NEW ORGANOCATALYTIC METHODS FOR C–C AND C–O BOND FORMATION

Dissertation

zur Erlangung des Doktorgrades der Naturwissenschaften

Dr. rer. nat.

an der Fakultät für Chemie und Pharmazie

der Universität Regensburg

vorgelegt von

Christopher Rose

aus Forchheim

Regensburg 2011

Der experimentelle Teil dieser Arbeit wurde in der Zeit zwischen Januar 2008 und Januar 2011 unter Anleitung von Dr. Kirsten Zeitler am Lehrstuhl für Organische Chemie der Universität Regensburg angefertigt. Meiner Betreuerin danke ich herzlich für die Überlassung dieses interessanten Projektes sowie für die hervorragende Betreuung und Unterstützung.

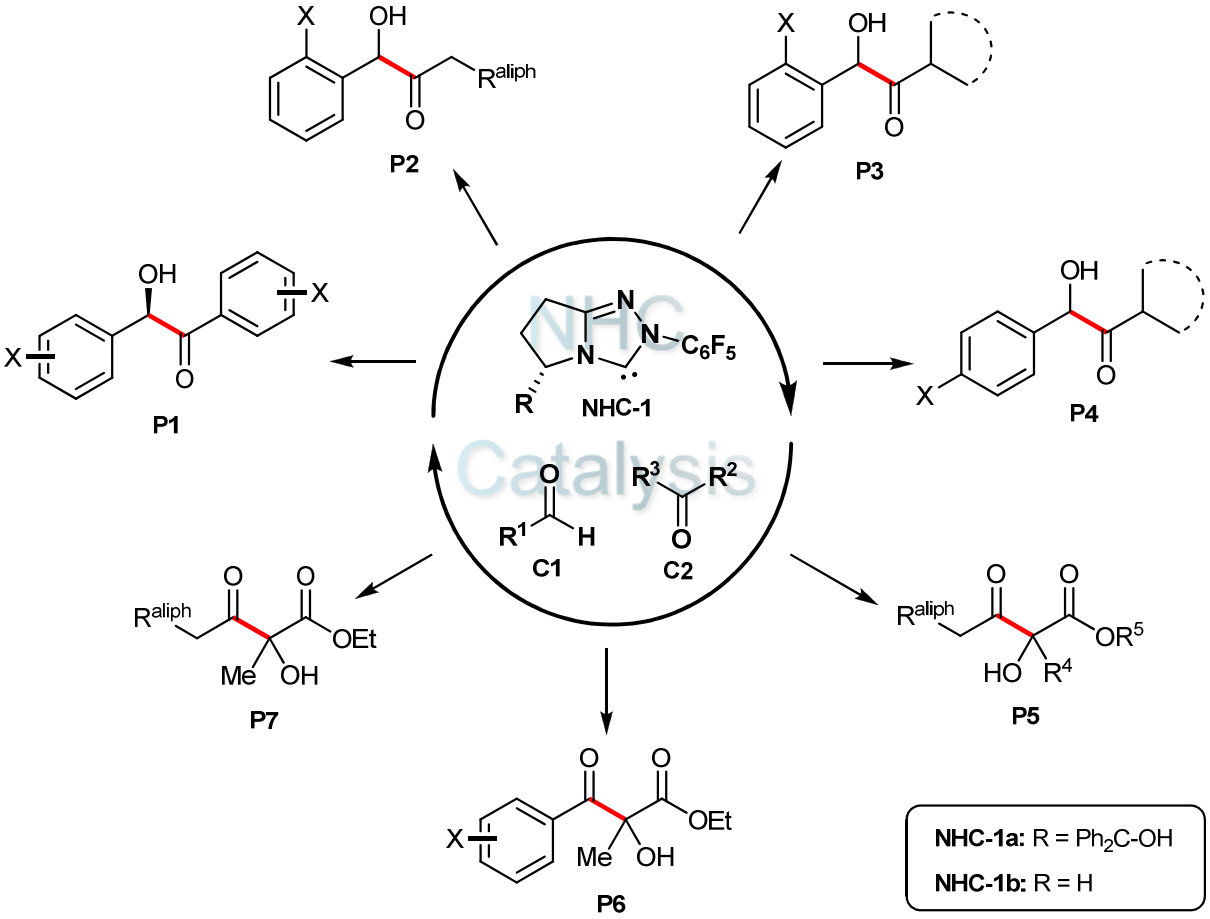
Die Arbeit wurde angeleitet von:		Dr. Kirsten Zeitler
Promotionsgesuch eingereicht am:		13.04.2011
Promotionskolloquium am:		31.05.2011
Prüfungsausschuss:	Vorsitz	Prof. Dr. Joachim Wegener
	Erstgutachter	Dr. Kirsten Zeitler
	Zweitgutachter	Prof. Dr. Oliver Reiser
	Dritter Prüfer	Prof. Dr. Henri Brunner

Chemical research and mountaineering have much in common. If the goal or the summit is to be reached, both initiative and determination as well as perseverance are required. But after the hard work it is a great joy to be at the goal or peak with its splendid panorama. (Georg Wittig, Nobel Lecture, 8 December 1979)

Table of Contents

Summary

The present dissertation deals with novel carbene catalyzed processes for C–C and C–O bond formation. Chapter 1 covers (chemo- and/or stereo-)selective nucleophilic acylation reactions between aldehydes **C1** and carbonyl electrophiles **C2** (Scheme 1).



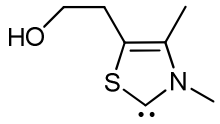
Scheme 1: Product scope of carbene catalyzed nucleophilic acylation reactions between aldehydes **C1** and carbonyl electrophiles **C2**.

After a brief introduction (chapter 1.1), a highly enantioselective (homo-)benzoin condensation is described in chapter 1.2. For the first time, the concept of hydrogen bonding was successfully introduced to control enantioselectivity. Pyroglutamic acid-derived, bifunctional carbene **NHC-1a** equipped with a protic, substituent R effectuates good to high yields and excellent *ee* values of the homocoupling products **P1**. The presence of a pentafluorophenyl substituent adjacent to the carbene carbon was demonstrated to be prerequisite to ensure a high catalytic activity.

The extension to crossed benzoin-type condensations is presented in chapter 1.3: based on a synergism between a highly reactive catalyst system and substrate control, chemoselective cross condensations

between aliphatic and *ortho*-substituted benzaldehydes (yielding cross products **P2** and **P3**) were accomplished. Contrary to previous alternative methods, a prefunctionalization of substrates is not required. The *o*-substituent ensures high selectivity and can be smoothly removed in case of bromine, thus serving as a temporary and traceless directing group.

Chapter 1.4 tries to shed light on the interplay between catalyst and substrate control in crossed acyloin condensation reactions. For this purpose, the relative performance of achiral pentafluorphenyl-substituted carbene **NHC-1b** and thiazolium-derived carbene **NHC-2**, previously introduced by Stetter, was evaluated. Triazolium derived carbene **NHC-1b** was found to be more reactive not only than its thiazole counterpart **NHC-2**, but also compared to various other frequently applied heterazolium salts.



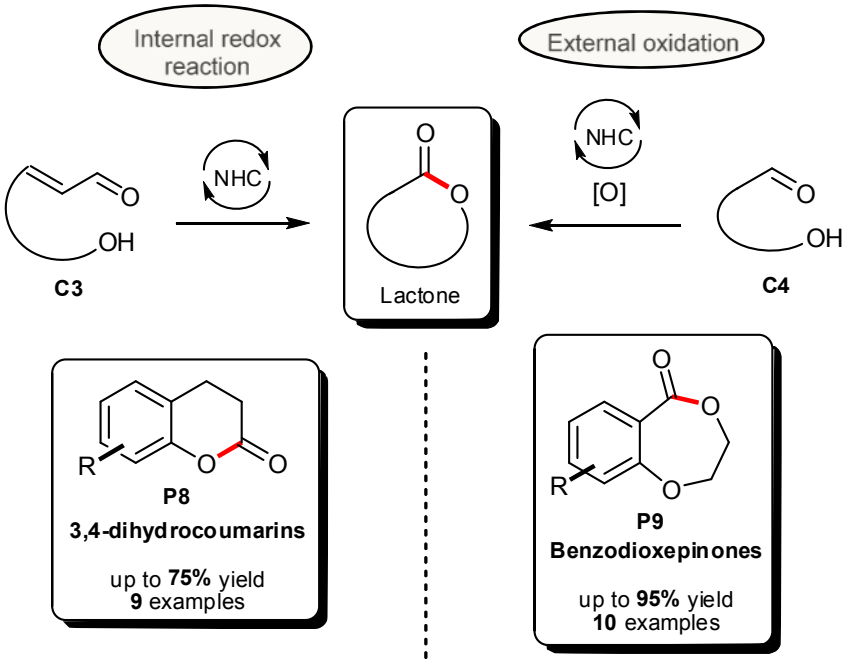
NHC-2

Figure 1: Thiazolium-derived carbene **NHC- 2** utilized by Stetter in his report on cross acyloin condensations.

In cross acyloin condensations between α-branched aliphatic aldehydes and benzaldehydes employing achiral triazolium precatalyst **NHC-1b**, moderate to good selectivities towards cross products **P4** can be achieved *without ortho*-substitution of the aromatic aldehyde. Moreover, an error in literature was corrected during these studies.

One of the hitherto rare examples of a carbene catalyzed cross coupling process between aldehydes and ketones is disclosed in chapter 1.5. Pursuing a rational mechanistic approach with relatively electron deficient carbene **NHC-1b** playing the key role, the novel, bioinspired method provides a modular access to α-hydroxy-β-ketoesters **P5** to **P7**. The substrate scope – all employing readily available compounds – is remarkable, ranging from aliphatic to aromatic aldehydes, as well as differently substituted α-ketoesters.

Chapter 2 is devoted to carbene catalyzed C–O bond forming reactions. In particular, new NHC catalyzed lactonization strategies either relying on an internal redox reaction of α,β-unsaturated aldehydes **C3** or external oxidation of substrates **C4** are presented (Scheme 2).



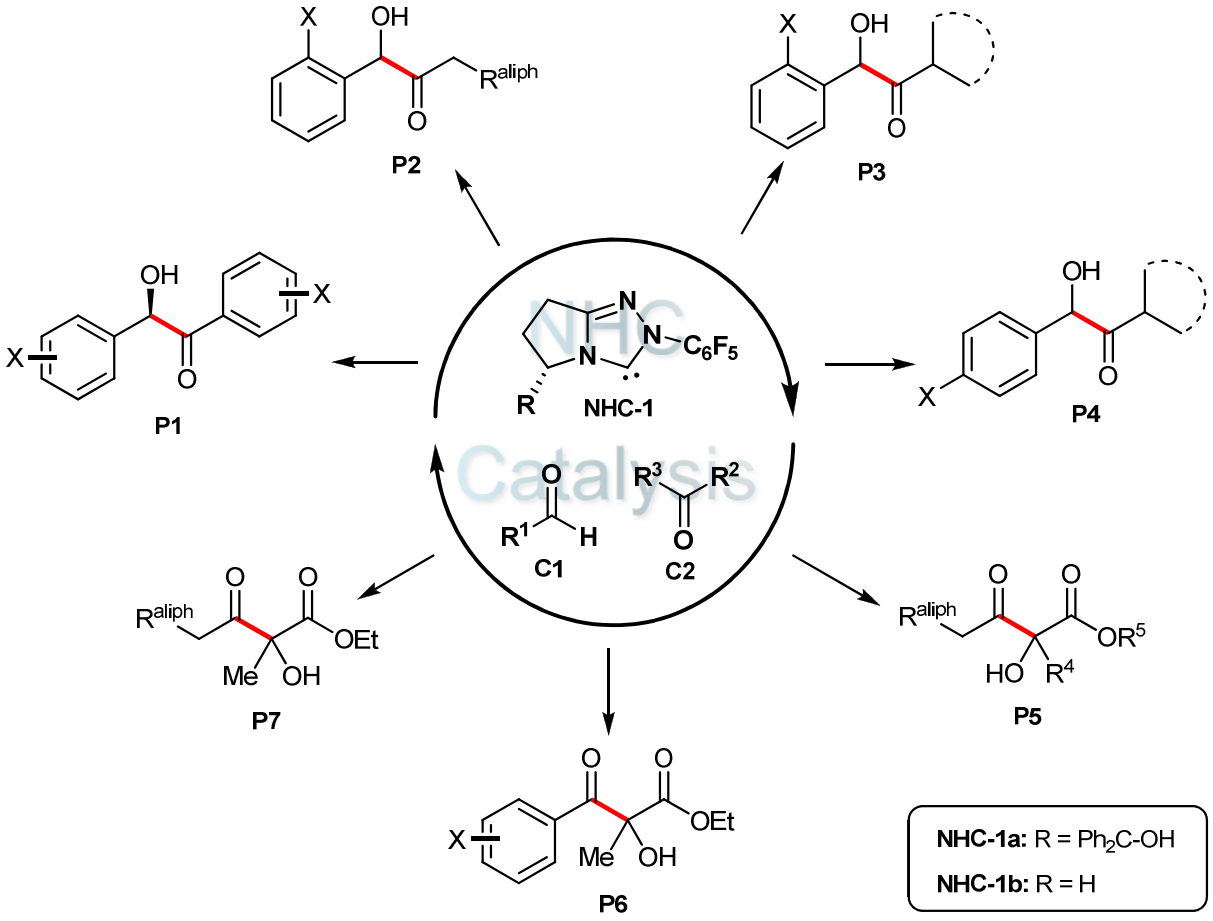
Scheme 2: Carbene catalyzed lactonization strategies for the synthesis of benzolactones.

After an introductory overview of these approaches (chapter 2.1), a carbene catalyzed access to 3,4-dihydrocoumarins **P8** *via* redox lactonization of the corresponding cinnamaldehyde derivatives is presented in chapter 2.2. The transformation involves a homoenolate protonation-cyclization sequence and gives rise to lactone products in moderate to good yields. As a result of a competing oxidative pathway, coumarins are observed in minor amounts.

Finally, a carbene catalyzed oxidative lactonization process was applied to the synthesis of benzodioxepinones **P9** (chapter 2.3). In this non-high dilution procedure, $FeCl_3$ is utilized as formal terminal oxidant. Seven membered lactones are formed in good to excellent yields, selected examples exhibit interesting properties as odorants, as revealed in collaboration with Dr. Philip Kraft (Givaudan AG, Switzerland).

Zusammenfassung

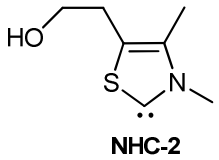
Die vorliegende Dissertation beschäftigt sich mit neuen, carbenkatalysierten Prozessen zur C–C bzw. C–O Bindungsknüpfung. Im Kapitel 1 werden (chemo- bzw. stereo-)selektive nukleophile Acylierungsreaktionen zwischen Aldehyden **C1** und Carbonyl-Elektrophilen **C2** behandelt (Schema 1).



Schema 1: Carbenkatalysierte nukleophile Acylierungsreaktionen zwischen Aldehyden **C1** und Carbonyl-Elektrophilen **C2**: Produktspektrum.

Nach einer kurzen Einführung (Kapitel 1.1) wird in Kapitel 1.2 eine hoch enantioselektive (Homo-) Benzoinkondensation beschrieben. Hierbei wurde zum ersten Mal erfolgreich das Konzept der Wasserstoffbrückenbindung zur Stereokontrolle eingeführt. Das von Pyroglutaminsäure abgeleitete, bifunktionelle Carben **NHC-1a** mit einem protischen Rest R erzielt dabei gute bis sehr gute Ausbeuten und exzellente Enantiomerenüberschüsse der Homokupplungsprodukte **P1**. Um eine hohe katalytische Aktivität zu gewährleisten, ist ein Pentafluorophenyl-Substituent in Nachbarschaft zum Carben-Kohlenstoffatom unbedingte Voraussetzung.

Die Erweiterung auf gekreuzte benzoinartige Kondensationen wird in Kapitel 1.3 vorgestellt: Basierend auf einem Synergismus zwischen einem hochreaktiven, katalytischen System und Substratkontrolle, konnten chemoselektive gekreuzte Acyloinkondensationen zwischen einer Reihe aliphatischer Aldehyde und *o*-substituierter Benzaldehyde durchgeführt werden (Kreuzprodukte **P2**, **P3**). Im Gegensatz zu bisherigen, alternativen Methoden ist eine Präfunktionalisierung der Substrate dabei nicht nötig. Der *o*-Substituent gewährleistet eine hohe Selektivität und kann – falls erwünscht - im Falle von Bromid leicht wieder entfernt werden. Er dient somit als temporäre, dirigierende Gruppe.
Kapitel 1.4 beleuchtet das Zusammenspiel von Katalysator- und Substratkontrolle in gekreuzten Acyloinkondensationen. Zu diesem Zweck wurde ein direkter Vergleich des pentafluorphenyl-substituierten Carbens **NHC-1b** und des von Stetter für Acyloinkondensationen eingesetzten, Thiazolium-basierten Carbens **NHC-2** durchgeführt, wobei eine höhere katalytische Aktivität von **NHC-1b** gegenüber **NHC-2** deutlich wurde.

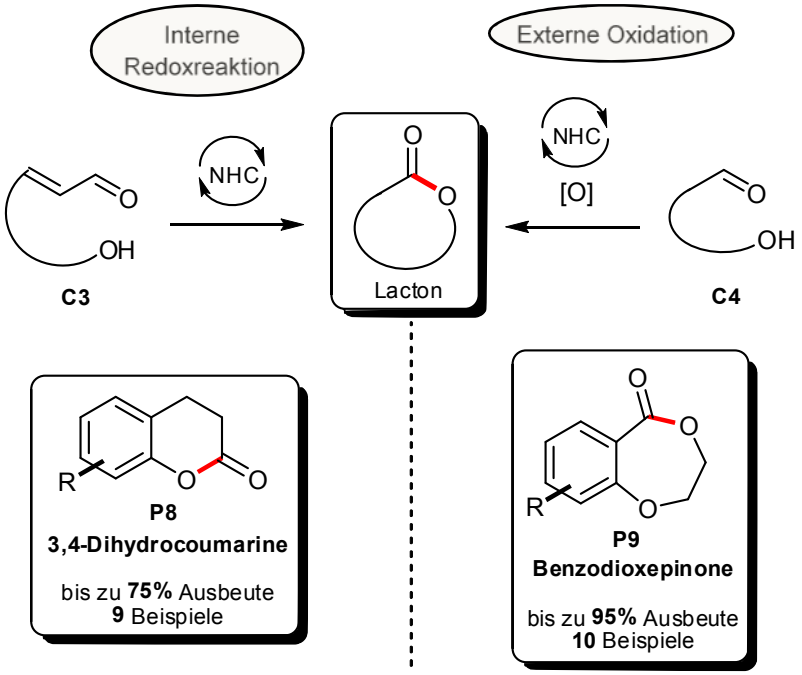


NHC-2

Abb. 1: Das von Stetter für gekreuzte Acyloinkondensationen eingesetzte Thiazolium-basierte Carben **NHC-2**.

Auch im Vergleich mit einigen anderen häufig verwendeten Heterazoliumsalzen besitzt **NHC-1b** eine Sonderstellung. Letztendlich können unter den von uns etablierten Bedingungen auch gekreuzte Acyloinkondensationen zwischen gehinderten aliphatischen und *nicht o*-substituierten Benzaldehyden mit moderaten bis guten Ausbeuten der Kreuzprodukte **P4**, erreicht werden. Zusätzlich wurde im Zuge der Untersuchungen ein Fehler in der Literatur aufgedeckt und berichtigt.
Eines der bisher wenigen Beispiele für einen carbenkatalysierten Kupplungsprozess zwischen Aldehyden und Ketonen wird in Kapitel 1.5 vorgestellt. Bei der Entwicklung der dabei zum Tragen kommenden, biomimetischen Methode verfolgten wir einen rationalen mechanistischen Ansatz, wobei dem als elektronenarm zu bezeichnenden Carben **NHC-1b** die Schlüsselrolle zukommt. Unter Verwendung von leicht verfügbaren Aldehyden und α-Ketoestern als Ausgangsmaterialien können damit α-Hydroxy-β-Ketoester **P5** bis **P7** modular und unter sehr milden Reaktionsbedingungen synthetisiert werden. Die enorme Substratbreite (aliphatische und aromatische Aldehyde sowie verschieden substituierte α-Ketoester) ist hierbei besonders bemerkenswert.

Kapitel 2 widmet sich carbenkatalysierten C–O Bindungsknüpfungen. Konkret vorgestellt werden dabei neue, NHC katalysierte Lactonisierungsstrategien, die entweder auf interner Redoxreaktion der α,β-ungesättigten Aldehyde **C3** oder externer Oxidation der Substrate **C4**, basieren (Schema 2).



Schema 2: Carbenkatalysierte Lactonisierungsstrategien für die Synthese von Benzolactonen.

Nach einer einführenden Vorstellung der zugrunde liegenden Strategien (Kapitel 2.1), wird in Kapitel 2.2 ein carbenkatalytischer Zugang zu 3,4-Dihydrocoumarinen **P8** über Redoxlactonisierung (interne Redoxreaktion) der entsprechenden Zimtaldehydderivate behandelt. Der Prozess beinhaltet eine Homoenolat-Protonierung-Cyclisierungs-Sequenz und liefert die jeweiligen Lactone in moderaten bis guten Ausbeuten. Bedingt durch einen konkurrierenden oxidativen Reaktionspfad werden Coumarine als Nebenprodukte in geringen Mengen beobachtet.

Ein carbenkatalysierter oxidativer Lactonisierungsprozess (externe Oxidation) wird schließlich für die Synthese von Benzodioxepinonderivaten **P9** angewandt (Kapitel 2.3). In dieser Lactonisierung, die nicht unter hochverdünnten Bedingungen erfolgen muss, dient $FeCl_3$ als formales terminales Oxidans. Die Produkte werden in guten bis exzellenten Ausbeuten erhalten, ausgewählte Beispiele zeigen interessante Eigenschaften als Geruchsstoffe, wie in Zusammenarbeit mit Dr. Philip Kraft (Givaudan Schweiz AG) ermittelt wurde.

1 Carbene Catalyzed C–C Bond Forming Reactions

1.1 Introduction

Organic molecules exhibit more or less complex frameworks of diversely connected carbon atoms. Hence, methods for the formation of carbon-carbon bonds have been fundamental in organic synthesis. First reports concerning this type of transformation date back to the mid-19th century: during their experimentations with bitter almond oil (which contains predominantly benzaldehyde (**1**) and a small amount of hydrocyanic acid), Liebig and Wöhler discovered the benzoin condensation (Figure **2**, eq. 1).[1]

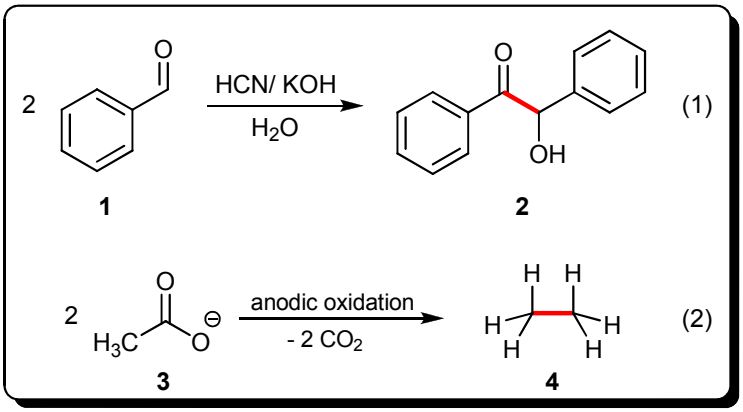
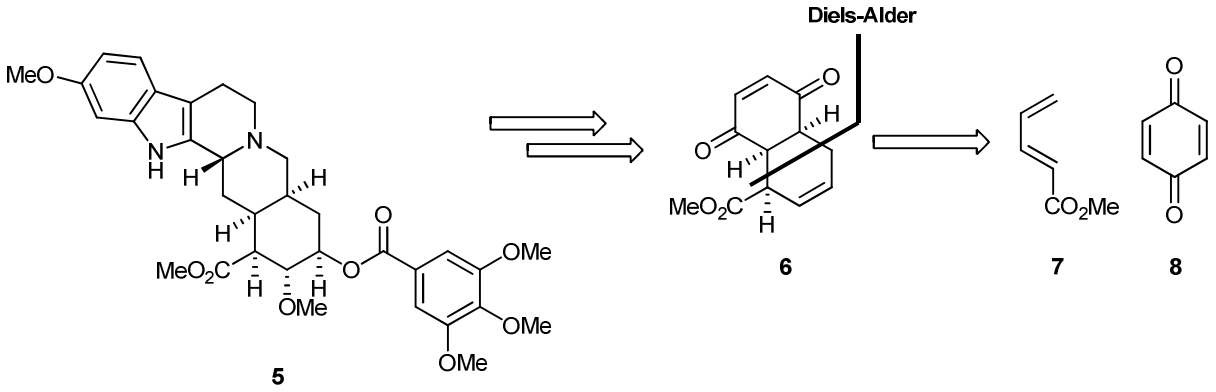


Figure 2: Two of the first documented C–C coupling reactions: the cyanide mediated benzoin condensation according to Liebig and Wöhler (eq. 1) and the Kolbe electrolysis (eq. 2).

Thirteen years later, German chemist Hermann Kolbe reported on the formation of ethane (**4**) (and CO_2) upon anodic oxidation of acetate – a transformation which is known today as Kolbe electrolysis.[2] Owing to the curiosity and commitment of countless chemists, many highly valuable, yet often non-catalytic C–C coupling processes were developed during the ensuing years and decades. In many instances, these involve enolate chemistry, organometallic reagents or pericyclic reactions. Based on this early methodology pool, the total synthesis of natural products has flourished as an independent discipline in organic chemistry since the end of World War II.[3] Vice versa, by being showcased in a complex molecule synthesis, the significance of a particular transformation was evidenced. The Nobel Prize-awarded Diels-Alder reaction,[4] which served as a cornerstone in Woodward`s landmark synthesis of reserpine (**5**), may be mentioned as an example (Scheme 3).[5]



Scheme 3: The Diels-Alder reaction as starting point for the total synthesis of reserpine (**5**) according to Woodward et al. 1958.

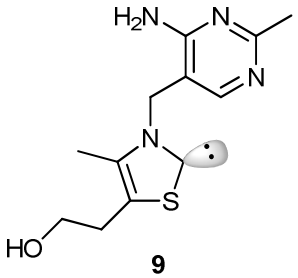
Great importance on the part of academic and industrial research is attached to catalytic methods in light of their high efficiency.[i] With respect to today`s arsenal of metal catalyzed C–C coupling protocols, the development of the Wacker Process[7] (i.e. the palladium (II)-catalyzed transformation of ethylene into acetaldehyde) by the end of the 1950`s, represented an important accomplishment. Stimulated by the success of this industrial process, many chemists devoted their work to transition metal catalyzed C–C couplings in the following years. Intensive research has finally brought forth outstanding achievements, contemporary organic synthesis would be unthinkable without.[8] Just recently, two methodologies which evolved during this period of time have been awarded the Nobel Prize in chemistry: the development of olefin metathesis[9] (2005) and palladium catalyzed cross couplings[10] (2010).

Until the end of the 20th century, it was expected that metal- and enzymatic catalysis would dominate (asymmetric) synthesis for years to come.[11] Contrary to this prospect, catalysis with "purely organic" molecules (i.e. Organocatalysis) has succeeded in becoming the third pillar, witnessing an exponential growth of publications since 2000.[12] In general, organocatalytic processes are considered to be more robust, less toxic and less expensive than their metal-mediated counterparts, thus becoming attractive for synthetic applications.[13]

[i] Meanwhile, more than 80% of all chemical products worldwide are synthesized in catalytic processes. [6]

N–Heterocyclic Carbenes as Organocatalysts

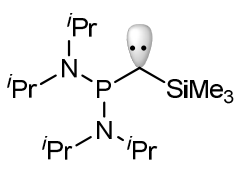
In view of an increasing need for complex chemicals, e.g. pharmaceuticals, agrochemicals or materials, the development of new and selective methods for carbon carbon bond formation is an ongoing objective in organic chemistry. In this context, chemists have been inspired by nature for hundreds of years, trying to understand and imitate its elegant and highly efficient processes.[14]
Regarding the biomimetic archetype of carbene organocatalysis, the identification of a thiazolium-derived *N*-heterocyclic carbene as active species in thiamine dependent enzymes[15] was a seminal event (Figure 3).[16]



9

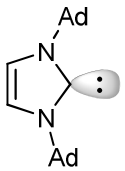
Figure 3: Prototype for NHC organocatalysts: coenzyme thiamine (**9**) (vitamin B1).

However, during the ensuing almost forty years, reports involving heterazolium derived carbenes as catalytically active species appeared only sporadically.[17] For contemporary chemists, those molecules were more elusive reactive intermediates than a promising class of compounds. Two reports on the synthesis and characterization of heteroatom substituted, nucleophilic carbenes **10** and **11,** being stable at room temperature, changed this attitude and ultimately paved the way for NHCs into chemical laboratories (Figure 4).[18] Only few years later, Enders et al. presented the first "bottle-able" carbene **12**,[19] which is even commercially available.[ii]



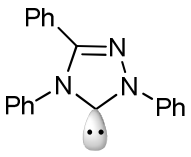
10

Bertrand et al. 1988
The first stable nucleophilic carbene.



11

Arduengo et al. 1991
The first isolable (crystalline) carbene.



12

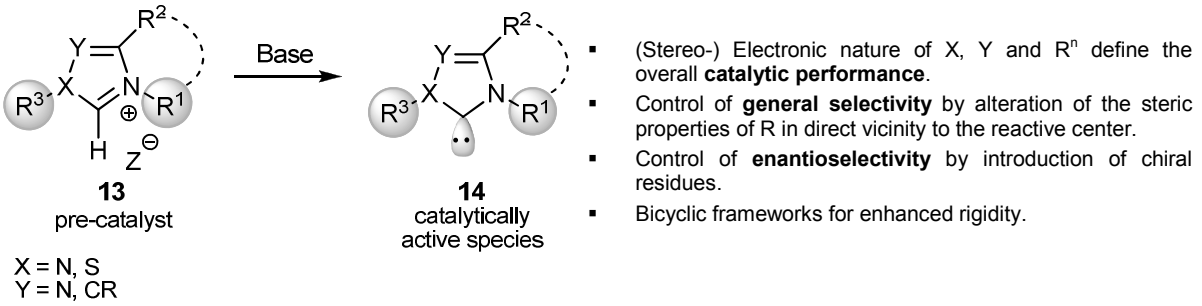
Enders et al. 1995
The first N-heterocyclic carbene to be commercially available.

Figure 4: The evolution of stable carbenes: important compounds.

[ii] CAS: 166773-08-6. 1g→263.70€ (Acros Organics, prize retrieved on 14.03.2011).

Since then, *N*-heterocyclic carbenes have been enriching the synthetic organic toolbox with a variety of powerful methods, especially for the construction of carbon-carbon bonds.[20] Meanwhile, they constitute one major class of organocatalysts.[21]

The generation of the active catalyst **14** commonly occurs *via* in situ deprotonation of the corresponding heterazolium salt **13** (Scheme 4). The reactive center is a divalent carbon atom, which is embedded in a heterocyclic ring system. By exhibiting π-donating and σ-withdrawing properties, the adjacent heteroatoms ensure sufficient overall thermodynamic stability.[22] The catalytic performance is predominantly determined by the nature of the azole ring[23] (substituents X, Y) and stereoelectronic properties of the attached substituents.[24] These factors ultimately become measurable as acidity of C2-hydrogen in the parent heterazolium salt.[25] Acid-base relationships have been demonstrated to significantly influence the reaction outcome.[26] Altering the steric configuration in direct vicinity to the reactive center may directly impact the catalyst's selectivity.[27]

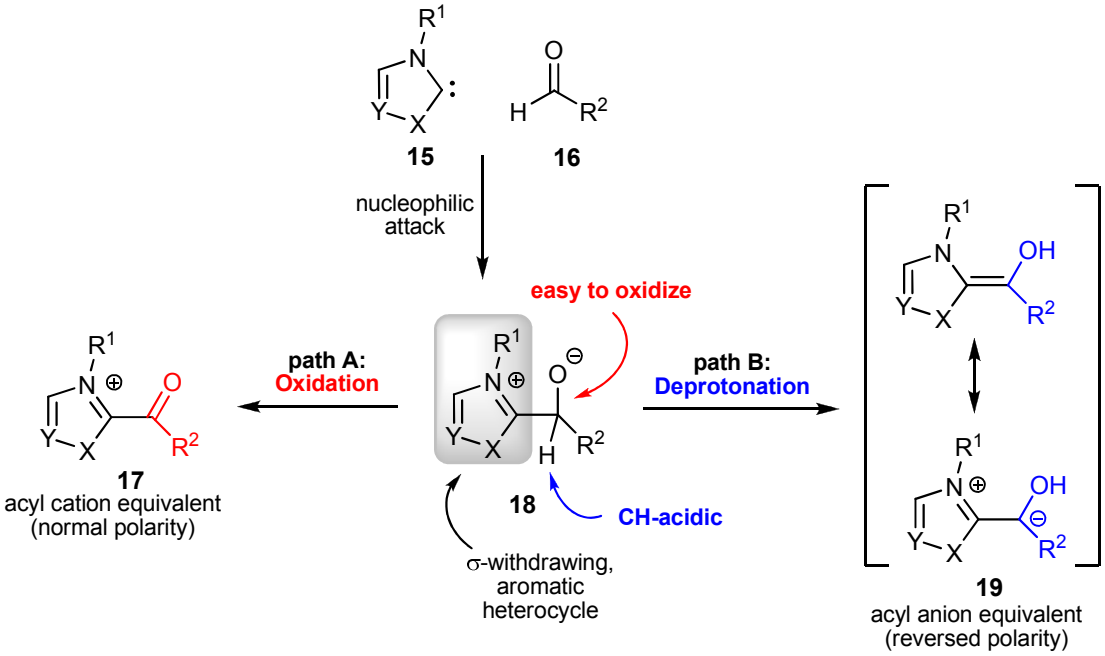


Scheme 4: Formation of the active catalyst and general structural features of *N*-heterocyclic carbenes.

Introduction of stereocenters, particularly in combination with bi- or polycyclic systems offering enhanced rigidity, renders the NHC suitable for enantioselective catalysis.[28]

Given the nucleophilic nature of *N*-heterocyclic carbenes, they can interact with various electrophiles. A nucleophilic attack of NHC **15** to an aldehyde moiety **16** (which is prevalent[29, 30, 31, 32, 33, 34, 35 36] in NHC Organocatalysis), results in a tetrahedral intermediate **18** (Scheme 5). In this initially formed adduct, the heterazolium unit both effects a higher susceptibility to oxidation and acidifies the former carbonyl hydrogen atom. In case no α-reducible functional groups are present,[iii] the further reaction process depends upon the applied reaction conditions. Compound **19** that would result from a deprotonation step (path B), represents a synthetic equivalent for an acyl anion and is commonly referred to as the Breslow Intermediate.[17c]

[iii] These may effect a cooperative interaction within the intermediate ("extended Umpolung").[20a]



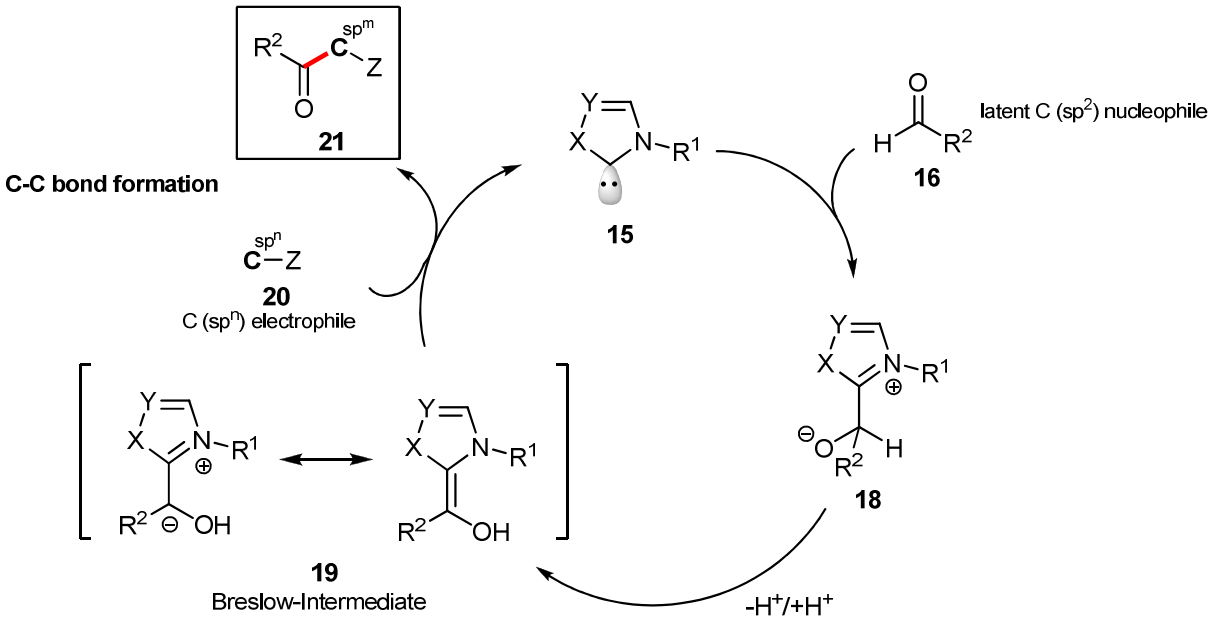
Scheme 5: Lewis base activation of aldehydes by NHCs: reaction pathways.

Contrary to acyl cation **17**[37] this species exhibits reversed polarity ("Classical Umpolung"[38, 20a]), which in turn allows for unconventional synthetic strategies, i.e. *nucleophilic* acylation reactions. Prominent examples which take advantage of this catalytic[iv] methodology are the Stetter Reaction and the Benzoin Condensation. The introduction of NHCs as competent catalysts for this coupling of two molecules of benzaldehyde was reported only in 1943 by Ukai et al.[40] Interestingly, though, this happened more than 10 years before the thiazol-2-ylidene involvement in thiamine dependent transformations was proven.[17c]

[iv] An important example for a non-catalytic nucleophilc acylation methodology is the Corey-Seebach reaction.[39]

Carbene Catalyzed C–C Couplings *via* Nucleophilic Acylation Reactions

Nucleophilic acylation reactions are likely to proceed according to Breslow`s mechanistic proposal from 1958:[17c] nucleophilic attack of the free carbene **15** to the electrophilic carbonyl carbon of aldehyde **16**, followed by de-/reprotonation leads to Breslow intermediate **19**, which can then undergo C–C bond formation with electrophile **20** (Scheme 6). Release of ketone product **21** concomitantly regenerates the active catalyst. In analogy to metal catalyzed cross coupling reactions, a classification (sp^2–sp, sp^2–sp^2 or sp^2–sp^3) depending on the hybridization of the electrophilic center can be carried out.



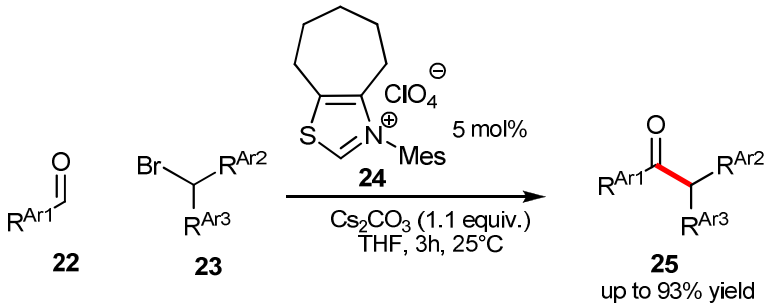
Scheme 6: $C(sp^2)$–$C(sp^n)$ couplings: general mechanism of NHC-catalyzed nucleophilic acylation reactions.

A study of the relevant literature reveals, that sp^2–sp^2 cross couplings constitute the main part, whereas sp- and sp^3 electrophiles are relatively rare. If one considers the fame of the Benzoin or Stetter reaction, this is not entirely surprising.

The following section highlights three recent reports on NHC catalyzed nucleophilic acylation reactions which represent each of the aforementioned coupling types.

NHC–Catalyzed Nucleophilic Acylation of Activated Alkyl Halides

As already mentioned, the coupling of acyl anion equivalents with sp^3 electrophiles is – compared to their sp^2 counterparts – largely underrepresented in literature. In 2010, the group of Glorius accomplished a nucleophilic acylation of activated alkyl halides **23**, taking advantage of NHC-catalyzed Umpolung methodology (Scheme 7).[41]



Scheme 7: A Carbene catalyzed $C(sp^2)$–$C(sp^3)$ coupling: nucleophilic acylation of activated alkyl halides as reported by Glorius et al.

Their novel[42] concept is applicable to different *meta*- and *para*-substituted aryl aldehydes and heteroaryl aldehydes **22**. In contrast, *o*-substituted aryl aldehydes as well as aliphatic aldehydes proved incompatible with this methodology. It was shown that apart from some symmetrical and one unsymmetrical diaryl bromides **23**, α–bromo ketones and α–bromo esters can be converted to the corresponding aryl ketones. Among a set of heterazolium salts, only the bicyclic mesityl substituted thiazolium-precatalyst **24** provides high yields. A direct comparison between bicyclic triazoliumsalts **26** and **27** nicely exemplifies the impact of azole substituents (Figure 5).

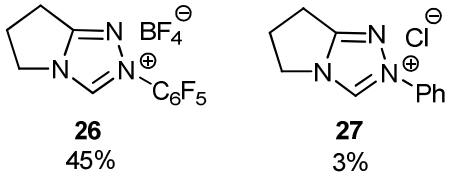


Figure 5: Direct comparison of triazolium precatalysts with different stereoelectronic properties (for reaction conditions see **Scheme** 7: R^{Ar1} = (*p*-Cl)Ph; R^{Ar2}, R^{Ar3} = Ph; 1.2 equiv. K_2CO_3 instead of Cs_2CO_3; 2h instead of 3h; 10 mol % triazoliumsalt **26** or **27** instead of 5 mol% **24**).

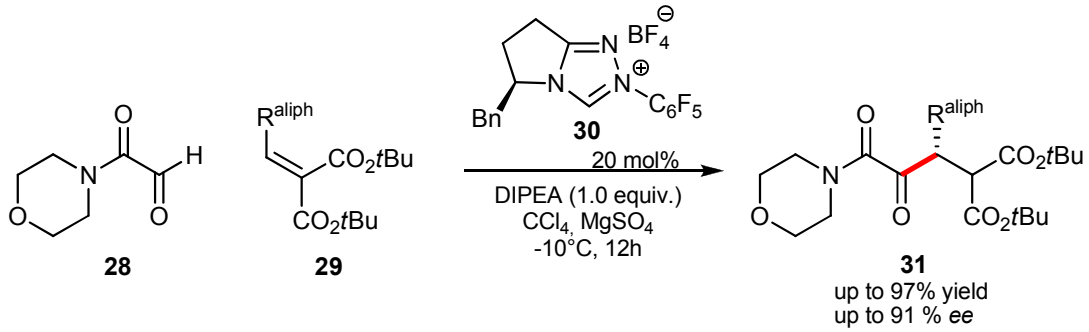
The stoichiometric use of base is required to maintain excellent conversion – presumably to provide a sufficient amount of free carbene in the reaction mixture.

Moreover, benzoin formation is reversible[43] to a certain extent: when using this masked aldehyde, the corresponding alkylated product can still be isolated in 55% yield. In order to establish a mechanistic

hypothesis, competition experiments were conducted. Based on these findings, a S_N1-type mechanism is likely to be favored over a potential concerted or a S_N2-like pathway, respectively.

NHC–Catalyzed Asymmetric Nucleophilic Acylation of Alkylidene Malonates

The conjugate addition of acyl anion equivalents to activated alkenes, is commonly referred to as the Stetter Reaction. Despite numerous reports on catalytic enantioselective intramolecular variants of this sp^2–sp^2 coupling, corresponding intermolecular processes are relatively rare. In 2008, Rovis and co-workers presented an NHC catalyzed asymmetric Stetter reaction between glyoxamides **28** and alkylidene malonates **29** (Scheme 8).[44]

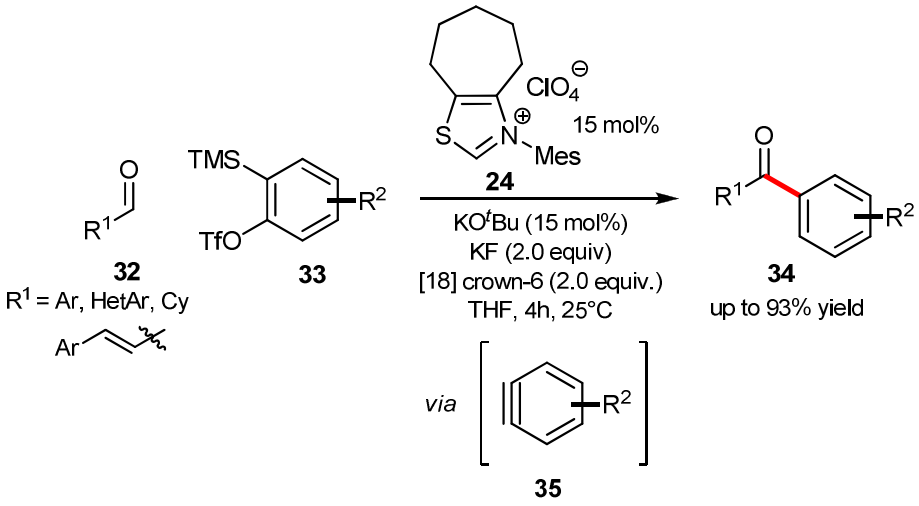


Scheme 8: A Carbene catalyzed C(sp^2)–C(sp^2) coupling: asymmetric Stetter reaction between glyoxamides and alkylidene malonates as reported by Rovis et al.

Generally, the scope of their method is somehow limited to glyoxamides derived from tertiary cyclic amines with morpholine derivative being the best reaction partner. In the course of optimization studies the authors revealed that *tert*-butyl malonates are crucial for achieving high *ee* values. Less sterically hindered esters (Me, ^{i}Pr) result in inferior stereoinduction. The enantiomeric excess is relatively constant (~ 80% *ee*) in a variety of polar and nonpolar solvents. However, reasonable yields are only obtained in nonpolar solvents with carbon tetrachloride being optimal. To suppress the observed erosion of the newly formed stereocenter, the reaction temperature was decreased to – 10° C along with the application of a bulkier base (DIPEA). It was further demonstrated that in β position of the alkylidene malonate, a variety of alkyl substituents are tolerated.

NHC Catalyzed Nucleophilic Acylation of Arynes

Owing to the introduction of 2-(trimethylsilyl) aryl triflates **33** as precursors of arynes, their application in organic synthesis has witnessed a rapid growth during the past few years. It was already demonstrated that these highly reactive intermediates can be successfully formally inserted into carbon–carbon-, carbon–heteroatom- and heteroatom–hydrogen bonds *via* transition metal free reactions. In 2010, Glorius reported the first (hydro-)acylation of arynes **35** derived from **33**, capitalizing on NHC catalyzed Umpolung methodology (Scheme 9).[45]



Scheme 9: A Carbene catalyzed C(sp^2)–C(sp) coupling: hydroacylation of arynes as reported by Glorius et al.

Within a series of heterazolium precatalysts tested, only the bicyclic sterically demanding thiazolium salt **23** results in satisfactory amounts of product. Other frequently applied carbene precursors such as **36** or **37** (Figure 6) either fail completely or only provide low yields.

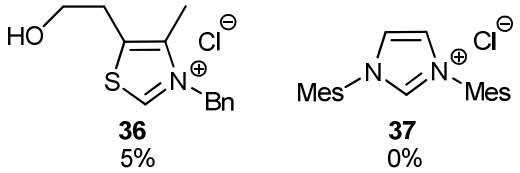


Figure 6: Evaluation of thiazolium- and imidazolium pre-catalysts (for reaction conditions, see Scheme 9: R^1 = (*p*-Br)Ph; R^2 = H; 20 mol % K_2CO_3 instead of 15 mol % KO*t*Bu; 10 mol % heterazoliumsalt **36** or **37** instead of 15 mol % **24**).

Under optimized conditions, the authors neither observe products stemming from an attack of the NHC to the aryne nor from a conceivable attack of the aryne **35** to the aldehyde **32**. It was demonstrated that various donor- and acceptor substituted aryl aldehydes are competent reaction partners, albeit *o*-substituted benzaldehydes furnish only moderate yield of the corresponding benzophenone products **34**. Even challenging aldehydes such as ferrocenecarboxaldehyde,

α,β-unsaturated aldehydes, heteroaromatic aldehydes and cyclohexanecarboxaldehyde undergo the desired transformation.

As expected, symmetrical aryne precursors produce benzophenones as a single product, whereas unsymmetrical arynes furnish mixtures of regioisomers. In order to shed light on a potential reaction mechanism, the authors performed comparison experiments with variable substrate combinations. The observation give clear evidence that the electronical nature of the aryne does not affect the reaction rate. On the contrary, the electronic nature of the aldehyde seriously impacts the rate of reaction: electron deficient ones react faster than their donor substituted counterparts.

The mechanistic proposal involves the formation of the Breslow Intermediate as rate determining step followed by its stepwise or concerted attack of the aryne. Final release of the NHC catalyst closes the catalytic cycle under concomitant formation of the ketone product.

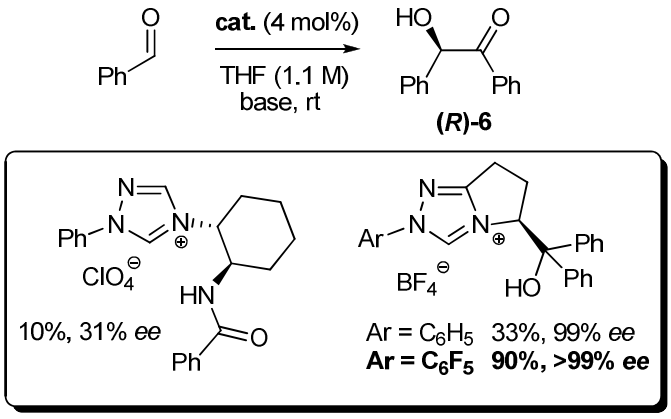
References:

(1) F. Wöhler, J. Liebig, *Ann. Pharm.* **1832**, *3*, 249.
(2) H. Kolbe, *Ann. Chem. Pharm.* **1849**, *69*, 257.
(3) a) K. C. Nicolaou, E. J. Sørensen, *Classics in Total Synthesis*, VCH, Weinheim, **1996**; b) J. Mulzer, *Nachr. Chem.* **2007**, *55*, 731.
(4) O. Diels, K. Alder, *Liebigs Ann. Chem.* **1928**, *460*, 98.
(5) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *J. Am. Chem. Soc.* **1956**, *78*, 2023.
(6) a) *Roadmap der deutschen Katalyseforschung*, German Catalysis Society, Frankfurt am Main, **2010**; b) *Katalyse - Heterogene Katalysatoren Gestern, Heute, Morgen*, BASF SE, Ludwigshafen, **2008**; c) F. Schüth, *Chem. Unserer Zeit* **2006**, *40*, 92.
(7) a) J. Smidt, W. Hafner, R. Jira, J. Sedlmeier, R. Sieber, R. Ruttinger, H. Kojer, *Angew. Chem.* **1959**, *71*, 176; b) R. Jira, *Angew. Chem. Int. Ed.* **2009**, *48*, 9034.
(8) *Metal-catalyzed Cross-coupling Reactions*, Wiley-VCH, Weinheim, **1998**.
(9) a) A. H. Hoveyda, A. R. Zhugralin, *Nature* **2007**, *450*, 243; b) *Handbook of Metathesis*, Wiley-VCH, Weinheim, **2003**; c) P. Ahlberg, in *Advanced information on the Nobel Prize in Chemistry 2005 (available online: www.nobelprize.org)*, The Royal Swedish Academy of Sciences, Stockholm, **2005**.
(10) a) X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 9047; b) O. Reiser, *Chem. Unserer Zeit* **2001**, *35*, 94; c) J.-E. Bäckvall, in *Scientific Background on the Nobel Prize in Chemistry 2010 (available online: www.nobelprize.org)*, The Royal Swedish Academy of Sciences, Stockholm, **2010**.
(11) For a perspective on organic synthesis, see: D. Seebach, *Angew. Chem.* **1990**, *102*, 1363.
(12) For selected recent reviews on organocatalysis, see: a) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; b) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; c) Special issue on organocatalysis: *Chem. Rev.* **2007**, *107*, 5413; d) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**; e) B. List, J. W. Yang, *Science* **2006**, *313*, 1584.
(13) For reviews on the application of organocatalytic methods in the total synthesis of natural products, see: a) R. M. de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575; b) E.

Marqués-López, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138; c) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167.
(14) D. Enders, A. A. Narine, *J. Org. Chem.* **2008**, *73*, 7857.
(15) M. Pohl, B. Lingen, M. Müller, *Chem. Eur. J.* **2002**, *8*, 5288.
(16) S. Mizuhara, P. Handler, *J. Am. Chem. Soc.* **1954**, *76*, 571.
(17) a) J. C. Sheehan, D. H. Hunneman, *J. Am. Chem. Soc.* **1966**, *88*, 3666; b) J. C. Sheehan, T. Hara, *J. Org. Chem.* **1974**, *39*, 1196; c) R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719.
(18) a) A. J. Arduengo III, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361; b) A. Igau, H. Grützmacher, A. Baceiredo, G. Bertrand, *J. Am. Chem. Soc.* **1988**, *110*, 6463; c) A. J. Arduengo, III, R. Krafczyk, *Chem. Unserer Zeit* **1998**, *32*, 6.
(19) D. Enders, K. Breuer, G. Raabe, J. Runsink, J. H. Teles, J.-P. Melder, K. Ebel, S. Brode, *Angew. Chem. Int. Ed.* **1995**, *34*, 1021.
(20) a) K. Zeitler, *Angew. Chem. Int. Ed.* **2005**, *44*, 7506; b) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534; c) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; d) N. Marion, S. Diez-Gonzalez, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; e) J. S. Johnson, *Angew. Chem. Int. Ed.* **2004**, *43*, 1326; f) J. L. Moore, T. Rovis, *Top. Curr. Chem.* **2010**, *291*, 77; g) F. Glorius, K. Hirano, *Ernst Schering Found. Symp. Proc.* **2008**, 159; h) K. Zeitler, *Ernst Schering Found. Symp. Proc.* **2008**, 183; i) J. W. Bode, P.-C. Chiang, in *RSC Catalysis Series No. 6* (Ed.: S. Díez-González), **2011**.
(21) For an overview on asymmetric organocatalysis including a classification of organocatalysts, see: J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719.
(22) a) F. E. Hahn, M. C. Jahnke, *Angew. Chem. Int. Ed.* **2008**, *47*, 3122; b) R. Brückner, *Reaktionsmechanismen*, Spektrum, Akad. Verl., Heidelberg, **2003**.
(23) For a direct comparison of the catalytic performances of otherwise identical triazolium- and imidazolium precatalysts, see: J. R. Struble, J. Kaeobamrung, J. W. Bode, *Org. Lett.* **2008**, *10*, 957.
(24) For early work studying the influence of triazolium substituents on formoin-condensations, see: J. H. Teles, J.-P. Melder, K. Ebel, R. Schneider, E. Gehrer, W. Harder, S. Brode, D. Enders, K. Breuer, G. Raabe, *Helv. Chim. Acta* **1996**, *79*, 61.
(25) For contributions involving the determination of pK_a-values of heterazolium salts, see: a) R. W. Alder, P. R. Allen, S. J. Williams, *J. Chem. Soc., Chem. Commun.* **1995**, 1267; b) T. L. Amyes, S. T. Diver, J. P. Richard, F. M. Rivas, K. Toth, *J. Am. Chem. Soc.* **2004**, *126*, 4366; c) C. D. Campbell, N. Duguet, K. A. Gallagher, J. E. Thomson, A. G. Lindsay, A. C. O'Donoghue, A. D. Smith, *Chem. Commun.* **2008**, 3528; d) Y.-J. Kim, A. Streitwieser, *J. Am. Chem. Soc.* **2002**, *124*, 5757; e) A. M. Magill, K. J. Cavell, B. F. Yates, *J. Am. Chem. Soc.* **2004**, *126*, 8717; f) Y. Chu, H. Deng, J.-P. Cheng, *J. Org. Chem.* **2007**, *72*, 7790.
(26) For examples revealing the crucial role of acid-base relationships in NHC catalyzed reactions, see: a) J. Kaeobamrung, M. C. Kozlowski, J. W. Bode, *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20661; b) S. S. Sohn, J. W. Bode, *Org. Lett.* **2005**, *7*, 3873; c) H. Takikawa, K. Suzuki, *Org. Lett.* **2007**, *9*, 2713; d) L. Baragwanath, C. A. Rose, K. Zeitler, S. J. Connon, *J. Org. Chem.* **2009**, *74*, 9214.
(27) For examples exemplifying the impact of sterically demanding *N*-aryl substituents, see: a) K. Hirano, I. Piel, F. Glorius, *Adv. Synth. Catal.* **2008**, *350*, 984; b) K. Zeitler, *Org. Lett.* **2006**, *8*, 637; c) C. Burstein, S. Tschan, X. Xie, F. Glorius, *Synthesis* **2006**, 2418.
(28) T. Rovis, *Chem. Lett.* **2008**, *37*, 2.
(29) For examples involving ketenes as electrophiles, see: a) N. Duguet, C. D. Campbell, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 1108; b) X.-L. Huang, X.-Y. Chen, S. Ye, *J. Org. Chem.* **2009**, *74*, 7585; c) X.-L. Huang, L. He, P.-L. Shao, S. Ye, *Angew. Chem. Int. Ed.* **2009**, *48*, 192; d) H. Lv, L. You, S. Ye, *Adv. Synth. Catal.* **2009**, *351*, 2822; e) H. Lv, Y.-R. Zhang, X.-L. Huang, S. Ye, *Adv. Synth. Catal.* **2008**, *350*, 2715; f) X.-N. Wang, H. Lv, X.-L. Huang, S. Ye, *Org. Biomol. Chem.* **2009**, *7*, 346; g) Y.-R. Zhang, H. Lv, D. Zhou, S. Ye, *Chem. Eur. J.* **2008**, *14*, 8473; h) X.-N. Wang, P.-L. Shao, H. Lv, S. Ye, *Org. Lett.* **2009**, *11*, 4029.

(30) For examples involving carbon dioxide as electrophile, see: a) L.-Q. Gu, Y.-G. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 914; b) Y. Kayaki, M. Yamamoto, T. Ikariya, *Angew. Chem. Int. Ed.* **2009**, *48*, 4194.
(31) For examples involving esters as electrophiles, see: a) C. Fischer, S. W. Smith, D. A. Powell, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 1472; b) S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2009**, *131*, 14176; c) J. E. Thomson, K. Rix, A. D. Smith, *Org. Lett.* **2006**, *8*, 3785; d) G. A. Grasa, R. M. Kissling, S. P. Nolan, *Org. Lett.* **2002**, *4*, 3583; e) G. A. Grasa, R. Singh, S. P. Nolan, *Synthesis* **2004**, 971.
(32) For a minireview on the application of silicon based electrophiles, see: M. J. Fuchter, *Chem. Eur. J.* **2010**, *16*, 12286.
(33) For the application of enones as electrophiles in NHC mediated Morita-Baylis-Hillman reactions, see: a) L. He, T.-Y. Jian, S. Ye, *J. Org. Chem.* **2007**, *72*, 7466; b) L. He, Y.-R. Zhang, X.-L. Huang, S. Ye, *Synthesis* **2008**, 2825.
(34) For an example involving boron based electrophiles, see: K.-s. Lee, A. R. Zhugralin, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 7253.
(35) For an example involving imines as electrophile, see: D.-D. Chen, X.-L. Hou, L.-X. Dai, *J. Org. Chem.* **2008**, *73*, 5578.
(36) For an example involving α-ketoacids as electrophile, see: H. Stetter, G. Lorenz, *Chem. Ber.* **1985**, *118*, 1115.
(37) For examples involving oxidative generation of acyl heterazoliumions, see: a) S. De Sarkar, A. Studer, *Org. Lett.* **2010**, *12*, 1992; b) S. De Sarkar, A. Studer, *Angew. Chem. Int. Ed.* **2010**, *49*, 9266; c) J. Guin, S. De Sarkar, S. Grimme, A. Studer, *Angew. Chem. Int. Ed.* **2008**, *47*, 8727; d) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Org. Lett.* **2007**, *9*, 371; e) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Tetrahedron* **2009**, *65*, 3102; f) B. E. Maki, K. A. Scheidt, *Org. Lett.* **2008**, *10*, 4331; g) S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, *132*, 1190; h) M. Yoshida, Y. Katagiri, W.-B. Zhu, K. Shishido, *Org. Biomol. Chem.* **2009**, *7*, 4062; i) C. Noonan, L. Baragwanath, S. J. Connon, *Tetrahedron Lett.* **2008**, *49*, 4003; j) C. A. Rose, K. Zeitler, *Org. Lett.* **2010**, *12*, 4552.
(38) D. Seebach, *Angew. Chem. Int. Ed.* **1979**, *18*, 239.
(39) a) E. J. Corey, D. Seebach, *Angew. Chem. Int. Ed.* **1965**, *4*, 1075; b) D. Seebach, *Synthesis* **1969**, *1*, 17.
(40) T. Ukai, R. Tanaka, T. Dokawa, *J. Pharm. Soc. Jpn.* **1943**, *63*, 296.
(41) M. Padmanaban, A. T. Biju, F. Glorius, *Org. Lett.* **2011**, *13*, 98.
(42) J. He, J. Zheng, J. Liu, X. She, X. Pan, *Org. Lett.* **2006**, *8*, 4637.
(43) a) D. Enders, A. Henseler, *Adv. Synth. Catal.* **2009**, *351*, 1749; b) P.-C. Chiang, M. Rommel, J. W. Bode, *J. Am. Chem. Soc.* **2009**, *131*, 8714; c) P.-C. Chiang, Y. Kim, J. W. Bode, *Chem. Commun.* **2009**, 4566; d) S. E. O'Toole, C. A. Rose, S. Gundala, K. Zeitler, S. J. Connon, *J. Org. Chem.* **2011**, *76*, 347.
(44) Q. Liu, S. Perreault, T. Rovis, *J. Am. Chem. Soc.* **2008**, *130*, 14066.
(45) A. T. Biju, F. Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 9761.

1.2 Highly Enantioselective Benzoin Condensation Reactions Involving a Bifunctional Protic Pentafluorophenyl-Substituted Triazolium Precatalyst[i]



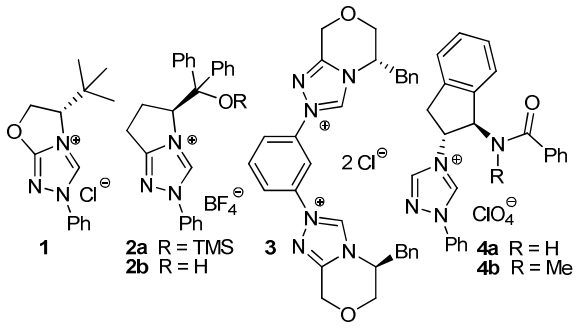
Improved catalyst design by incorporating a hydrogen-bond donating substituent to improve enantiocontrol together with an acidifying pentafluorophenyl substituent to enhance catalyst efficiency results in a triazolium ion precatalyst that promotes the asymmetric archetypal benzoin condensation with excellent efficiency and unprecedented enantioselectivity.[ii]

[i] Reproduced with permission from: L. Baragwanath, C. A. Rose, K. Zeitler, S. J. Connon, *J. Org. Chem.* **2009**, *74*, 9214 – 9217. Copyright 2009 American Chemical Society.

[ii] The investigations concerning the influence of catalyst`s electronics on yield were performed by C. A. R. The other experiments including the preparation of the chiral bifunctional catalyst and its application in enantioselective benzoin condensations were performed by L. B.

1.2.1 Introduction

First discovered in 1832,[1] the benzoin condensation (BC)[2] is a catalytic carbon-carbon bond forming process of considerable synthetic utility which allows the construction of an α-hydroxy ketone motif from two aldehyde molecules with the formation of a new stereocenter. Initial attempts to develop an asymmetric variant of the reaction using chiral thiazolium ion precatalysts in the presence of a base resulted in low-moderate product enantiomeric excess,[3] however seminal work by Enders[4] and then by Leeper[5] later demonstrated the clear superiority of chiral triazolium ion precatalysts – which culminated in 2002 with the isolation of benzoin from the condensation of benzaldehyde in greater than 90% *ee* (83% yield) catalyzed by the carbene derived from the chiral bicyclic triazolium ion **1** (Scheme 1).[6] As had been observed in previous systems, both catalyst efficacy and selectivity were highly dependent on the steric and electronic characteristics of the aromatic aldehyde used: activated aldehydes gave lower product *ee*, while electron rich analogues afforded benzoins with higher levels of enantiopurity at the expense of product yield.



Scheme 1: Chiral triazolium catalysts for the benzoin condensation.

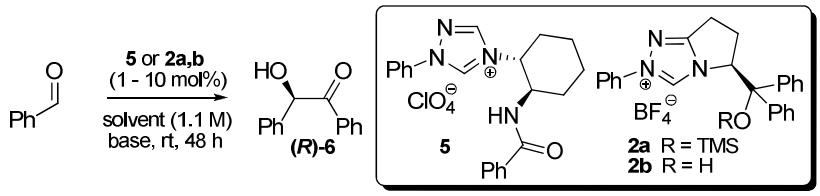
Very recently three reports have emerged which have prompted us to report our results in this field: Enders disclosed that the pyroglutamic acid-derived precatalyst **2a** could promote the BC of benzaldehyde in an outstanding 95% *ee* (66% yield) in toluene using KHMDS as the base, however as has traditionally been the case, substrates either more or less electron rich than benzaldehyde proved problematic.[7] You and coworkers[8] demonstrated that the *bis*-triazolium precatalyst **3** could promote BC reactions with high-excellent enantioselectivity (84-95% *ee*) and moderate-excellent product yields (41-95%) while also very recently, Ye *et al*. reported the use of **2a** and its desilylated derivative **2b** (along with related analogs) for the promotion of highly enantioselective ketene dimerisations,[9] Staudinger cycloadditions[10] and aza-Baylis-Hillman reactions.[11]

Recently Connon *et al*.[12] reported the first example of the use of hydrogen-bond donation as a control element in an asymmetric BC reaction:[13] precatalyst **4a** incorporating a secondary amide substituent could promote the BC of benzaldehyde with a maximum enantiomeric excess of 62%, while its *N*-methylated analogue **4b** furnished the same product in 13% *ee*. While this study established proof of

concept, neither product yield nor enantioselectivity reached synthetically useful levels. We therefore considered exploring the potential of these systems further through the synthesis of the rigid, bicyclic alcohol **2b**[14] and the 1,2-diaminocyclohexane-derived triazolium salt **5** – where the relative positioning of the nucleophile-generating and electrophile activating components would differ subtly from those associated with catalyst **4a**.

1.2.2 Results and Discussion

In preliminary experiments these were evaluated as precatalysts for the BC reaction in the presence of a variety of bases known to be suitable (from our previous study) for use in the BC (Table 1). While **5** did not represent an improvement over **4a**, the silylated precatalyst **2a** (4 mol%) furnished **(*R*)-6** with moderate enantioselectivity and low yield (entries 1-3).



entry	cat.	catalyst loading (mol%)	base	base loading (mol%)	yield (%)[a]	*ee* (%)[b]
1	**5**	4	K_2CO_3/KOH	2.88/0.64	0	–
2	**5**	4	K_2CO_3	3.2	10	31[c]
3	**2a**	4	K_2CO_3/KOH	2.88/0.64	18	53
4	**2b**	4	K_2CO_3/KOH	2.88/0.64	33	99
5	**2b**	2	K_2CO_3/KOH	1.44/0.32	14	96
6	**2b**	10	K_2CO_3/KOH	7.19/1.62	25	96
7	**2b**	4	NEt_3	6.4	22	93
8	**2b**	4	DBU	6.4	0	0
9	**2b**	4	Cs_2CO_3	3.2	32	98
10	**2b**	4	Rb_2CO_3	3.2	29	>99
11	**2b**	1	KO^{t}Bu	6.4	0	0
12[d]	**2b**	10	KHMDS	9.81	14	96

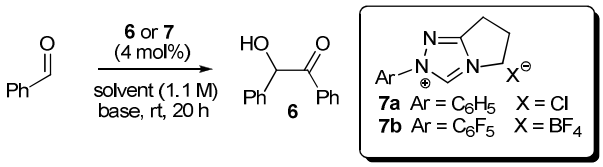
[a]Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [b]Determined by CSP-HPLC. [c]**(*S*)-6** obtained. [d]In toluene (1.0 M).

Table 1. The asymmetric benzoin reaction: initial studies.

The protic precatalyst **2b** (which had not previously been evaluated as a BC precatalyst) furnished the product in almost enantiopure form under identical conditions, albeit in disappointing yield (entry 4). Attempts to optimize the reaction conditions (base, solvent, catalyst/base loading) to improve catalyst efficiency met with failure (entries 4-13), although it is notable that **2b** possessed a reproducibly higher selectivity profile when used in conjunction with Rb_2CO_3 than with other bases (entry 10).

It was clear at this stage that while **2b** represents a solution to the enantioselectivity issue which often bedevils the BC, product yields using this system (*ca.* 30%) were unacceptable – therefore modification of the catalyst structure to improve catalyst efficacy was necessary. Speculating that the low yield may be related in part to the ability of benzoin to reprotonate the carbene, we were intrigued to read a report from Suzuki's group[15] where the judicious modification of triazolium ion substituents[16] to render them more electron-withdrawing in nature led to higher product yields in intramolecular BC reactions involving enolizable substrates prone to aldol side reactions. To test this hypothesis, the achiral salt **7a** and its pentafluorophenyl analogue **7b** were prepared[17] and evaluated as precatalysts for the BC reaction under conditions compatible with **2b**.[18]

The results of these experiments are outlined in Table 2. Under conditions in which the phenyl-substituted model catalyst **7a** either fails completely (entries 1, 5 and 8) or produces trace amounts of **6**, the pentafluoro analogue **7b** promotes highly efficient BC reactions with product yields as high as 98% (entries 2-4, 6-7 and 9) at low catalyst loadings. Precatalyst **7b** was also of sufficient acidity to form the carbene in the presence of mild amine bases (entry 9).

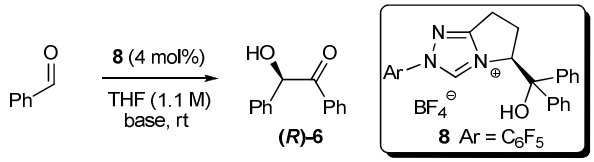


entry	cat.	solvent	base	base loading (mol%)	yield (%)[a]
1	**7a**	THF	K_2CO_3	3.2	0
2	**7b**	THF	K_2CO_3	3.2	98
3	**7b**	THF	Cs_2CO_3	3.2	87
4	**7b**	THF	Rb_2CO_3	3.2	75
5	**7a**	THF	Cs_2CO_3	3.2	0
6	**7b**	PhMe	K_2CO_3	3.2	39
7	**7b**	CCl_4	K_2CO_3	3.2	11
8	**7a**	THF	$^iPr_2NEt$	4.0	4
9	**7b**	THF	$^iPr_2NEt$	4.0	84

[a]Determined by ^1H NMR spectroscopy using an internal standard.

Table 2: Evaluating the influence of catalyst electronics on yield.

We were therefore prompted to prepare the novel triazolium salt **8** – a structure which aspires towards a marriage of the highly enantioselective catalysis associated with the core structure **2b** with the catalytic efficiency of **7b**. Gratifyingly, on evaluation of **8** as a promoter of the BC reaction (Table 3) this proved to be the case: uniformly high-excellent product yields and enantioselectivities were obtained under a variety of conditions – the optimization of which (entry 10) allowed the use of 4 mol% of precatalyst **8** at ambient temperature to generate **(*R*)-6** in 90% yield and >99% *ee* – *the highest level of enantiopurity achieved to date using an artificial catalyst system to the best of our knowledge*. The precatalyst could also mediate highly enantioselective BC reactions at lower loadings of 2 mol% (entry 5) and was also compatible with triethylamine – a convenient and inexpensive base (entry 13).



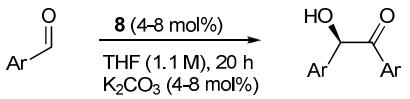
entry	base	base loading (mol%)	time (h)	yield (%)[a]	*ee* (%)[b]
1	K_2CO_3/KOH	2.88/0.64	21	85	98
2	K_2CO_3	3.20	20	84	96
3	Cs_2CO_3	3.20	20	81	98
4	Rb_2CO_3	3.20	20	87	98
5[c]	Rb_2CO_3	2.00	20	84	96
6	Rb_2CO_3	4.00	20	90	97
7	Rb_2CO_3	6.00	20	87	96
8	Rb_2CO_3	3.20	20	86	99
9	Rb_2CO_3	4.00	20	89	99
10	Rb_2CO_3	4.00	24	90	>99
11	K_2CO_3/KOH	2.88/0.64	21	85	98
12	NEt_3	6.40	21	76	92

[a]Determined by 1H NMR spectroscopy using (E)-stilbene as an internal standard. [b]Determined by CSP-HPLC. [c]2 mol% of both catalyst and base used.

Table 3: The asymmetric benzoin reaction using catalyst **8**.

With a highly active and selective precatalyst in hand we next turned to the question of substrate scope (Table 4) – an issue which has severely limited the utility of the BC reaction in the past. We evaluated the performance of **8** in BC reactions involving a range of aromatic aldehydes (including the little-tested 2-substituted analogs) and were pleased to find the catalyst of relatively broad scope. 2-napth-aldehyde (**9**) proved an excellent substrate (entry 1), while as expected 2-chlorobenzaldehyde (**10**)

proved difficult to convert with high selectivity (entry 2). Chlorobenzaldehydes **11** and **12** could be transformed into **(*R*)-19** and **(*R*)-20** with high yield and enantioselectivity at either ambient temperature or at 0 °C (entries 3-7), while the excellent activity of **8** is illustrated by its ability to promote the conversion of the challenging (from an enantioselectivity standpoint) substrate furfural (**13**) to **(*R*)-22** at -60 °C with 92% *ee* and 90% isolated yield (entry 10).



9 Ar = 2-naphthyl
10 Ar = 2-Cl-C_6H_4
11 Ar = 3-Cl-C_6H_4
12 Ar = 4-Cl-C_6H_4
13 Ar = 2-furyl
14 Ar = 2-CH_3-C_6H_4
15 Ar = 4-CH_3-C_6H_4
16 Ar = 2-MeO-C_6H_4
17 Ar = 4-MeO-C_6H_4

(*R*)-18 Ar = 2-naphthyl
(*R*)-19 Ar = 2-Cl-C_6H_4
(*R*)-20 Ar = 3-Cl-C_6H_4
(*R*)-21 Ar = 4-Cl-C_6H_4
(*R*)-22 Ar = 2-furyl
(*R*)-23 Ar = 2-CH_3-C_6H_4
(*R*)-24 Ar = 4-CH_3-C_6H_4
(*R*)-25 Ar = 2-MeO-C_6H_4
(*R*)-26 Ar = 4-MeO-C_6H_4

entry	substrate	temp. (°C)	cat. loading (mol%)	yield (%)[a]	*ee* (%)[b]
1	**9**	18	4	86	94
2	**10**	18	4	17	43
3	**11**	18	4	64	67
4	**11**	0	4	83	83
5	**11**	-20	8	86	83
6	**12**	18	4	75	89
7	**12**	0	4	91	92
8	**13**	18	4	100	40
9	**13**	0	4	100	47
10	**13**	-60	4	92	90
11	**14**	18	4	0	0
12	**15**	18	4	87	95
13	**16**	18	4	11	64
14	**16**	0	8	21	82
15	**17**	18	4	13	93
16	**17**	18	8	26	97

[a]Isolated yield. [b]Determined by CSP-HPLC.

Table 4: Evaluation of catalyst scope.

In line with the findings of our previous study[12] the little utilized *o*-tolualdehyde (**14**) proved resistant to the BC, however the corresponding *para*-isomer **15** underwent reaction at ambient temperature without difficulty and with excellent enantioselectivity (entries 11-12). The traditionally problematic

deactivated anisaldehyde substrates underwent slow reactions and furnished products in lower yields but with high-excellent enantioselectivity (entries 13-16).

1.2.3 Conclusion

In summary, we have developed the concept of utilizing hydrogen-bonding to control the stereochemical outcome of the BC reaction further through the introduction of the novel triazolium salt **8** – a rigid bicyclic precatalyst not only incorporating a chiral protic substituent that improves product enantioselectivity, but also a pentafluorophenyl moiety which dramatically enhances catalyst efficacy. Salt **8** is readily accessible from pyroglutamic acid and is active at low loadings of 2-4 mol%. At room temperature it promotes the BC of benzaldehyde with the highest levels of enantiocontrol (to the best of our knowledge) reported for this reaction using an artificial catalyst and it can convert a wide spectrum of aromatic aldehydes to the corresponding benzoins - in several cases also with unprecedented enantioselectivity.

1.2.4 Experimental Section

General Methods

Proton Nuclear Magnetic Resonance spectra were recorded on 400 MHz and 600 MHz spectrometers in $CDCl_3$ referenced relative to residual $CHCl_3$ (δ = 7.26 ppm), DMSO-d_6 referenced relative to residual DMSO (H) (δ = 2.51 ppm) and CD_3CN referenced relative to residual CH_3CN (δ = 1.96 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Fluorine 19 spectra were referenced externally (0.05% trifluorotoluene: –62.7 ppm). Carbon NMR spectra were recorded on the same instruments (100 MHz and 150 MHz) with total proton decoupling. All melting points are uncorrected. Infrared spectra were obtained using neat samples on a FT-IR spectrometer equipped with a universal ATR sampling accessory. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualized by either UV irradiation or $KMnO_4$ staining. Optical rotation measurements are quoted in units of 10^{-1} deg cm^2 g^{-1}. Toluene, ether and THF were distilled from sodium. Methylene chloride and triethylamine were distilled from calcium hydride. Analytical CSP-HPLC was performed using Daicel CHIRALCEL AD (4.6 mm x 25 cm) and CHIRALCEL OD-H (4.6 mm x 25 cm) and CHIRALCEL OJ-H (4.6 mm x 25 cm) columns. Unless otherwise stated, all chemicals were obtained from commercial sources and used as received. All reactions were carried out in oven-dried glassware with magnetic stirrers under an atmosphere of argon, unless specified.

Reaction conditions

Optimised conditions – Rb_2CO_3 as base

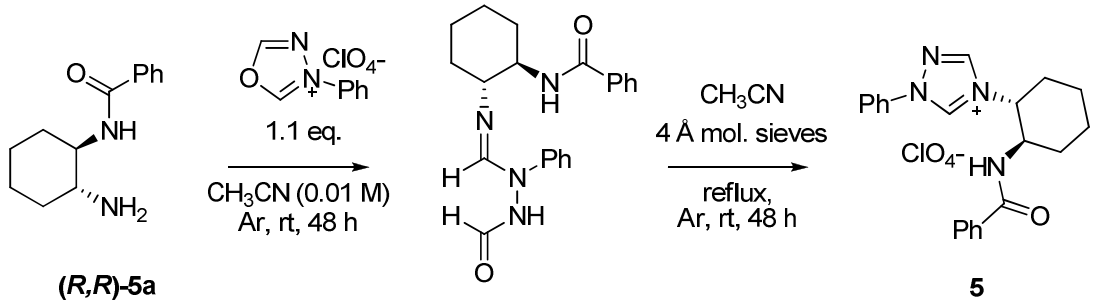
To a 5 mL round bottom flask, equipped with a magnetic stirring bar, Rb_2CO_3 (99.995%, anhydrous, 0.044 mmol, 10.16 mg) that had been finely ground using a mortar and pestle, was added. The reaction vessel was put under vacuum and heated with a heat gun for 1 minute over two-minute intervals for a total of 4 minutes. Upon cooling, the appropriate catalyst (0.044 mmol) and (*E*)-stilbene (0.138 mmol, 24.78 mg) were added and the flask was fitted with a septum seal. The reaction was evacuated for 4 min and put under an atmosphere of Ar. The required aldehyde was distilled under vacuum and used directly. THF (1.1 M) was charged to the reaction, followed by the aldehyde (1.100 mmol). The reaction was stirred at room temperature for 20 h after which CH_2Cl_2 (3.0 mL) and deionised H_2O (3.0 mL) were added. The lower organic layer was removed and the aqueous layer was washed with

CH_2Cl_2 (4 x 3.0 mL). The organic layers were combined, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The product was purified using column chromatography.

Characterization data

Synthesis of catalysts

4-(2-Benzoylamino-cyclohexyl)-1-phenyl-1*H*-[1,2,4]triazol-4-ium perchlorate (5)



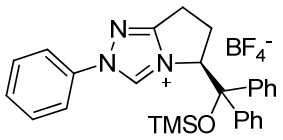
(*R,R*)-5a **5**

A 10 mL round bottom flask, containing a stirring bar, was charged with oxadiazolium perchlorate (2.07 mmol, 0.5097 g). The flask was fitted with a septum and placed under an Ar atmosphere (balloon). **5a** (1.880 mmol, 0.398 g) dissolved in CH_3CN (20.0 mL) was added dropwise, *via* syringe, to the flask and the reaction was stirred at room temperature for 45 min. The crude reaction mixture was concentrated *in vacuo* and recrystallization from hot CH_3CN gave the acylic intermediate (0.420 mmol, 0.1530 g) as a white solid. A 10 mL round bottom flask containing a stirring bar was charged with the resulting crystalline solid (0.420 mmol, 0.153 g) and 4 Å molecular sieves (0.100 g). The flask was fitted with a reflux condenser and septum and placed under an Ar atmosphere (balloon). CH_3CN (2.0 mL) was added *via* syringe and the resulting solution heated, under reflux, at 90 °C for 48 h. The reaction mixture was filtered to remove the molecular sieves and washed with CH_3CN (3 x 5 mL). The resulting solution was concentrated *in vacuo* resulting in a pale yellow solid. Recrystallization from hot acetonitrile gave **5** (0.054 g, 6 %) as a white crystalline solid, m.p. 218-219 °C, $[\alpha]_D^{20}$ = -94.2 (c 0.60 in CH_3OH).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.40 – 1.52 (m, 2H), 1.67 – 1.78 (m, 1H), 1.86 – 2.01 (m, 3H), 2.11 – 2.26 (m, 1H), 2.30 – 2.39 (m, 1H) 4.22 – 4.47 (m, 2H), 7.42 (app. t, 2H), 7.45 – 7.55 (m, 1H), 7.56-7.75 (m, 5H), 7.85 (d, J = 12.0 Hz, 2H), 8.60 (d, J = 11.3 Hz, 1H), 9.43 (s, 1H), 11.18 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 24.6, 24.7, 32.1, 32.4, 51.7, 61.4, 120.2, 127.8, 128.5, 128.6, 130.3,

131.7, 135.0 (q), 140.6 (q), 154.7, 160.1, 167.1 (C=O). IR (neat)/cm^{-1} 721, 972, 1044, 1318, 1519, 1572, 1651, 3391. HRMS (ES) Found: 347.1862 (M^+ -ClO_4^-) $C_{21}H_{23}N_4O$ requires 347.1872.

(*S*)-5-(Diphenyl-trimethylsilanyloxy-methyl)-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-c][1,2,4] triazol-2-ium tetrafluoroborate (2a)

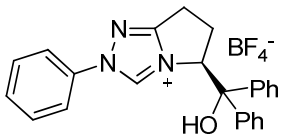


2a

This compound was synthesised according to the literature. Recrystallization from hot MeOH gave **2a** (1.578 g, 58 %) as pale yellow crystals, m.p. 199-200 °C, lit.[19] 196-198 °C. $[\alpha]_D^{20}$ = -122.6 (c 0.50 in CH_3CN), lit.[19] $[\alpha]_D^{20}$ = -113.8 (c 0.50 in CH_3CN).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 9H), 2.06 – 2.10 (m, 1H), 2.76 – 2.82 (m, 1H), 2.89 – 2.94 (m, 1H), 3.30 – 3.36 (m, 1H), 6.14 (d, J = 9.01 Hz, 1H), 7.30 – 7.36 (m, 2H), 7.38 – 7.43 (m, 5H), 7.48 – 7.52 (m, 3H), 7.58 – 7.61 (m, 3H), 7.71 – 7.73 (m, 2H), 8.90 (s, 1H).

(*S*)-5-[Hydroxy(diphenyl)methyl]-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (2b)

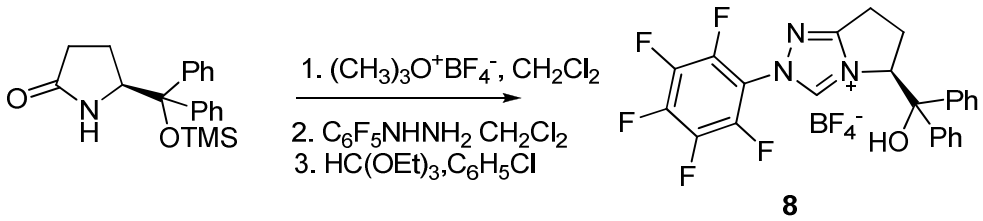


2b

A 100 mL round bottom flask was charged with **2a** (1.352 mmol, 0.7132g). The flask was fitted with a rubber septum and placed under an atmosphere of Ar (balloon). MeOH (67.5 mL) was added *via* syringe. To this reaction mixture TMSBr (10 % solution in MeOH) (3.4 mL) was added *via* syringe. The reaction mixture was stirred at room temperature for 2 h and then concentrated *in vacuo* to give **2b** (0.615 g, 99 %) as an off-white crystalline solid, m.p. 197-180 °C. $[\alpha]_D^{20}$ = -55.4 (c 0.5, CH_3OH), lit.[20] $[\alpha]_D^{20}$ = -58.6 (c 0.5, CH_3CN).

^{1}H NMR (600 MHz, DMSO-d_6) δ 2.50 – 2.59 (m, 1H), 2.93 – 2.95 (m, 2H), 3.13 – 3.16 (m, 1H), 6.13 (d, J = 9.8 Hz, 1H), 6.58 (s, 1H), 7.30 (t, J = 7.2 Hz, 1H), 7.37 – 7.59 (m, 3H), 7.45 (app. t, 2H), 7.52 (d, J = 7.8 Hz, 2H), 7.58 (d, J = 7.8 Hz, 2H), 7.63-7.68 (m, 3H), 7.78 (d, J = 7.8 Hz, 2H), 9.60 (s, 1H). HRMS (ES) Found: 368.1754 (M^+ -BF_4^-) $C_{24}H_{22}N_3O$ requires 368.1763.

5-(Hydroxy-diphenyl-methyl)-2-pentafluorophenyl-6,7-dihydro-5*H*-pyrrolo[2,1-c][1,2,4] triazol-2-ium tetrafluoroborate (8)



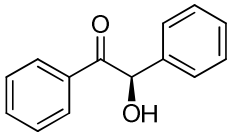
8

A 100 mL round bottom flask was charged with (*S*)-5-(diphenyl-trimethylsilanyloxy-methyl)-pyrrolidin-2-one (5.891 mmol, 2.00 g). CH_2Cl_2 (28 mL) was added *via* syringe followed by trimethyloxonium tetrafluoroborate (5.891 mmol, 0.8713 g). The flask was fitted with a rubber septum and placed under an atmosphere of Ar (balloon) and the resulting solution stirred at room temperature for 15 h. Pentafluorophenylhydrazine (5.891 mmol, 1.1669 g) was added to the reaction, which was then allowed stir at room temperature for 2 h. The crude reaction mixture was concentrated *in vacuo* resulting in a pale yellow residue. Chlorobenzene (54 mL) was added, followed by triethylorthoformate (2.5 mL) and the mixture was heated under reflux at 120 °C for 12 h. Additional triethylorthoformate (2.5 mL) was added and reflux was continued for a further 12 h. Upon cooling, the reaction mixture was concentrated *in vacuo* resulting in a pale brown residue. A 100 mL round bottom flask was charged with the crude reaction material (6.787 mmol, 4.1900g). The flask was fitted with a rubber septum and placed under an atmosphere of Ar (balloon). MeOH (200 mL) was added *via* syringe. To this reaction mixture TMSBr (10 % solution in MeOH) (1.69 mL) was added *via* syringe. The reaction mixture was stirred at room temperature for 24 h and then concentrated *in vacuo*. Recrystallization from EtOAc gave **8** (1.141 g, 31 %) as a pale yellow crystalline solid m.p. 225-226 °C, $[\alpha]_D^{20}$ = -205.5 (c 1.0, CH_3Cl).

^{1}H NMR (600 MHz, DMSO-d_6) δ 2.70 (app. t., 1H), 2.89 – 2.93 (m, 1H), 3.01 – 3.05 (m, 1H), 3.19 – 3.21 (m, 1H), 6.16 (d, J = 6.6 Hz, 1H), 6.80 (s, 1H), 7.32 (app. t., 1H), 7.36 – 7.40 (m, 3H), 7.43 – 7.47 (m, 4H), 7.55 (d, J = 7.4 Hz, 2H), 9.61 (s, 1H). ^{13}C NMR (600 MHz, DMSO-d_6) δ 21.4, 29.7, 68.1, 78.8 (q), 111.2 (q), 126.1, 127.7, 128.1, 128.5, 128.9, 136.6 (m), 138.2 (m), 141.7 (m), 142.2 (m), 142.8 (q), 143.2 (q), 143.5, 164.7 (q). ^{19}F NMR (376 MHz, DMSO-d_6) δ -145.5 (d, J = 5.6 Hz, 1F), -147.7 (t, J = 6.2 Hz, 1F), -160.1 (dd, J = 5.6, 2.7 Hz, 1F). IR (neat)/cm^{-1} 694, 872, 1002, 1071, 1523, 3185. HRMS (ES) Found: 458.1294 (M^+-BF_4^-) $C_{24}H_{17}N_3OF_5$ requires 458.1292.

Synthesis of benzoins

(*R*)-2-Hydroxy-1,2-diphenyl-ethanone (6)



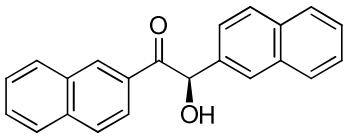
(*R*)-6

Prepared according to the optimised reaction conditions (above) using catalyst **8**. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.2) gave **(*R*)-6** (105 mg, 90%) as a white solid, m.p. 131-132 °C, lit.[21] 132-133 °C, 99.8 % *ee*. $[\alpha]_D^{20}$ = -35.1 (c 1.0 in CH_3OH), lit.[22] $[\alpha]_D^{20}$ = -113.8 (c 1.5 in CH_3COCH_3), for *R* enantiomer with 99 % *ee*.

Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min^{-1}, r.t., UV detection at 220 nm, retention times: 20.4 min (major enantiomer) and 26.9 (minor enantiomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (bs, 1H), 5.98 (s, 1H), 7.29-7.40 (m, 5H (overlapping with $CHCl_3$ resonance)), 7.43 (app. t, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H).

(*R*)-2-Hydroxy-1,2-di-naphthalen-2-yl-ethanone (18)



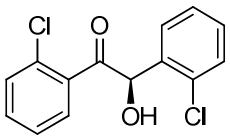
(*R*)-18

Prepared according to the optimised reaction conditions (above) using catalyst **8**. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.1) gave **(*R*)-18** (147.9 mg, 86%) as a white solid, m.p. 124-125 °C, lit.[23] 125-126 °C, 94 % *ee*. $[\alpha]_D^{20}$ = +105.5 (c 0.5 in CH_3OH), lit.[24] $[\alpha]_D^{20}$ = -48.3 (c 0.5 in CH_3OH) for *S* enantiomer with 92 % *ee*.

Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 8/2, 1.0 mL min^{-1}, r.t., UV detection at 254 nm, retention times: 26.4 min (major enantiomer) and 44.8 (minor enantiomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (bs, 1H), 6.31 (s, 1H), 7.48-7.66 (m, 5H), 7.78-7.85 (m, 5H), 7.90 (d, J = 8.0 Hz, 1H), 7.95 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.54 (s, 1H).

(*R*)-1,2-Bis-(2-chloro-phenyl)-2-hydroxy-ethanone (19)



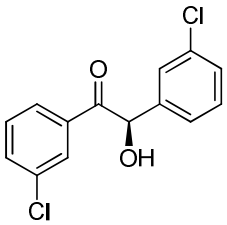
(*R*)-19

Prepared according to the optimised reaction conditions (above) using catalyst **8**. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.2) gave **(*R*)-19** (26.6 mg, 17%) as a pale yellow solid, m.p. 65-66 °C, lit.[25] 64 °C, 43 % *ee*. $[\alpha]_D^{20}$ = -25.1 (c 1.0 in $CHCl_3$), lit.[22] $[\alpha]_D^{20}$ = -46.0 (c 1.0 in $CHCl_3$) for *R* enantiomer with 97 % *ee*.

Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 0.8 mL min^{-1}, r.t., UV detection at 254 nm, retention times: 22.2 min (minor enantiomer) and 24.9 (major enantiomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (bs, 1H), 6.38 (s, 1H), 7.23-7.26 (m, 5H (overlapping with $CHCl_3$ resonance)), 7.31 – 7.40 (m, 3H).

(*R*)-1,2-Bis-(3-chloro-phenyl)-2-hydroxy-ethanone (20)

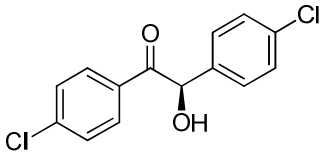


(*R*)-20

Prepared according to the optimised reaction conditions (above) using catalyst **8**. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.3) gave **(*R*)-20** (134.2 mg, 87%) as a white solid, m.p. 77-78 °C, lit.[25] 76-77 °C, 83 % *ee*. $[\alpha]_D^{20}$ = -100.5 (c 1.1 in $CHCl_3$), lit.[22] $[\alpha]_D^{20}$ = -31.0 (c 1.2 in $CHCl_3$) for *R* enantiomer with 99 % *ee*.
Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 0.8 mL min^{-1}, r.t., UV detection at 254 nm, retention times: 19.5 min (major enantiomer) and 26.6 (minor enantiomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (bs, 1H), 5.91 (s, 1H), 7.23-7.29 (m, 3H (overlapping with $CHCl_3$ resonance)), 7.35 – 7.38 (m, 2H) 7.51 (d, J = 7.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.92 (s, 1H).

(*R*)-1,2-Bis-(4-chloro-phenyl)-2-hydroxy-ethanone (21)



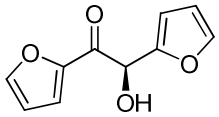
(*R*)-21

Prepared according to the optimised reaction conditions using catalyst **8**. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.3) gave **(*R*)-21** (139.7 mg, 91%) as a white solid, m.p. 87-88 °C, lit.[25] 87-88 °C, 92 % *ee*. $[\alpha]_D^{20}$ = -31.1 (c 1.0 in CH_3OH), lit.[26] $[\alpha]_D^{20}$ = -12.3 (c 1.0 in CH_3OH), for *R* enantiomer with 29% *ee*.

Chiralpak OJ-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.6 mL min^{-1}, r.t., UV detection at 220 nm, retention times: 34.1 min (minor enantiomer) and 36.2 (major enantiomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (bs, 1H), 5.90 (s, 1H), 7.26-7.27 (d, 2H (overlapping with $CHCl_3$ resonance)), 7.32 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 7.8 Hz, 2H), 7.84 (d, J = 7.8 Hz, 2H).

(*R*)-1,2-Di-furan-2-yl-2-hydroxy-ethanone (22)



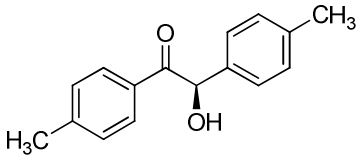
(*R*)-22

Prepared according to the optimised reaction conditions using catalyst **8**. Purification by column chromatography (CH_2Cl_2, R_f 0.2) gave **(*R*)-22** (97.5 mg, 92%) as a white solid, m.p. 137-138 °C, lit.[27] 135-136 °C, 90 % *ee*. $[\alpha]_D^{20}$ = -40.9 (c 1.0 in CH_3OH), lit.[22] $[\alpha]_D^{20}$ = -21.6 (c 1.0 in CH_3OH) for *R* enantiomer with 92 % *ee*.

Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 0.8 mL min^{-1}, r.t., UV detection at 254 nm, retention times: 26.5 min (minor enantiomer) and 32.1 (major enantiomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (bs, 1H), 5.82 (bs, 1H), 6.37 (dd, J = 3.0, 1.5 Hz, 1H), 6.42 (d, J = 3.5Hz, 1H), 6.56 (dd, J = 4.0, 2.2 Hz, 1H), 7.27 (m, 1H (overlapping with $CHCl_3$ resonance)), 7.39 (d, J = 1.5 Hz, 1H), 7.63 (app. s, 1H).

(*R*)-1,2-Bis-(4-chloro-phenyl)-2-hydroxy-ethanone (24)



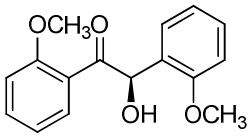
(*R*)-24

Prepared according to the optimised reaction conditions using catalyst **8**. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.1) gave **(*R*)-24** (116.1 mg, 87%) as a white solid, m.p. 89-90 °C, lit.[25] 89-90 °C, 95 % *ee*. $[\alpha]_D^{20}$ = -90.8 (c 1.0 in CH_3OH), lit.[28] $[\alpha]_D^{20}$ = -130.8 (c 1.0 in CH_3OH) for *R* enantiomer with 92 % *ee*.

Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 0.8 mL min^{-1}, r.t., UV detection at 254 nm, retention times: 28.8 min (major enantiomer) and 33.1 (minor enantiomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.38 (s, 3H), 4.57 (bs, 1H), 5.92 (bs, 1H), 7.14-7.15 (d, J = 7.5 Hz, 2H), 7.20-7.27 (m, 4H), 7.84 (d, J = 8.5 Hz, 2H).

(*R*)-2-Hydroxy-1,2-bis-(2-methoxy-phenyl)ethanone (25)

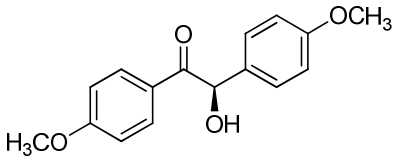


(R)-25

Prepared according to the optimised reaction conditions using catalyst **8**. Purification by column chromatography (CH_2Cl_2, R_f 0.2) gave **(*R*)-25** (30.8 mg, 21%) as an off white solid, m.p. 99-100 °C, lit.[29] m.p. 98-99 °C, 82 % *ee*. $[\alpha]_D^{20}$ = -43.1 (c 0.3 in $CHCl_3$), lit.[22] $[\alpha]_D^{20}$ = -125.0 (c 0.9 in $CHCl_3$) for *R* enantiomer with 99 % *ee*.
Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA: 85/15, 0.5 mL min^{-1}, r.t., UV detection at 254 nm, retention times: 30.8 min (major enantiomer) and 43.7 (minor enantiomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.74 (s, 3H), 4.50 (d, J = 5.5 Hz, 1H), 6.13 (d, J = 5.5 Hz, 1H), 6.78 (app. t, 2H), 6.85 (app. t, 1H), 6.94 (app. t, 1H), 7.18 (m, 2H), 7.38 (m, 1H), 7.70 (dd, J = 5.9, 1.8 Hz, 1H).

(*R*)-2-Hydroxy-1,2-bis-(4-methoxy-phenyl)-ethanone (26)



(R)-26

Prepared according to the optimised reaction conditions using catalyst **8**. Purification by column chromatography (CH_2Cl_2, R_f 0.2) gave **(*R*)-26** (38.3 mg, 21%) as a white solid, m.p. 111-112 °C, lit.[27] m.p. 109-110°C, 97 % *ee*. $[\alpha]_D^{20}$ = -13.1 (c 1.1 in CH_3OH), lit.[22] $[\alpha]_D^{20}$ = -90.4 (c 1.0 in CH_3OH) for *R* enantiomer with 99 % *ee*.

Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 75/25, 0.95 mL min^{-1}, r.t., UV detection at 254 nm, retention times: 27.2 min (major enantiomer) and 32.0 (minor enantiomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.84 (s, 3H), 4.61 (bs, 1H), 5.87 (s, 1H), 6.84 – 6.90 (m, 4H), 7.25 – 7.29 (d, 2H (overlapping with $CHCl_3$ resonance)), 7.92 (d, J = 8.9 Hz, 2H).

→Please find supporting information including **^{1}H- and ^{13}C-NMR spectra** on the enclosed CD.

1.2.5 References

(1) Wöhler, F.; Liebig, J. *Ann. Pharm*. **1832**, 3, 249.

(2) Recent reviews: (a) Enders, D; Niemeier, O; Henseler, A. *Chem. Rev*. **2007**, *107*, 5506. (b) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem. Int. Ed*. **2007**, *46*, 2988. (c) Zeitler, K. *Angew. Chem. Int. Ed*. **2005**, *44*, 7506. (d) Christmann, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 2632. (e) Enders, D.; Balensiefer, T. *Acc. Chem. Res*. **2004**, *37*, 534. (f) Johnson, J. S. *Angew. Chem. Int. Ed*. **2004**, *43*, 1326. (g) Zeitler, K. *E. Schering Found. Symp. Proc.* **2007***, 2*, 183.

(3) (a) Sheehan, J.; Hunnemann, D. H. *J. Am. Chem. Soc*. **1966**, *88*, 3666. (b) Sheehan, J.; Hara, T. *J. Org. Chem*. **1974**, *39*, 1196. (c) Dvorak, C. A.; Rawal, V. H. *Tetrahedron Lett*. **1998**, *39*, 2925. (d) Takagi, W.; Tamura, Y.; Yano, Y. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 478. (e) Marti, J.; Castells, J.; Lopez-Calahora, F. *Tetrahedron Lett*. **1993**, *34*, 521. (f) Tachibana, Y.; Kihara, N.; Takata, T. *J. Am. Chem. Soc*. **2004**, *126*, 3438. (g) Knight, R. L.; Leeper, F. J. *Tetrahedron Lett*. **1997**, *38*, 3611. (h) Gerhard, A. U.; Leeper, F. J. *Tetrahedron Lett*. **1997**, *38*, 3615. (i) Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 1891. (j) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem*. **2004**, 2025.

(4) Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta*. **1996**, *79*, 1217.

(5) Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891.

(6) Enders, D.; Kallfass, U. *Angew. Chem. Int. Ed*. **2002**, *41*, 1743.

(7) Enders, D.; Han, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1367.

(8) Ma, Y.; Wei, S.; Wu, J.; Yang, F.; Liu, B.; Lan, J.; Yang, S.; You, J. *Adv. Synth. Catal*. **2008**, *350*, 2645.

(9) He, L.; Zhang, Y. -R.; Huang, X. -L.; Ye, S. *Synthesis* **2008**, 2825.

(10) Zhang, Y. -R.; He, L.; Wu, X.; Shao, P. -L.; Ye, S. *Org. Lett*. **2008**, *10*, 277.

(11) Lv, H.; Zhang, Y. -R.; Huang, X. -L.; Ye, S. *Adv. Synth. Catal*. **2008**, *350*, 2715.

(12) O'Toole, S. E.; Connon, S. J. *Org. Biomol. Chem*. **2009**, *7,* 3584.

(13) Miller had previously designed chiral H-bond donating thiazolium ion precatalysts for the promotion of intramolecular Stetter reactions and intermolecular aldehyde-imine couplings, see: (a) Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun*. **2005**, 195. (b) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc*. **2005**, *127*, 1654.

(14) We were prompted by success we have had in using similar hydrogen bond-donating motifs to control stereochemistry in the design of catalysts for enantioselective acylation chemistry previously (see following refs), however it should be acknowledged that Ye disclosed the design of **2b** (refs 9-11) while this project was in progress: (a) O' Dálaigh, C.; Hynes, S. J.; Maher, D. J.; Connon, S. J.*Org. Biomol. Chem*. **2005**, *3*, 981. (b) O' Dálaigh, C.; Hynes, S. J.; O'Brien, J. E.; McCabe, T.; Maher, D. J.; Watson, G. W.; Connon, S. J. *Org. Biomol. Chem*. **2006**, *4*, 2785. (c) O' Dálaigh, C.; Connon, S. J. *J. Org. Chem*. **2007**, 72, 7066. (d) Gleeson, O.; Tekoriute, R.; Gun'ko, Y. K.; Connon, S. J. *Chem. Eur. J*. **2009**, *15*, 5669.

(15) Takikawa, H.; Suzuki, K. *Org. Lett*. **2007**, *9*, 2713.

(16) For an account detailing the importance of the *N*-aryl substituents see: Rovis, T. *Chem. Lett.* **2008**, *37*, 1.

(17) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem*. **2005**, *70*, 5725.

(18) Recently the pKa of catalyst **7a** (H_2O) has been determined to be 17.7: Campbell, C. D.; Duguet, N.; Gallagher, K. A.; Thomson, J. E.; Lindsay, A. G.; O'Donoghue, A. C.; Smith, A. D. *Chem. Commun*. **2008**, 3528.

(19) Zhang, Y. –R.; He, L.; Wu, X.; Shao, P. –L.; Ye, S. *Org. Lett.* **2008**, *10*, 277.

(20) He, L.; Zhang, Y. –R.; Huang, X. –L.; Ye, S. *Synthesis* **2008**, *17*, 2825.

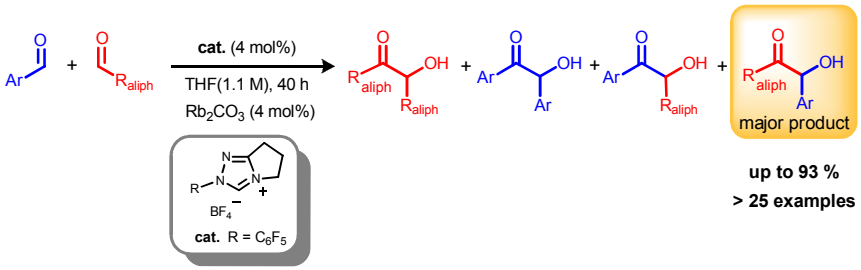
(21) Kenyon, J.; Patel, R. L. *J. Chem. Soc.* **1965**, 435.

(22) Demir, A. S.; Müller, M. *et al. Adv. Synth. Catal.* **2002**, *344*, 96.

(23) Fulton, R. *J. Chem. Soc.* **1939**, 200.

(24) Ma, Y.; Wei, S.; Wu, J.; Yang, F.; Liu, B.; Lan, J.; Yang, S.; You, J. *Adv. Synth. Catal.* **2008**, *350*, 2645.
(25) Cumper, C. W. N.; Thurston, A. P. *J. Chem. Soc. Perkin Trans. 2* **1972**, 106.
(26) Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1217.
(27) Stetter, H.; Rämsch, Y.; Kuhlmann, H. *Synthesis* **1976**, 733.
(28) Knight, R. L.; Leeper, F. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 1891.
(29) Clecak, N. J.; Cox, R. J. *Chem. Abstr.* **1970**, *73*, 89166.

1.3 Highly Chemoselective Direct Crossed Aliphatic – Aromatic Acyloin Condensations with Triazolium-Derived Carbene Catalysts[i]



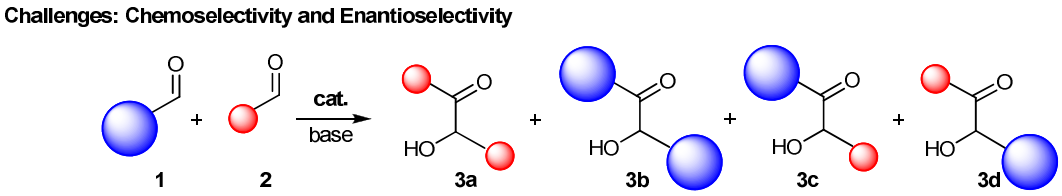
It has been shown for the first time that triazolium pre-catalysts promote (in the presence of base) highly chemoselective crossed acyloin condensation reactions between aliphatic and *ortho*-substituted aromatic aldehydes. An *o*-bromine atom can serve as a temporary directing group to ensure high chemoselectivity (regardless of the nature of the other substituents on the aromatic ring) which then can be conveniently removed. The process is of broad scope and is operationally simple as it does not require the pre-activation of any of the coupling partners to ensure selectivtiy. Preliminary data indicates that highly enantioselective variants of the reaction are feasible using chiral pre-catalysts.[ii]

[i] Reproduced with permission from: S. E. O`Toole, C. A. Rose, S. Gundala, K. Zeitler, S. J. Connon, *J. Org. Chem* **2011**, *76*, 347 – 357. Copyright 2011 American Chemical Society.

[ii] The study concerning the general applicability of known crossed acyloin procedures (Table 1), the evaluation of branched aldehydes as substrates (Scheme 4), as well as the experiments illustrating the impact of the catalytic system on chemo-selectivity (Scheme 5) were performed by C. A. R. The remaining experiments including evaluation of linear aldehydes, the debromination procedure and the enantioselective crossed acyloin condensation were performed by either S. E. O`T. or S. G.

1.3.1 Introduction

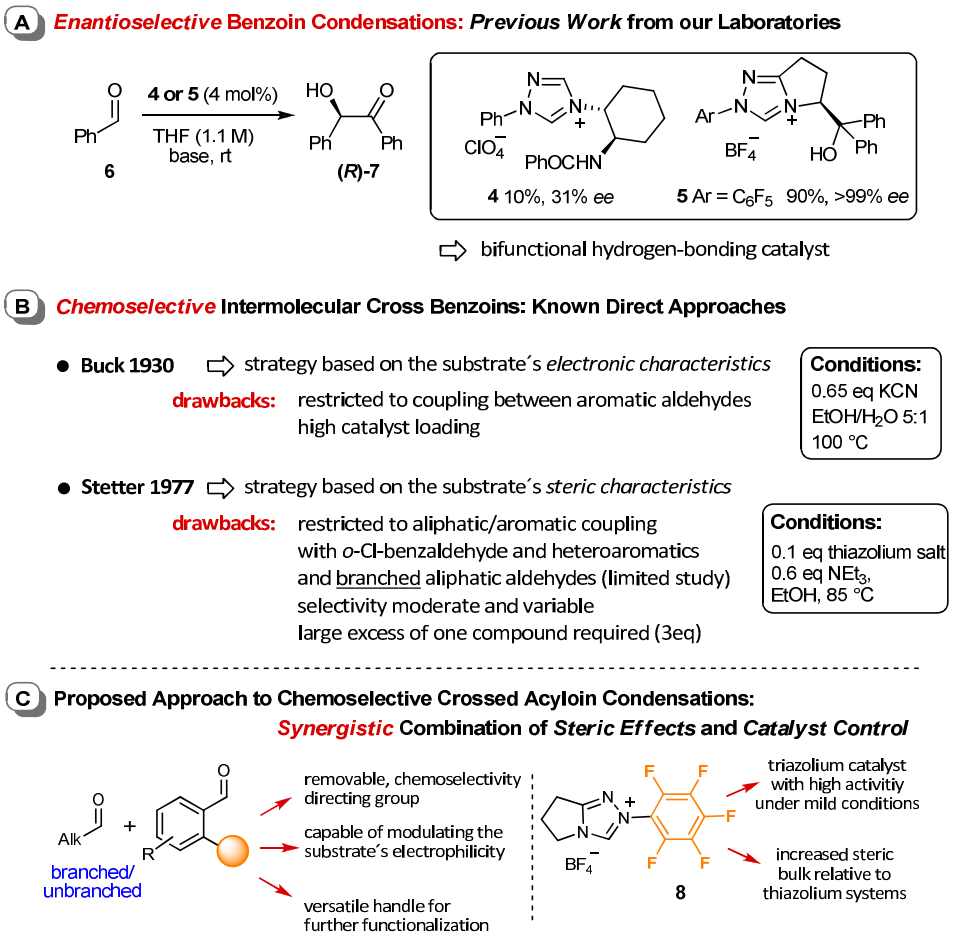
α-Hydroxy ketones are highly useful building blocks for the synthesis of heterocycles, natural products, agrochemicals and (inter alia[1]) pharmaceuticals.[2] In addition, the unsymmetrical nature of the building block allows for access to other important synthetic precursors, such as chiral 1,2-diols and amino alcohols.[3] As a consequence, the development of routes to these compounds *via* metal-catalyzed heteroatom transfer[4] and organocatalytic α-oxidation chemistry[5] have been extensively investigated recently.[6]



Scheme 1: The challenges associated with direct crossed acyloin condensations.

The acyloin condensation (AC) is one of the oldest carbon-carbon bond forming reactions in organic chemistry – with a rich history dating back to the pioneers Liebig and Wöhler in 1832.[7] For much of the intervening time, it has proven first an interesting mechanistic challenge[8, 9] and later a process which inspired the development of a suite of *N*-heterocyclic carbene-based catalysts.[10] While significant advances in the catalysis of the (asymmetric) carbene-catalyzed homo-AC reaction have been made recently,[11,12,13,14,15] the absence of a *selective* carbene-mediated methodology capable of promoting the intermolecular reaction[16] between two different aldehydes in a chemo- and enantio-selective fashion, curtails the utility of the process. The challenges associated with the development of an efficient and selective crossed acyloin condensation protocol are considerable – the objective is to exercise control (*via* the catalyst) over the process to the extent that a single major adduct is formed from 8 possible products (4 chiral ketones **3a-d** × 2 enantiomers each, Scheme 1) in good yield.[17]

Known Approaches. In 1930, Buck *et al*. published a report concerning the crossed benzoin condensation of *aromatic* aldehyde partners of contrasting electronic character in the presence of high loadings of cyanide ion (Scheme 2B).[18,19] Over 30 years ago Stetter *et al*.,[20] in an attempt to develop efficient routes to 1,2-diketones, reported in a short, limited study that an achiral thiazolium salt-derived carbene catalyzed the crossed AC between aromatic and aliphatic aldehydes: good crossed product yields could be obtained if the aliphatic aldehyde was utilized in quite high excess (3.0 equiv), however chemoselectivity was both highly variable and substrate dependent.[21,22,23]

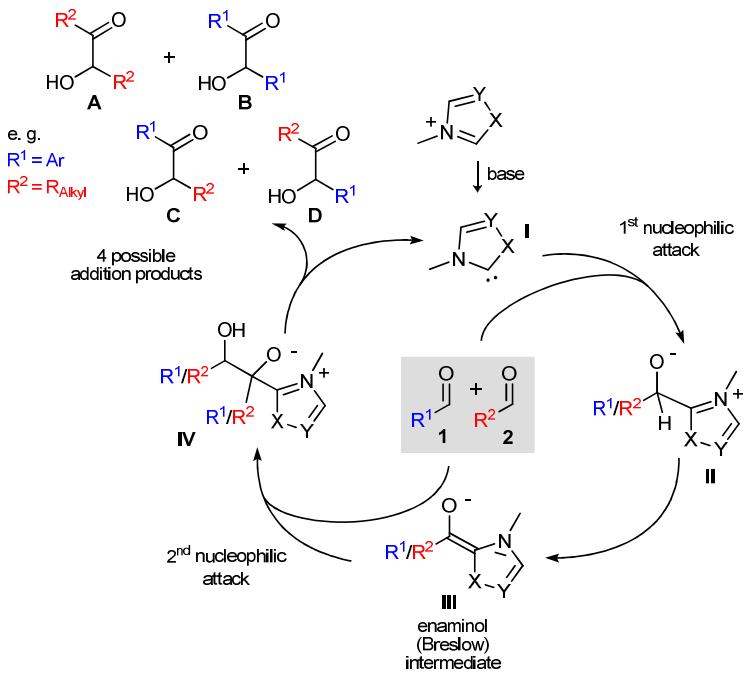


Scheme 2: Previous approaches and the proposed strategy detailed in this work.

Miller *et al*. carried out a single *intermolecular* AC reaction reported to be selective involving *o*-tolualdehyde and hexanal in the presence of stoichiometric loadings of a triazolium ion precatalyst. However the yield of the only isolable product was low (16%).[24] Other approaches to the catalytic synthesis of products (formally) derived from intermolecular AC reactions have been developed, including the use of enzyme catalysts[25] and polymer bound aldehydes,[26] in addition to indirect methods where chemoselectivity is derived from the pre-formation of an *umpolung* reagent, such as acyl-silanes,[27] acyl-phosphonates[28] and aldehyde-thiazolium carbene adducts.[29] Enders recently disclosed that aromatic aldehydes could be coupled to α,α,α-trifluoroacetophenone in good to excellent yields under the influence of triazolium carbene catalysis,[30] however, *to the best of our knowledge a general carbene-catalyzed process capable of promoting the direct, chemoselective*[31] *(and enantioselective) crossed AC reaction between two different aldehydes remains elusive*.[32]

1.3.2 Results and Discussion

In approaching this problem, we considered what we regarded as the key question: the aldehyde is the electrophile in both the Breslow intermediate (BI, Scheme 3: **III**)- and product- (and stereocenter-) forming steps, so if, for instance, aldehyde **2** is the superior electrophile in the BI-formation step (Scheme 3: **I→III**), on what basis (using traditional catalyst design strategies) can we expect **2** not to be the superior electrophile in the subsequent stereocentre-forming step (Scheme 3: **III→IV**) – leading to the homodimer **3a** instead of cross product **3d** (Scheme 1B and Scheme 3: **A** resp. **D**)?



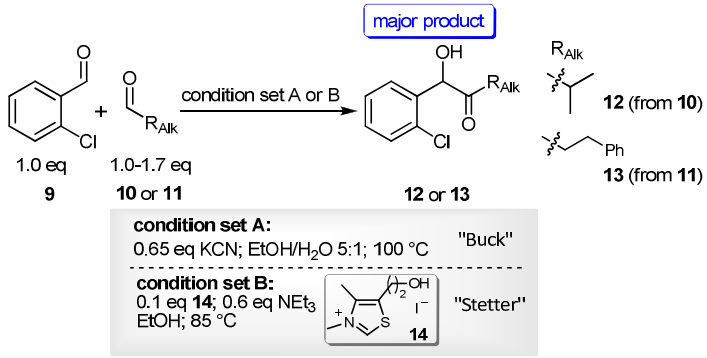
Scheme 3: General mechanism for NHC-catalyzed benzoin/acyloin condensations.

Recently we reported that hydrogen bonding could be utilized as a control element in enantioselective homo-benzoin condensation reactions.[33, 34] The pentafluorophenyl-substituted triazolium precatalyst **5** (which followed our first generation system **4**) could promote the formation of benzoin (**7**) from benzaldehyde (**6**) with excellent efficiency and stereocontrol (Scheme 2A). We postulated that the rigid, hindered nature of **5**, coupled with the presence of a catalyst hydrogen bond-donating group,[35] would allow the catalyst to potentially distinguish between the *two* aldehyde electrophiles based on the recognition of *two different substrate properties* – steric bulk and Brønsted basicity. However, as a important further control element in addition to catalyst control,[36] we envisaged that a degree of *synergistic substrate control* could be brought to bear on the process in the form of a removable chemoselectivity-enhancing substituent in the *ortho* position of the aromatic aldehyde. Stetter *et al.*[20] had reported that *o*-chloro-substituted benzaldehydes participated in more selective crossed AC

reactions than their unsubstituted counterparts. Thus we proposed that a halogen atom could be used in this capacity, which could later be either easily removed by hydrogenolysis or utilized as a functional handle in further structural elaboration of the product (Scheme 2C).

Before testing this hypothesis, we wished to be certain that highly chemoselective direct crossed acyloin chemistry was not possible using existing technology. For instance, while Buck *et al*.[18] did not employ aliphatic aldehydes in their study and Stetter[20] utilized a large excess of one aldehyde component, we felt it prudent to first examine these two protocols to ensure that the dearth of a chemoselective protocol in the literature is not due to either a simple oversight or omission by previous researchers. Aiming for a widely applicable, practical procedure that would also allow for the implementation of higher advanced aldehyde building blocks, we focussed on conditions which would not employ a large excess of either of both coupling partners (*i.e.* aliphatic aldehyde ≤ 1.7 eq).[37]

Accordingly we carried out experiments examining the reaction between an aliphatic and an aromatic aldehyde under the influence of either cyanide (conditions defined by Buck *et al*.)[18] or thiazolium derived carbene (conditions defined by Stetter *et al*.)[20] catalysis (Table 1). In the presence of cyanide ion (65 mol%) the reaction between **9** and isobutyraldehyde (**10**) produced a poor yield of **12** as the major product, while reaction with the unbranched hydrocinnamaldehyde (**11**) failed to generate cross product at all (entries 1-2). Utilization of Stetter's conditions proved somewhat more successful, with the isolation of 36-38% yields of a 'major' cross product possible when 1-1.7 equivalents of the aliphatic aldehyde component were employed (entries 3-6)



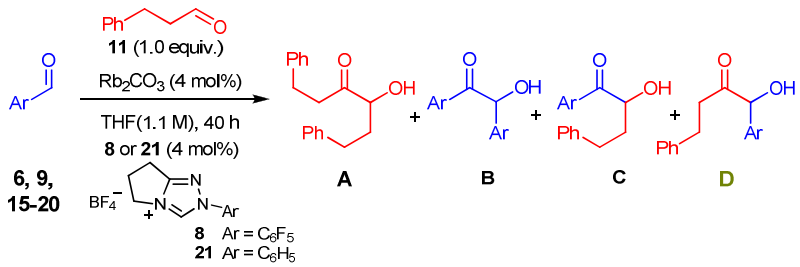
Entry	Condition[a]	Equivalents of $R_{Alk}CHO$	'Aliphatic' Aldehyde $R_{Alk}CHO$	Yield (%)
1	**A**	1.0	**10**	**12** 21
2	**A**	1.0	Ph **11**	0
3	**B**	1.0	**10**	**12** 38
4	**B**	1.7	**10**	**12** 36
5	**B**	1.0	Ph **11**	**13** 38
6	**B**	1.7	Ph **11**	**13** 39

[a] For details see experimental section.

Table 1: Short study on the general applicability of known direct cross acyloin procedures using branched and unbranched aliphatic aldehydes with *o*-chloro benzaldehyde as aromatic aldehyde partner.

From an analysis of the results of this study, a clear picture of the limited potential of the current benchmark protocols for the direct crossed AC reaction emerged: both do not tolerate reduced amounts of the aliphatic aldehyde and also fail to produce synthetically useful amounts of cross-product if unbranched aldehydes are employed. This encouraged us to return our attention to the original proposal involving the use of triazolium salt-derived systems.

Before attempting to examine the potential of hydrogen-bonding as a control element in these reactions,[36] we first wished to orient ourselves with respect to the natural bias (if any) a triazolium-derived carbene devoid of protic substituents would display towards one of the coupling partners in a crossed AC reaction. As a model process we chose the AC reaction between a range of substituted benzaldeyhdes **9** and **15-20** (of variable steric and electronic characteristics) and the relatively unhindered hydrocinnamaldehyde (**11**) in the presence of the achiral precatalysts **8** or **21** and base (*i.e.* conditions which had proven conducive to the promotion of homo-benzoin condensation reactions in our previous studies[33,34a]). The results of these experiments are outlined in Table 2.



Entry	Ar		Prod.	Yield **A** (%)[a]	Yield **B** (%)[a]	Yield **C** (%)[a]	Yield **D** (%)[a]	
1[b]	Ph	**6**	**22**	>2	8	>2	10	
2	Ph	**6**	**22**	26	20 (**7**)	11	48	
3	4-Cl-C_6H_4	**15**	**23**	53	44	2	43	
4	3-Cl-C_6H_4	**16**	**24**	44	34	6	50	1:1 ratio of ArCHO and HCA (**11**)
5	2-Cl-C_6H_4	**9**	**13**	8	15	9	51	
6	2-F-C_6H_4	**17**	**25**	52	45	14	34	
7	2-MeO-C_6H_4	**18**	**26**	20	16	21	59	
8	2-CF_3-C_6H_4	**19**	**27**	8	6	10	81	
9	2-Br-C_6H_4	**20**	**28**	0	9	8	49	
10[c]	2-Br-C_6H_4	**20**	**28**	4	10	5	73	
11[d]	2-Br-C_6H_4	**20**	**28**	5	10	6	76	
12[e]	2-Br-C_6H_4	**20**	**28**	>2	6	10	79	
13[f]	2-Br-C_6H_4	**20**	**28**	>2	21	11	74	variable ratios of ArCHO and HCA (**11**)
14[g]	2-Br-C_6H_4	**20**	**28**	31	4	7	84	
15[h]	2-Br-C_6H_4	**20**	**28**	61	3	7	89	
16[i]	2-Br-C_6H_4	**20**	**28**	68	0	10	90	

[a] Yield determined by ^{1}H NMR spectroscopy using styrene as an internal standard. Note: yields of **13** and **22-28a** and **22-28b** account for the 2:1 stoichiometry. To obtain the mol% of these materials divide the yield by 2. [b] Phenyl-substituted triazolium precatalyst **21** was used instead. [c] 8 mol% catalyst. [d] With 10 mol% catalyst loading. [e] With 1.3 equiv of **20** and 8 mol% catalyst. [f] With 1.5 equiv of **20** and 8 mol% catalyst. [g] With 1.3 equiv of **11** and 8 mol% catalyst. [h] 1.5 equiv of **11** and 8 mol% catalyst. [i] With 1.7 equiv of **11** and 8 mol% catalyst.

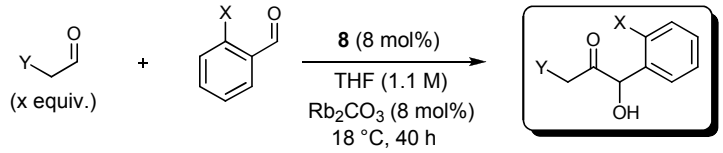
Table 2: Crossed AC reactions with unbranched aldehydes: preliminary experiments.

As expected the pentafluorophenyl-substituted catalyst **8** proved a superior system to **21** under these conditions (entries 1-2).[34] The coupling of benzaldehyde (**6**) and **11** proceeded with poor chemoselectivity – while a marked preference for the formation of products derived from the aliphatic Breslow intermediate (e.g. *via* initial attack of the catalyst on **11** (*i.e.* **22a+22d** *vs* **22b+22c**)) was observed, all four possible products (homodimers **22a**/**22b** and crossed products **22c**/**22d**) were formed without any one being present at synthetically useful levels. The activation of the aromatic aldehyde component with a chlorine atom in either the *m*- or *p*-position failed to influence chemoselectivity to any appreciable extent (entries 3-4) the preference for the cross-coupled products **D** was slightly improved, at the expense of the formation of increased amounts of the aryl homobenzoins **B**. However, the use of the *o*-substituted analogue **9** generated **13d** as the dominant

product in moderate yield (entry 5). Further investigation revealed that the improved chemoselectivity associated with the use of *o*-substituted aldehydes is primarily related to the steric requirement of the substituent, although its electronic characteristics do also seem to play a minor role. For instance, the small but highly electronegative fluorine atom does not confer high chemoselectivity (entry 6), however use of larger units such as the electron releasing methoxy- and the electron withdrawing trifluoromethyl-substituents (entries 7 and 8 respectively) allow relatively selective crossed AC reactions to occur – with the latter suppressing the pathways leading to **27a-c** to the extent that **27d** was formed in 81% yield.

Particularly gratifying was the performance of the *o*-bromo derivative **20**. This coupling partner is of considerable potential interest for two reasons: firstly, the bromine atom in the product (*i.e.* **28d**) can serve as a functional handle for further elaboration (radical generation, participation in transition metal catalyzed coupling reactions *etc*.), while secondly, as mentioned earlier (*vide supra*), we envisaged that it should be possible to cleanly remove the halogen from the product – which allows one to aspire towards the use of an *o*-bromo substituent as a removable tool to control chemoselectivity in these processes, thereby providing access to products (after debromination) which would be otherwise difficult to prepare in good yield *via* carbene-catalyzed crossed AC chemistry. It was found that **20** coupled to **11** with *very good chemoselectivity* and moderate yield initially (entry 9), which could already drastically improved by employing 8 mol% of catalyst **8** (entry 10). Subsequent optimization of the reaction conditions (entries 10-16) allowed the synthesis of **28d** in 90% yield by employing a small excess of **11** (1.7 equiv.) in the presence of 8 mol% of **8**.[38]

The scope of the process with respect to the 'aliphatic' or '*umpolung*' aldehyde component was next investigated. *o*-substituted electrophiles **19** and **20** were coupled to a range of unbranched aldehydes **11** and **29-32** under our optimized conditions in the presence of catalyst **8** at room temperature (Table 3). Acetaldehyde (**29**) proved a challenging substrate to utilize at ambient temperature due to its low boiling point (entry 1), however use of a tenfold excess (feasible due to the low cost of this reagent) resulted in good yield of its cross product with **19** (*i.e.* **33**, entry 2). The less volatile unbranched aldehydes *n*-propanal (**30**, entries 3-5), *n*-pentanal (**31**, entries 6-7), hydrocinnamaldehyde (**11**, entries 8-9) and phenylacetaldehyde (**32**, entries 10-11) could be efficiently coupled to either **19** or **20** with good product yields without difficulty using a smaller excess of 1.7-2.5 equiv.



29 Y = H
30 Y = CH_3
31 Y = *n*-C_3H_7
11 Y = CH_2Ph
32 Y = Ph

19 X = CF_3
20 X = Br

33 Y = H, X = CF_3
34 Y = CH_3, X = CF_3
35 Y = CH_3, X = Br

36 Y = *n*-C_3H_7, X = CF_3
37 Y = *n*-C_3H_7, X = Br
38 Y = Ph, X = CF_3
39 Y = Ph, X = Br

Entry	'Aliphatic' Aldehyde	X	'Aromatic' Aldehyde	Product	Yield D[38] (%)
1	**29**	1.7	**19**	**33**	50[a]
2	**29**	10.0	**19**	**33**	78
3	**30**	1.7	**19**	**34**	79
4	**30**	1.7	**20**	**35**	68[a]
5	**30**	2.5	**20**	**35**	73
6	**31**	1.7	**19**	**36**	84
7	**31**	1.7	**20**	**37**	77
8[b]	**11**	1.7	**19**	**27d**	60[a]
9[c]	**11**	1.7	**19**	**27d**	86
10	**32**	1.7	**19**	**38**	81
11	**32**	1.7	**20**	**39**	76

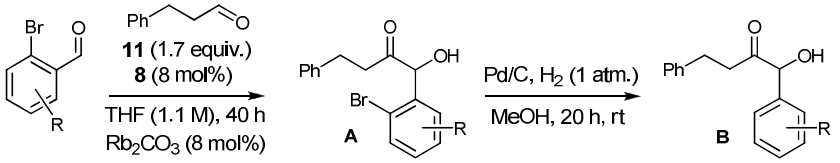
[a] Yield determined by ^{1}H NMR spectroscopy using styrene as an internal standard. [b] At 5 °C: 17% and 16% yields of homo- and heterocoupling products (**B** and **C**) respectively derived from initial attack of the catalyst on **19** were obtained. [c] At 18 °C: 10% yields of both homo- and heterocoupling products (**B** and **C**) derived from initial attack of the catalyst on **19** were obtained.

Table 3: Evaluation of substrate scope: unbranched aldehydes.

It is perhaps interesting to note that coupling of **11** (1.7 equiv.) to **19** at 5 °C is less chemoselective than an otherwise identical reaction at 18 °C (entries 8-9). In the case of the reaction at the lower temperature, **27d** was still obtained as the major product, however significantly elevated levels of products derived from initial attack of the catalyst on **19** (*i.e.* **27b** and **27c**) were detected, indicating that these coupling reactions may proceed under a significant degree of thermodynamic control.[39]

To demonstrate the potential of the use of an *ortho*-bromo substituent as a solution to circumvent the inherent lack of chemoselectivity in crossed AC reactions involving aromatic aldehydes and unbranched aliphatic aldehydes, we carried out the coupling of a variety of *o*-bromobenzaldehydes (**20** and **40-42**) equipped with both electron neutral (entry 1), electron donating (entries 2-3) and electron withdrawing (entry 4) substituents with **11** (Table 4). Good to excellent yields of coupled products were obtained in each case under standard conditions. Adducts **28d** and **43-45** were then smoothly and conveniently debrominated under an atmosphere of hydrogen in the presence of Pd/C to give

hydroxyketones **18d** and **46-48** respectively in uniformly excellent yields. Thus we would submit, that the *o*-bromo substituent can be employed as a temporary directing group which can first divert the course of an otherwise relatively unselective (see Table 1, entry 2 *vs.* entries 9 and 16) coupling reaction towards the formation of a single major product (irrespective of the overall electronic nature of the aromatic aldehyde coupling partner), and then either serve as a functional handle if required or be cleanly removed to give debrominated products *not otherwise accessible in high yield directly from a operationally simple carbene-catalyzed AC process*.



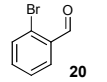
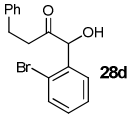
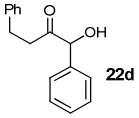
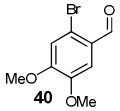
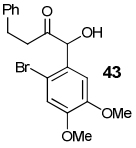
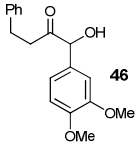
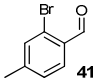
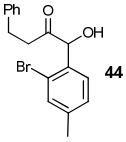
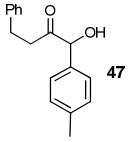
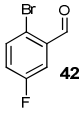
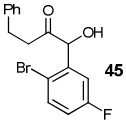
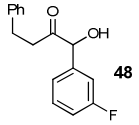
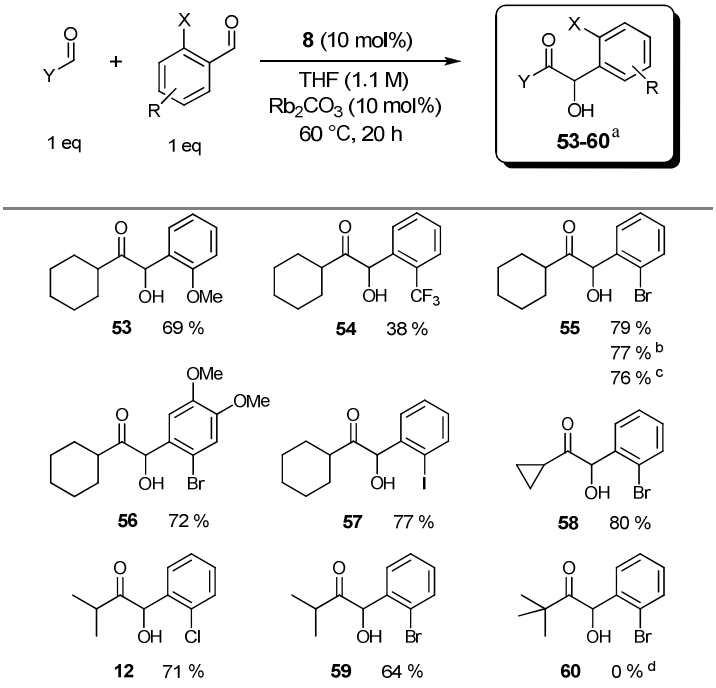
Entry	Aldehyde	Acyloin Product (**A**)	Yield (%)	Reduction Product (**B**)	Yield (%)
1	 **20**	 **28d**	90	 **22d**	90
2	 **40**	 **43**	93	 **46**	96
3	 **41**	 **44**	88	 **47**	93
4	 **42**	 **45**	80	 **48**	92

Table 4: Exploitation of a removable 2-bromo substituent.

For this methodology to be genuinely synthetically useful, its scope with respect to the 'nucleophilic' component must not be limited to unbranched aldehydes. Initial experiments involving the coupling of α-substituted aldehydes at room temperature resulted in poor conversion (<50%) even after prolonged reaction times. At 60 °C however, these substrates will participate in efficient crossed AC reactions (Scheme 4). The reaction between cyclohexane carbaldehyde (**49**) and *o*-anisaldehyde (**18**) furnished **53** in good yield. We found that *o*-trifluoromethyl benzaldehyde **19** performed unsatisfactorily under these conditions (the stability of product **54** under the reaction conditions appears to be problematic,

vide infra[39]; product **54**). *o*-bromobenzaldehydes **20** and **40** both coupled with cyclohexane-carbaldehyde (**49)** to afford **55** and **56** respectively in good yield. *o*-iodobenzaldehyde (**52**) is also compatible with the methodology (the first time this aldehyde has been evaluated as a AC substrate, product **57**). The use of the interesting substrate **50** led to the formation of the densely functionalized cyclopropyl-substituted ketone **58** in 80% yield. 2-Methylpropanal (**10**) proved a challenging substrate due to its low boiling point but could still be converted to **12** and **59** in good yields in the presence of **9** resp. **20**, while at this stage it appears that pivaldehyde is too bulky a substrate to form a nucleophilic Breslow intermediate under these conditions. Importantly, this cross coupling procedure employing branched aldehydes does not require an excess of one of the coupling partners, thus providing a catalytic and relatively waste-free, selective access to such valuable cross acyloin products.



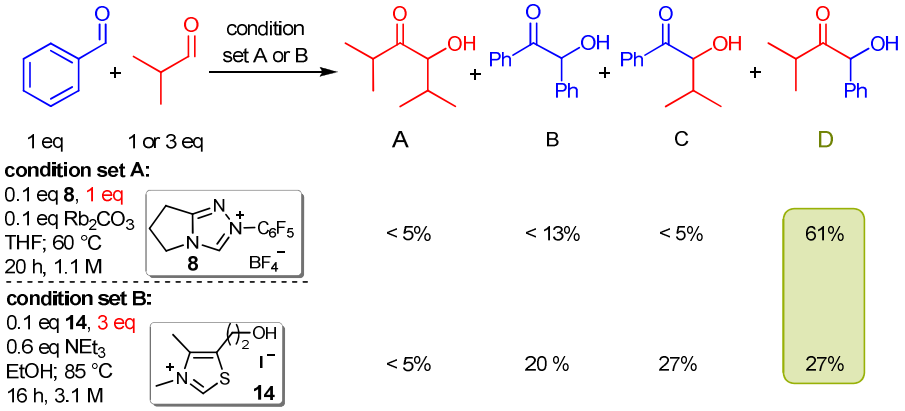
[a] Neither the homobenzoins nor cross-product **C** are formed in significant amounts; sometimes formation of corresponding acids can be observed. [b] 1.5 equiv. of aldehyde **49**. [c] K_2CO_3 used instead of Rb_2CO_3. [d] No cross AC product detected; only 16% of aromatic homocoupled product was obtained (yield determined by ^{1}H NMR spectroscopy using stilbene as an internal standard).

Scheme 4: Evaluation of substrate scope: branched aldehydes

The question regarding the origin of the chemoselectivity observed is both intriguing and difficult to definitively answer at this juncture. It is reasonable to assume that the presence of the *o*-substituent retards the rate of attack of the carbene on the aromatic aldehyde, resulting in increased concentrations of the Breslow intermediate derived from initial attack on the aliphatic aldehyde. What is unclear, is why this intermediate (rather counter intuitively) then prefers to react with the presumably more hindered *o*-substituted benzaldehyde over another molecule of aliphatic aldehyde?

There are several possible explanations, such as a π-iminium interaction in the developing TS as the enolamine attacks the aromatic aldehyde,[27, 40] a stabilising (and selectively formed) hydrogen bond between the more basic aromatic aldehyde carbonyl oxygen and the enolamine hydroxyl group, or perhaps most importantly given the supporting evidence uncovered as this study progressed – a degree of thermodynamic product control. Based on the well-established mechanistic picture of acyloin/benzoin condensations,[10e, 41] it is also reasonable to assume that the properties of the Breslow intermediate should also be dependant to a significant extent on the nature of the catalyst it is derived from. What is certain is that these issues are now ripe for investigation.

We were first interested in examining the influence of the choice of catalyst on the outcome of these reactions from a chemoselectivity perspective. We challenged our optimized catalytic system (condition set A, Scheme 5) with the reaction between benzaldehyde, lacking the selectivity-controlling *ortho*-substituent, and *iso*butyraldehyde and then repeated the experiment under Stetter´s conditions (condition set B, Scheme 4) employing a thiazolium derived carbene instead of the triazolium pre-catalyst. In contrast to the results reported by Stetter,[20] in our hands condition set B provides both cross-products and the homo arylbenzoin in a *ca*. 1:1:1 ratio (combined yield of cross-acyloin products: 54%).[42] Use of condition set A on the other hand, involving the triazolium catalyst **8**, results in remarkably high selectivity for the cross-coupled acyloin **D**, which could be isolated in 61% yield. Neither the cross-coupled **C** nor homobenzoin **B** was formed in significant amounts. It is therefore clear that the catalyst exerts a significant degree of control over the process from a chemoselectivity standpoint.



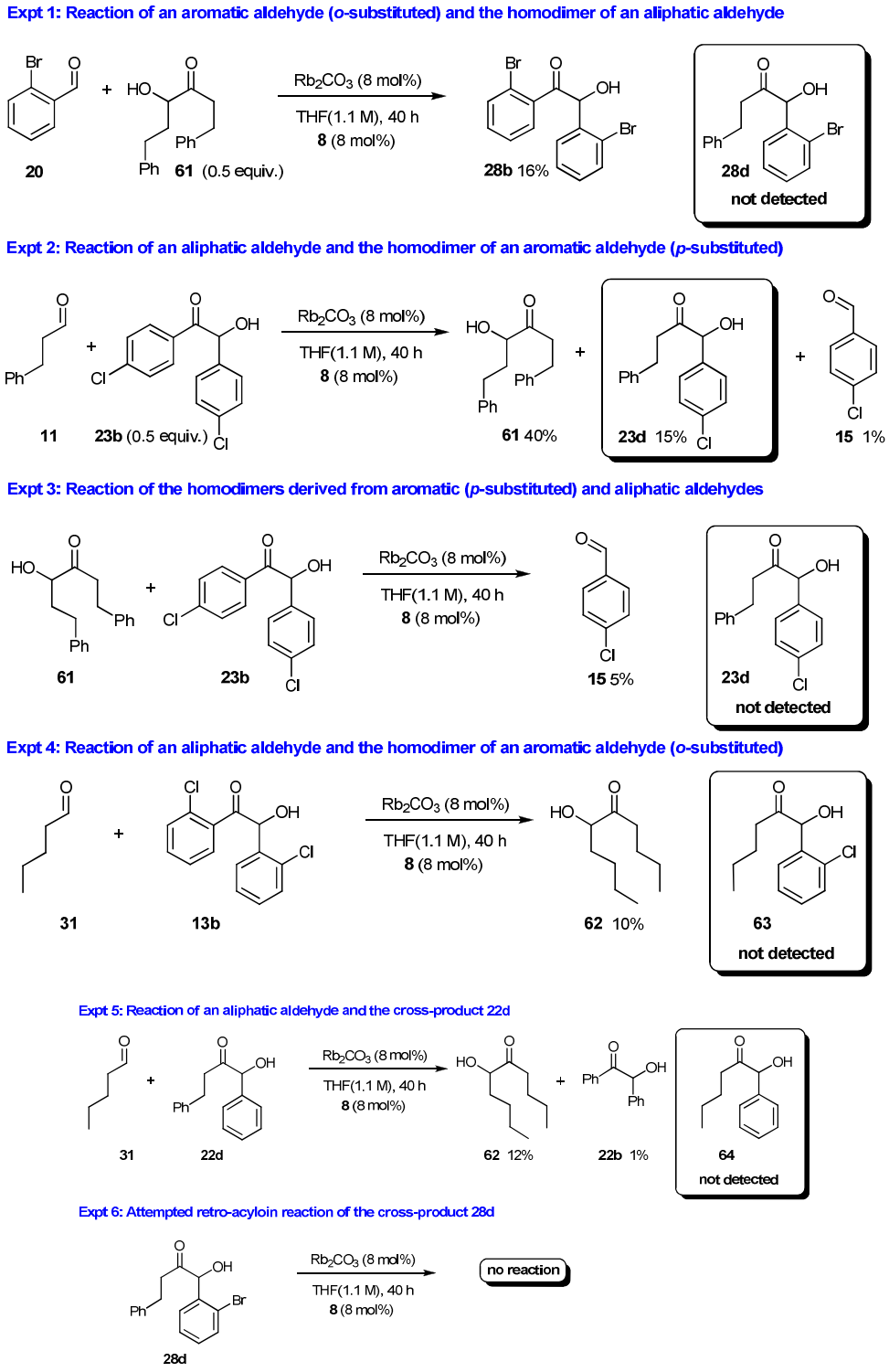
[a] Yields determined by ^{1}H NMR spectroscopy using stilbene as internal standard. See experimental section for details.

Scheme 5: Influence of the catalytic system on chemoselectivity.[a]

In an attempt to further shed light on the origins of the observed chemoselectivity a number of crossover experiments were carried out. The results of these experiments are outlined below (Scheme 6). In the first instance, we wished to establish the degree of reversibility of these processes. We therefore treated the *o*-substituted aldehyde **20** with the catalyst **8** under our standard conditions in the presence of homodimer **61** (Expt 1). The slow dimerization of **20** was observed but no products (such as **28d**) derived from the retro-acyloin of **61** could be detected. Next we investigated the opposite pairing of starting materials, *i.e.* an 'aliphatic' aldehyde **11** and a homodimer derived from a (*para*-substituted) aromatic aldehyde (*i.e.* **23b**, Expt 2**)**. Interestingly, this experiment afforded significant amounts of the cross-product **23d**, along with free aldehyde **15** (which also stems from a retro-acyloin reaction) and the homodimer **61**. When the experiment was repeated where the aliphatic aldehyde **11** was replaced with its homodimers **61** (Expt 3), again retroacyloin of **23b** was observed but in this case no coupling to form cross-product **23d** occurred. These results seemed to indicate that the benzoin **23b** is able to revert to its parent aldehyde under the reaction conditions, whereas the homodimer **61** derived from hydrocinnamaldehyde is not. To probe this further, the *ortho*-isomer of benzoin **23b** (*i. e.* **13b**, Expt 4) was treated with an aliphatic aldehyde **31** in the presence of the catalyst. Gratifyingly, no cross product **63** was detected in this experiment (Expt 4).

Thus it would appear that the *o*-substituted **13b** is more stable towards the catalyst than its *p*-isomer **23b**, which, together with the rather slow rate of dimerization of *o*-bromobenzaldehyde (**20**) and hydrocinnamaldehyde (**11**) and the reluctance of the 'aliphatic' homodimer **61** to undergo a retro-acyloin reaction, goes some way towards explaining the chemoselectivity observed in these processes.

In a similar cross-over experiment involving the cross product **22d** and the aliphatic aldehyde **31** we observed trace amounts of benzoin (**22b** - which could only arise from the retroacyloin of **22d)** and homodimer **62** (Expt 5). No cross product **64** was detected. Finally, exposure of the cross product **28d** derived from reaction of *o*-bromobenzaldehyde (**20**) and hydrocinnamaldehyde (**11**) to the catalyst under standard conditions failed to produce any products.



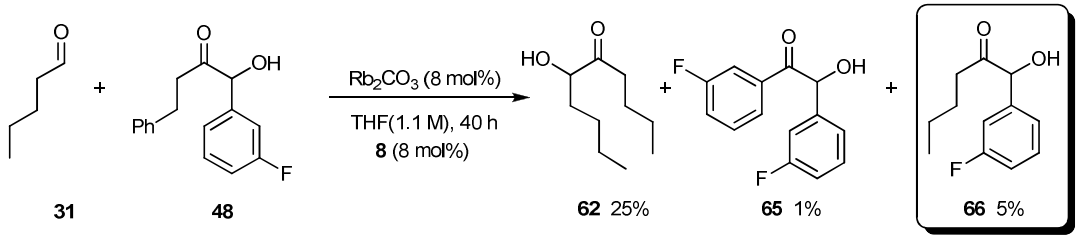
Scheme 6: Crossover experiments under optimized conditions using triazolium precatalyst **8**.

A number of conclusions can be drawn from these reactions:

'Aliphatic' and *o*-substituted benzaldehydes dimerize, but do so only slowly (Expts 1, 2 and 4-5). This is central to attaining high chemoselectivity in these processes. The homodimers derived from 'aliphatic' aldehydes do not participate in retro-acyloin chemistry under these conditions and are

essentially formed irreversibly (Expts 1 and 3). Unhindered benzoins (*i.e.* homodimers of aromatic aldehydes) will participate in retro-acyloin chemistry under these conditions, whereas *o*-substituted isomers will not (Expts 2-4). The α-arylketone cross-product (the major product under our conditions) from the reaction of an 'aliphatic' and an aromatic aldehyde undergoes retro-acyloin either slowly (Expt 5) or not at all (Expt 6). The crossed acyloin reactions involving unhindered benzaldehydes are subject to a far greater degree of thermodynamic control than those involving hindered analogues (Expts 1-6). Given that the energy differences between the acyloin products are likely to be small – this results in relatively unselective reactions where benzaldehydes devoid of *o*-substitution are employed.[43]

To support the theory that cross-products derived from reactions involving activated, unhindered benzaldehydes are more amenable to retro-acyloin reactions (and hence are formed in lower yields) we synthesized **48** and subjected it to the reaction conditions in the presence of pentanal (**31**). We were pleased to observe increased levels of products derived from the retro-acyloin reaction of **48** relative to those observed using benzaldehyde as the reacting partner (see Scheme 7 and Exp 6, Scheme 6). Thus it is clear that the reversibility of the process is also influenced by the electronic nature of the benzaldehyde partner, with more activated aldehydes participating in less chemoselective reactions.



Scheme 7: Investigation of the use of cross products derived from activated yet unhindered aldehydes.

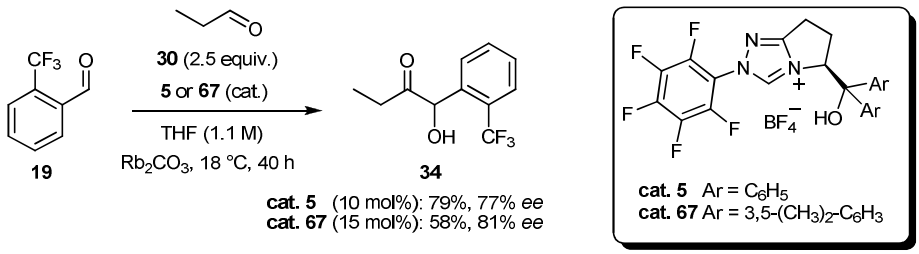
Overall, it is clear that crossed-coupling is facilitated by the slow dimerizability of the aliphatic aldehyde and *o*-substituted benzaldehydes. Given that none of the products derived from the cross-coupling of these aldehydes could demonstrably participate in retro-acyloin reactions, why cross-coupling is faster than dimerization and why the α-arylketone cross-product is favored over the other still require explanation. We would propose that it is reasonable to assume that initial attack of the carbene on the aliphatic aldehyde is preferred on electronic grounds – *i. e.* the more electron rich benzaldehyde carbonyl moieties make for poorer electrophiles in the first step of the catalytic cycle. This is supported by the observation that the use of more activated, halogen-substituted benzaldehydes generates greater levels of homobenzoin products derived from initial attack on the benzaldehyde moiety (see entries 3-6 and 9, Table 2). In the case of *o*-substituted benzaldehydes this preference for the aliphatic partner as the initial site of attack would obviously be exaggerated for steric reasons; this argument can be underlined by the decreasing amount of these homobenzoins detected with increasing

size of the *ortho*-halogen substituent (*o*-F, *o*-Cl, *o*-Br with 45%, 15% and 9% of homo-coupled product, see entries 5, 6 and 9, Table 2).

It is difficult to establish why the BI then prefers to attack the hindered aromatic aldehyde over another molecule of aliphatic aldehyde. In a natural product synthesis study involving an intramolecular AC step Miller[24] has suggested that a stabilizing interaction between orthogonally aligned carbonyl and aromatic moieties known to exist in α-phenyl ketones (in cases where it is stereoelectronically permitted) may influence the chemoselective outcome of AC reactions between aliphatic and aromatic aldehyde components. It is tempting to draw parallels in this study, *i.e.* that the observed preference for the α-arylketone cross product over the α-substituted aromatic ketone analogue is related to the contribution of this interaction, which presumably results in greater reversibility of the latter cross-product over the former. However, it should be pointed out that the seemingly logical extension of this argument to account for the preference for cross-product formation over aliphatic aldehyde dimerization is less sound at this juncture, since we could not observe any retro-acyloin chemistry involving the aliphatic dimers.

What can be safely inferred is that chemoselectivity in these processes is not governed by a single factor alone but rather a confluence of factors depending on the catalyst employed and the steric and electronic nature of the reactants. That being said, it is clear that one can achieve high selectivity in the diverse array of AC reactions examined in this study by using catalyst **8** in the presence of an aromatic aldehyde incorporating an (removable) *o*-bromo substituent, irrespective of other substrate characteristics.

While the methodologies outlined above allow one to carry out highly chemoselective crossed AC reactions using a combination of catalyst properties and the steric effects of the substrates, the ability to control the stereochemical outcome of these reactions is of course the ultimate goal. To this end **19** was coupled with **30** in the presence of the bifunctional chiral triazolium salt **5** (10 mol%) to afford the expected product **34** in good yield and enantiomeric excess (Scheme 8).



Scheme 8: Chemo- and enantioselective crossed acyloin condensation.

The novel precatalyst **67**, which possesses a larger diarylcarbinol unit, is less active than **5** but promoted the same reaction with improved enantioselectivity (81% *ee*). While this aspect of the study

is currently at an early stage of development, it is clear from analysis of these preliminary data that the process is amenable to the efficient transfer of stereochemical information from catalyst to product.

1.3.3 Conclusion

In summary, we have developed the first chemoselective intermolecular crossed AC reactions between two aldehyde partners involving triazolium precatalysts. A key discovery is the use of an *o*-bromo substituent as a temporary chemoselectivity-controlling group which can subsequently be removed in high yield. The methodology is of very broad scope: hindered, activated and electron-rich aromatic aldehydes are compatible, as are both unbranched and more hindered branched aliphatic aldehydes. Importantly, unlike the previous benchmark study in the literature involving a thiazolium catalyst, in these reactions the expected product from the cross-coupling of two aldehydes can be confidently predicted beforehand, and the methodology is generally complementary to existing methodologies based on enzymatic catalysis. The feasibility of highly enantioselective crossed AC reactions has also been established – investigations aimed at further refining the asymmetric catalysis and elucidating the origins of the chemoselectivity are now underway.

1.3.4 Experimental Section

General Methods

Unless otherwise noted, all commercially available compounds were used as provided without further purification.

NMR spectra were recorded on 300 (300.13 MHz), 400 MHz (400.13 MHz) or 600 MHz (600.13 MHz) spectrometers using the solvent peak as internal reference ($CDCl_3$: δ H 7.26; δ C 77.0 and DMSO-d_6: δ H 2.51; δ C 39.5). Multiplicities are indicated, s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet)); coupling constants (*J*) are in Hertz (Hz). Mass spectra (MS ESI) were recorded using a mass spectrometer equipped with a TOF analyser. All reactions were monitored by thin-layer chromatography using gel plates 60 F_{254}; visualization was accomplished with UV light and/or staining with appropriate stains ($KMnO_4$, anisaldehyde, vaniline, ninhydrin or phosphomolybdic acid). Standard flash chromatography procedures were followed (particle size 40−63 μm). Infrared spectra were obtained using neat samples on spectrometers equipped with a universal ATR (attenuated total reflectance) sampling accessory. Optical rotation measurements are quoted in units of 10^{-1} deg cm^2 g^{-1}. Analytical CSP-HPLC was performed using a Daicel CHIRALCEL OJ-H (4.6 mm x 25 cm) column.

Tetrahydrofuran was distilled from sodium/benzophenone. All reactions were carried out under a protective atmosphere of dry nitrogen or argon using oven-dried glassware unless otherwise stated.

Catalyst **5** was prepared as per the procedure described by Connon, Zeitler et al.[44] and catalyst **8** as per the method described by Rovis.[45]

General Procedures

<u>General Procedure 1</u> (for the synthesis of catalyst 67)

An oven-dried 25 cm^3 round bottomed flask, equipped with a magnetic stirrer, was charged with the selected TMS-protected pyrrolidinone (500 mg, 1.27 mmol) and the reaction put under an atmosphere of Argon. CH_2Cl_2 (6.00 cm^3) was injected *via* syringe to give a solution. Trimethyloxonium tetrafluoroborate (187 mg, 1.27 mmol) was added and the reaction returned to an atmosphere of Ar. The reaction was stirred for 12 h resulting in a pale orange suspension. Pentafluorophenyl hydrazine (251 mg, 1.27 mmol) was added to the reaction. After 2 h the orange solution was concentrated *in vacuo*. The crude reaction was equipped with a reflux condenser and put under an Ar atmosphere.

Chlorobenzene (12 cm^3), followed by triethyl orthoformate (530 μL, 3.16 mmol), were charged to the vessel and the reaction was stirred at 120 °C for 12 h. Additional triethylorthoformate (530 μL, 3.16 mmol) was added and the reflux continued for a further 12 h. Upon cooling, the reaction mixture was concentrated *in vacuo* resulting in a brown residue. MeOH (37 cm^3) was added to the reaction, the flask was fitted with a rubber septum seal and placed under an atmosphere of Ar. To the resulting solution was added TMSBr (630 μL, 4.88 mmol) in 5.70 cm^3 MeOH. The reaction mixture was stirred at room temperature for 24 h and solvent removed under reduced pressure. Column chromatography (EtOAc) and subsequent recrystallization from EtOAc gave **67** as a pale yellow solid, mass 292 mg, yield 38%.

General Procedure 2 (for the Crossed Acyloin Condensation with Unbranched Aldehydes)

To a 5 cm^3 round-bottomed flask, equipped with a magnetic stirring bar, was added Rb_2CO_3 (99.8%) that had been finely ground using a mortar and pestle. The reaction vessel was put under vacuum and heated with a heat gun for 4 one-minute intervals. When cooled to ambient temperature the appropriate catalyst (0.09 mmol) was added and the flask was fitted with a septum seal. The flask was evacuated for 1 min and put under an atmosphere of Ar. The required aldehydes were distilled under vacuum and used directly. THF was charged to the reaction, followed by consecutive addition of each aldehyde. The reaction was stirred at room temperature for 40 h. CH_2Cl_2 (3.0 cm^3) and deionised H_2O (3.0 cm^3) were added. The organic layer was removed and the aqueous layer was washed with CH_2Cl_2 (4 x 3.0 cm^3). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The product was purified using column chromatography.

General Procedure 3 (for the Hydro-debromination of Crossed Acyloin Condensation Products)

To a 25 cm^3 round bottomed flask, equipped with a stirring bar, was added brominated crossed acyloin (0.3 mmol), 10% Pd/C (6 wt.%), Et_3N (1.2 eq.) and MeOH (0.36M). The flask was evacuated and then purged with N_2. This cycle was performed twice. The reaction was stirred vigorously at ambient temperature (ca. 20 ºC) under an atmosphere of hydrogen (hydrogen generator), overnight. The reaction mixture was filtered and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 cm^3) and H_2O (10 cm^3), the organic layer was washed with brine (10 cm^3), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The product was purified using column chromatography.

General Procedure 4 (for the Crossed Acyloin Condensation with α-Branched Aldehydes)

A flame-dried Schlenk flask equipped with a magnetic stirring bar was charged with Rb_2CO_3 (12 mg, 0.05 mmol). The reaction vessel was evacuated, heated to 650° C for 1 minute and cooled to r.t. under N_2. After this procedure had been repeated once, triazolium-precatalyst **8** (18 mg, 0.05 mmol) was added. The precatalyst/base-mixture was put under vacuum and dried at r.t. for 45 min. Subsequently, absolute THF (0.45 ml) was added and the resulting mixture was allowed to stir at r.t. for 15 min. After sequential addition of the appropriate benzaldehyde (0.5 mmol) and α-branched aldehyde (0.5 mmol), the reaction vessel was equipped with a reflux condenser and stirred at 60 °C under an atmosphere of N_2.After 20h the reaction mixture was allowed to cool to r.t., diluted with 5 mL of $CHCl_3$ and extracted with H_2O. The aqueous layer was back-extracted twice with 5 mL of $CHCl_3$ and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent under reduced pressure affords the crude product which was purified by column chromatography.

General Procedure 5 ("Stetter"-type Conditions for the Crossed Acyloin Condensation)

A flame-dried Schlenk flask ("tube shape")[46] equipped with a magnetic stirring bar was charged with 14 mg (0.05 mmol = 10 mol%) thiazolium iodide precatalyst **14** (and 25 mol% stilbene, if required) and put under high vacuum. After having dried the solids for 1h at ambient temperature, 0.16 ml of EtOH was added and the resulting solution stirred for 5 min. Now 0.5 mmol (1 eq) of the aromatic aldehyde as well as 1.5 mmol (3 eq) of the aliphatic aldehyde were added. After final addition of 0.3 mmol (0.6 eq) triethylamine, the reaction vessel was equipped with a reflux condenser and heated for 16 h (ca. 90 °C) under an inert atmosphere.

To determine the yields of the benzoin products, residual starting material etc. *via* quantitative NMR, the reaction vessel was allowed to cool to room temperature. In order to transfer the crude reaction mixture into an NMR tube, a pasteur-pipet (without cap) was dipped four times into the solution (whereupon it is becoming partly solid in most cases). Finally, an appropriate amount of $CDCl_3$ was added.

For the isolation of the corresponding benzoin products the crude mixture was evaporated and purified by column chromatography.

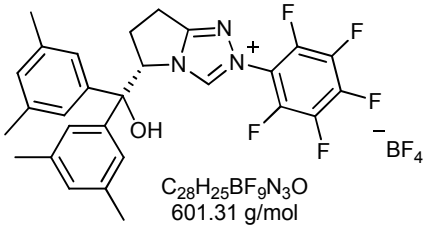
General Procedure 6 (Crossover Experiments)

To a 5 cm^3 round-bottomed flask, equipped with a magnetic stirring bar, was added Rb_2CO_3 (99.8%) that had been finely ground using a mortar and pestle. The reaction vessel was put under vacuum and heated with a heat gun for 4 one-minute intervals. When cooled to ambient temperature the appropriate catalyst (8 mol%) was added and the flask was fitted with a septum seal. The flask was evacuated for 1 min and put under an atmosphere of Ar.

The flask was evacuated for 1 min and put under an atmosphere of Ar. THF was added, followed by the consecutive addition of the benzoin to be checked and the aldehyde (distilled under vacuum and used directly). The reaction was stirred at room temperature for 40 h. After 40 h styrene was added as internal standard and the reaction analysed by ^{1}H NMR spectroscopy.

Experimental Data for Catalyst Synthesis

(5*S*)-[Bis-(3,5-dimethyl-phenyl)-hydroxy-methyl]-2-pentafluorophenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate (67)

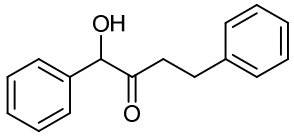


according to the **general procedure 1**: yield 0.292 g; 38 %, as pale yellow solid, 292 mg, 38%, m.p. 165-167 °C, (dec.). R_f (EtOAc) 0.20. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.38 (s, 1H), 7.13 (s, 2H), 7.07 (s, 2H), 6.98 (s, 1H), 6.95 (s, 1H), 6.59 (s, 1H), 6.05 (dd, 1H, *J* = 8.7, 1.9), 3.21-3.17 (m, 1H), 3.07-3.01 (m, 1H), 2.98-2.92 (m, 1H), 2.71-2.68 (m 1H), 2.29 (s, 6H), 2.27 (s, 6H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 164.7, 143.2, 143.1, 142.9, 142.1 (d of m, *J* = 255.6), 141.6 (d of m, *J* = 255.4), 137.8, 137.4, 136.5 (d of m, *J* = 250.0), 129.4, 129.0, 123.7, 123.6, 111.0 (t, *J* = 12.8), 78.5, 68.4, 29.7, 21.4, 21.1, 21.0. ^{19}F NMR (376 MHz, DMSO-d_6): δ -157.48 (app. t, 2F), -145.05 (t, 1F, *J* = 24.9), -143.15 (d, 2F, *J* = 22.1). HRMS ($C_{28}H_{25}N_3OF_5$ - BF_4): calcd.: 514.1918, found: 514.1918. IR (cm^{-1})**:** $\tilde{\nu}$ = 3399, 3215, 3034, 2956, 2919, 1635, 1594, 1526, 1504, 1486, 1068, 999, 866, 856, 810, 730. $[\alpha]_D^{20}$ = -168.0 (*c* 1.39 in $CHCl_3$) for *S* enantiomer.

Experimental Data for Crossed Acyloin Products

Experimental Data for Crossed Acyloins with Unbranched Aliphatic Aldehydes

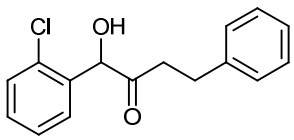
1-Hydroxy-1,4-diphenyl-butan-2-one (22d, Table 2, entry 2)



$C_{16}H_{16}O_2$
240.30 g/mol

according to the **general procedure 2**: yield 127 mg; 48 %, white solid, m.p. 63-65 ºC. R_f (CH_2Cl_2/hexanes 3/2) 0.28. Procedure used Rb_2CO_3 (10.2 mg, 0.04 mmol), catalyst **8** (16.0 mg, 0.04 mmol), benzaldehyde (**6**) (111.7 µL, 1.10 mmol), hydrocinnamaldehyde (**11**) (144.9 µL, 1.10 mmol) and THF (710 µL). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40-7.35 (m, 3H), 7.29 (d, 2H, *J* = 7.2), 7.27-7.25 (app. t, 2H), 7.19 (t, 1H, *J* = 7.3), 7.06 (d, 2H, *J* = 7.2), 5.07 (s, 1H), 4.31 (s (broad), 1H), 2.94-2.89 (m, 1H), 2.84-2.79 (m, 1H), 2.75-2.63 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 208.6, 140.2, 137.8, 129.1, 128.7, 128.5, 128.2, 127.4, 126.3, 79.2, 39.5, 29.7. HRMS ($C_{16}H_{16}O_2$ + Na): calcd.: 263.1048, found: 263.1050. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3427, 3084, 3028, 2923, 1713, 1601, 1495, 1452, 1062, 748, 715.

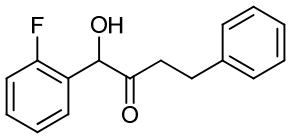
1-(2-Chloro-phenyl)-1-hydroxy-4-phenyl-butan-2-one (13d, Table 1 and Table 2 entry 5)



$C_{16}H_{15}ClO_2$
274.74 g/mol

according to the **general procedure 2**: yield 154 mg; 51 %, colourless to pale yellow oil. R_f (CH_2Cl_2/hexanes 2/3) 0.10. Procedure used Rb_2CO_3 (10.2 mg, 0.04 mmol), **8** (16.0 mg, 0.04 mmol), *ortho*-chlorobenzaldehyde (**9**) (123.9 µL, 1.10 mmol), hydrocinnamaldehyde (**11**) (144.9 µL, 1.10 mmol) and THF (700 µL). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, 1H, *J* = 7.5), 7.31-7.28 (m, 2H), 7.27-7.24 (app. t, 2H), 7.22-7.18 (app. t, 2H), 7.08 (d, 2H, *J* = 7.5), 5.58 (s, 1H), 4.36 (s (broad), 1H), 2.97-2.92 (m, 1H), 2.89-2.84 (m, 1H), 2.83-2.79 (m, 1H), 2.70-2.64 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 207.9, 140.1, 135.5, 133.5, 130.1, 129.9, 129.1, 128.5, 128.2, 127.5, 126.3, 76.2, 39.4, 29.6. HRMS ($C_{16}H_{15}ClO_2$ + Na): calcd.: 297.0658, found: 297.0666. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3456, 3063, 3028, 2926, 1714, 1593, 1604, 1574, 1475, 1454, 1440, 1032, 751, 699.

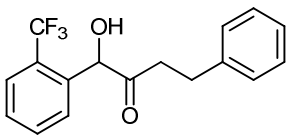
1-(2-Fluoro-phenyl)-1-hydroxy-4-phenyl-butan-2-one (25d, Table 2, entry 6)



$C_{16}H_{15}FO_2$
258.29 g/mol

according to the **general procedure 2**: yield 97 mg; 34 %, pale yellow oil. R_f (CH_2Cl_2/hexanes 3/2) 0.12. Procedure used Rb_2CO_3 (10.2 mg, 0.04 mmol), **8** (16.0 mg, 0.04 mmol), *ortho*-fluorobenzaldehyde (**17**) (115.9 µL, 1.10 mmol), hydrocinnamaldehyde **11** (144.9 µL, 1.10 mmol) and THF (740 µL). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (d, 1H, *J* = 6.4), 7.29-7.09 (m, 8H), 5.40 (s, 1H), 4.29 (s (broad), 1H), 2.98-2.93 (m, 1H), 2.89-2.85 (m, 1H), 2.82-2.77 (m, 1H), 2.71-2.66 (m 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 207.8, 160,4 (d, *J* = 247.5), 140.1, 130.4 (d, *J* = 8.8), 128.9 (d, *J* = 3.3), 128.5, 128.2, 126.3, 125.1 (d, *J* = 14.3), 124.8 (d, *J* = 3.3), 115.8 (d, *J* = 20.9), 73.4, (d, *J* = 3.3), 39.2, 29.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ -129.7. HRMS ($C_{16}H_{15}FO_2$ + Na): calcd.: 281.0954, found: 281.0944. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3459, 3064, 3028, 2926, 2857, 1717, 1611, 1587, 1490, 1455, 1277, 1232, 1056, 756, 698.

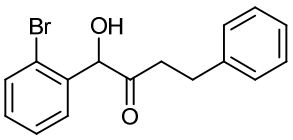
1-Hydroxy-4-phenyl-1-(2-trifluoromethyl-phenyl)-butan-2-one (27d, Table 2, entry 8)



$C_{17}H_{15}F_3O_2$
308.30 g/mol

according to the **general procedure 2**: yield 275 mg; 81 %, colorless to pale yellow oil. R_f (CH_2Cl_2/hexanes 3/2) 0.25. Procedure used Rb_2CO_3 (20.3 mg, 0.09 mmol), **8** (31.9 mg, 0.09 mmol), α,α,α-trifluoromethyl benzaldehyde (**19**) (145.1 µL, 1.10 mmol), hydrocinnamaldehyde (**11**) (246.2 µL, 1.87 mmol) and THF (610 µL). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.74 (d, 1H, *J* = 7.5), 7.51-7.45 (m, 2H), 7.26-7.23 (app. t, 2H), 7.18 (t, 1H, *J* = 7.4), 7.12 (d, 1H, *J* = 7.5), 7.06 (d, 2H, *J* = 7.5), 5.48 (s, 1H), 4.39 (s (broad), 1H), 2.95-2.86 (m, 2H), 2.75-2.70 (m, 1H), 2.58-2.53 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 207.6, 139.8, 136.3, 132.5, 128.8, 128.8 (q, *J* = 30.2), 128.6, 128.4, 128.0, 126.2, 126.1 (q, *J* = 5.5), 124.0 (q, *J* = 274.1), 74.5, 39.4, 29.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ -57.59. HRMS ($C_{17}H_{15}F_3O_2$ + Na): calcd.: 331.0922, found: 331.0923. IR (cm^{-1}): $\tilde{\nu}$ = 3456, 3031, 2930, 1717, 1605, 1497, 1454, 1311, 1159, 1108, 1034, 768, 747, 696.

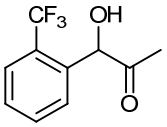
1-(2-Bromo-phenyl)-1-hydroxy-4-phenyl-butan-2-one (28d, Table 2, entry 16)



$C_{16}H_{15}BrO_2$
319.19 g/mol

according to the **general procedure 2**: yield 316 mg; 90 %, colorless to pale yellow oil. R_f (CH_2Cl_2/hexanes 2/3) 0.17. Procedure used Rb_2CO_3 (20.3 mg, 0.09 mmol), **8** (31.9 mg, 0.09 mmol), *ortho*-bromobenzaldehyde (**20**) (128.4 µL, 1.10 mmol), hydrocinnamaldehyde (**11**) (246.2 µL, 1.87 mmol) and THF (630 µL). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61 (d, 1H, J = 8.1), 7.28 (t, 1H, J = 7.3), 7.27-7.24 (app. t, 2H), 7.23-7.17 (m, 3H), 7.09 (d, 2H, J = 7.3), 5.59 (s, 1H), 4.39 (s (broad), 1H), 2.98-2.93 (m, 1H), 2.88-2.82 (m, 2H), 2.70-2.64 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 207.8, 139.9, 137.1, 133.3, 130.0, 129.0, 128.4, 128.1, 128.0, 126.2, 123.7, 78.3, 39.4, 29.5. HRMS ($C_{16}H_{15}BrO_2$ + Na): calcd.: 341.0153, found: 341.0152. IR (cm^{-1}): $\tilde{\nu}$ = 3456, 3063, 3028, 2925, 1713, 1536, 1496, 1454, 1024, 749, 698, 672.

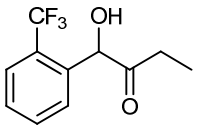
1-Hydroxy-1-(2-trifluoromethyl-phenyl)-propan-2-one (33, Table 3, entry 2)



$C_{10}H_9F_3O_2$
218.17 g/mol

according to the **general procedure 2**: yield 187 mg; 78 %, pale yellow oil. R_f (CH_2Cl_2/hexanes 3/2) 0.25. Procedure used Rb_2CO_3 (20.3 mg, 0.09 mmol), **8** (31.9 mg, 0.09 mmol), α,α,α-trifluoromethyl benzaldehyde (**19**) (145.1 µL, 1.10 mmol), acetaldehyde (**29**) (617.3 µL, 11.00 mmol) and THF (240 µL). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, 1H, J = 7.9), 7.62-7.59 (app. t, 1H), 7.52-7.49 (app. t, 1H), 7.29 (d, 1H, J = 7.2), 5.51 (s, 1H), 4.41 (s (broad), 1H), 2.20 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 206.2, 136.7, 132.7, 128.91, 128.90 (q, J = 30.8), 128.8, 126.3 (q, J = 5.5), 124.2 (q, J = 274.3), 74.9 (q, J = 2.2), 25.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ -57.7. HRMS ($C_{10}H_9F_3O_2$ + Na): calcd.: 241.0452, found: 241.0456. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3454, 2971, 2902, 1717, 1608, 1586, 1497, 1454, 1311, 1158, 1108, 1036, 768, 672.

1-Hydroxy-1-(2-trifluoromethyl-phenyl)-butan-2-one (34, Scheme 2 resp. Table 3, entry 3)



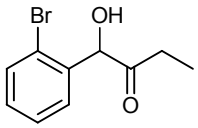
$C_{11}H_{11}F_3O_2$
232.20 g/mol

according to the **general procedure 2**: yield 202 mg; 79 %, 77 % *ee*, pale yellow oil. R_f (CH_2Cl_2/hexanes 3/2) 0.24. Procedure used Rb_2CO_3 (25.4 mg, 0.11 mmol), **67** (60.0 mg, 0.11 mmol), α,α,α-trifluoromethyl benzaldehyde (**19**) (145.1 µL, 1.10 mmol), propionaldehyde (**30**) (200.2 µL, 2.75 mmol) and THF (650 µL). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, 1H, J = 7.9), 7.60-7.58 (app. t, 1H), 7.50-7.48

(app. t, 1H), 7.26 (d, 1H, *J* = 7.9), 5.51 (s, 1H), 4.45 (s (broad), 1H), 2.39 (d of q, 1H, *J* = 18.2, 7.2), 2.23 (d of q, 1H, *J* 18.2, 7.2), 1.05 (t, 3H, *J* = 7.2). ^{13}C NMR (150 MHz, $CDCl_3$): δ 209.3, 137.1, 132.6, 129.1, 128.9 (q, *J* = 30.6), 128.75, 126.3 (q, *J* = 5.5), 125.9 (q, *J* = 274.0), 74.3, (q, *J* = 2.2), 31.4, 7.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ -57.7. HRMS ($C_{11}H_{11}F_3O_2$ + Na): calcd.: 255.0609, found: 255.0618. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3460, 2981, 2922, 2854, 1718, 1608, 1586, 1497, 1455, 1311, 1159, 1102, 1058, 1033, 768, 657. $[\alpha]_D^{20}$ = -178.2 (*c* 1.14 in $CHCl_3$, 77% *ee*).

Enantiomeric excess (77%) was determined by CSP-HPLC analysis (Chiralpak OJ-H 4.6 mm x 25 cm), solvent hexane/IPA: 98.5/1.5, flow rate 0.3 mL min^{-1}, r.t., λ = 220 nm, retention times 45.1 min (major enantiomer) and 49.6 min (minor enantiomer).

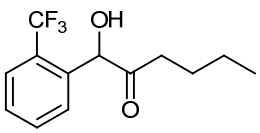
1-(2-Bromo-phenyl)-1-hydroxy-butan-2-one (35, Table 3, entry 5)



$C_{10}H_{11}BrO_2$
243.10 g/mol

according to the **general procedure 2**: yield 195mg; 73 %, pale yellow oil. R_f (CH_2Cl_2/hexanes 3/2) 0.18. Procedure used Rb_2CO_3 (20.3 mg, 0.09 mmol), **8** (31.9 mg, 0.09 mmol), *ortho*-bromobenzaldehyde (**20**) (128.4 µL, 1.10 mmol), propionaldehyde (**30**) (200.2 µL, 2.75 mmol) and THF (670 µL). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, 1H, *J* = 7.9), 7.37-7.34 (app. t, 1H), 7.26-7.22 (m, 2H), 5.63 (d, 1H, *J* = 2.8), 4.44 (d, 1H, *J* = 2.8), 2.52 (dq, 1H, *J* = 17.8, 7.2), 2.33 (dq, 1H, *J* = 17.8, 7.2), 1.07 (t, 3H, *J* = 7.2). ^{13}C NMR (150 MHz, $CDCl_3$): δ 209.4, 137.8, 133.4, 130.1, 129.1, 128.1, 123.8, 78.1, 31.4, 7.6. HRMS ($C_{10}H_{11}BrO_2$ + Na): calcd.: 264.9840, found: 264.9831. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3455, 3064, 2979, 2939, 1714, 1589, 1567, 1470, 1438, 1378, 1351, 1087, 1021, 974, 754, 724, 666.

1-Hydroxy-1-(2-trifluoromethyl-phenyl)-hexan-2-one (36, Table 3, entry 6)

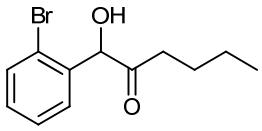


$C_{13}H_{15}F_3O_2$
260.25 g/mol

according to the **general procedure 2**: yield 240 mg; 84 %, pale yellow oil. R_f (CH_2Cl_2/hexanes 3/2) 0.16. Procedure used Rb_2CO_3 (20.3 mg, 0.09 mmol), **8** (31.9 mg, 0.09 mmol), α,α,α-trifluoromethyl benzaldehyde (**19**) (145.1 µL, 1.10 mmol), pentanal (**31**) (198.8 µL, 1.87 mmol) and THF (630 µL). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, 1H, *J* = 7.9), 7.61-7.58 (app. t, 1H), 7.51-7.48 (app. t, 1H), 7.26 (d, 1H, *J* = 7.5), 5.50 (s, 1H), 4.45 (s (broad), 1H), 2.42-2.37 (m 1H), 2.26-2.20 (m 1H), 1.60-1.48 (m, 2H), 1.29-1.18 (m 2H), 0.83 (t, 3H, *J* = 7.3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 208.9, 136.9 (q, *J* = 1.4), 132.6 (q, *J* = 1.3), 129.02 (q, *J* = 30.4), 128.96, 128.8, 126.2 (q, *J* = 5.7), 124.2 (q, *J* = 274.3), 74.4 (q, *J* = 2.3), 37.7, 25.6, 22.0, 13.6. ^{9}F NMR (376 MHz, $CDCl_3$): δ -

57.6. HRMS ($C_{13}H_{15}F_3O_2$ + Na): calcd.: 283.0922, found: 283.0923. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3464, 2961, 2935, 2875, 1716, 1608, 1587, 1455, 1311, 1159, 1113, 1033, 768, 658.

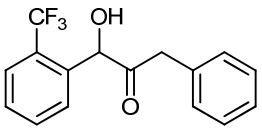
1-(2-Bromo-phenyl)-1-hydroxy-hexan-2-one (37, Table 3, entry 7)



$C_{12}H_{15}BrO_2$
271.15 g/mol

according to the **general procedure 2**: yield 230 mg; 77 %, pale yellow oil. R_f (CH_2Cl_2/hexanes 3/2) 0.17. Procedure used Rb_2CO_3 (20.3 mg, 0.09 mmol), **8** (31.9 mg, 0.09 mmol), *ortho*-bromobenzaldehyde (**20**) (128.4 µL, 1.10 mmol), pentanal (**31**) (198.8 µL, 1.87 mmol) and THF (640 µL). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, 1H, *J* = 7.5), 7.37-7.34 (app. t, 1H), 7.25-7.22 (m, 2H), 5.62 (s, 1H), 4.45, (s (broad), 1H), 2.48 (d of t, 1H, *J* = 8.0, 6.8), 2.31 (d of t, 1H, *J* = 8.0, 6.8), 1.62-1.49 (m, 2H), 1.29-1.21 (m, 2H), 0.84 (t, 3H, *J* = 7.5). ^{13}C NMR (150 MHz, $CDCl_3$): δ 209.2, 137.6, 133.4, 130.1, 129.1, 128.1, 123.9, 78.2, 37.8, 25.9, 22.3, 13.6. HRMS ($C_{12}H_{15}BrO_2$ + Na): calcd.: 293.0153, found: 293.0163. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3455, 3066, 2958, 2931, 2873, 1713, 1589, 1569, 1468, 1438, 1379, 1022, 754, 671.

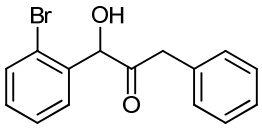
1-Hydroxy-3-phenyl-1-(2-trifluoromethyl-phenyl)-propan-2-one (38, Table 3, entry 10)



$C_{16}H_{13}F_3O_2$
294.27 g/mol

according to the **general procedure 2**: yield 262 mg; 81 %, pale yellow oil. R_f (CH_2Cl_2/hexanes 3/2) 0.24. Procedure used Rb_2CO_3 (20.3 mg, 0.09 mmol), **8** (31.9 mg, 0.09 mmol), α,α,α-trifluoromethyl benzaldehyde (**19**) (145.1 µL, 1.10 mmol), phenylacetaldehyde (**32**) (209.0 µL, 1.87 mmol) and THF (650 µL). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80 (d, 1H, *J* = 7.9), 7.57-7.55 (app. t, 1H), 7.53-7.50 (app. t, 1H), 7.28-7.23 (m, 4H), 7.02 (d, 2H, *J* = 6.8), 5.64 (s, 1H), 4.33 (s (broad), 1H), 3.67 (d, 1H, *J* = 15.8), 3.59 (d, 1H, *J* = 15.8). ^{13}C NMR (150 MHz, $CDCl_3$): δ 206.2, 136.2, 132.6, 132.5, 129.4, 129.3, 129.2 (q, *J* = 34.1), 129.0, 128.6, 127.3, 126.4 (q, *J* = 5.5), 124.2 (q, *J* = 274.1), 74.5 (q, *J* = 2.2), 44.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ -57.5. HRMS ($C_{16}H_{13}F_3O_2$ + Na): calcd.: 317.0765, found: 317.0767. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3456, 3067, 3033, 2929, 1721, 1606, 1586, 1497, 1455, 1311, 1158, 1114, 1033, 768, 699, 660.

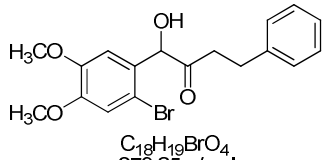
1-(2-Bromo-phenyl)-1-hydroxy-3-phenyl-propan-2-one (39, Table 3, entry 11)



$C_{15}H_{13}BrO_2$
305.17 g/mol

according to the **general procedure 2**: yield 255 mg; 76 %, pale yellow oil. R_f (CH_2Cl_2/hexanes 3/2) 0.22. Procedure used Rb_2CO_3 (20.3 mg, 0.09 mmol), **8** (31.9 mg, 0.09 mmol), *ortho*-bromobenzaldehyde (**20**) (128.4 µL, 1.10 mmol), phenylacetaldehyde (**32**) (209.0 µL, 1.87 mmol) and THF (630 µL). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, 1H, *J* = 8.1), 7.35-7.33 (app. t, 1H), 7.29-7.24 (m, 4H), 7.22 (d, 1H, *J* = 7.5), 7.06 (d, 2H, *J* = 6.4), 5.74 (s, 1H), 4.34 (s (broad), 1H), 3.76 (d, 1H, *J* = 15.6), 3.69 (d, 1H, *J* = 15.6). ^{13}C NMR (150 MHz, $CDCl_3$): δ 206.3, 137.0, 133.5, 132.6, 130.4, 129.6, 129.3, 128.6, 128.2, 127.3, 124.1, 78.2, 44.8. HRMS ($C_{15}H_{13}BrO_2$ + Na): calcd.: 326.9997, found: 327.0010. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3457, 3063, 3030, 2923, 1717, 1586, 1568, 1496, 1471, 1454, 1022, 752, 723, 701.

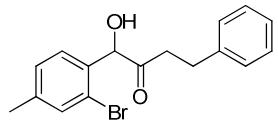
1-(2-Bromo-4, 5-dimethoxy-phenyl)-1-hydroxy-4-phenyl-butan-2-one (43, Table 4, entry 2)



$C_{18}H_{19}BrO_4$
379.25 g/mol

according to the **general procedure 2**: yield 388 mg; 93 %, yellow oil. R_f (CH_2Cl_2/hexanes 3/2) 0.08. Procedure used Rb_2CO_3 (20.3 mg, 0.09 mmol), **8** (31.9 mg, 0.09 mmol), 6-bromoveratraldehyde (**40**) (269.6 mg, 1.10 mmol), hydrocinnamaldehyde (**11**) (246.2 µL, 1.87 mmol) and THF (1000 µL). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25-7.16 (m, 3H), 7.07 (d, *J* = 8.1, 2H), 7.03 (s, 1H), 6.53 (s, 1H), 5.53 (s, 1H), 4.35 (s, br., 1H), 3.90 (s, 3H), 3.77 (s, 3H), 2.96-2.68 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.2, 149.7, 148.9, 139.9, 128.7, 128.2, 128.0, 126.1, 115.3, 113.8, 110.3, 78.1, 56.1, 55.8, 39.1, 29.5. HRMS ($C_{18}H_{19}BrO_4$ + Na): calcd: 401.0364, found: 401.0358. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3446, 3007, 2929, 2842, 1709, 1695, 1598, 1501, 1454, 1436, 1377, 1289, 1255, 1231, 1204, 1157, 1108, 1059, 1025, 995, 965, 757, 700.

1-(2-Bromo-4-methyl-phenyl)-1-hydroxy-4-phenyl-butan-2-one (44, Table 4, entry 3)

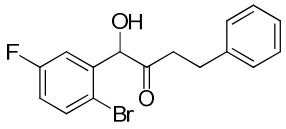


$C_{17}H_{17}BrO_2$
333.22 g/mol

according to the **general procedure 2**: yield 323 mg; 88 %, yellow oil. R_f (hexanes/CH_2Cl_2 1/4) 0.13. Procedure used Rb_2CO_3 (20.3 mg, 0.09 mmol), **8** (31.9 mg, 0.09 mmol), 2-bromo-4-methylbenzaldehyde (**41**) (218.9 mg, 1.10 mmol), hydrocinnamaldehyde (**11**) (246.2 µL, 1.87 mmol) and THF (1000 µL). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.25-7.13 (m, 3H), 7.07

(app. d, *J* = 7.0, 3H), 7.00 (d, *J* = 7.9, 1H), 5.51 (s, 1H), 4.34 (s, br. 1H), 3.00-2.74 (m, 3H), 2.69-2.57 (m, 1H), 2.32 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.2, 140.5, 140.1, 134.1, 133.7, 129.0, 129.0, 128.5, 128.2, 126.2, 123.5, 78.2, 39.5, 29.7, 20.8. HRMS ($C_{17}H_{17}O_2Br$ + Na): Calcd: 355.0310, found: 355.0312. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3457, 3027, 2923, 1712, 1603, 1561, 1491, 1453, 1361, 1271, 1195, 1141, 1112, 1078, 1056, 1035, 988, 868, 815, 746, 697.

1-(2-Bromo-5-fluorophenyl)-1-hydroxy-4-phenyl-butan-2-one (45, Table 4, entry 4)

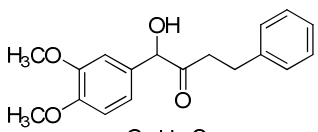


$C_{16}H_{14}BrFO_2$
337.18 g/mol

according to the **general procedure 2**: yield 297mg; 80 %, colourless to pale yellow oil. R_f (hexanes/CH_2Cl_2 2/3) 0.08. Procedure used Rb_2CO_3 (20.3 mg, 0.09 mmol), **8** (31.9 mg, 0.09 mmol), 2-bromo-5-fluorobenzaldehyde (**42**) (223.3 mg, 1.10 mmol), hydrocinnamaldehyde (**11**) (246.2 µL, 1.87 mmol) and THF (1000 µL). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 9.0, 5.2, 1H), 7.28-7.17 (m, 3H), 7.08 (app. d, *J* = 6.9, 2H), 6.97-6.91 (m, 1H), 6.88 (dd, *J* = 9.0, 3.1, 1H), 5.55 (d, *J* = 3.5, 1H), 4.43 (d, *J* = 3.5, 1H), 2.99-2.81 (m, 3H), 2.75-2.64 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.4, 162.1 (d, *J* = 249.1), 139.7, 139.2, 139.1, 134.4 (d, *J* = 7.5), 128.4, 128.0, 126.3, 117.4 (d, *J* = 22.0), 115.9 (d, *J* = 23.1), 78.0, 39.4, 29.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ -113.0. HRMS ($C_{16}H_{14}BrFO_2$ + Na): calcd.: 359.0059, found:359.0069. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3448, 3065, 3028, 2927, 1715, 1603, 1580, 1496, 1467, 1454, 1404, 1361, 1264, 1229, 1147, 1100, 1079, 1055, 1025, 990, 964, 875, 812, 745, 697.

Experimental Data for Debromination of Crossed Acyloins with Pd/C

1-(3,4-Dimethoxyphenyl)-1-hydroxy-4-phenylbutan-2-one (46, Table 4, entry 2)

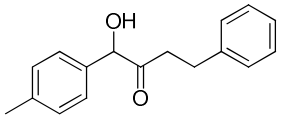


$C_{18}H_{20}O_4$
300.35 g/mol

according to the **general procedure 3**: yield 87 mg; 96 %, yellow oil. R_f (hexanes/CH_2Cl_2 1/4) 0.9. Procedure used **43** (113.7 mg, 0.30 mmol), NEt_3 (50.1 µL, 0.36 mmol), 10% Pd/C (6.8 mg), MeOH (6.0 cm^3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18-7.06 (m, 3H), 6.97 (d, *J* = 7.0, 2H), 6.77 (d, *J* = 2.1, 2H), 6.59 (s, 1H), 4.91 (d, *J* = 4.1, 1H), 4.18 (d, *J* = 4.1, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 2.87-2.69 (m, 2H), 2.60 (t, *J* = 7.5, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.0, 149.5, 149.3, 139.7, 130.1, 128.3, 128.0, 126.2, 120.5, 111.5, 109.8, 79.8, 55.8, 55.7, 39.4, 29.6. HRMS ($C_{15}H_{20}O_3$ + Na):

calcd.: 323.1259, found: 323.1244. IR (cm^{-1}): $\tilde{\nu}$ = 3448, 3064, 3028, 2927, 1715, 1603, 1580, 1496, 1467, 1454, 1404, 1361, 1264, 1229, 1147, 1100, 1079, 1055, 1025, 964, 875, 812, 745.

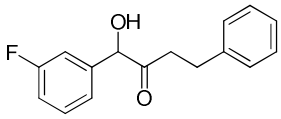
1-Hydroxy-4-phenyl-1-*p*-tolylbutan-2-one (47, Table 4, entry 3)



$C_{17}H_{18}O_2$
254.32 g/mol

according to the **general procedure 3**: yield 71 mg; 93 %, yellow oil. R_f (hexanes/CH_2Cl_2 1/4) 0.12. Procedure used **44** (99.7 mg, 0.30 mmol), NEt_3 (50.1 µL, 0.36 mmol), 10% Pd /C (6.0 mg), MeOH (6.0 cm^3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (s, 2H), 7.26 (t, *J* = 7.4, 2H), 7.22-7.12 (m, 3H), 7.07 (d, *J* = 7.4, 2H), 5.03 (s, 1H), 4.26 (s, br., 1H), 2.96-2.85 (m, 1H), 2.87-2.76 (m, 1H), 2.75-2.61 (m, 2H), 2.37 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.7, 140.1, 138.4, 134.7, 129.6, 128.4, 128.1, 127.2, 126.1, 79.6, 39.3, 29.6, 21.0. HRMS ($C_{17}H_{17}O_2$ + Na): Calcd. 277.1204, found: 277.1205. IR (**cm^{-1}**)**:** $\tilde{\nu}$ = 3464, 3028, 2980, 1674, 1713, 1496, 1453, 1232, 1180, 1057, 972, 826, 749, 699.

1-(3-Fluorophenyl)-1-hydroxy-4-phenylbutan-2-one (48, Table 4, entry 4)

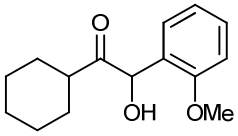


$C_{16}H_{15}FO_2$
258.29 g/mol

according to the **general procedure 3**: yield 71 mg; 92 %, yellow oil. R_f (hexanes/CH_2Cl_2 1/4) 0.15. Procedure used **45** (100.8 mg, 0.3 mmol), NEt_3 (50.1 µL, 0.36 mmol), 10% Pd /C (6.0 mg), MeOH (6.0 cm^3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.20 (m, 5H), 7.10-7.04 (m, 3H), 7.00 (d, *J* = 8.8, 1H), 5.05 (s, 1H), 4.33 (s, 1H), 2.95-2.11 (m, 1H), 2.87-2.82 (m, 1H), 2.77-2.65 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.9, 163.05 (d, *J* = 247.6), 140.2, 140.0, 130.6 (d, *J* = 8.8), 128.5, 128.1, 126.4, 123.1 (d, *J* = 3.3), 115.7 (d, *J* = 20.9), 114.3 (d, *J* = 23.1), 79.3, 39.4, 29.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ -112.2. HRMS ($C_{16}H_{15}FO_2$ + Na): calcd.: 281.0953, found: 281.09873. IR (**cm^{-1}**)**:** $\tilde{\nu}$ = 3459, 3027, 2927, 1713, 1603, 1518, 1476, 1470, 1455, 1438, 1362, 1272, 1191, 1079, 1058, 1025, 995, 751.

Experimental Data for Crossed Acyloins with α–Branched Aliphatic Aldehydes

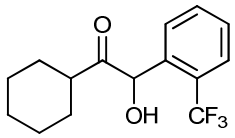
1-Cyclohexyl-2-hydroxy-2-(2-methoxyphenyl)ethanone (53, Table 5)



$C_{15}H_{20}O_3$
248.32 g/mol

according to the **general procedure 4**: yield 86 mg; 69 %, colourless to pale yellow oil. R_f (10% Et_2O/*n*-pentane) 0.08. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 – 7.27 (m, 1H), 7.20 (dd, *J* = 7.6 Hz, 1.78 Hz, 1H), 7.00 – 6.88 (m, 2H), 5.51 (d, *J* = 5.2 Hz, 1H), 4.28 (d, *J* = 5.2 Hz, 1H), 3.85 (s, 3H), 2.40 (tt, *J* = 11.1 Hz, *J* = 3.7 Hz, 1H), 1.95 – 1.83 (m, 1H), 1.81 – 1.53 (m, 3H), 1.50 – 0.96 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 212.8, 157.1, 129.9, 129.3, 126.5, 121.1, 111.1, 73.2, 55.5, 45.8, 29.9, 27.7, 25.9, 25.6, 25.1. MS (EI): m/z (%) 248 (1) [M^+], 137 (100), 107 (17). HRMS ($C_{15}H_{20}O_3$): calcd.: 248.1412, found: 248.1412. IR (cm^{-1}): $\tilde{\nu}$ = 3456, 2931, 2854, 1704, 1600, 1492, 1464, 1450, 1368, 1330, 1290, 1246, 1188, 1121, 1050, 1026, 993, 895, 754, 632, 541, 495.

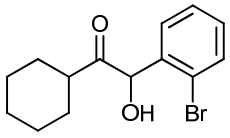
1-Cyclohexyl-2-hydroxy-2-(2-(trifluoromethyl)phenyl)ethanone (54, Table 5)



$C_{15}H_{17}F_3O_2$
286.29 g/mol

according to the **general procedure 4**: yield 54 mg; 38 %, colourless oil. R_f (10% Et_2O/*n*-pentane) 0.16. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.4 Hz, 1H), 7.61 – 7.40 (m, 2H), 7.18 (d, *J* = 7.7 Hz, 1H), 5.59 (d, *J* = 4.4 Hz, 1H), 4.42 (d, *J* = 4.4 Hz, 1H), 2.32 (tt, *J* = 11.3 Hz, 3.4 Hz, 1H), 1.93 – 0.91 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 211.9, 136.6, 132.5, 129.1, 128.8, 126.4 (q, *J* = 5.65 Hz), 126.0, 122.4, 73.0 – 72.8 (m), 46.3, 29.9, 27.8, 25.6, 25.5, 24.9. MS (EI): m/z (%) 155 (28), 111 (53) [$C_6H_{11}CO]^+$, 83 (100) [$C_6H_{11}]^+$. HRMS ($C_{15}H_{17}F_3O_2$ + H): calcd.: 287.1259, found: 287.1254. IR (cm^{-1}): $\tilde{\nu}$ = 2933, 2857, 1710, 1607, 1586, 1495, 1451, 1371, 1311, 1160, 1119, 1060, 1034, 993, 769, 629, 605, 534, 494.

2-(2-Bromophenyl)-1-cyclohexyl-2-hydroxyethanone (55, Table 5)

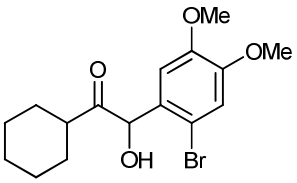


$C_{14}H_{17}BrO_2$
297.19 g/mol

according to the **general procedure 4**: yield 117 mg; 79 %, colorless to pale yellow oil. R_f (10% Et_2O/*n*-pentane) 0.18. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66–7.57 (m, 1H), 7.31 (td, *J* = 7.5 Hz, 1.3 Hz, 1H), 7.24 – 7.14 (m, 2H), 5.71 (d, *J* = 4.7 Hz, 1H), 4.45 (d, *J* = 4.7 Hz, 1H), 2.46 (tt, *J* = 11.3 Hz, 3.4 Hz, 1H), 2.04

– 1.92 (m, 1H), 1.84 – 1.55 (m, 3H), 1.51–0.96 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 211.9, 137.4, 133.4, 130.1, 129.2, 128.1, 124.1, 76.6 (overlapping with $CDCl_3$ resonance), 46.2, 29.9, 27.7, 25.7, 25.5, 25.0. MS (EI): m/z (%) 217 (13) $[M\text{-}Br]^+$, 185 (19), 111 (52) $[C_6H_{11}CO]^+$, 83 (100) $[C_6H_{11}]^+$. HRMS ($C_{14}H_{17}BrO_2$ + H): calcd.: 297.0490, found: 297.0497. IR (cm^{-1}): $\tilde{\nu}$ = 3452, 2930, 2854, 1707, 1470, 1448, 1369, 1313, 1192, 1127, 1058, 1023, 993, 754, 632, 537, 495.

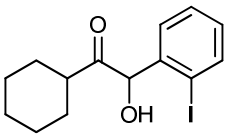
2-(2-Bromo-4,5-dimethoxyphenyl)-1-cyclohexyl-2-hydroxyethanone (56, Table 5)



$C_{16}H_{21}BrO_4$
357.24 g/mol

according to the **general procedure 4**: yield 129 mg; 72 %, pale yellow oil. R_f (Et_2O/*n*-pentane 1/3) 0.11. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03 (s, 1H), 6.58 (s, 1H), 5.63 (s, 1H), 4.39 (br s, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 2.58 – 2.35 (m, 1H), 2.04 – 0.97 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 212.4, 149.7, 149.0, 129.1, 115.4, 114.4, 110.5, 76.4, 56.2, 56.1, 46.1, 29.9, 27.8, 25.7, 25.5, 25.1. MS (EI): m/z (%) 356 (3) $[M^+]$, 277 (6) $[M\text{-}Br]^+$, 245 (100), 138 (57). HRMS ($C_{16}H_{21}BrO_4$): calcd.: 356.0623, found: 356.0621. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3458, 2930, 2853, 1705, 1601, 1504, 1440, 1378, 1258, 1222, 1157, 1028, 994, 820, 634, 493cm^{-1}.

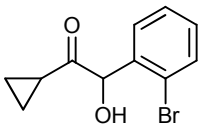
1-Cyclohexyl-2-hydroxy-2-(2-iodophenyl)ethanone (57, Table 5)



$C_{14}H_{17}IO_2$
344.19 g/mol

according to the **general procedure 4**: yield 133 mg; 77 %, colourless oil. R_f (10% Et_2O/*n*-pentane) 0.16. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 7.9 Hz, 1.1 Hz, 1H), 7.33 (td, *J* = 7.6 Hz, 1.3 Hz, 1H), 7.10 (dd, *J* = 7.7 Hz, 1.7 Hz, 1H), 7.07- 6.97 (m, 1H), 5.60 (d, *J* = 4.7 Hz, 1H), 4.48 (d, *J* = 4.4 Hz, 1H), 2.45 (tt, *J* = 11.3 Hz, 3.5 Hz, 1H), 2.08 – 1.91 (m, 1H), 1.84 – 1.54 (m, 3H), 1.49 – 0.97 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 211.0, 139.4, 139.0, 129.3, 127.9, 127.6, 99.3, 80.1, 45.4, 28.9, 26.6, 24.7, 24.5, 24.0. MS (EI): m/z (%) 233 (34), 217 (30) $[M\text{-}I]^+$, 111 (54) $[C_6H_{11}CO]^+$, 83 (100) $[C_6H_{11}]^+$. HRMS ($C_{14}H_{17}IO_2$ + H): calcd.: 345.0351, found: 345.0334. IR **(**cm^{-1}**):** $\tilde{\nu}$ = 3454, 2928, 2853, 1705, 1584, 1564, 1448, 1369, 1312, 1264, 1243, 1191, 1146, 1124, 1057, 1010, 992, 751, 632, 595, 542, 497.

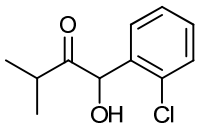
2-(2-Bromophenyl)-1-cyclopropyl-2-hydroxyethanone (58, Table 5)



$C_{11}H_{11}BrO_2$
255.11 g/mol

according to the **general procedure 4**: yield 102 mg; 80 %, colorless oil. R_f (10% Et_2O/*n*-pentane) 0.13.^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 – 7.59 (m, 1H), 7.38 – 7.29 (m, 1H), 7.25 – 7.17 (m, 2H), 5.78 (d, *J*= 4.1 Hz, 1H), 4.45 (d, *J* = 4.1 Hz, 1H), 1.94 (tt, *J* = 7.5 Hz, 4.9 Hz, 1H), 1.27 – 1.15 (m, 1H), 1.11 – 0.96 (m, 2H), 0.90 – 0.79 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 209.1, 137.6, 133.3, 130.1, 129.4, 128.2, 124.2, 78.7, 17.6, 12.8, 12.6. MS (EI): m/z (%) 185 (56) $[M\text{-}C_4H_5O^+]$, 175 (31) $[M\text{-}Br]^+$, 77 (43) $[C_6H_5]^+$, 69 (100) $[C_4H_5O]^+$. HRMS ($C_{11}H_{11}BrO_2$ + H): calcd.: 255.0021, found: 255.0012. IR (cm^{-1}): $\tilde{\nu}$ = 3450, 3009, 1695, 1568, 1471, 1438, 1373, 1271, 1193, 1134, 1051, 1017, 907, 757, 732, 672, 632, 531, 499.

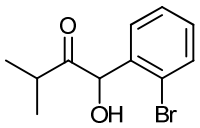
1-(2-Chlorophenyl)-1-hydroxy-3-methylbutan-2-one (12, Table 2 and Table 5)



$C_{11}H_{13}ClO_2$
212.67 g/mol

according to the **general procedure 4**: yield 76 mg; 71 %, pale yellow oil. R_f (*n*-pentane/Et_2O 5/1) 0.25. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 – 7.38 (m, 1H), 7.30 – 7.18 (m, 3H), 5.73 (d, *J* = 4.39Hz, 1H), 5.41 (d, *J* = 4.67 Hz, 1H), 2.70 (sept, *J* = 6.86 Hz, 1H), 1.17 (d, *J* = 7.14 Hz, 3H), 0.88 (d, *J* = 6.86 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 212.9, 135.7, 133.8, 130.1, 129.9, 129.3, 127.5, 74.6, 36.2, 19.5, 17.9. MS (FAB): m/z (%) 213 (38) $[MH]^+$, 195 (39) $[MH\text{-}H_2O]^+$. HRMS ($C_{11}H_{13}ClO_2$ + H): calcd.: 213.0682, found: 213.0686. IR (**cm^{-1}**)**:** $\tilde{\nu}$ = 3440, 2973, 1713, 1473, 1385, 1015, 758, 632, 536, 499.

1-(2-Bromophenyl)-1-hydroxy-3-methylbutan-2-one (59, Table 5, entry 9)

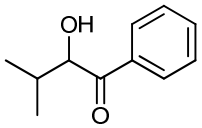


$C_{11}H_{13}BrO_2$
257.12 g/mol

according to the **general procedure 4**: yield 82 mg; 64 %, colourless oil. R_f (10% Et_2O/*n*-pentane) 0.21. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 – 7.56 (m, 1H), 7.37 – 7.27 (m, 1H), 7.24 – 7.13 (m, 2H), 5.73 (d, *J* = 4.7 Hz, 1H), 4.43 (d, *J* = 4.4 Hz, 1H), 2.72 (sept, *J* = 6.8 Hz, 1H), 1.17 (d, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 213.0, 137.4, 133.4, 130.2, 129.3, 128.1, 124.1, 76.8, 36.3, 19.6, 17.9. HRMS ($C_{11}H_{13}BrO_2$ + H): calcd.: 257.0177, found: 257.0173. IR (**cm^{-1}**)**:** $\tilde{\nu}$ = 3465, 2972, 2934, 2876, 1712, 1469, 1438, 1384, 1270, 1190, 1128, 1098, 1018, 758, 666, 632, 536, 496.

Experimental Data for Testing the Influence of the Catalytic System on Chemoselectivity

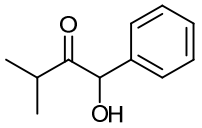
2-Hydroxy-3-methyl-1-phenylbutan-1-one (C in Scheme 4)



$C_{11}H_{14}O_2$
178.23 g/mol

according to the **general procedure 5**: yield 24 mg; 27 %, colourless oil. R_f (*n*-pentane/Et_2O 5/1) 0.28. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 – 7.86 (m, 2H), 7.66 – 7.58 (m, 1H), 7.54 – 7.46 (m, 2H), 4.98 (dd, *J* = 6.31 Hz, 2.47 Hz, 1H), 3.61 (d, *J* = 6.31 Hz, 1H), 2.13 (sept-d, *J* = 6.79 Hz, 2.58 Hz, 1H), 1.16 (d, *J* = 7.14 Hz, 3H), 0.65 (d, *J* = 6.86 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 202.3, 134.2, 133.9, 128.9, 128.5, 77.3, 32.7, 20.2, 14.4. IR (cm^{-1})**:** $\tilde{\nu}$ = 3490, 2964, 2930, 1676, 1449, 1263, 1137, 1034, 990, 760, 693, 532, 497.

1-Hydroxy-3-methyl-1-phenylbutan-2-one (D in Scheme 4)



$C_{11}H_{14}O_2$
178.23 g/mol

according to the **general procedure 4**: yield 54 mg; 61 %, colourless to pale yellow crystals. R_f (*n*-pentane/Et_2O 5/1) 0.19. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 – 7.27 (m, 5H), 5.22 (d, *J* = 4.67 Hz, 1H), 4.39 (d, *J* = 4.67 Hz, 1H), 2.70 (sept, *J* = 7.00 Hz, 1H), 1.14 (d, *J* = 6.86 Hz, 3H), 0.83 (d, *J* = 6.59 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 213.5, 137.9, 129.0, 128.7, 127.6, 78.3, 36.0, 19.4, 18.0. HRMS ($C_{11}H_{14}O_2$): calcd.: 178.0994, found: 178.0996. IR (cm^{-1})**:** $\tilde{\nu}$ = 3440, 3402, 2976, 1707, 1455, 1384, 1129, 1011, 839, 756, 722, 697, 507.

→Please find supporting information including **^{1}H- and ^{13}C-NMR spectra** on the enclosed CD.

1.3.5 References

(1) For use as photocleavable protecting groups see: Pirrung, M. C.; Shuey, S. W. J. Org. Chem. 1994, 59, 3890. b) For use as an anchoring group for materials see: Fuhrmann, G.; Nelles, G.; Zilai, B.; Obermaier, M. WO 2010/049042 A2

(2) Hoyos, P.; Sinisterra, J. -V.; Molinari, F.; Alcántara, A. R.; Domínguez de María, P. *Acc. Chem. Res*. **2010**, *43*, 288.

(3) For instance, (-)-ephedrine is available from a thiamine-dependent enzyme catalyzed reaction which produces (*R*)-phenylacetylcarbinol: Rosche, B.; Sandford, V.; Breuer, M.; Hauer, B.; Rogers, P. L. *J. Mol. Catal. B: Enzym*. **2002**, *19*, 109.

(4) For selected reviews see: a) Plietker, B. *Tetrahedron Asymmetry* **2005**, *16*, 3453; b) Davis, F. A.; Chen, B. C.; *Chem. Rev*. **1992**, *92*, 919.

(5) For selected examples on organocatalytic α-hydroxylations and α-oxyaminations, see: a) Zhong, G. *Angew. Chem. Int. Ed*. **2003**, *42*, 4247; b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2003**, *125*, 10808; c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino H. *Adv. Synth. Catal*. **2004**, *346*, 1435; d) Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc*. **2007**, *129*, 4124; e) Gotoh, H.; Hayashi, Y. *Chem. Commun*. **2009**, 3083; f) Palomo, C.; Vera, S.; Velila, I.; Mielgo, A.; Gomez-Bengoa, E. *Angew. Chem. Int. Ed*. **2007**, *46*, 8054; g) Koike, T. Akita, M. *Chem. Lett*. **2009**, *38*, 166; h) Poe, S. L.; Bogdan, A. R.; Mason, B: P.; Steinbacher, J. L.; Opalka, S. M.; McQuade, D. T. *J. Org. Chem*. **2009**, *74*, 1574.

(6) Recent reviews: a) Merino, P.; Tejero, T. *Angew. Chem. Int. Ed*. **2004**, *43*, 2995; b) Marigo, M.; Jørgensen, K. A. α-*Heteroatom functionalization.* In *Enantioselective Organocatalysis* **2007**, Wiley, Weinheim.

(7) Wöhler, F.; Liebig, J. *Ann. Pharm.* **1832**, *3*, 249.

(8) Breslow, R. *J. Am. Chem. Soc*. **1958**, *80*, 3719.

(9) For a more recent kinetic study see: White, M. J.; Leeper, F. J. *J. Org. Chem*. **2001**, *66*, 5124.

(10) Recent reviews: a) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2009**, *291*, 77; b) Enders, D., Narine A. A. *J. Org. Chem*. **2008**, *73*, 7857; c) Rovis, T. *Chem. Lett*. **2008**, *37*, 1; d) Zeitler, K. *E. Schering Found. Symp. Proc.* **2007***, 2*, 183; e) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev*. **2007**, *107*, 5506; f) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed*. **2007**, *46*, 2988; g) Zeitler, K. *Angew. Chem., Int. Ed*. **2005**, *44*, 7506; h) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632; i) Enders, D.; Balensiefer, T. *Acc. Chem. Res*. **2004**, *37*, 534; j) Johnson, J. S. *Angew. Chem., Int. Ed*. **2004**, *43*, 1326.

(11) Enders, D.; Breuer, K.;. Teles, J. H. *Helv. Chim. Acta*. **1996**, *79*, 1217.

(12) Knight, R. L.; Leeper, F. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 1891.

(13) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed*. **2002**, *41*, 1743.

(14) Enders, D.; Han, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1367.

(15) Ma, Y.; Wei, S.; Wu, J.; Yang, F; Liu, B.; Lan, J.; Yang, S.; You, J. *Adv. Synth. Catal*. **2008**, *350*, 2645.

(16) Highly enantioselective intermolecular AC reactions between aldehydes and ketones are known. For representative examples see: a) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed*. **2006**, *45*, 1463; b) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed*. **2006**, *45*, 3492; c) Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431; d) Li, Y.; Feng, Z.; You, S. –L. *Chem. Commun*. **2008**, 2263. e) For a recent example on a sterically controlled intramolecular aldehyde-ketone AC reaction in the context of a multicatalytic cascade sequence, see: Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc*. **2009**, *131*, 13628.

(17) In addition, the use of enolizable aldehydes is potentially problematic due to competitive aldol pathways under the basic reaction conditions.

(18) W. S.; Buck, J. S. *Org. React*. **1948**, *4*, 269.

(19) It is noteworthy that establishing the levels of chemoselectivity in this study proved difficult due to the reactivity of the benzoins in the derivatization process to establish the structures of the products. For a ^{1}H NMR spectroscopy based structural assignement also see ref. 23.

(20) a) Stetter, H.; Dämbkes, G. *Synthesis* **1977**, 403; b) Stetter, H.; Dämbkes, G. *Synthesis*, **1980**, 309.

(21) For a related report using aliphatic aldehydes see: Heck, R.; Henderson, A. P.; Köhler, B.; Rétey, J.; Golding, B. T. *Eur. J. Org. Chem.* **2001,** 2623.

(22) For a later demonstration of the potential utility of formaldehyde as a coupling partner in these reactions see: Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem*. **1985**, *50*, 603.

(23) In addition, most likely due to the lack of highfield NMR instrumentation and the focus of the study on the oxidized benzil products (*cf.* their NMR characterization data), we have found that in some instances the chemoselectivity reported in this study was over estimated due to misassignment of products in the crude ^{1}H NMR spectra. Further details will be reported in due course. For a more recent report using NMR spectroscopy for the structural assignment in mixed aromatic benzoin systems, see: Simion, C.; Simion, A. M.; *U.P.B. Sci. Bull., Series B*, **2007**, *69*, 49.

(24) Mennen, S. M.; Miller, S. J. *J. Org. Chem*. **2007**, *72*, 5260.

(25) a) Lehwald, P.; Richter, M.; C. Röhr, C.; Liu, H.-W.; Müller, M. *Angew. Chem., Int. Ed*. **2010**, *49*, 2389; b) Müller, M.; Gocke, D.; Pohl, M. *FEBS J.*, **2009**, *276*, 2894; c) Demir, A. S.; Şeşengolu, Ö.; Dünkelmann, P.; Müller, M. *Org. Lett*. **2003**, *5*, 2047; d) Dünkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Linden, B.; Baumann, M.; Pohl, M.; Müller, M. *J. Am. Chem. Soc*. **2002**, *124*, 12084; e) Demir, A. S.; Şeşengolu, Ö.; Eren, E.; Hosrik, B.; Pohl, M.; Janzen, E.; Kolter, D.; Feldmann, R.; Dünkelmann, P.; Müller, M. *Adv. Synth. Catal*. **2002**, *344*, 96; f) Pohl, M.; Lingen, B.; Müller, M. *Chem. Eur. J*. **2002**, *8*, 5288; g) Demir, A. S.; Pohl, M.; Janzen, E.; Müller, M. *J. Chem. Soc. Perkin Trans. 1* **2001**, 633.

(26) a) Kuriakose, S.; Rajasekharan Pillai, V. N. *Eur. Polym. J*. **1994**, *30*, 881; b) Kuriakose, S; Rajasekharan Pillai, V. N. *Angew. Makromol. Chem*. **1994**, *221*, 53; c) Kuriakose, S; Rajasekharan Pillai, V. N. *Polymer*, **1994**, *35*, 1339.

(27) a) Linghu, X.; Johnson, J. S. *Angew. Chem., Int. Ed*. **2003**, *42*, 2534; b) Linghu, X.; Potnick, J. R.;. Johnson, J. S. *J. Am. Chem. Soc*. **2004**, *126*, 3070; c) Bausch, C. C.; Johnson, J. S. *J. Org. Chem*. **2004**, *69*, 4283; d) Linghu, X.; Bausch, C. C; Johnson, J. S. *J. Am. Chem. Soc*. **2005**, *127*, 1833; e) Tarr, J. C.; Johnson, J. S. *Org. Lett*. **2009**, *11*, 3870.;

(28) a) Demir, A. S.; Esiringü, I.; Göllü, M.; Reis, Ö. *J. Org. Chem*. **2009**, *74*, 2197; b) Demir, A. S.; Reis, B.; Reis, Ö.; Eymür, S.; Göllü, M.; Tural, S.; Saglam, G. *J. Org. Chem*. **2007**, *72*, 7439; c) Demir, A. S.; Reis, Ö.; Esiringü, I.; Reis, B.; Baris, S. *Tetrahedron* **2007**, *63*, 160; d) Demir, A. S.; Reis, Ö.; Ciğdem, C.; Esiringü, I.; Eymur, S. *J. Org. Chem*. **2005**, *70*, 10584; e) Bausch, C. C.; Johnson, J. S. *Adv. Synth. Catal*. **2005**, *347*, 1207.

(29) a) Mathies, A. K.; Mattson, A. E.; Scheidt, K. A. *Synlett*, **2009**, 377; b) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc*. **2006**, *128*, 4932. c) Mattson, A. E.; Scheidt, K. A. *J. Am. Chem. Soc*. **2007**, *129*, 4508.

(30) a) Enders, D.; Henseler, A. *Adv. Synth. Catal*. **2009**, *351*, 1749. b) Enders, D.; Grossmann, A.; Fronert, J.; Raabe, G. *Chem. Comm.* **2010**, *46*, 6282.

(31) For contributions to the ongoing discussion on the importance of chemoselectivity for efficient syntheses, see: a) Trost, B. M., *Science* **1983**, *219*, 245. b) Shenvi, R. A.; O'Malley, D. P.; Baran, P. S. *Acc. Chem.* Res. **2009**, *42*, 530. c) Maurigo, M.; Melchiorre, P. *ChemCatChem* **2010**, *2*, 621.

(32) For an example of a preceding intermolecular aldehyde-ketone cross acyloin reaction in the context of a cyclopentene-forming annulation *via* NHC-catalyzed acyloin-oxy-Cope reaction, see: Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520.

(33) O'Toole, S. E.; Connon, S. J. *Org. Biomol. Chem*. **2009**, *7*, 3584.

(34) a) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem*. **2009**, *74*, 9214; b) The pK_a of catalyst **8** (H_2O) has been determined to be 17.7. To the best of our knowledge the

corresponding pK_a of **21** has yet to be determined: Campbell, C. D.; Duguet, N.; Gallagher, K. A.; Thomson, J. E.; Lindsay, A. G.; O'Donoghue, A. C.; Smith, A. D. *Chem. Commun*. **2008**, 3528.

(35) For a recent report on the synthesis of a bifunctional thiourea carbene catalyst, see: Brand, J. P.; Siles, J. I.Osuna; Waser, J. *Synlett* **2010**, 881.

(36) Our investigations on catalyst control are ongoing and will be reported in due course.

(37) Conducting the experiment with an excess of 3 eq. of the aliphatic aldehyde (here: *iso*-butyraldehyde) provides a main cross product[23] in 64% yield in accordance with the results of Stetter et al.;[20, 23] however, application of similar conditions to unbranched aldehydes such as **11** clearly revealed the limitations of the process as this – even in combination with the potentially "privileged" *o*-substituted aryl aldehydes – only yields a major product in 40% yield (together with significant amounts of the homo dimer of hydrocinnamaldehyde), providing some evidence for the requirement of both large excess of aliphatic aldehydes and sterical demand of the aryl aldehyde for successful transformations.

(38) The concurrently formed homodimer **28a** can be easily separated by column chromatography. In our subsequent studies employing unbranched aliphatic aldehydes in 1.7 eq (table 3 and table 4) we only report the yields of the cross product **D** for clarity reasons.

(39) Carrying out the coupling reaction at temperatures higher than 18 °C invariably led to lower overall yields due to decomposition of the *o*-trifluoromethylbenzaldehyde. See also the results outlined in Scheme 4.

(40) Duddling, T.; Houk, K. N. *Proc. Nat. Acad. USA* **2004**, *101*, 5770.

(41) White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124.

(42) Stetter et al.[20] report a combined yield of 56% for the cross-acyloins **C** and **D** in a ratio of 1.9:1; no information is provided on the amount of homobenzoin **B**.

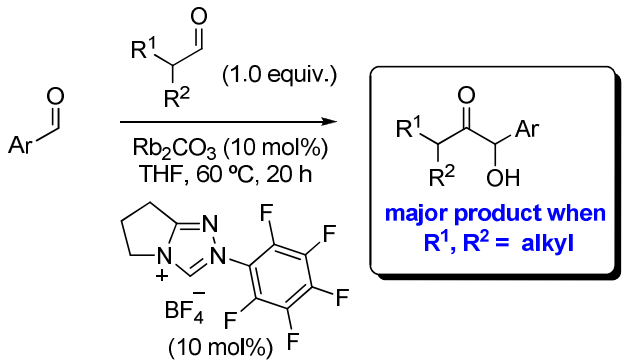
(43) Calculation of the free energy of the two regioisomers of the cross acyloin products of *o*-chlorobenzaldehyde (**9**) and *iso*butyraldehyde (**10**) revealed a preference for the α-aryl ketone **13d** as compared to the aromatic ketone **13c** by 3.60 kcal/mol. Similar results were obtained for the calculation using unbranched *n*-propanal as aliphatic aldehyde for the cross acyloins (lower energy for of then α-aryl ketone *vs.* aromatic ketone: 3.43 kcal/mol). Calculations of the free energy were performed with SPARTAN-06© by geometry optimization using Hartree-Fock methods (6-31G) starting from the corresponding minimun conformer as obtained in a PM3-based Monte Carlo conformer search.

(44) L. H. Baragwanath, C. A. Rose, K. Zeitler, S. J. Connon, *J. Org. Chem.* **2009**, *74*, 9124.

(45) M. S. Kerr, J. Read de Alaniz and T. Rovis, *J. Org. Chem.* **2005**, *70*, 5725.

(46) The concentration of the reaction performed by Stetter was quite high (ca. 3 M); in order to reproduce this accordingly on a smaller scale we found a tube shaped flask better suited to handle smaller amounts of solvent.

1.4 Chemoselective Crossed Acyloin Condensations: Catalyst and Substrate Control[i]



The interplay between catalyst and substrate control in crossed acyloin condensation reactions has been studied. It was found that a pentafluorophenyl-substituted triazolium ion derived catalyst was capable of catalyzing highly chemoselective processes between a range of aliphatic and aromatic aldehydes utilized in a 1:1 ratio.[ii]

[i] Reprinted with permission from: Rose, C. A.; Gundala, S.; Connon, S. J; Zeitler, K. *Synthesis* **2011**, *2*, 190 – 198. Copyright 2011 Georg Thieme Verlag Stuttgart · New York.

[ii] S. G. performed the crossed acyloin experiments with thienylcarbaldehyde (Table 1, entries 14 & 15), the evaluation of linear aliphatic aldehydes in crossed acyloin condensations (Scheme 1) and the crossed acyloin condensation between *p*-anisaldehyde and *iso*butyraldehyde (Scheme 2). All other experiments & studies were performed by C. A. R.

1.4.1 Introduction

The benzoin condensation (BC) is among the most well-known, time-honored transformations in organic chemistry. Discovered in 1832,[1] it is taught in most undergraduate courses around the world as an example of *umpolung* chemistry – two molecules of benzaldehyde react: one serves as an electrophile whereas the other behaves as a formal nucleophile in the presence of a catalyst.[2]

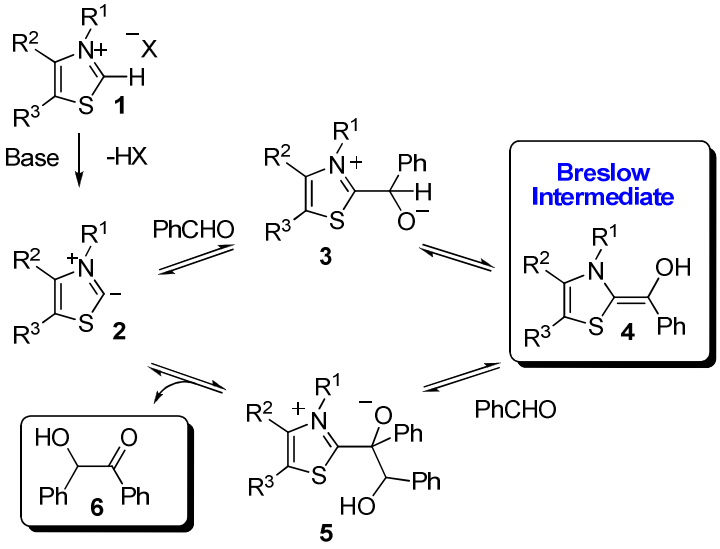


Figure 1: The mechanism of the thiazolium ion mediated benzoin condensation.

The process was initially promoted by cyanide ion, however more than 100 years after its discovery a thiazolium ion mediated process (under basic conditions) was developed by Ukai *et al*.[3] While studying thiamine dependent enzymes and their biological transformations the mechanism of the thiazolium ion mediated benzoin condensation was established in 1958 by Breslow[4] as involving the intermediacy of the carbene **2** (Figure 1), formed from initial deprotonation of the thiazolium salt **1**. This then adds to benzaldehyde to afford adduct **3**, which then undergoes proton transfer to yield the Breslow Intermediate (BI) **4**. This nucleophilic species adds to a second molecule of benzaldehyde (for example) to afford **5**, which eliminates benzoin (**6**) leading to the regeneration of carbene **2**, which is then available to re-enter the cycle and attack another benzaldehyde substrate molecule *etc*.[5]

In the 1990s, Enders pioneered the development of triazolium ion-derived carbene catalysts for the BC reaction.[6] A distinct advantage associated with the use of these systems was their amenability to modification for the purposes of asymmetric catalysis – leading to impressive recent developments in the corresponding (enantioselective) homo-BC reaction.[7,8]

However, the standing of the BC as a useful synthetic methodology, especially as a intermolecular C-C coupling process, is not high among the synthetic community, due to an inherent chemoselectivity problem: while excellent product yields are possible in the homo-BC reaction, when the two reacting

aldehyde moieties are not identical it is usual that no single α-hydroxy ketone of the four possible products (Figure 2) dominates. This is perhaps not entirely surprising upon cursory analysis of the mechanism (Figure 1): if one of the aldehydes is more electrophilic than the other, it is likely to undergo nucleophilic attack faster in the steps to form both the BI (*i.e.* **2** → **3**) and the C-C bond forming step (*i.e.* **4** → **5**). Therefore in the absence of any thermodynamic bias toward one product or the other, poor chemoselectivity would result.

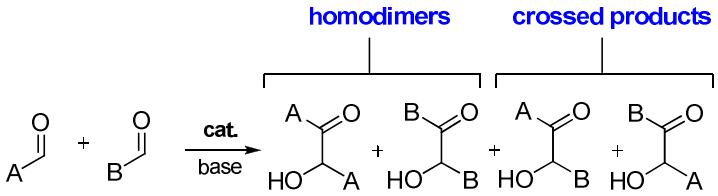


Figure 2: The four possible products from a crossed intermolecular BC reaction

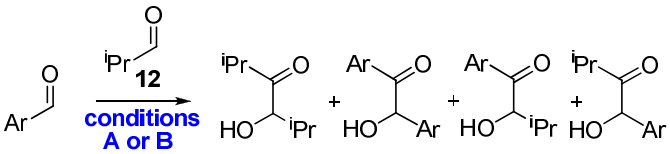
The first attempts to find a solution to this chemoselectivity problem were made by Buck *et al*.,[9] who examined this influence of electronic effects in the cyanide ion catalyzed crossed BC of aromatic aldehydes – no general trends leading to chemoselective methodologies were uncovered. Later, Stetter and coworkers[10] studied the thiazolium ion mediated reaction between aliphatic and aromatic aldehydes. When the aliphatic aldehyde was utilized in threefold excess good crossed product yields could be obtained. A curious finding was that chemoselectivity was highly substrate dependent: efficient, selective coupling was only observed in cases where the aromatic aldehyde either incorporated a π-excessive heterocycle or a chlorine atom in the *ortho* position.[11]

While a number of intramolecular examples of crossed aldehyde-ketone benzoin reactions have been accomplished,[12] more recently, Enders *et al*. demonstrated that 2,2,2-trifluoromethylacetophenone can serve as an electrophilic reaction partner in intermolecular crossed acyloin condensation (AC) reactions with electron rich heterocyclic aldehydes.[13,14,15] The choice of electrophile was crucial – the ketone is reactive enough to be attacked by the BI but is incapable of participating in BI-formation as it is devoid of an aldehyde proton. In general, an efficient, *N*-heterocyclic carbene (NHC)-catalyzed chemoselective intermolecular crossed AC methodology of broad scope remains outside the orbit of current technology, which has prompted the development of several useful either indirect[16] or enzyme-catalyzed[17] methodologies for the synthesis of these products.

1.4.2 Results and Discussion

With the objective of developing upon a recent finding that *ortho*-substituted benzaldehydes could participate in chemoselective crossed acyloin reactions with aliphatic aldehydes[17c] in the presence of triazolium salt-derived carbenes,[18] we began to investigate the influence of both substrate- and catalyst structure on the chemoselective outcome of the crossed AC reaction – we were particularly interested in the performance differential between Stetter's thiazolium ion precatalyst **18**[10a] and a triazolium analogue **19** which we have recently found to serve as an excellent promoter of both BC[8e] and crossed AC reactions.[18]

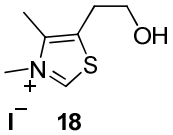
Since it appeared that single aspects of Stetter's findings (in particular the chemoselectivity associated with the use of *o*-chlorobenzaldehyde as a coupling partner) seemed at odds with our recent study,[18] we decided to repeat selected examples from Stetter's original work (condition set A), and compare the results with those an analogous reaction involving triazolium ion **19** under conditions optimized for its use (condition set B). The results of these experiments are outlined in Table 1. The reactions under investigation involved the coupling of benzaldehydes **7-11** with isobutyraldehyde (**12**) in either a 3:1 (condition set A 'Stetter') or a 1:1 ratio (condition set B) respectively. As Stetter had originally reported, benzaldehyde (**7**) participated in a broadly unselective process (save the expected absence of the hindered homo-AC product **13a**) hitherto typical of these types of coupling reactions (entries 1-2).[19] Using the triazolium ion precatalyst however (condition set B, entry 3) a considerably more selective process takes place: cross product **13d** (*via* the intermediacy of a BI derived from initial attack of the catalyst on **12**) is dominant, with small amounts of benzoin (**13b**) also formed.



7	Ar = C_6H_5	**13a**	**13b**	**13c**	**13d**
8	Ar = 2-Cl-C_6H_4		**14b**	**14c**	**14d**
9	Ar = 4-Cl-C_6H_4		**15b**	**15c**	**15d**
10	Ar = 2-furanyl		**16b**	**16c**	**16d**
11	Ar = 2-thienyl		**17b**	**17c**	**17d**

Condition set A (Stetter)

(3.0 equiv. aliphatic aldehyde)



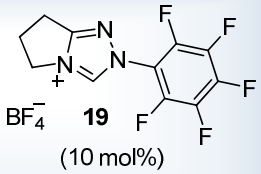
18

(10 mol%)

NEt_3 (60 mol%)
EtOH, reflux, 16 h

Condition set B

(1:1 ratio of aldehydes)



19

(10 mol%)

Rb_2CO_3 (10 mol%)
THF, 60 °C, 20 h

Entry	Cond. set	Prod.	Yield **a** (%)[a]	Yield **b** (%)[a]	Yield **c** (%)[a]	Yield **d** (%)[a]
1	**A** (ref.[b])	**13**	-	-	20	36
2	**A** (rep.[c])	**13**	<2	20	27	27
3	**B**	**13**	<2	13	<2	61
4	**A** (ref.[b])	**14**	-	-	81	0
5	**A** (rep.[c])	**14**	<2	8	<2	64
6	**B**	**14**	<2	<2	<2	68
7	**A** (ref.[b])	**15**	-	-	34	41
8	**A** (rep.[c])	**15**	5	12	27	26
9	**B**	**15**	0	7	12	63
10	**A** (ref.[b])	**16**	-	-	84	4
11	**A** (rep.[c])	**16**	5	<2	78	7
12	**B**	**16**	<2	13	33	28
13	**A** (ref.[b])	**17**	-	-	79	0
14	**A** (rep.[c])	**17**	<2	9	44	<2
15	**B**	**17**	<2	14	31	0

[a]Yield determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. Note: yields of **13-17a** and **13-17b** account for the 2:1 stoichiometry. [b]Data from ref. 10a. [c]Repeat of the experiment outlined in ref. 10a – data from the average of a minimum of two experiments.

Table 1: Crossed AC reactions under either Stetter's original conditions (reference and repeated) or under optimized conditions using a triazolium ion precatalyst.

In our hands, the coupling of *o*-substituted aldehyde **8** under Stetter's conditions did result in a chemoselective process; however, rather than the reported formation of **14c** as the sole product (entry 4), **14d** was identified as the major constituent of the reaction mixture in 64% yield (entry 5). In the triazolium ion-mediated reaction **14d** was also formed as the sole product in similar yield (entry 6). It is certain that the assignment of the major product from the reaction involving thiazolium ions as **14c** instead of **14d** by Stetter is an error, most likely related to the disparate focus of Stetter´s study (which concentrated on the mixed *oxidized* benzil-type products) and the limitations of NMR instrumentation at the time. In the case of the *p*-chlorobenzaldehyde isomer (**9**), the chemoselectivity profile of the reaction was similar to that observed using benzaldehyde: a low-yielding unselective process was observed in the presence of **18** (entries 7-8), while **19** facilitated the generation of **15d** in 63% yield (entry 9).

Another aspect of Stetter's work we found intriguing was the reversal of the chemoselectivity observed in the presence of π-excessive heterocyclic aldehydes. For instance, as Stetter had disclosed previously (entry 10), we found that furfural (**10**) could be added to **12** in the presence of thiazolium salt **18** to furnish **16c** (*via* a BI derived from initial attack of the catalyst on the aromatic aldehyde) as the major product in high yield (entry 11). To our surprise, the corresponding reaction catalyzed by the triazolium-derived carbene proved reproducibly inefficient and unselective (entry 12). In addition, thiophene-2-carbaldehyde (**11**) underwent selective crossed AC reactions with **12** in the presence of either **18** or **19** to produce **17c**; with the thiazolium salt-derived carbene providing higher product yields (entries 13-15).

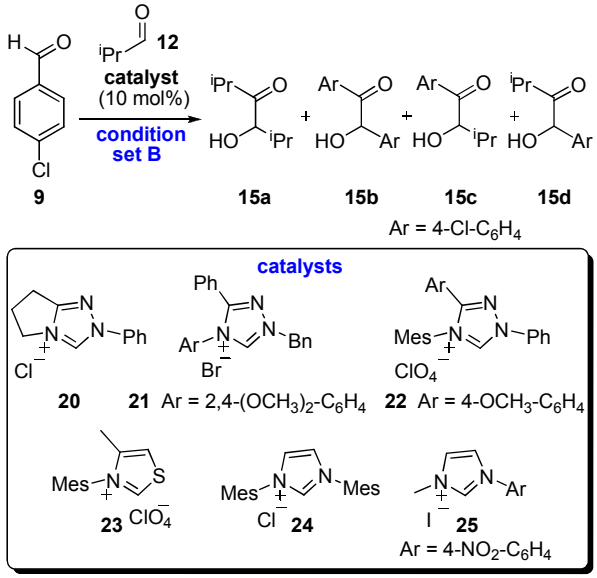
It is clear from these investigations that (as expected) *o*-substitution of the benzaldehyde component allows selective crossed AC reactions favoring the cross-product derived from initial catalyst attack on the aliphatic aldehyde to take place, regardless of the catalyst employed. However, in the absence of an *o*-substituent the thiazolium precatalyst **18** mediates unselective reactions, whereas the triazolium salt-derived carbene is capable of promoting the formation of **15d** as the dominant product in good overall yield.

It would also appear that BIs derived from attack of the carbene on π-excessive heterocyclic aldehydes are very different in character to those derived from benzaldehydes. Here the thiazolium ion-based catalyst promoted almost completely chemoselective reactions where the major product forms after initial attack on the heterocyclic aldehyde, while in the triazolium case the catalyst behaves differently if presented with either a furan or thiophene-based electrophile; promoting selective reactions in the former case and unselective processes in the latter. Thus a complex picture emerges where chemoselectivity can derive from either catalyst or substrate control, or a confluence of both factors.

Given the important role that the catalyst appears to play in bringing about a chemoselective outcome, we next investigated the use of other precatalysts in the reaction of **9** with **12** under condition set B (Table 2). We began by modifying the triazolium ion structure: precatalyst **20** (an analogue of **19** in

which the pentafluorophenyl unit has been replaced with a phenyl moiety) mediated a relatively unselective crossed AC reaction: while **15c** and **15d** dominated over homo AC products **15a** and **15b**, the crossed products were formed in almost equal amounts (entry 1).

The trisubstituted triazolium precatalyst **21** exhibited a very similar activity (entry 2) and chemo-selectivity profile to **20**, while **22** (which is characterized by the presence of two aromatic moieties flanking the acidic central CH-position, one of which is a bulky mesityl group) mediated an almost completely unselective reaction: only the formation of **15a** was avoided and the marked increase in the levels of the homo-BC reaction product (*i.e.* **15b**) obtained is noteworthy (entry 3).



Entry	Cat.	Yield **15a** (%)	Yield **15b** (%)	Yield **15c** (%)	Yield **15d** (%)
1	**20**	0	4	44	40
2	**21**	0	8	50	35
3	**22**	0	24	26	36
4	**23**	0	26	<2	<2
5	**24**	0	61	<2	<2
6	**25**	0	6	<2	12

[a]Yield determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. Note: yields of **15a** and **15b** account for the 2:1 stoichiometry.

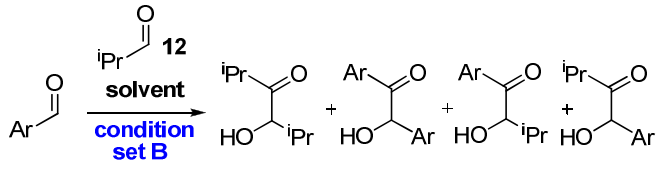
Table 2: Crossed AC reactions: investigation of the influence of catalyst structure.

It is also interesting to note that the mesityl-substituted thiazolium ion **23** provided **15b** as the sole detectable product in 26% yield (entry 4). This observation is in stark contrast with the performance of precatalyst catalyst **18** under condition set A (see Table 1, entries 7-8). Likewise, the *bis*-mesityl substituted bulky imidazolium ion **24** did not mediate the crossed AC process at all – only **15b** was

formed, albeit in moderately good yield (entry 5) while the less bulky 4-nitrophenyl substituted imidazolium ion **25** proved completely unsuitable as a catalyst precursor (entry 6).
From analysis of these results two conclusions can be drawn:

1) The pentafluorophenyl unit plays a key role in controlling selectivity in crossed AC reactions in the presence of precatalyst **19** – all triazolium catalysts (*i.e.* **20-22**) devoid of this substituent failed to promote selective processes.
2) Irrespective of the nature of the heterocyclic core, the presence of bulky groups (in particular the mesityl group) flanking the carbene carbon either significantly diminishes or destroys the catalyst's ability to promote crossed AC reactions. Using these catalyst systems elevated levels of homo BC products are detected.

Since the crossed BC reaction proceeds through charged intermediates – the stability of which we speculated would be impacted upon by the polarity of the reaction medium – we next evaluated the influence of solvent on the process (Table 3). Surprisingly, it was found that the reaction proceeded with comparable levels of efficiency and chemoselectivity in solvents ranging from the very polar and protic (entries 1 and 2 respectively) to the moderately polar and apolar (entries 3 and 4 respectively).

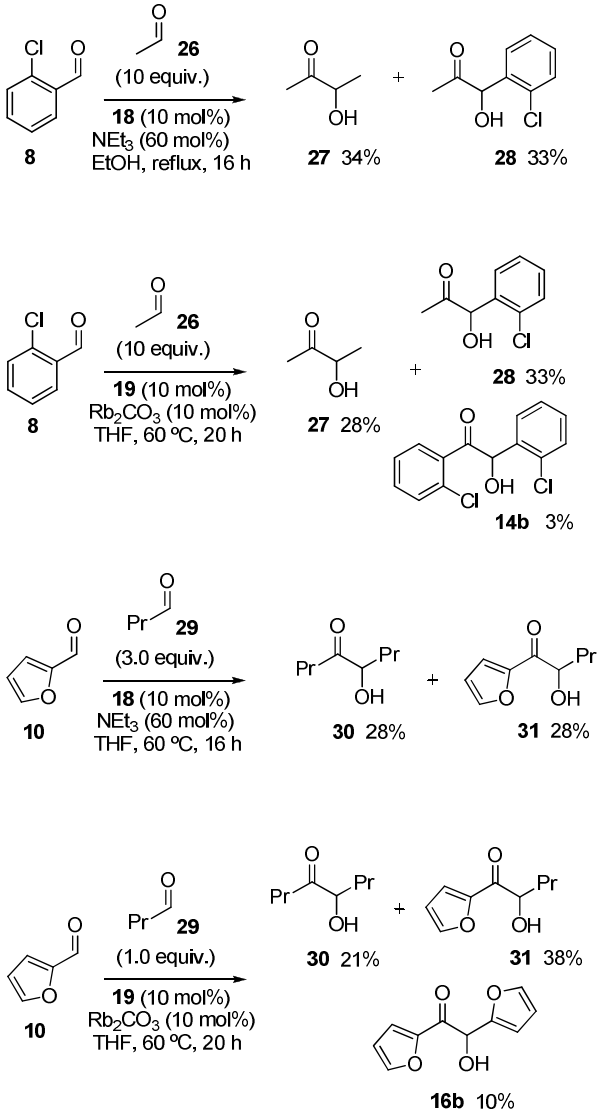


Entry	Solvent	Yield **15a** (%)[a]	Yield **15b** (%)[a]	Yield **15c** (%)[a]	Yield **15d** (%)[a]
1[b]	THF	0	7	12	63
2	EtOH	0	18	11	65
3	$CHCl_3$	0	10	10	70
4	PhMe	0	9	12	65

[a]Yield determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. Note: yields of **15a** and **15b** account for the 2:1 stoichiometry. [b]Data from Table 1, entry 9.

Table 3: Crossed AC reactions: investigation of the influence of solvent

The behaviour of unbranched aliphatic aldehydes in these reactions was also briefly examined (Scheme 1). Acetaldehyde (**26**) could be coupled with **8** in the presence of either the thia- or the triazolium ion precatalyst.



Scheme 1: Crossed AC reactions of aliphatic aldehydes.

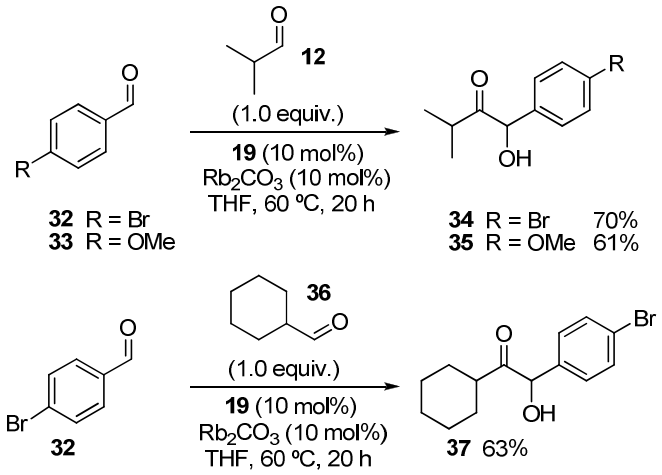
The aliphatic partner was required in 10 fold excess due to its volatility. These reactions were inefficient in general: the smaller, less hindered aldehyde readily formed the homodimer **27** in both cases at levels approximately equal to that of the expected crossed product **28**. It is perhaps of note that the triazolium precatalyst also mediates the formation of trace amounts of benzoin derivative **14b**, which was not observed in the reaction catalyzed by the thiazolium ion derived carbene. In a similar fashion, the reaction between furfural (**10**) and butanal (**29**) furnished equivalent (but moderate) yields of homodimer **30** and the crossed-product **31** under condition set A.

In the presence of the triazolium ion marginally higher yields of **31** were obtained, and again low levels of the dimer derived from homo-BC of **10** (*i.e.* **16b**) were observed. When this reaction is

compared to the equivalent transformation involving isobutyraldehyde (*i.e.* Table 1, entry 12), one notices the absence of the crossed product derived from the initial attack of the catalyst on **29**. Presumably this is related to the less hindered nature of **29**, which results in all of that BI being converted to homodimer **30**.

The general superiority of catalyst **19** is further underlined by the finding that the levels of chemoselectivity observed in the presence of **18** and **19** were very similar, despite the thiazolium system operating under Stetter's original conditions involving the use of 3.0 equivalents of aliphatic aldehyde, while the triazolium dervied carbene mediated reactions in which the aldehydes were present in stoichiometric amounts.

Finally, the potential of **19** to serve as a catalyst for the promotion of selective and synthetically useful crossed AC reactions involving benzaldehydes devoid of an *ortho*-substituent was evaluated (Scheme 2). Gratifyingly, lack of steric bulk at the *ortho* position is no impediment to a chemoselective process in the presence of precatalyst **19**. Reaction of one equivalent of **12** with either an activated or a deactivated benzaldehyde (*i.e.* **32** and **33**) afforded **34** and **35** respectively in good isolated yield. Cyclohexane carbaldehyde (**36**) could also participate in these processes – reaction with benzaldehyde generated coupled product **37** in 63% yield.



Scheme 2: Crossed AC reactions of unhindered benzaldehydes

1.4.3 Conclusion

In summary, we have evaluated the relative performance of thiazolium and triazolium ion precatalysts in crossed AC reactions. In general, a complex picture emerges where both catalyst and substrate control play important roles in determining the outcome of the process from both efficiency and chemoselectivity perspectives. The triazolium catalyst **19** proved more useful over a wide range of substrates than its thiazolium counterpart **18**, and an error in the literature concerning the performance of **18** in the reaction to generate **14** has been corrected.

Substrate features demonstrated to be important in the control of chemoselectivity include the presence of either *o*-substitution or a π-excessive heterocycle substituted at position 2 in the benzaldehyde component (features which interestingly result in opposing chemoselectivity), and a disubstituted α-carbon on the aliphatic aldehyde coupling partner. The requirement for the *o*-substituent on the aromatic aldehyde can be obviated through the use of the triazolium-derived carbene catalyst – in which the pentafluorophenyl moiety and the absence of steric bulk adjacent to the carbene carbon atom were demonstrated to be key factors contributing to highly chemoselective catalysis.

1.4.4 Experimental Section

General Methods

Unless otherwise noted, all commercially available compounds were used as provided without further purification. All reactions were carried out under a protective atmosphere of dry nitrogen or argon using oven-dried glassware unless otherwise stated.
NMR spectra were recorded on a Bruker Avance 300 (300.13 MHz), 400 MHz (400.13 MHz) or a Bruker Advance 600 (600.13 MHz) and using the solvent peak as internal reference ($CDCl_3$: δ H 7.26; δ C 77.0 and DMSO-d_6: δ H 2.51; δ C 39.5). Multiplicities are indicated, s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), app. sept (app. septet), m (multiplet)); coupling constants (*J*) are in Hertz (Hz). Mass spectra (MS ESI) were recorded using a Micromass/Waters mass spectrometer equipped with a TOF analyser, using ESI, and also with a Finnigan MAT 95 or Varian MAT 311A. All reactions were monitored by thin-layer chromatography using Merck silica gel plates 60 F_{254}; visualization was accomplished with UV light and/or staining with appropriate stains ($KMnO_4$, anisaldehyde, vaniline, ninhydrin or phosphomolybdic acid). Standard flash chromatography procedures were followed (particle size 40−63 μm). Infrared spectra were obtained using neat samples on a Perkin Elmer FT-IR spectrometer, respectively on a Biorad Excalibur FTS 3000 Spectrometer equipped with a universal ATR sampling accessory.
Tetrahydrofuran was distilled from sodium/benzophenone. Catalyst **19** was prepared according to the method described by Rovis.[20]

Crossed Acyloin Condensation Using 'Stetter' Conditions:
General Procedure for *Condition Set A*

A flame-dried Schlenk flask ('tube shape')[21] equipped with a magnetic stirring bar was charged with 14 mg (0.05 mmol = 10 mol%) thiazolium iodide precatalyst **18** (and 25 mol% (*E*)-stilbene, if required) and placed under high vacuum. After having dried the solids for 1 h at ambient temperature, 0.16 mL of EtOH was added and the resulting solution stirred for 5 min. Now 0.5 mmol (1 equiv.) of the aromatic aldehyde as well as 1.5 mmol (3 equiv.) of the aliphatic aldehyde were added. After final addition of 0.3 mmol (0.6 equiv) triethylamine, the reaction vessel was equipped with a reflux condenser and heated for 16 h (ca. 90 °C) under an inert atmosphere.
To determine the yields of the benzoin products, residual starting material etc. *via* quantitative NMR, the reaction vessel was allowed to cool to room temperature. In order to transfer the crude reaction mixture into an NMR tube, a Pasteur-pipette (without cap) was dipped four times into the solution

(whereupon it is becoming partly solid in most cases). Finally, an appropriate amount of $CDCl_3$ was added.

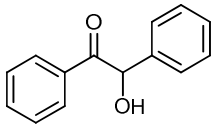
For the isolation of the corresponding benzoin products the crude mixture was evaporated and purified by column chromatography.

Crossed Acyloin Condensation: General Procedure for *Condition Set B*

A flame-dried Schlenk flask equipped with a magnetic stirring bar was charged with Rb_2CO_3 (12 mg, 0.05 mmol). The reaction vessel was evacuated, heated to 650° C for 1 min and cooled to r.t. under N_2. After this procedure had been repeated once, triazolium-precatalyst **19** (18 mg, 0.05 mmol) was added. The precatalyst/base-mixture was placed under vacuum and dried at r.t. for 1 h. Subsequently, absolute THF (0.45 ml) was added and the resulting mixture was allowed to stir at r.t. for 15 min. After sequential addition of the appropriate aromatic aldehyde (0.5 mmol) and α-branched aldehyde (0.5 mmol), the reaction vessel was equipped with a reflux condenser and stirred at 60 °C for 20 h under an atmosphere of N_2. The reaction mixture was allowed to cool to r.t., followed by evaporation of the solvent under reduced pressure. The crude product was purified by column chromatography (silica gel, solvent mixture as indicated).

Experimental Data

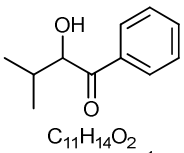
2-Hydroxy-1,2-diphenyl-ethanone (13b)



$C_{14}H_{12}O_2$
212.24 gmol^{-1}

m.p. 131-132 °C (Lit.[8f,22a] 131–132 °C). R_f (CH_2Cl_2/hexane 3/2) = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.43 (app. t, 2H), 7.29-7.40 (m, 5H (overlapping with $CHCl_3$ resonance)), 5.98 (s, 1H), 4.58 (bs, 1H).

2-Hydroxy-3-methyl-1-phenylbutan-1-one (13c)

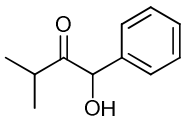


$C_{11}H_{14}O_2$
178.23 gmol^{-1}

according to the **general procedure '*Cond. Set A*'**: yield after column chromatography (silica gel, *n*-pentane/Et_2O 10/1) 17 mg (19 %), colourless oil. R_f (*n*-pentane/Et_2O 5/1) = 0.28. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 – 7.86 (m, 2H), 7.66 – 7.58 (m, 1H), 7.54 – 7.46 (m, 2H), 4.98 (dd, *J* = 6.3 Hz, 2.5 Hz, 1H), 3.61 (d, *J* =

6.3 Hz, 1H), 2.13 (app. sept-d, *J* = 6.8 Hz, 2.6 Hz, 1H), 1.17 (d, *J* = 7.1 Hz, 3H), 0.65 (d, *J* = 6.9 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 202.3, 134.2, 133.9, 128.9, 128.5, 77.3, 32.7, 20.2, 14.4. IR (neat): $\tilde{\nu}$ = 3490, 2964, 2930, 1676, 1449, 1263, 1137, 1034, 990, 760, 693, 532, 497 cm^{-1}.

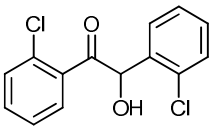
1-Hydroxy-3-methyl-1-phenylbutan-2-one (13d)



$C_{11}H_{14}O_2$
178.23 gmol^{-1}

according to the **general procedure '*Cond. Set B*'**: yield after column chromatography (silica gel, *n*-pentane/Et_2O 10/1): 48 mg (54 %), colourless to pale yellow crystals. m.p. 44 - 45 °C. R_f (*n*-pentane/Et_2O 5/1) = 0.19. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 – 7.27 (m, 5H), 5.22 (d, *J* = 4.7 Hz, 1H), 4.39 (d, *J* = 4.7 Hz, 1H), 2.70 (app. sept, *J* = 7.0 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 213.5, 137.9, 129.0, 128.7, 127.6, 78.3, 36.0, 19.4, 18.0. HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{11}H_{14}O_2$: 178.0994, found: 178.0996. IR (neat): $\tilde{\nu}$ = 3440, 3402, 2976, 1707, 1455, 1384, 1129, 1011, 839, 756, 722, 697, 507 cm^{-1}.

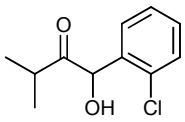
1,2-Bis-(2-chloro-phenyl)-2-hydroxy-ethanone (14b)



$C_{14}H_{10}Cl_2O_2$
281,13 gmol^{-1}

m.p. 65-66 °C (Lit.[8f, 22b] 64–66 °C). R_f (CH_2Cl_2/hexane 3/2) = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 - 7.40 (m, 3H), 7.23-7.26 (m, 5H (overlapping with $CHCl_3$ resonance)), 6.38 (s, 1H), 4.46 (bs, 1H).

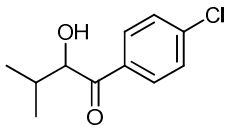
1-(2-Chlorophenyl)-1-hydroxy-3-methylbutan-2-one (14d)



$C_{11}H_{13}ClO_2$
212.67 gmol^{-1}

according to the **general procedure '*Cond. Set B*'**: yield after column chromatography (silica gel, *n*-pentane/Et_2O 10/1): 75 mg (71 %), pale yellow oil. R_f (*n*-pentane/Et_2O 5/1) = 0.25. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 – 7.38 (m, 1H), 7.30 – 7.18 (m, 3H), 5.73 (d, *J* = 4.4 Hz, 1H), 4.41 (d, *J* = 4.7 Hz, 1H), 2.70 (app. sept, *J* = 6.9 Hz, 1H), 1.17 (d, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 212.9, 135.7, 133.8, 130.1, 129.9, 129.3, 127.5, 74.6, 36.2, 19.5, 17.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{11}H_{14}ClO_2$: 213.0682, found: 213.0686. IR (neat): $\tilde{\nu}$ = 3440, 2973, 1713, 1473, 1385, 1015, 758, 632, 536, 499 cm^{-1}.

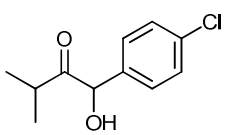
1-(4-Chlorophenyl)-2-hydroxy-3-methylbutan-1-one (15c)



$C_{11}H_{13}ClO_2$
212.67 gmol^{-1}

according to the **general procedure '*Cond. Set A*'**: yield after column chromatography (silica gel, *n*-pentane/Et_2O 20/1): 20 mg (19 %), pale yellow oil. R_f (*n*-pentane/Et_2O 5/1) = 0.22. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 – 7.81 (m, 2H), 7.52 – 7.44 (m, 2H), 4.93 (dd, *J* = 6.6 Hz, 2.5 Hz, 1H), 3.53 (d, *J* = 6.6 Hz, 1H), 2.10 (app. sept-d, *J* = 6.8 Hz, 2.6 Hz, 1H), 1.17 (d, *J* = 7.1 Hz, 3H), 0.65 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 201.1, 140.4, 132.4, 129.9, 129.3, 77.3, 32.7, 20.1, 14.4. HRMS (EI): *m/z* $[M]^+$ calcd.for $C_{11}H_{13}ClO_2$: 212.0604, found: 212.0599. IR (neat): $\tilde{\nu}$ = 3483, 2961, 2930, 2873, 1669, 1589, 1491, 1387, 1307, 1279, 1258, 1090, 1032, 939, 807, 605, 532, 460 cm^{-1}.

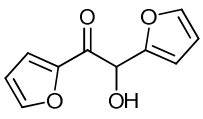
1-(4-Chlorophenyl)-1-hydroxy-3-methylbutan-2-one (15d)



$C_{11}H_{13}ClO_2$
212.67 gmol^{-1}

according to the **general procedure '*Cond. Set B*'**: yield after column chromatography (silica gel, *n*-pentane/Et_2O 10/1): 62 mg (58 %), colourless crystals. m.p. 45-46 °C. R_f (*n*-pentane/Et_2O 5/1) = 0.14. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 – 7.33 (m, 2H), 7.28 – 7.23 (m, 2H), 5.19 (d, *J* = 4.7 Hz, 1H), 4.37 (d, *J* = 4.7 Hz, 1H), 2.68 (app. sept, *J* = 6.9 Hz, 1H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 213.0, 136.5, 134.7, 129.2, 128.9, 77.6, 36.0, 19.4, 18.0. HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{11}H_{13}ClO_2$: 212.0604, found: 212.0605. IR (neat) : $\tilde{\nu}$ = 3426, 2968, 2934, 1711, 1592, 1491, 1386, 1213, 1093, 1013, 808, 534, 480 cm^{-1}.

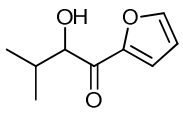
1,2-Di-furan-2-yl-2-hydroxy-ethanone (16b)



$C_{10}H_8O_4$
192.17 gmol^{-1}

m.p. 137-138 °C (Lit.[22] 135–136 °C). R_f (CH_2Cl_2) = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63 (app. s, 1H), 7.39 (d, *J* = 1.5 Hz, 1H),), 7.27 (m, 1H (overlapping with $CHCl_3$ resonance)), 6.56 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.42 (d, *J* = 3.5Hz, 1H), 6.37 (dd, *J* = 3.0, 1.5 Hz, 1H), 5.82 (bs, 1H), 4.22 (bs, 1H).

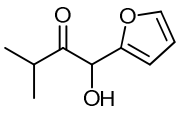
1-(Furan-2-yl)-2-hydroxy-3-methylbutan-1-one (16c)



$C_9H_{12}O_3$
168.19 gmol^{-1}

according to the **general procedure '*Cond. Set A*'**: yield after column chromatography (silica gel, *n*-pentane/Et_2O 10/1): 30 mg (36% - not optimized), yellowish crystals. m.p. 36–37 °C. R_f (*n*-pentane/Et_2O 5/1) = 0.11. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 – 7.57 (m, 1H), 7.28 – 7.23 (m, 1H), 6.54 (dd, *J* = 3.6 Hz, 1.6 Hz, 1H), 4.67 (br s, 1H), 3.38 – 3.25 (m, 1H), 2.20 (app. sept-d, *J* = 6.9 Hz, 2.7 Hz, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.69 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 190.6, 150.6, 147.0, 118.8, 112.5, 77.7, 32.7 20.0, 14.8. MS (EI): *m/z* (%) = 168 (1) [$M^{+\bullet}$], 167 (5) [$M^{+\bullet}$-$H^{\bullet}$], 150 (2) [$M^{+\bullet}$-H_2O], 97 (40) [$M^{+\bullet}$-$C_4H_7O^+$]. IR (neat) : $\tilde{\nu}$ = 3442, 3126, 2975, 2933, 1656, 1466, 1410, 1270, 1146, 1030, 990, 814, 764, 589, 510 cm^{-1}.

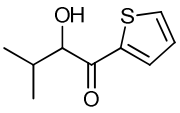
1-(Furan-2-yl)-1-hydroxy-3-methylbutan-2-one (16d)



$C_9H_{12}O_3$
168.19 gmol^{-1}

according to the **general procedure '*Cond. Set B*'** (here: 2 mmol): yield after column chromatography (silica gel, petroleum ether/ethyl acetate 10/1): 16 mg (5 % - not optimized), yellow oil. R_f (petroleum ether/ethyl acetate 5/1) = 0.29. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (br s, 1H), 6.42 – 6.36 (m, 2H), 5.28 (d, *J* = 5.2 Hz, 1H), 4.15 (d, *J* = 4.9 Hz, 1H), 2.71 (app. sept, *J* = 6.9 Hz, 1H), 1.13 (d, *J* = 7.1 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 211.0, 150.6, 143.2, 110.9, 109.6, 71.4, 36.4, 19.2, 17.6.

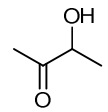
2-Hydroxy-3-methyl-1-(thiophen-2-yl)butan-1-one (17c)



$C_9H_{12}O_2S$
184.26 gmol^{-1}

according to the **general procedure '*Cond. Set A*'**: yield after column chromatography (silica gel, *n*-pentane/Et_2O 20/1): 40 mg (43 %), colourless to pale yellow needles. m.p. 37–38 °C. R_f (*n*-pentane/Et_2O 5/1) = 0.17. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 – 7.69 (m, 2H), 7.20 – 7.14 (m, 1H), 4.77 (dd, *J* = 6.9 Hz, 2.7 Hz, 1H), 3.42 (d, *J* = 6.9 Hz, 1H), 2.22 (app. sept-d, *J* = 6.8 Hz, 2.9 Hz, 1H), 1.16 (d, *J* = 7.1 Hz, 3H), 0.75 (d, *J*= 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 194.5, 140.3, 134.6, 132.9, 128.3, 78.3, 34.0, 20.1, 14.8. HRMS (EI): *m/z* [$M]^+$ calcd. for $C_9H_{12}SO_2$: 184.0558, found: 184.0558. IR (neat): $\tilde{\nu}$ = 3506, 3470, 3085, 2970, 2930, 2873, 1646, 1518, 1412, 1359, 1260, 1139, 1063, 1019, 908, 813, 749, 689, 472, 430 cm^{-1}.

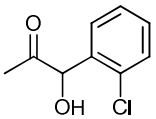
3-Hydroxybutan-2-one (27)



$C_4H_8O_2$
88.11 gmol^{-1}

according to the **general procedure '*Cond. Set A*'**: yield after column chromatography (silica gel, hexane/Et_2O 4/1): 30 mg (30 %), colourless liquid. R_f (silica gel, hexane/Et_2O 4/1) = 0.13. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.28 (dq, J =7.2, J = 4.3 Hz, 1H), 3.53 (d, J = 4.3 Hz, 1H, OH), 2.23 (s, 3H). 1.43 (d, J = 7.2 Hz, 3H), 1.28 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 210.0, 72.8, 24.7, 19.5. HRMS (EI): *m/z* $[M]^+$ calcd. for $C_4H_8O_2$: 88.1096, found: 88.1109. IR (neat): $\tilde{\nu}$ = 3454, 2924, 1690, 1460, 1052, 732 cm^{-1}.

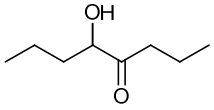
1-(2-Chlorophenyl)-1-hydroxypropan-2-one (28)



$C_9H_9ClO_2$
184.62 gmol^{-1}

according to the **general procedure '*Cond. Set A*'**: yield after column chromatography (silica gel, hexane/Et_2O 4/1): 62 mg (33 %), yellow oil. R_f (silica gel, hexane/Et_2O 4/1) = 0.16. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.43 (m, 1H), 7.31-7.29 (m, 3H), 5.61 (d, J = 4.3 Hz, 1H), 4.38 (d, J = 4.3 Hz, 1H, OH), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.2, 135.7, 133.4, 130.0, 129.9, 128.9, 127.5, 76.4, 25.2. HRMS (CI): *m/z* $[M+H]^+$ calcd. for $C_9H_9ClO_2$: 185.0369, found: 185.0366. IR (neat): $\tilde{\nu}$ = 3447, 1716, 1592, 1474, 1358, 1225, 1179, 1035, 966, 885, 752, 688 cm^{-1}.

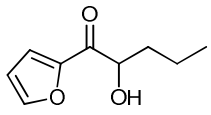
5-Hydroxyoctan-4-one (30)



$C_8H_{16}O_2$
144.21 gmol^{-1}

according to the **general procedure '*Cond. Set A*'**: yield after column chromatography (silica gel, hexane/Et_2O 4/1): 41 mg (28 %). R_f (silica gel, hexane/Et_2O 4/1) = 0.15. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.20-4.16 (m, 1H), 3.52 (d, J = 5.0 Hz, 1H, OH), 2.53-2.38 (m, 2H), 1.84-1.75 (m, 1H), 1.72-1.65 (m, 2H), 1.57-1.35 (m, 3H), 0.98-0.93 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 212.2, 76.1, 39.6, 35.7, 18.0, 17.0, 13.7, 13.6. HRMS (EI): *m/z* $[M]^+$ calcd. for $C_8H_{16}O_2$: 144.1150, found: 144.1144. IR (neat): $\tilde{\nu}$ = 3474, 2961, 1708, 1459, 1275, 1080, 852, 742 cm^{-1}.

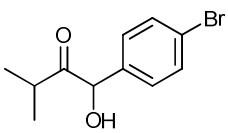
1-(Furan-2-yl)-2-hydroxypentan-1-one (31)



$C_9H_{12}O_3$
168.19 gmol^{-1}

according to the **general procedure '*Cond. Set A*'**: yield after column chromatography (silica gel, hexane/Et_2O 4/1): 47 mg (28 %). m.p. 63 - 66 °C. R_f (silica gel, hexane/Et_2O 4/1) = 0.18. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.6 (s, 1H),7.33 (d, J = 3.5 Hz, 1H), 6.62 (dd, J = 3.5, 1.5 Hz, 1H), 4.86 (m, 1H), 3.47 (d, J = 5.5 Hz 1H, OH), 1.94 - 1.87 (m, 1H), 1.68-1.45 (m, 3H), 0.97 (t, J = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.3, 149.8, 146.6, 118.4, 112.1, 72.9, 37.3, 17.4, 13.4. HRMS (ES): *m/z* $[M+Na]^+$ calcd. for $C_9H_{12}O_3$: 191.0684, found: 191.0691

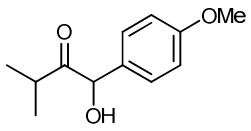
1-(4-Bromophenyl)-1-hydroxy-3-methylbutan-2-one (34)



$C_{11}H_{13}BrO_2$
257.12 gmol^{-1}

according to the **general procedure '*Cond. Set B*'**: yield after column chromatography (silica gel, *n*-pentane/Et_2O 10/1): 90 mg (70 %). m.p. 58–59°C. R_f (silica gel, *n*-pentane/Et_2O 5/1) = 0.14. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 – 7.47 (m, 2H), 7.22 – 7.15 (m, 2H), 5.17 (d, J = 4.7 Hz, 1H), 4.39 (d, J = 4.7 Hz, 1H), 2.67 (app. sept, J = 6.9 Hz, 1H), 1.13 (d, J = 7.1 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 212.9, 137.0, 132.1, 129.2, 122.8, 77.6, 36.0, 19.4, 18.0. HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{11}H_{13}BrO_2$: 256.0099, found: 256.0109. IR (neat): $\tilde{\nu}$ = 3436, 2968, 1709, 1588, 1486, 1385, 1223, 1008, 806, 741, 641, 581, 521 cm^{-1}.

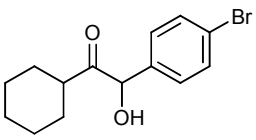
1-Hydroxy-1-(4-methoxyphenyl)-3-methylbutan-2-one (35)



$C_{12}H_{16}O_3$
208.25 gmol^{-1}

according to the **general procedure '*Cond. Set B*'**: yield after column chromatography (silica gel, hexane/Et_2O 4/1): 126 mg (61 %). m.p. 83 - 85 °C. R_f (silica gel, hexane/Et_2O 4/1) = 0.17. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 5.19 (d, J = 4.5 Hz, 1H), 4.35 (d, J = 4.5 Hz , 1H, OH), 3.83 (s, 3H), 2.71 (app. sept, J = 6.7 Hz 1H), 1.14 (d, J = 7.2 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.3, 159.4, 129.5, 128.4, 114.0, 77.3, 54.8, 35.5, 18.9, 17.5. HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{12}H_{16}O_3$: 208.1099, found: 208.1097. IR (neat): $\tilde{\nu}$ = 3432, 2967, 1711, 1587, 1455, 1382, 1222, 1009, 813, 784, 731, 692, 531 cm^{-1}.

2-(4-Bromophenyl)-1-cyclohexyl-2-hydroxyethanone (37)



$C_{14}H_{17}BrO_2$
297.19 gmol^{-1}

according to the **general procedure '*Cond. Set B*'**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 10/1): 93 mg (63 %), colourless solid. m.p. 102-103 °C. R_f (silica gel, petroleum ether/ethylacetate 5/1) = 0.29. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.46 (m, 2H), 7.21–7.13 (m, 2H), 5.14 (d, J = 4.7 Hz, 1H), 4.39 (d, J = 4.7 Hz, 1H), 2.39 (tt, J = 11.3 Hz, 3.5 Hz, 1H), 1.91–1.72 (m, 2H), 1.68–1.56 (m, 2H), 1.44–0.94 (m, 6H). ^{13}C NMR (75,5 MHz, $CDCl_3$): δ 211.9, 137.0, 132.1, 129.3, 122.8, 77.6, 46.0, 29.6, 27.9, 25.6, 25.5, 25.0. HRMS (EI): *m/z* $[M]^+$ calcd. for $C_{14}H_{17}BrO_2$: 296.0412, found: 296.0410. IR(neat): $\tilde{\nu}$ = 3430, 2930, 2851, 1705, 1447, 1059, 993, 820, 638, 521 cm^{-1}.

1.4.5 References

(1) Wöhler, F.; Liebig, F. *Ann. Pharm.* **1832**, *3*, 249.

(2) For recent reviews see: (a) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2009**, *291*, 77. (b) Enders, D. *J. Org. Chem*. **2008**, *73*, 7857. (c) Rovis, T. *Chem. Lett*. **2008**, *37*, 1. (d) Zeitler, K. *E. Schering Found. Symp. Proc.* **2007***, 2*, 183. (e) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev*. **2007**, *107*, 5506. (f) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed*. **2007**, *46*, 2988. (g) Zeitler, K. *Angew. Chem., Int. Ed*. **2005**, *44*, 7506. (h) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632. (i) Enders, D.; Balensiefer, T. *Acc. Chem. Res*. **2004**, *37*, 534. (j) Johnson, J. S. *Angew. Chem., Int. Ed*. **2004**, *43*, 1326.

(3) Ukai, T.; Tanaka R.; Dokawa, T. *J. Pharm. Soc. Jpn.* **1943**, *63*, 269.

(4) Breslow, R. *J. Am. Chem. Soc*. **1958**, *80*, 3719.

(5) Leeper later carried out a detailed kinetic study of the process, see: White, M. J.; Leeper, F. J. *J. Org. Chem*. **2001**, *66*, 5124.

(6) (a) Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta*. **1996**, *79*, 1217. (b) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J. -P.; Ebel, K.; Brode, S. *Angew. Chem. Int. Ed*. **1995**, *34*, 1021. (c) Teles, J. H.; Melder, J.-P.; Ebel, K.; Schneider, R.; Gehrer, E.; Harder, W.; Brode, S.; Enders, D.; Breuer, K.; Raabe, G. *Helv. Chim. Acta* **1996**, *79*, 61.

(7) For selected examples of thiazolium ion-mediated asymmetric BC reactions see: (a) Sheehan, J.; Hunnemann, D. H. *J. Am. Chem. Soc*. **1966**, *88*, 3666. (b) Sheehan, J.; Hara, T. *J. Org. Chem*. **1974**, *39*, 1196. (c) Dvorak, C. A.; Rawal, V. H. *Tetrahedron Lett*. **1998**, *39*, 2925. (d) Takagi, W.; Tamura, Y.; Yano, Y. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 478. (e) Marti, J.; Castells, J.; Lopez-Calahora, F. *Tetrahedron Lett*. **1993**, *34*, 521. (f) Tachibana, Y.; Kihara, N.; Takata, T. *J. Am. Chem. Soc*. **2004**, *126*, 3438. (g) Knight, R. L.; Leeper, F. J. *Tetrahedron Lett*. **1997**, *38*, 3611. (h) Gerhard, A. U.; Leeper, F. J. *Tetrahedron Lett*. **1997**, *38*, 3615. (i) Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 1891. (j) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem*. **2004**, 2025. (k) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc*. **2005**, *127*, 1654.

(8) For selected examples of triazolium ion-mediated asymmetric BC reactions see: (a) Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta*. **1996**, *79*, 1217. (b) Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891. (c) Enders, D.; Kallfass, U. *Angew. Chem. Int. Ed*. **2002**, *41*, 1743. (d) Enders, D.; Han, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1367. (e) Ma, Y.;

Wei, S.; Wu, J.; Yang, F.; Liu, B.; Lan, J.; Yang, S.; You, J. *Adv. Synth. Catal*. **2008**, *350*, 2645. (f) O'Toole, S. E.; Connon, S. J. *Org. Biomol. Chem*. **2009**, *7*, 3584. (g) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem*. **2009**, *74*, 9214. (h) Brand, J. P.; Osuna Siles J. –I.; Waser, J. *Synlett* **2010**, 881.

(9) Ide, W. S.; Buck, J. S. *Org. React*. **1948**, *4*, 269.

(10) (a) Stetter, H.; Dämbkes, G. *Synthesis* **1977**, 403. (b) Stetter, H.; Dämbkes, G. *Synthesis*, **1980**, 309.

(11) Miller *et al*. reported one example of a crossed AC reaction using *o*-tolualdehyde and hexanal mediated by a triazolium ion precatalyst (stoichiometric loadings). The yield of the isolated product was 16%. Mennen, S. M.; Miller, S. J. *J. Org. Chem*. **2007**, 72, 5260.

(12) *Intramolecular* enantioselective AC reactions between aldehydes and ketones are known. For representative examples, see: (a) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed*. **2006**, *45*, 1463. (b) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int.Ed.* **2006**, *45*, 3492. (c) Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431. (d) Li, Y.; Feng, Z.; You, S.-L. *Chem. Commun*. **2008**, 2263. (e) Ema, T.; Oue, Y.; Akihara, K.; Miyazaki, Y.; Sakai, T. *Org. Lett.* **2009**, *11*, 4866. (f) For a recent example in the context of a multicatalytic cascade sequence, see: Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628.

(13) Enders, D.; Henseler, A. *Adv. Synth. Catal*. **2009**, *351*, 1749.

(14) For a recent report detailing asymmetric variants of this process see: Enders, D.; Grossmann, A.; Fronert, J.; Raabe, G. *Chem. Commun*. **2010**, *46*, 6282.

(15) For an extension of this methodology to include ketimine substrates see: Enders, D.; Henseler, Lowins, S. *Synthesis* **2009**, 4125.

(16) (a) Kuriakose, S.; Rajasekharan Pillai, V. N. *Eur. Polym. J*. **1994**, *30*, 881. (b) Kuriakose, S; Rajasekharan Pillai, V. N. *Angew. Makromol. Chem*. **1994**, *221*, 53. (c) Kuriakose, S; Rajasekharan Pillai, V. N. *Polymer*, **1994**, *35*, 1339. (d) Linghu, X.; Johnson, J. S. *Angew. Chem., Int. Ed*. **2003**, *42*, 2534. (e) Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc*. **2004**, *126*, 3070. (f) Bausch, C. C.; Johnson, J. S. *J. Org. Chem*. **2004**, *69*, 4283. (g) Linghu, X.; Bausch, C. C; Johnson, J. S. *J. Am. Chem. Soc*. **2005**, *127*, 1833. (h) Tarr, J. C.; Johnson, J. S. *Org. Lett*. **2009**, *11*, 3870. (i) Demir, A. S.; Esiringü, I.; Göllü, M.; Reis, Ö. *J. Org. Chem*. **2009**, *74*, 2197. (j) Demir, A. S.; Reis, B.; Reis, Ö.; Eymür, S.; Göllü, M.; Tural, S.; Saglam, G. *J. Org. Chem*. **2007**, *72*, 7439. (k) Demir, A. S.; Reis, Ö.; Esiringü, I.; Reis, B.; Baris, S. *Tetrahedron* **2007**, *63*, 160. (l) Demir, A. S.; Reis, Ö.; Ciğdem, C.; Esiringü, I.; Eymur, S. *J. Org. Chem*. **2005**, *70*, 10584. (m) Bausch, C. C.; Johnson, J. S. *Adv. Synth. Catal*. **2005**, *347*, 1207. (n) Mathies, A. K.; Mattson, A. E.; Scheidt, K. A. *Synlett* **2009**, 377. (o) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc*. **2006**, *128*, 4932. (p) Mattson, A. E.; Scheidt, K. A. *J. Am. Chem. Soc*. **2007**, *129*, 4508.

(17) (a) Lehwald, P.; Richter, M.; Röhr, C.; Liu, H. -W.; Müller, M. *Angew. Chem. Int. Ed*. **2010**, *49*, 2389. (b) Müller, M.; Gocke, D.; Pohl, M. *FEBS J.*, **2009**, *276*, 2894. (c) Gocke, D.; Nguyen, C. L.; Pohl, M.; Stillger, T.; Walter, L.; Müller, M. . *Adv. Synth. Catal*. **2007**, *349*, 1425. (d) Demir, A. S.; Şeşengolu, Ö.; Dünkelmann, P.; Müller, M. *Org. Lett*. **2003**, *5*, 2047. (e) Dünkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Linden, B.; Baumann, M.; Pohl, M.; Müller, M. *J. Am. Chem. Soc*. **2002**, *124*, 12084. (f) Demir, A. S.; Şeşengolu, Ö.; Eren, E.; Hosrik, B.; Pohl, M.; Janzen, E.; Kolter, D.; Feldmann, R.; Dünkelmann, P.; Müller, M. *Adv. Synth. Catal*. **2002**, *344*, 96. (g) Pohl, M.; Lingen, B.; Müller, M. *Chem. Eur. J*. **2002**, *8*, 5288. (h) Demir, A. S.; Pohl, M.; Janzen, E.; Müller, M. *J. Chem. Soc. Perkin Trans. 1,* **2001**, 633.

(18) O'Toole, S. E.; Rose, C. A.; Gundala, S.; Zeitler, K.; Connon, S. J. *J. Org. Chem*. **2011**, 76, 347.

(19) We have previously reported that thiazolium ions can mediate the oxidation of aldehydes in the presence of a stoichiometric oxidant. Triazolium ions were poor catalysts for this process. In recalcitrant reactions involving **18** and protic solvent it is possible that the presence of

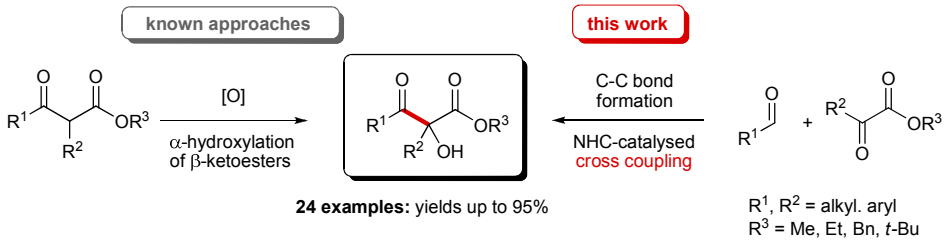
adventitious oxygen may be responsible for low product yields: Noonan, C.; Baragwanath, L.; Connon, S. J. *Tetrahedron Lett*. **2008**, *49*, 4003.

(20) Vora, H. U.; Lathrop, S. P.; Reynolds, N. T.; Kerr, M. T.; Read de Alaniz, J; Rovis, T. *Org. Synth.* **2010**, *87*, 350.

(21) In order to reproduce the conditions accordingly on a smaller scale we found a tube shaped flask better suited to handle smaller amounts of solvent (cf. high concentration of the reactions performed by Stetter (ca. 3 M)).

(22) (a) Stetter, H.; Rämsch, R. Y.; Kuhlmann, H. *Synthesis* **1976**, 733. (b) Cumper, C. W. N.; Thurston, A. P. *J. Chem. Soc. Perkin Trans 2*, **1972**, 106.

1.5 Hydroacylation Avoided: NHC-Catalyzed, Completely Chemoselective Crossed Acyloin Reactions[i]



It has been shown for the first time that relatively electron deficient triazolium pre-catalysts promote (at low loadings in the presence of base) highly chemoselective crossed acyloin condensation reactions between aldehydes and α-ketoesters to afford densely products incorporating a quaternary stereocentre of considerable synthetic potential. Hydroacylation pathways which have hitherto been dominant in these reactions can be completely avoided. The scope of the process is extraordinarily broad with respect to both coupling partners, and a preliminary study has established the principle that a high degree of stereochemical control over the reaction can also be exercised *via* the use of a chiral NHC precursor. It has also been shown for the first time that coupling of benzyl α-ketoesters with aldehydes followed by acylation and simple hydrogenolysis furnishes a product formally derived from the chemoselective 1:1 coupling of two different aliphatic aldehydes in high yield with absolute control over which coupling partner behaves as the acyl-anion equivalent.[ii]

---

[i] C. A. Rose, S. Gundala, S. J. Connon, K. Zeitler, *manuscript submitted for publication*.

[ii] S. G. performed the cross-coupling experiments between ethylpyruvate and propanal (Table 2, entry 2), ethylpyruvate and butanal (Table 2, entry 3) as well as ethylpyruvate and crotonaldehyde (Table 2, entry 9). S. G. carried out experimentations resulting in entries 5 and 6 (Table 4), the asymmetric crossed acyloin condensation (Scheme 2) and the acylation-de-carboxylation sequence (Scheme 3). All other experiments & studies were performed by C. A. R.

1.5.1 Introduction

α-Hydroxy-β-ketoacid derivatives incorporating a quaternary stereogenic centre in the α–position (*i.e.* **1**, Figure 1) are structural features in a range of natural products.[1] In addition, they are densely functionalised, highly synthetically-pliable molecules which can serve as useful precursors to the α-hydroxy acid/α-hydroxy ketone motifs remarkably common in naturally occurring biomolecules,[2] tetracycline/glycylcycline antibiotics,[3] artificial β-amino acids/alcohols and α,β-dihydroxylated acids (in addition to a plethora of other useful building blocks). The undoubted synthetic utility of these materials is curtailed by the synthetic routes to these compounds – which are based in the main on often functional-group sensitive α-oxidation methods (*e.g.* **2**→**1**, Figure 1).[4,5]

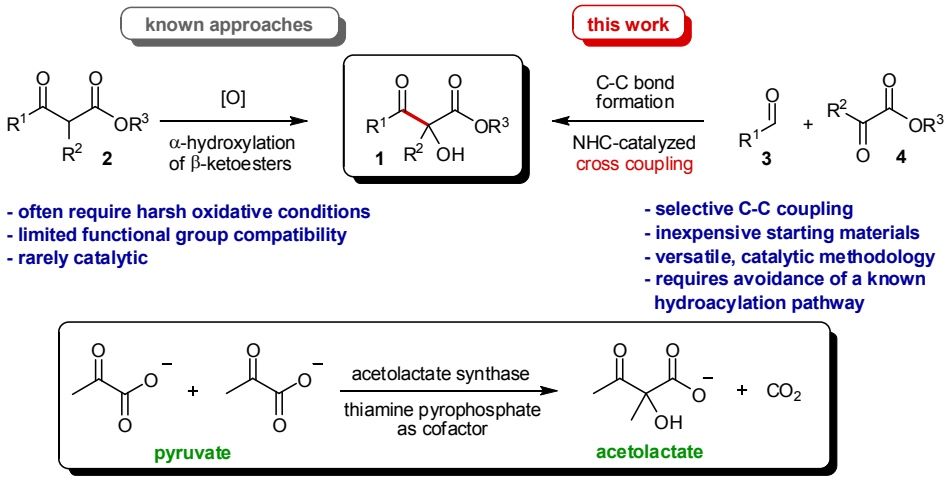


Figure 1: α-Hydroxy-β-ketoacid derivatives: known approaches and a proposed direct catalytic C-C bond forming route.

Inspired by the mode of action of the thiamine pyrophosphate-dependent enzyme acetolactate synthase, which catalyses the coupling of two molecules of pyruvate to generate acetolactate (a precursor to valine, leucine and isoleucine, Figure 1),[6,7] we envisaged the possibility of developing an analogous route to **1** from the direct *N*-Heterocyclic Carbene (NHC)-catalysed coupling of an aldehyde **3** and an α-ketoester **4** in a chemoselective crossed acyloin condensation (AC) reaction (Figure 1, *right*).

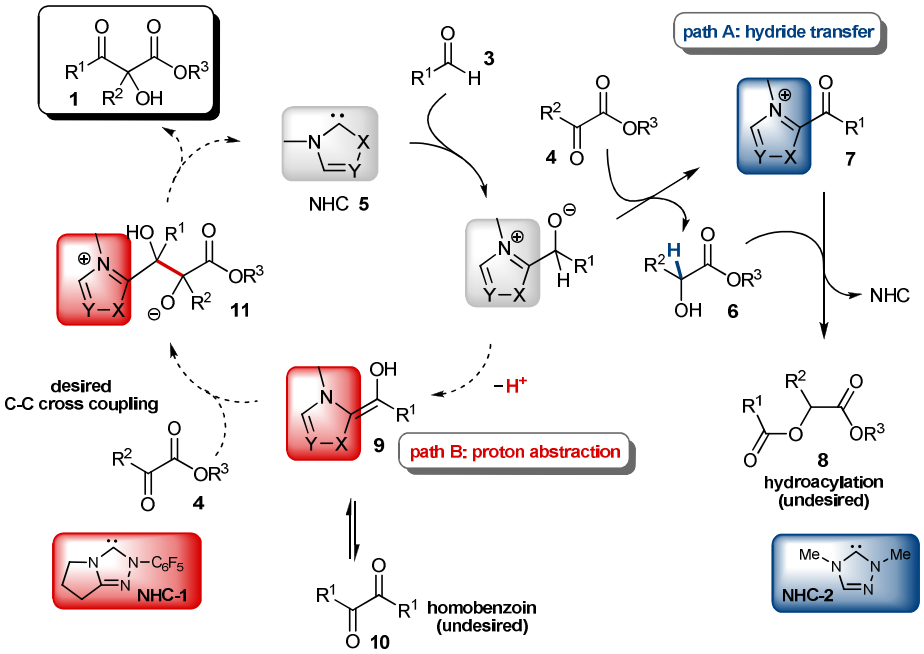
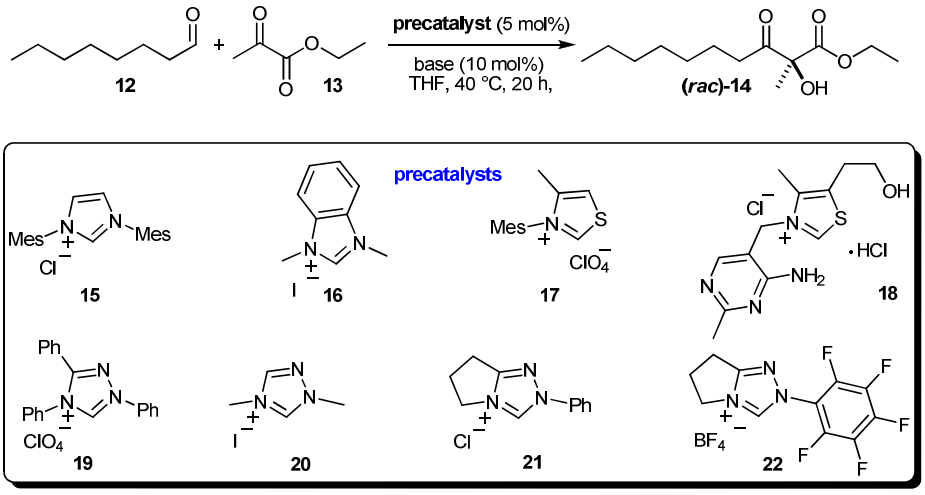


Figure 2: Three possible pathways involving the reaction of **3** and **4** in the presence of either electron-rich or electron deficient carbenes.

While such a coupling process would obviously represent a considerable advance over literature methods (which often require the use of excess of one coupling partner) in terms of greater synthetic flexibility, two major barriers (outlined in Figure 2) to its development were identified. Firstly, in previous studies involving the NHC-catalysed reaction of aldehydes and α-ketoesters,[8,9] upon reaction of carbene **5** with the aldehyde **3**, *hydride transfer* to from the hydroacylation product **8** *via* the coupling of the initially formed alcohol **6** and acyl-triazolium ion **7** was observed. We noted that these hydroacylation reactions[8–10] were promoted by relatively electron-rich NHCs (e .g. **NHC–2**). This led to the proposal that the use of a carbene incorporating a powerful inductive electron withdrawing substituent (*i.e.* **NHC–1**) would destabilise developing positive charge in the transition state leading to acyl-triazolium ion and hence disfavour the hydride transfer pathway in favour of a proton-transfer step leading to the nucleophilic Breslow intermediate **9**. Next, for chemoselective cross coupling to occur **9** must eschew reaction with **3** (leading to homobenzoin **10**[11]) and add preferentially to ketoester **4** to afford the cross-coupled product **1** *via* adduct **11**. Examples of intermolecular chemoselective crossed-acyloin reactions involving two aldehydes are very rare,[12] and to the best of our knowledge the only ketone substrates that have been shown to participate in these processes[13] are highly activated heterocyclic trifluoromethylketones.[14] We have previously studied the performance of **NHC–1**[15,16] in (crossed)[12e,f] acyloin conden-sations involving two different aldehydes and were confident – given a combination of the relatively mild reactivity of **NHC–1** and superior electrophilicity of **4** over **3** in previously reported hydroacylation studies – that if **9** could be formed selectively the crossed acyloin pathway would be dominant.[17]

1.5.2 Results and Discussion

Our study began with the reaction between octanal (**12**) and one equivalent of the inexpensive ethyl pyruvate (**13**) in the presence of a range of azolium ions and bases (Table 1). Imidazolium-, thiazolium and triazolium ions devoid of σ-withdrawing substituents (*i.e.* **15**-**20**), failed to mediate the formation of **14** above trace levels in the presence of K_2CO_3 (entries 1-2, 3-4 and 5-6 respectively).



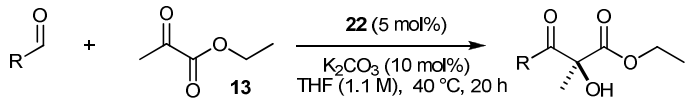
Entry	Precatalyst	Base	Yield (%)[a]
1	**15**	K_2CO_3	<5
2	**16**	K_2CO_3	<5
3	**17**	K_2CO_3	<5
4	**18**	K_2CO_3	<5
5	**19**	K_2CO_3	<5
6	**20**	K_2CO_3	<5
7	**21**	K_2CO_3	9
8	**22**	K_2CO_3	>95 (92)[b]
9	**22**	KO*t*-Bu	34
10	**22**	NaH	<5
11	**22**	K_3PO_4	>95
12	**22**	DBU	28
13	**22**	*i*-PrNEt$_2$	>95

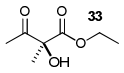
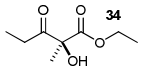
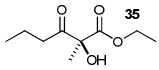
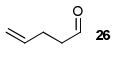
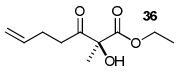
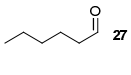
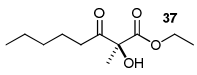
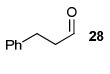
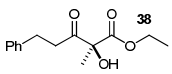
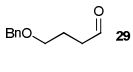
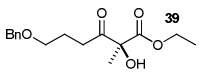
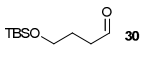
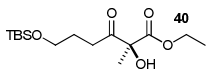
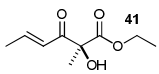
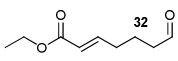
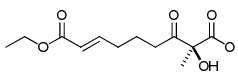
[a] Yield determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [b] Isolated yield in parenthesis.

Table 1: Crossed AC reactions: preliminary experiments.

Use of the simple *N*-phenyl triazolium ion did result in a modest amount of cross-coupling (entry 7), however, we were pleased to observe the clear superiority of the *N*-pentafluorophenyl substituted precatalyst **22**, which furnished the coupled product in excellent yield (entry 8). Exchange of the carbonate base for either sodium hydride or potassium *tert*-butoxide resulted in inefficient catalysis (entries 9-10), while potassium phosphate was found to be a suitable substitute (entry 11). Two tertiary amine bases were also evaluated: DBU failed to facilitate clean cross-coupling while excellent product yields were obtained using Hünig's base (entries 12-13).

With chemoselective cross coupling established and convenient conditions identified, we next turned to a systematic examination of the reaction scope. Beginning with aliphatic aldehydes (Table 2), we were pleased to find that substrates incorporating hydrocarbon chains **23**-**28** were converted to the corresponding α-hydroxy-β-ketoesters **33**-**38** in uniformly excellent isolated yields (entries 2-6). Protected hydroxy functionality is well tolerated (*i.e*. **39** and **40**, entries 7-8) as are peripheral double bonds (*i.e.* **37**, entry 4), however isolation of **41** is more problematic due to a competitive Stetter reaction pathway, nonetheless the highly functionalised α,β-unsaturated product can be isolated in appreciable yield (entry 9). It is noteworthy that not only are homobenzoin and hydroacylation pathways excluded here, a lactone-generating reaction *via* a homoenolate pathway reported by You[18] in the presence of more electron-rich carbenes was also avoided. Of particular interest is the observation that **32** (which incorporates a less activated Michael acceptor yet which is – from a stereoelectronic perspective – well-disposed towards a 5-*exo*-trig Stetter cyclisation reaction) undergoes exclusive 1:1 intermolecular coupling with **13** (entry 10) in excellent yield.

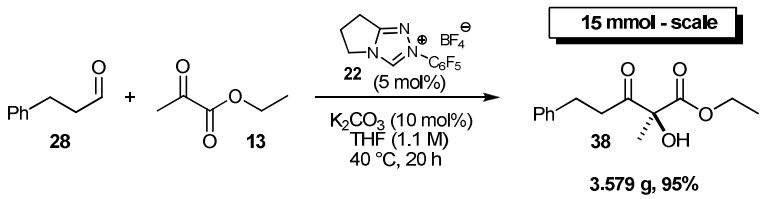


Entry	Aldehyde	Product	Yield (%)[a]
1			92[b]
2			93
3			94
4			87
5			91
6			95
7			88
8			76
9			48
10			90

[a] Isolated yield [b] Yield determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard.

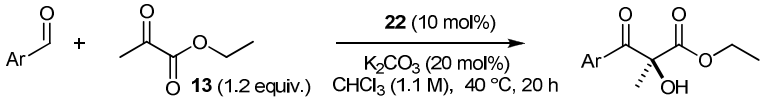
Table 2: Coupling of aliphatic aldehydes to ethyl pyruvate.

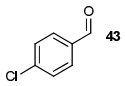
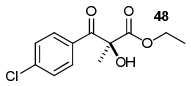
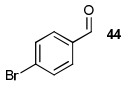
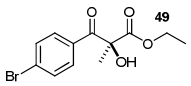
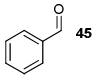
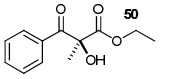
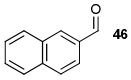
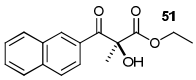
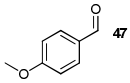
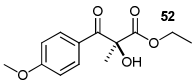
To evaluate the utility of these reactions on a more synthetically relevant scale, 15 mmol of pyruvate ester **13** was coupled to a stoichiometric amount of **28**, resulting in the formation of multigram quantities of **38** in excellent yield (Scheme 1).



Scheme 1: A crossed AC reaction on preparative scale.

Initially, the efficiency of the corresponding coupling reactions involving aromatic aldehydes (Table 3) was disappointing – for example the crossed AC reaction between *p*-chlorobenzaldehyde (**43**) and **13** proceeded in 56% yield (entry 1). After considerable experimentation it was found that the use of chloroform as the reaction solvent allowed the circumvention of this difficulty.[19] Thus, **43** could be converted to **48** in 83% yield in the presence of **22** (10 mol%) in this solvent (entry 2). In a similar fashion, activated- (*i.e.* **44**, entry 3), electron-neutral (*i.e.* **45-46**, entries 4-5) and deactivated (*i.e.* **47**, entry 6) aromatic aldehydes could be coupled with **13** to afford **49-52** respectively in good isolated yields.

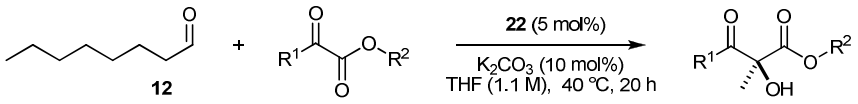


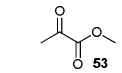
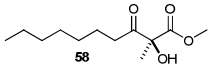
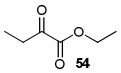
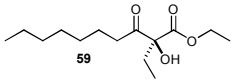
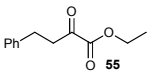
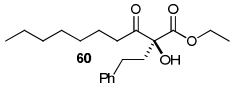
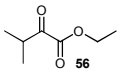
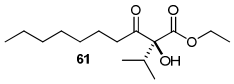
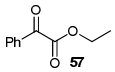
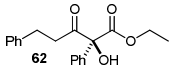
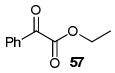
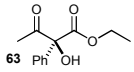
Entry	Aldehyde	Product	Yield (%)[a]
1[b]			56
2			83
3			76
4			86
5			84
6[c]			93

[a] Isolated yield. [b] Reaction conditions: **22** (10 mol%), K_2CO_3 (20 mol%), 1 equiv. of **13**, THF (1.1 M), 40 °C, 16 h. [c] reaction time: 48 h.

Table 3: Coupling of aromatic aldehydes to ethyl pyruvate.

The methodology is not limited to the use of **13** and is also applicable to other α-ketoester coupling partners (Table 4). For instance, methyl pyruvate (**53**) could be coupled to **12** with excellent efficiency (entry 1), while high yields were also obtained from α-ketoesters with elongated chains (entries 2-3). The hindered ketone **56** reacted sluggishly under standard conditions resulting in a lower isolated yield of 40% (entry 4). Aromatic ketoesters also proved difficult substrates, however these reactions responded well to a change of solvent from THF to chloroform,[19] which allowed the formation of **62** and **63** in yields ≥80% (entries 5-6).

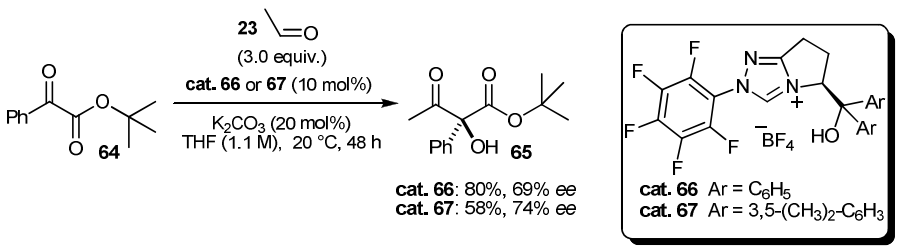


Entry	α-Ketoester	Product	Yield (%)[a]
1			90
2			90
3[b]			70
4			40
5[c]			80
6[d]			82

[a] Isolated yield. [b] Using **22** (8 mol%) and K_2CO_3 (15 mol%). [c] Using **28** as the aldehyde partner. Reaction conditions: **22** (10 mol%), K_2CO_3 (20 mol%), $CHCl_3$ (1.1 M), 40 °C, 20 h, rt. [d] Using **23** as the aldehyde partner. Reaction conditions: **22** (10 mol%), K_2CO_3 (20 mol%), $CHCl_3$ (1.1 M), 40 °C, 20 h, rt.

Table 4: Coupling of octanal to various α–ketoesters.

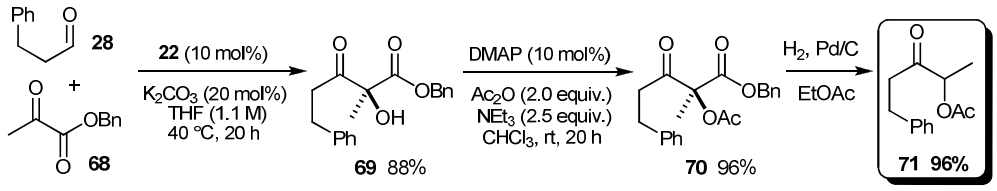
With the scope of the process systematically explored, we were ready to examine the possibility of carrying out asymmetric variants of these reactions. We were gratified to find that augmentation of the steric requirement of the α-ketoester derivative resulted in improved levels of product enantiomeric excess relative to that obtained using ethyl pyruvate. For instance, protection of the acid functionality as the easily removed *tert*-butyl ester (*i.e.* **64**, Scheme 2) allowed coupling with acetaldehyde[20] to occur in 58-80% yield and 69-74% *ee* using the chiral precatalysts **66** and **67**.



Scheme 2: Asymmetric crossed AC using chiral precatalysts.

While the level of asymmetric induction is not yet optimal, it is of interest that a high degree of stereochemical control is exercisable over the process using current benchmark catalyst technology. We are currently designing new catalysts to perfect this quaternary stereocentre-generating reaction from an enantioselectivity standpoint.

Finally, while the potential utility of such densely functionalised adducts as synthetic building blocks is reasonably obvious, we were also interested in investigating the use of the pyruvate unit as a 'masked aldehyde' in crossed acyloin reactions between two aliphatic aldehydes. While there has been a recent surge in interest in the investigation of the factors which influence the outcome of crossed acyloin reactions,[12-14] in all cases where useful selectivity was observed the system consisted of the reaction between one aliphatic aldehyde and one aromatic aldehyde – where the inherent differences in electrophilicity and steric bulk of the two substrates can be exploited to bring about a measure of selective (although rarely completely chemoselective) coupling. However, *no examples of chemoselective crossed acyloin reactions between two aliphatic aldehydes catalysed by an artificial catalyst are known*. Given that the AC reactions detailed above (Tables 1-4) are 100% chemoselective, we reasoned that coupling of an α-ketobenzyl ester with an aliphatic aldehyde would, on hydrogenolysis of the benzyl group, result in *in situ* decarboxylation to give a product formally derived from the chemoselective coupling of two aliphatic aldehydes. This hypothesis was validated as follows: aldehyde **28** was coupled with benzyl pyruvate (**68**) in the presence of **22** (5 mol%) in excellent yield (Scheme 3). After acylation of the tertiary alcohol, hydrogenolysis of **70** in the presence of Pd/C led to the clean formation of **71 -** which is formally derived from the completely chemoselective crossed AC reaction between **28** and one equivalent of acetaldehyde (**23**).[21] Thus by utilising an α-ketoester partner with the requisite α-substituent followed by a simple acylation/hydrogenolysis protocol it is now conceivable to generate the acylated product derived from the AC reaction between any two aliphatic aldehydes (within the substrate scope outlined in Tables 2-4) with complete control over which aldehyde formally acts as the acyl-anion synthon.[22]



Scheme 3: An α-ketoester as a masked aldehyde in an AC reaction.

1.5.3 Conclusion

To conclude, we have developed the first entirely chemoselective, intermolecular crossed AC reactions between aldehydes and inexpensive α-ketoesters catalysed by an NHC catalyst. Through the selection of a more electron-deficient carbene promoter the hitherto dominant hydroacylation pathways can be completely avoided. In contrast with the majority of previous attempts to effect such transformations in the literature, in this reaction the two partners can react in a 1:1 ratio to furnish densely functionalised products of high potential synthetic utility containing a quaternary stereocentre in good to excellent yields. The scope of the process is extraordinarily broad: both aliphatic and aromatic aldehydes are well tolerated, while also both aromatic and aliphatic substituents at the α-carbon (in addition to various ester functionalities) are accommodated in the α–ketoester electrophile. A preliminary study has established that a high degree of stereochemical control over the reaction can also be exercised *via* the use of a chiral NHC precursor. In addition, a benzyl α-ketoester can be utilised as a masked aldehyde equivalent – thus practitioners can synthesise (*via* a chemoselective AC reaction) acylated AC products formally derived from the 1:1 coupling of two aldehydes (even if they have very similar steric/electronic characteristics) with absolute control over which partner will behave as the acyl-anion equivalent and which will serve as the electrophile. Investigations to further develop the utility/enantioselectivity of these reactions are underway.

1.5.4 Experimental Section

General Methods

Unless otherwise noted, all commercially available compounds were used as provided without further purification. NMR spectra were recorded on 300 MHz (300.13 MHz), 400 MHz (400.13 MHz) or 600 MHz (600.13 MHz) spectrometers using the solvent peak as internal reference ($CDCl_3$: δ H 7.26; δ C 77.0 and DMSO-d_6: δ H 2.51; δ C 39.5). Multiplicities are indicated, s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet)); coupling constants (*J*) are in Hertz (Hz). Mass spectra (MS ESI) were recorded using a Finnigan MAT 95 or Varian MAT 311A. All reactions were monitored by thin-layer chromatography using using Merck silica gel plates 60 F_{254}; visualization was accomplished with UV light and/or staining with appropriate stains ($KMnO_4$, anisaldehyde, vaniline, ninhydrin or phosphomolybdic acid). Standard flash chromatography procedures were followed (particle size 40−63 μm). Infrared spectra were obtained using neat samples on spectrometers equipped with a universal ATR (attenuated total reflectance) sampling accessory. Optical rotation measurements are quoted in units of 10^{-1} deg cm^2 g^{-1}. Analytical CSP-HPLC was performed using a Daicel CHIRALCEL OJ-H (4.6 mm x 25 cm) column. Tetrahydrofuran was distilled from sodium/benzophenone. All reactions were carried out under a protective atmosphere of dry nitrogen or argon using oven-dried glassware unless otherwise stated. Liquid aldehydes and α-ketoesters were distilled over EDTA prior to use. Solid aldehydes were washed acid-free with 10% aq. K_2CO_3-solution prior to use. For the cross coupling experiments, K_2CO_3 was finely ground prior to use. Triazolium pre-catalyst **22** was synthesized according to the procedure described by Rovis et al.[iii] and catalysts **67** and **68** were prepared as described earlier.[iv] Aldehydes **23-28, 31** and **43-47** are commercially available. Aldehyde **29**,[v] **30**[vi] and **32**[vii] were prepared according to known protocols. Ketoesters **13, 53, 55** and **57** are commercially available. Ketoester **54**[viii] **56**[ix] and **64**[x] **a**nd **68**[xi] were prepared according to known literature procedures.

[iii] a) M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Org. Chem.* **2005**, *70*, 5725; b) H. U. Vora, S. P. Lathrop, N. T. Reynolds, M. S. Kerr, J. Read de Alaniz, T. Rovis, *Org. Synth.* **2010**, *87*, 350.

[iv] a) L. Baragwanath, C. A. Rose, K. Zeitler, S. J. Connon, S. J., *J. Org. Chem.* **2009**, *74*, 9214; b) S. E. O'Toole, C. A. Rose, S. Gundala, K. Zeitler, S. J. Connon, *J. Org. Chem.* **2011**, *76*, 347

[v] C. Gennari, P. G. Cozzi, *J. Org. Chem.* **1988**, *53*, 4015-4021.

[vi] Y. Ikeda, J. Ukai, N. Ikeda, H. Yamamoto, *Tetrahedron* **1987**, *43*, 731-741.

[vii] R. M. de Figueiredo, R. Froelich, M. Christmann, *Angew. Chem. Int. Ed.* **2008**, *47*, 1450-1453.

[viii]. K. Nakamura, K. Inoue, K. Ushio, S. Oka, A. Ohno, *J. Org. Chem.* **1988**, *53*, 2589-2593.

[ix] M. Rambaud, M. Bakasse, G. Duguay, J. Villieras, *Synthesis* **1988**, 564-566.

[x] J. M. Domagala, *Tetrahedron Lett.* **1980**, *21*, 4997-5000.

[xi] S. Hu, D C. Neckers, *J. Org. Chem.* **1996**, *61*, 6407–6415.

General Procedures

General Procedure 1 (for the Cross coupling of Aliphatic Aldehydes and Ethyl Pyruvate)

A flame dried screw-capped Schlenk tube equipped with a magnetic stirring bar was charged with K_2CO_3 (7mg, 0.05 mmol, 10 mol%) and evacuated. The solid was then heated to 650 °C for 30 seconds and subsequently cooled to ambient temperature under N_2. After this procedure has been repeated once triazolium precatalyst (9 mg, 0.025 mmol, 5 mol%) was added.[xii] The solids were additionally dried for 1h under high vacuum at ambient temperature. Dry THF (0.45 mL) was added and the resulting mixture was stirred for 10 min at ambient temperature. To the orange suspension was added ethyl pyruvate (55 μL, 0.5 mmol, 1 equiv.) followed by the aliphatic aldehyde (0.5 mmol, 1 equiv.). The Schlenk tube was sealed with a cap and the reaction mixture was stirred for 20h at 40 °C under N_2.[xiii] After 20h the solvent was evaporated. The resulting mixture was subjected to column chromatography yielding the corresponding α-hydroxy-β-ketoester.

General Procedure 2 (for the Cross coupling of Aromatic Aldehydes and Ethyl Pyruvate)

A flame dried screw-capped Schlenk tube equipped with a magnetic stirring bar was charged with K_2CO_3 (14 mg, 0.1 mmol, 20 mol%) and evacuated. The solid was then heated to 650 °C for 30 seconds and subsequently cooled to ambient temperature under N_2. After this procedure has been repeated once triazolium precatalyst (18 mg, 0.05 mmol, 10 mol%) was added. The solids were dried for an additional 1h under high vacuum at ambient temperature. Dry $CHCl_3$ (0.45 mL) was added and the resulting mixture was stirred for 10 min at ambient temperature. To the orange suspension was added ethyl pyruvate (66 μL, 0.6 mmol, 1.2 equiv.) followed by the aromatic aldehyde (0.5 mmol, 1 equiv.). The Schlenk tube was sealed with a cap and the reaction mixture was stirred at 40 °C under N_2. After 20h the solvent was evaporated. The resulting mixture was subjected to column chromatography yielding the corresponding α-hydroxy-β-ketoester.

[xii] For quantitative NMR experiments *trans*-stilbene (23 mg, 0.125 mmol, 25 mol%) is additionally added at this stage.

[xiii] For quantification of products, residual starting material etc. *via* NMR spectroscopy, an aliquot of the reaction mixture was transferred into a NMR tube by dipping in a pasteur pipet (without cap) several times.

General Procedure 3 (for the Cross Coupling of Octanal and Various α-Ketoesters)

A flame dried screw-capped Schlenk tube equipped with a magnetic stirring bar was charged with K_2CO_3 (7 mg, 0.05 mmol, 10 mol%) and evacuated. The solid was then heated to 650 °C for 30 seconds and subsequently cooled to ambient temperature under N_2. After this procedure has been repeated once triazolium precatalyst (9 mg, 0.025 mmol, 5 mol%) was added. The solids were dried for a further 1h under high vacuum at ambient temperature. Dry THF (0.45 mL) was added and the resulting mixture was stirred for 10 min at ambient temperature. To the orange suspension was added α-ketoester (0.5 mmol, 1 equiv.) followed by octanal (77 µL, 0.5 mmol, 1 equiv.). The Schlenk tube was sealed with a cap and the reaction mixture was stirred at 40 °C under N_2. After 20h the solvent was evaporated. The resulting mixture was subjected to column chromatography yielding the corresponding α-hydroxy-β-ketoester.

General Procedure 4 (for Large Scale Cross Coupling)

A flame dried 50 mL Schlenk flask equipped with a magnetic stirring bar and a reflux condenser was charged with K_2CO_3 (206 mg, 1.5 mmol, 10 mol%) and evacuated The solid was then heated to 650 °C for 30 seconds and subsequently cooled to ambient temperature under N_2. After this procedure has been repeated once triazolium precatalyst (271 mg, 0.75 mmol, 5 mol%) was added. The solids were additionally dried for 1h under high vacuum at ambient temperature. Dry THF (14 mL) was added and the resulting mixture was stirred for 10 min at ambient temperature. To the orange suspension was added ethyl pyruvate (1.65 mL, 15 mmol, 1 equiv.) followed by the aldehyde (e. g. hydrocinnamaldehyde (1.96 mL, 15 mmol, 1 equiv.)). The reaction mixture was stirred for 20h at 40 °C under N_2. After 20h the reaction mixture was diluted with 50 mL dichloromethane and extracted with 20 mL H_2O. The aqueous layer was back-extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The resulting brown oil was subjected to column chromatography (silica gel).

General Procedure 5 (for Acetylation)

An oven-dried 10 mL round bottomed flask, equipped with a magnetic stirrer, was charged with the selected α-hydroxy-β-ketoester (1.0 mmol), DMAP (12.5 mg, 0.10 mmol, 10 mol%) and the reaction put under an atmosphere of Argon. CH_2Cl_2 (2.00 mL) was injected *via* syringe to give a solution followed by the addition of NEt_3 (2.5 mmol, 2.5 equiv.) and Ac_2O (2.0 mmol, 2.0 equiv.). The reaction

was stirred for 16 h; the resulting mixture was worked-up by the initial careful addition of water, followed by Na_2CO_3 until CO_2 evolution ceased and the aqueous layer remained basic. The product was extracted with CH_2Cl_2 dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The remaining residue was purified by column chromatography.

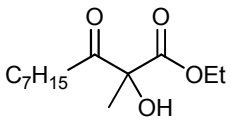
General Procedure 6 (for the Debenzyloxycarbonlyation of Cross Coupled α-Hydroxy-β-Ketoester)

To a 25 mL round bottomed flask, equipped with a magnetic stirring bar, was added the acetylated α-hydroxy-β-ketoester (0.5 mmol), 10% Pd/C (20 wt%) and EtOAc (0.05 m solution) together with 4Å molecular sieves. The flask was evacuated and then purged with N_2. This cycle was performed twice and finally the flask was evacuated and backfilled with hydrogen. The reaction was then stirred vigorously at ambient temperature under an atmosphere of hydrogen (hydrogen generator), overnight. After reaching full conversion the reaction mixture was filtered through celite® and concentrated *in vacuo*. The crude product was purified by column chromatography.

Experimental Data for Cross Coupled Products

Experimental Data for α-Hydroxy-ß-Ketoesters from Cross-Coupling of Aliphatic Aldehydes with Ethyl Pyruvate

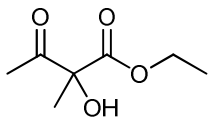
Ethyl-2-hydroxy-2-methyl-3-oxodecanoate (14)



$C_{13}H_{24}O_4$
244.33 g/mol

according to the **general procedure 1**: yield after column chromatography (silica gel, 20% Et_2O/*n*-pentane): 112 mg (92 %), colourless oil. R_f (petroleum ether/ethylacetate 5/1) 0.32. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.28 – 4.18 (m, 3H), 2.70 – 2.44 (m, 2H), 1.65 – 1.52 (m, 5H), 1.31 – 1.20 (m, 11H), 0.90 – 0.82 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 207.2, 171.5, 80.9, 62.5, 36.4, 31.6, 29.0 (2C), 23.5, 22.6, 21.8, 14.1, 14.0. HRMS (EI; $C_{13}H_{24}O_4$): calcd.: 244.1675, found: 244.1674. IR **:** $\tilde{\nu}$ = 3493, 2929, 2859, 1721, 1465, 1373, 1257, 1014, 632, 540 cm^{-1}.

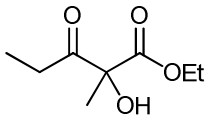
Ethyl 2-hydroxy-2-methyl-3-oxobutanoate (33, Table 2, entry 1)



$C_7H_{12}O_4$
160.17 g/mol

according to the **general procedure 1**: (using 2 equiv. of the aliphatic aldehyde instead of 1 equiv.): yield according to quantitative ^{1}H NMR (internal standard: *trans*-Stilbene): 92% ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.27 – 4.19 (m, 2H), 4.18 (br s, 1H), 2.25 (s, 3H), 1.57 (s, 3H), 1.27 (t, J = 7.14 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 204.9, 171.3, 81.0, 62.6, 24.2, 21.8, 14.0.[xiv]

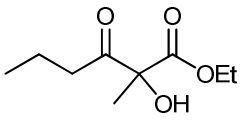
Ethyl 2-hydroxy-2-methyl-3-oxopentanoate (34, Table 2, entry 2)



$C_8H_{14}O_4$
174.19 g/mol

according to the **general procedure 1**: yield after column chromatography (silica gel, hexanes/Et_2O 4/1): 162 mg (93 %),[xv] colourless oil. R_f (hexanes/Et_2O 4/1) 0.28. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.26-4.20 (m, 3H), 2.72-2.65 (m, 1H), 2.58-2.54 (m, 1H), 1.58 (s, 3H), 1.28 (t, J = 7.5 Hz, 3H) 1.08 (t J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.6, 171.3, 80.6, 62.3, 29.6, 21.7, 13.8, 7.5. HRMS (ESI; $C_8H_{14}O_4$ + Na): calcd.: 197.0790, found: 197.0792. IR **:** $\tilde{\nu}$ = 3477, 2984, 2941, 1717, 1449, 1373, 1258, 1016, 807, 676 cm^{-1}.

Ethyl 2-hydroxy-2-methyl-3-oxohexanoate (35, table 2, entry 3)



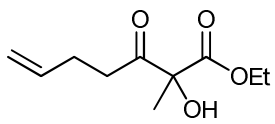
$C_9H_{16}O_4$
188.22 g/mol

according to the **general procedure 1**: yield after column chromatography (silica gel, hexanes/Et_2O 4/1): 177 mg (94 %),[xv] colourless oil. R_f (hexanes/Et_2O 4/1) 0.28. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.25-4.20 (m, 3H), 2.65-2.42 (m, 2H), 1.66-1.58 (m, 2H), 1.56 (s, 3H), 1.27 (t, J = 7.4 Hz, 3H) 0.89 (t, J = 7.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.8, 171.3, 80.7, 62.3, 38.0, 21.5, 16.8, 13.8, 13.3. HRMS (ESI; $C_9H_{16}O_4$ + Na): calcd. 211.0946, found: 211.0950. IR **:** $\tilde{\nu}$ = 3481, 2970, 2878, 1716, 1449, 1371, 1253, 1017, 825, 672 cm^{-1}.

[xiv] Experimental data in accordance to previously reported literature values: X. Baucherel, E. Levoirier, J. Uziel, S. Juge, *Tetrahedron Lett.* **2000**, *41*; 1385.

[xv] The reaction was performed using the double amount of the described size of the general procedure.

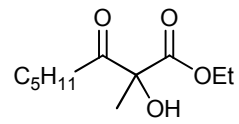
Ethyl 2-hydroxy-2-methyl-3-oxohept-6-enoate (36, Table 2, entry 4)



$C_{10}H_{16}O_4$
200.23 g/mol

according to the **general procedure 1**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 10/1): 87 mg (87 %), colourless oil. R_f (petroleum ether/ethylacetate 5/1) 0.27. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.84 – 5.68 (m, 1H), 5.08 – 4.93 (m, 2H), 4.23 (q, *J* = 7.14 Hz, 2H), 4.16 (s, 1H), 2.84 – 2.54 (m, 2H), 2.39–2.29 (m, 2H), 1.57 (s, 3H), 1.27 (t, *J*= 7.14 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 206.3, 171.5, 136.5, 115.6, 80.9, 62.6, 35.7, 27.4, 21.8, 14.0. HRMS (EI; $C_{10}H_{16}O_4$) calcd.: 200.1049, found: 200.1041. IR **:** $\tilde{\nu}$ = 3481, 2984, 1721, 1642, 1447, 1260, 1014, 916, 632, 538 cm^{-1}.

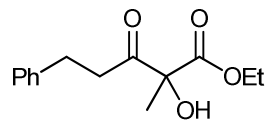
Ethyl 2-hydroxy-2-methyl-3-oxooctanoate (37, Table 2, entry 5)



$C_{11}H_{20}O_4$
216.27 g/mol

according to the **general procedure 1**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 10/1): 98 mg (91 %), colourless oil. R_f (petroleum ether/ethylacetate 5/1) 0.30. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.27 – 4.18 (m, 3H), 2.70 – 2.44 (m, 2H), 1.63 – 1.53 (m, 5H), 1.35 – 1.19 (m, 7H), 0.87 (t, *J* = 7.00 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 207.2, 171.5, 80.9, 62.5, 36.3, 31.2, 23.2, 22.4, 21.8, 14.0, 13.9. HRMS (EI; $C_{11}H_{20}O_4$): calcd.: 216.1362, found: 216.1362. IR **:** $\tilde{\nu}$ = 3480, 2960, 2873, 1720, 1449, 1374, 1260, 1019, 802, 632, 538 cm^{-1}.

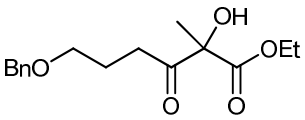
Ethyl 2-hydroxy-2-methyl-3-oxo-5-phenylpentanoate (38, Table 2, entry 6)



$C_{14}H_{18}O_4$
250.29 g/mol

according to the **general procedure 1**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 10/1): 119 mg (95 %), almost colourless oil. R_f (petroleum ether/ethylacetate 5/1) 0.22. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 – 7.13 (m, 5H), 4.20 – 4.09 (m, 3H), 3.08–2.78 (m, 4H), 1.54 (s, 3H), 1.22 (t, *J* = 7.14 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 206.2, 171.4, 140.5, 128.6, 128.4, 126.3, 81.0, 62.7, 38.3, 29.5, 21.7, 14.0. HRMS (EI; $C_{14}H_{18}O_4$): calcd.: 250.1205, found: 250.1208. IR **:** $\tilde{\nu}$ = 3480, 2986, 1720, 1454, 1259, 1160, 701, 632, 538 cm^{-1}.

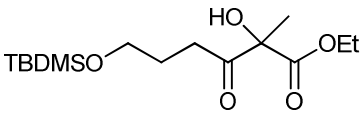
Ethyl 6-(benzyloxy)-2-hydroxy-2-methyl-3-oxohexanoate (39, Table 2, entry 7)



$C_{16}H_{22}O_5$
294.34 g/mol

according to the **general procedure 1**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 7/1): 129 mg (88 %), colourless oil. R_f (petroleum ether/ethylacetate 5/1) 0.22. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 – 7.24 (m, 5H), 4.47 (s, 2H), 4.27 – 4.16 (m, 3H), 3.47 (t, *J* = 6.04 Hz, 2H), 2.85 – 2.60 (m, 2H), 1.98 – 1.85 (m, 2H), 1.57 (s, 3H), 1.26 (t, *J* = 7.14 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 207.0, 171.5, 138.3, 128.4, 127.6 (2C), 80.9, 72.9, 68.9, 62.6, 33.2, 23.8, 21.9, 14.0. HRMS (EI; $C_{16}H_{22}O_5$): calcd.: 294.1467, found: 294.1459. IR **:** $\tilde{\nu}$ = 3455, 2870, 1721, 1454, 1367, 1260, 1113, 1026, 741, 632, 537 cm^{-1}.

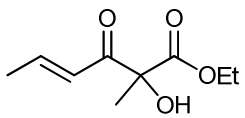
Ethyl 6-(*tert*-butyldimethylsilyloxy)-2-hydroxy-2-methyl-3-oxohexanoate (40, Table 2, entry 8)



$C_{15}H_{30}O_5Si$
318.48 g/mol

according to the **general procedure 1**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 10/1): 121 mg (76 %), colourless oil. R_f (petroleum ether/ethylacetate 5/1) 0.35. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25 – 4.16 (m, 3H), 3.58 (t, *J* = 6.04 Hz, 2H), 2.77 – 2.54 (m, 2H), 1.85 – 1.68 (m, 2H), 1.55 (s, 3H), 1.25 (t, *J* = 7.14 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 207.2, 171.5, 80.9, 62.5, 61.8, 32.8, 26.7, 25.9, 21.9, 18.3, 14.0, -5.4. HRMS (ESI; $C_{15}H_{31}O_5Si$): calcd.: 319.1941, found: 319.1941. IR **:** $\tilde{\nu}$ = 2937, 2858, 1722, 1473, 1259, 1101, 1201, 835, 632, 539 cm^{-1}.

(*E*)-Ethyl 2-hydroxy-2-methyl-3-oxohex-4-enoate (41, Table 2, entry 9)

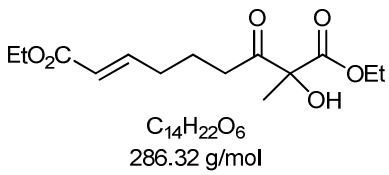


$C_9H_{14}O_4$
186.21 g/mol

according to the **general procedure 1**: yield after column chromatography (Silica gel, hexanes/ Et_2O 4/1): 90 mg (48 %),[xvi] colourless oil. R_f (hexanes/Et_2O 4/1) 0.32. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (m, 1H), 6.53 (m, 1H), 4.37 (s, 1H), 4.25 (q, *J* = 7.0 Hz, 2H), 1.97 (d, *J* = 7.0 Hz, 3H), 1.62 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 171.0, 147.0, 123.4, 79.6, 62.0, 21.6, 18.3, 13.5. HRMS (ESI; $C_9H_{14}O_4$ + Na): calcd.: 209.0799, found: 209.0790. IR **:** $\tilde{\nu}$ = 3471, 2938, 1736, 1444, 1375, 1252, 1014, 844, 669 cm^{-1}.

[xvi] The reaction was performed using the double amount of the described size of the general procedure.

(*E*)-Diethyl- 8-hydroxy-8-methyl-7-oxonon-2-enedioate (42, Table 2, entry 10)

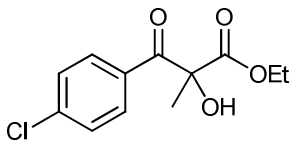


$C_{14}H_{22}O_6$
286.32 g/mol

according to the **general procedure 1**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 10/1): 129 mg (90 %), colourless oil. R_f (petroleum ether/ethylacetate 5/1) 0.16. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 – 6.83 (m, 1H), 5.85 – 5.76 (m, 1H), 4.28 – 4.11 (m, 5H), 2.70 (td, *J* = 18.20 Hz, 7.27 Hz, 1H), 2.53 (td, *J* = 18.20 Hz, 7.07 Hz, 1H), 2.25 – 2.14 (m, 2H), 1.83 – 1.71 (m, 2H), 1.56 (s, 3H), 1.27 (t, *J* = 7.13 Hz, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 206.5, 171.5, 166.5, 147.6, 122.2, 80.8, 62.7, 60.3, 35.5, 31.1, 21.9, 21.8, 14.3, 14.0. HRMS (EI; $C_{14}H_{22}O_6$): calcd: 286.1416, found: 286.1411. IR **:** $\tilde{\nu}$ = 2962, 1722, 1653, 1259, 1090, 1016, 795, 632, 537 cm^{-1}.

Experimental Data for α-Hydroxy-ß-Ketoesters from Cross-Coupling of Aromatic Aldehydes with Ethyl Pyruvate

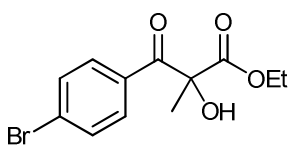
Ethyl 3-(4-chlorophenyl)-2-hydroxy-2-methyl-3-oxopropanoate (48, Table 3, entry 2)



$C_{12}H_{13}ClO_4$
256.68 g/mol

according to the **general procedure 2**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 10/1): 107 mg (83 %), colourless oil. R_f (petroleum ether/ethylacetate 5/1) 0.24. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 – 7.91 (m, 2H), 7.45 – 7.39 (m, 2H), 4.29 (s, 1H), 4.23 (q, *J* = 7.14 Hz, 2H), 1.72 (s, 3H), 1.17 (t, *J* = 7.14 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 194.6, 172.5, 140.2, 131.6, 131.0, 129.0, 79.6, 62.8, 23.5, 13.9. HRMS (EI; $C_{12}H_{13}O_4{}^{35}Cl$): calcd.: 256.0502, found: 256.0507. IR **:** $\tilde{\nu}$ = 3450, 3104, 2995, 1721, 1686, 1587, 1487, 1453, 1403, 1271, 1228, 1158, 1113, 1090, 1013, 991, 940, 844, 776, 739, 715, 683, 566, 530 cm^{-1}.

Ethyl 3-(4-bromophenyl)-2-hydroxy-2-methyl-3-oxopropanoate (49, Table 3, entry 3)

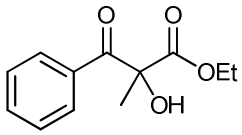


$C_{12}H_{13}BrO_4$
301.13 g/mol

according to the **general procedure 2**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 8/1): 115 mg (76 %), almost colourless oil. R_f (petroleum ether/ethylacetate 5/1) 0.26. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 – 7.83 (m, 2H), 7.61 – 7.55 (m, 2H), 4.31 – 4.28 (m, 1H), 4.27 – 4.18 (br q, *J* = 6.95 Hz, 2H), 1.71 (s, 3H), 1.17 (t, *J* = 7.14 Hz,

3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 194.8, 172.4, 132.1, 132.0, 131.0, 129.0, 79.6, 62.8, 23.5, 13.9. HRMS (EI; $C_{12}H_{13}O_4{}^{79}Br$): calcd.: 299.9997, found: 299.9997. IR **:** $\tilde{\nu}$ = 3452, 3101, 2992, 1721, 1686, 1581, 1475, 1452, 1399, 1268, 1227, 1160, 1113, 1070, 1010, 990, 940, 843, 774, 732, 679, 524 cm^{-1}.

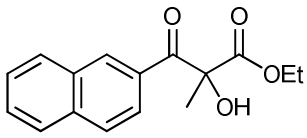
Ethyl 2-hydroxy-2-methyl-3-oxo-3-phenylpropanoate (50, Table 3, entry 4)



$C_{12}H_{14}O_4$
222.24 g/mol

according to the **general procedure 2**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 8/1): 96 mg (86 %), pale yellow oil. R_f (petroleum ether/ethylacetate 5/1) 0.21. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 – 7.95 (m, 2H), 7.61 – 7.54 (m, 1H), 7.49 – 7.41 (m, 2H), 4.46 (s, 1H), 4.22 (q, *J* = 7.14 Hz, 2H), 1.73 (s, 3H), 1.15 (t, *J* = 7.14 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 196.0, 172.3, 133.7, 133.1, 129.5, 128.6, 79.5, 62.5, 23.5, 13.8. HRMS (EI; $C_{12}H_{14}O_4$): calcd.: 222.0892, found: 222.0892. IR **:** $\tilde{\nu}$ = 3469, 2988, 1742, 1695, 1450, 1374, 1271, 1233, 1150, 632, 539 cm^{-1}.

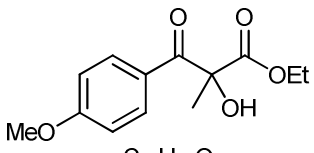
Ethyl 2-hydroxy-2-methyl-3-(naphthalen-2-yl)-3-oxopropanoate (51, Table 3, entry 5)



$C_{16}H_{16}O_4$
272.30 g/mol

according to the **general procedure 2**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 7/1): 115 mg (84 %), pale yellow oil. R_f (petroleum ether/ethylacetate 5/1) 0.21. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.04 – 7.84 (m, 4H), 7.66 – 7.52 (m, 2H), 4.55 (s, 1H), 4.24 (q, *J* = 7.14 Hz, 2H), 1.82 (s, 3H), 1.15 (t, *J* = 7.14 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 195.9, 172.5, 135.7, 132.3, 131.6, 130.4, 129.9, 129.1, 128.5, 127.7, 127.0, 124.8, 79.7, 62.6, 23.8, 13.9. HRMS (EI; $C_{16}H_{16}O_4$): calcd.: 272.1049, found: 272.1049. IR **:** $\tilde{\nu}$ = 3474, 3058, 2985, 1739, 1687, 1627, 1370, 1280, 1251, 1148, 1116, 1014, 632, 539 cm^{-1}.

Ethyl 2-hydroxy-3-(4-methoxyphenyl)-2-methyl-3-oxopropanoate (52, Table 3, entry 6)

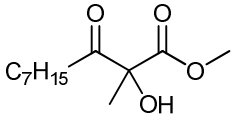


$C_{13}H_{16}O_5$
252.26 g/mol

according to the **general procedure 2** (note: reaction time 48h): yield after column chromatography (silica gel, petroleum ether/ethylacetate 7/1): 117 mg (93 %), colourless oil. R_f (petroleum ether/ethylacetate 5/1) 0.17. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 – 7.96 (m, 2H), 6.96 – 6.89 (m, 2H), 4.61 (s, 1H), 4.21 (q, *J* = 7.14 Hz, 2H), 3.87 (s, 3H), 1.73 (s, 3H), 1.16 (t, *J* = 7.14 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 194.4, 172.4, 164.0, 132.1, 125.6, 113.9, 79.2, 62.4, 55.6, 23.8, 13.9. HRMS (EI; $C_{15}H_{16}O_5$): calcd.: 252.0998, found: 252.1003. IR **:** $\tilde{\nu}$ = 2983, 1738, 1682, 1602, 1513, 1263, 1152, 1030, 632, 540 cm^{-1}.

Experimental Data for α-Hydroxy-ß-Ketoesters from Cross-Coupling with Various α–Ketoesters

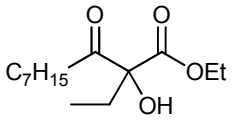
Methyl 2-hydroxy-2-methyl-3-oxodecanoate (58, Table 4, entry 1)



$C_{12}H_{22}O_4$
230.30

according to the **general procedure 3**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 20/1): 103 mg (90 %), colourless oil. R_f (petroleum ether/ethylacetate 5/1) 0.30. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22 (s, 1H), 3.78 (s, 3H), 2.70 – 2.46 (m, 2H), 1.63 – 1.53 (m, 5H), 1.30 – 1.21 (m, 8H), 0.90 – 0.83 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 207.2, 171.9, 81.0, 53.3, 36.3, 31.6, 29.0, 29.0, 23.5, 22.6, 22.0, 14.1. HRMS (EI; $C_{12}H_{22}O_4$): calcd. $C_{12}H_{22}O_4$: 230.1518, found: 230.1516. IR **:** $\tilde{\nu}$ = 3480, 2930, 2857, 1722, 1456, 1262, 1157, 632, 537 cm^{-1}.

Ethyl 2-ethyl-2-hydroxy-3-oxodecanoate (59, Table 4, entry 2)

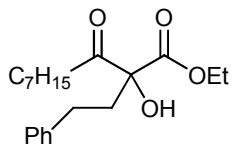


$C_{14}H_{26}O_4$
258.35 g/mol

according to the **general procedure 3**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 30/1): 116 mg (90 %), colourless oil. R_f (petroleum ether/ethylacetate 10/1) 0.27. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.31 – 4.17 (m, 2H), 4.16 s, 1H), 2.73 – 2.60 (m, 1H), 2.55 – 2.41 (m, 1H), 2.19 – 2.03 (m, 1H), 2.00 – 1.86 (m, 1H), 1.62 – 1.49 (m, 2H), 1.31 – 1.20 (m, 11H), 0.90 –

0.81 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 207.3, 171.1, 84.4, 62.5, 36.8, 31.6, 29.0 (2C), 28.3, 23.6, 23.5, 22.6, 14.1, 7.4. HRMS (EI ; $C_{14}H_{26}O_4$): calcd.: 258.1838, found: 258.1831. IR **:** $\tilde{\nu}$ = 3492, 2959, 2931, 2858, 1717, 1462, 1259, 1017, 804, 632, 537, 500 cm^{-1}.

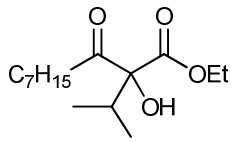
Ethyl 2-hydroxy-3-oxo-2-phenethyldecanoate (60, Table 4, entry 3)



$C_{20}H_{30}O_4$
334.45 g/mol

according to the **general procedure 3**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 50/1): 117 mg (70 %), colourless oil. R_f (petroleum ether/ethylacetate 10/1) 0.24. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 – 7.13 (m, 5H), 4.29 (s, 1H), 4.21 (q, *J* = 7.14 Hz, 2H), 2.78 – 2.36 (m, 5H), 2.26 – 2.13 (m, 1H), 1.62 – 1.50 (m, 2H), 1.33 – 1.20 (m, 11H), 0.91 – 0.84 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 207.0, 171.0, 141.0, 128.5, 128.5, 126.2, 83.8, 62.7, 37.1, 36.8, 31.6, 29.6, 29.0 (2C), 23.5, 22.6, 14.1. HRMS (EI; $C_{20}H_{30}O_4$): calcd.: 334.2144, found: 334.2147. IR **:** $\tilde{\nu}$ = 3485, 2930, 2857, 1716, 1497, 1455, 1368, 1247, 1190, 1126, 1095, 1074, 1019, 748, 699, 503 cm^{-1}.

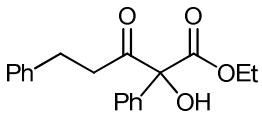
Ethyl 2-hydroxy-2-*iso*propyl-3-oxodecanoate (61, Table 4, entry 4)



$C_{15}H_{28}O_4$
272.38 g/mol

according to the **general procedure 3**: yield after column chromatography (silica gel, petroleum ether/ethylacetate 50/1): 54 mg (40 %), colourless oil. R_f (petroleum ether/ethylacetate 10/1) 0.35. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.33 – 4.16 (m, 2H), 4.10 (s, 1H), 2.82 – 2.64 (m, 2H), 2.54 (td, *J* = 18.20 Hz, 7.48 Hz, 1H), 1.64 – 1.47 (m, 2H), 1.35 – 1.18 (m, 11H), 0.95 – 0.83 (m, 6H), 0.77 (d, *J* = 6.86 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 208.0, 171.1, 87.7, 62.5, 37.2, 33.8, 31.7, 29.0 (2C), 23.5, 22.6, 16.8, 16.1, 14.1, 14.1. HRMS (EI; $C_{15}H_{28}O_4$): calcd.: 272.1986, found: 272.1987. IR **:** $\tilde{\nu}$ = 2962, 2930, 1716, 1251, 1037, 632, 544 cm^{-1}.

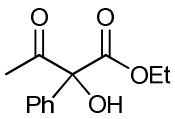
Ethyl 2-hydroxy-3-oxo-2,5-diphenylpentanoate (62, Table 4, entry 5)



$C_{19}H_{20}O_4$
312.36 g/mol

according to the **general procedure 2**: yield after column chromatography (silica gel, hexanes/Et_2O 4/1): 250 mg (80 %),[xvii] colourless oil. R_f (hexanes/Et_2O 4/1) 0.28. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.51 (m, 2H), 7.40-7.37 (m, 3H), 7.27-7.16 (m, 3H), 7.09 (app d, 2H), 4.72 (s, 1H), 4.38-4.24 (m, 2H), 3.02-2.82 (m, 4H), 1.32 (t, J = 7.4, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.8, 170.2, 140.4, 135.8, 128.3, 128.2, 128.1, 126.2, 126.0 84.2, 63.0, 38.9, 29.7, 13.8. 28.0. HRMS (ESI; $C_{19}H_{20}O_4$ + Na): calcd.: 335.1257, found: 335.1257. IR **:** $\tilde{\nu}$ = 3479, 2981, 1714, 1603, 1496, 1453, 1255, 1059, 859, 698 cm^{-1}.

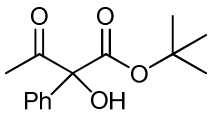
Ethyl 2-hydroxy-3-oxo-2-phenylbutanoate (63, Table 4, entry 6)



$C_{12}H_{14}O_4$
222.24 g/mol

according to the **general procedure 2**: yield after column chromatography (SiO_2, hexanes /Et_2O 4/1): 183 mg (82 %),[xvii] colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.56 (m, 2H), 7.46-7 42 (m, 3H), 4.78 (s, 1H), 4.40-4.28 (m, 2H), 2.24 (s, 3H), 1.34 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.5, 170.2, 136.1, 128.7, 128.4, 126.3, 84.5, 63.0, 25.0, 13.9. HRMS (ESI; $C_{12}H_{14}O_4$ + Na): calcd.: 245.0790, found: 245.0786. IR **:** $\tilde{\nu}$ = 3456, 2981, 1771, 1449, 1354, 1249, 1072, 857, 656 cm^{-1}.

***tert*-Butyl-2-hydroxy-3-oxo-2-phenylbutanoate (64)**

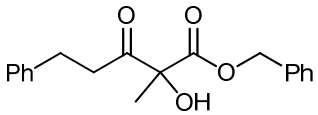


$C_{14}H_{18}O_4$
250.29 g/mol

according to the **general procedure 1** (at 20 °C, 40 h, using chiral catalyst **67** and 3 equiv. of volatile CH_3CHO): yield after column chromatography (SiO_2, hexanes/ Et_2O 4/1): 73 mg (58 %), colourless solid, m. p. 41-43 °C. R_f (hexanes/Et_2O 4/1) 0.34. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (m, 2H), 7.39 (m, 3H), 4.65 (s, 1H), 2.22 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.2, 169.0, 136.0, 128.0, 127.8, 126.0, 84.0, 83.9, 21.2, 24.3. HRMS (ESI; $C_{14}H_{18}O_4$ + Na): calcd.: 273.1096, found: 273.1032. IR **:** $\tilde{\nu}$ = 3447, 2979, 2933, 1721, 1449, 1369, 1257, 1074, 839, 661 cm^{-1}. $[\alpha]_D^{20}$ = + 73.63 (*c* 0.33 in acetone, 74% *ee*).[xviii].

[xvii] The reaction was performed using the double amount of the described size of the general procedure.
[xviii] See supporting information on enclosed CD for HPLC chromatograms.

Benzyl 2-hydroxy-2-methyl-3-oxo-5-phenylpentanoate (69)

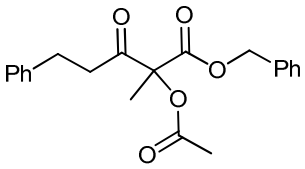


$C_{19}H_{20}O_4$
312.36 g/mol

according to the **general procedure 1**: yield after column chromatography (SiO_2, hexanes/ Et_2O 4/1): 275 mg (88 %),[xvii] white solid, m. p. 38-41 °C. R_f (hexanes/Et_2O 4/1) 0.27. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.37 (m, 3H), 7.34-7.31(m, 2H), 7.30-7.26 (m, 2H), 7.23-7.19 (m, 1H), 7.12-7.10 (m, 2H), 5.16 (d, *J* = 3.5 Hz, 2H), 4.20 (s, 1H), 2.97-2.75 (m, 4H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.5, 170.6, 139.9, 134.3, 128.3 (2C), 128.0 (2C), 127.9, 125.8, 80.6, 67.6, 37.8, 29.0, 21.2. HRMS (ESI; $C_{19}H_{20}O_4$ + Na): calcd. 335.1259, found: 335.1269. IR **:** $\tilde{\nu}$ = 3466, 3028, 2981, 1714, 1453, 1365, 1259, 1061, 745, 696 cm^{-1}.

Experimental Data for Decarboxylation Experiments

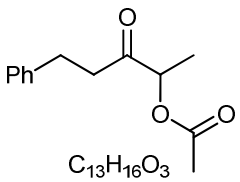
Benzyl 2-acetoxy-2-methyl-3-oxo-5-phenylpentanoate (70)



$C_{21}H_{22}O_5$
354.4 g/mol

according to the **general procedure 5**: yield after column chromatography (SiO_2, hexanes/ Et_2O 4/1): 340 mg (96 %), colourless oil. R_f (hexanes/Et_2O 4/1) 0.39. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.21 (m, 7H), 7.20-7.14 (m, 3H), 5.17 (s, 2H), 3.00-2.88 (m, 4H), 2.15 (s, 3H), 1.71(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9, 169.1, 167.0, 140.2, 134.5, 128.2, 128.1, 128.0, 127.9, 127.8, 125.7, 85.0, 67.4, 39.3, 29.1, 20.4, 19.5. HRMS (ESI, $C_{21}H_{22}O_5$ + Na): calcd.: 377.1368, found: 377.1365. IR **:** $\tilde{\nu}$ = 2942, 1714, 1497, 1370, 1116, 1056, 747, 696 cm^{-1}.

3-Oxo-5-phenylpentan-2-yl acetate (71)



$C_{13}H_{16}O_3$
220.26 g/mol

according to the **general procedure 6**: yield after column chromatography (SiO_2, hexanes/ Et_2O 4/1): 190 mg (96 %), colourless oil. R_f (hexanes/Et_2O 4/1) 0.32. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.29 (m, 2H), 7.22-7.20 (m, 3H), 5.1 (q, *J* = 7.2 Hz, 1H), 2.93-2.74 (m, 4H), 2.14 (s, 3H), 1.35 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 169.9, 140.3, 128.1, 127.9, 125.8, 74.2, 39.5, 28.7, 20.3, 15.5. HRMS (EI, $C_{13}H_{16}O_3$): calcd.: 220.1099, found: 220.1089. IR **:** $\tilde{\nu}$ = 2942, 1714, 1497, 1370, 1116, 1056, 747, 696 cm^{-1}.

→Please find supporting information including **^{1}H- and ^{13}C-NMR spectra** on the enclosed CD.

1.5.5 References

(1) For examples see: a) W. Herz, S. V. Bhat, *J. Org. Chem*. **1970**, *35*, 2605; b) L. Quljano, E. J. Oliweh, N. H. Fischer, *Phytochemistry*, **1980**, *19*, 1485; c) S. Schulz, *Liebigs Ann. Chem*. **1992**, 829; d) T. Tanaka, I. Koundo, G.–I. Nonaka, *Chem. Pharm. Bull.* **1996**, *44*, 34; e) J. Zhu, A. J. H. Klunder, B. Zwanenburg, *Tetrahedron Lett*. **1994**, *35*, 2787; f) Y. Shikishima, Y. Takaishi, G. Honda, M. Ito, Y. Takeda, M. Tori, S. Takaoka, O. K. Kodzhimatov, O. Ashurmetov, *J. Nat. Prod*. **2002**, *65*, 1897.

(2) a) G. Olack, H. Morrison, *J. Org. Chem*. **1991**, *56*, 4969; b) F. A. Davis, C. Clark, A. Kumar, B.–C. Chen, *J. Org. Chem*. **1994**, *59*, 1184; c) K. Tamaki, J. B. Shotwell, R. D. White, I. Drutu, D. T. Petsch, T. V. Nheu, H. He, Y. Hirokawa, H. Maruta, J. L. Wood, *Org. Lett*. **2001**, *3*, 1689; d) F. Neuser, H. Zorn, R. G. Berger, *J. Agric. Food Chem.* **2000,** *48,* 6191.

(3) a) P. E. Sum, P. Petersen, *Bioorg. Med. Chem. Lett*. **1999**, *9*, 1459; b) W. E. Rose, M. J. Rybak, *Pharmacotherapy* **2006**, *26*, 1099.

(4) Selected recent references: a) F. A. Davis, H. Liu, B.–C. Chen, P. Zhou, *Tetrahedron* **1998**, *54*, 1048; b) J. Christoffers, *J. Org. Chem*. **1999**, *64*, 766; c) T. Watanabe, T. Ishikawa, *Tetrahedron Lett.* **1999**, *40*, 7795; d) X. Baucherel, E. Levoirier, J. Uziel, S. Juge, *Tetrahedron Lett*. **2000**, *41*, 138; e) J. Christoffers, T. Werner, S. Unger, W. Frey, *Eur. J. Org. Chem*. **2003**, 425; f) S. V. Ley, T. D. Sheppard, R. M. Myers, M. S. Chorghade, *Bull. Chem. Soc. Jpn*. **2007**, *80*, 1451; g) Y. Monguchi, T. Takahashi, Y. Iida, Y. Fujiwara, Y. Inagaki, T. Maegawa, Hironao Sajiki, *Synlett* **2008**, 2291; h) P. Gans, O. Hamelin, R. Sounier, I. Ayala, M. A, Durá, C. D. Amero, M. Noirclerc-Savoye, B. Franzetti, M. J. Plevin, J. Boisbouvier, *Angew. Chem. Int. Ed.* **2010**, *49*, 1958.

(5) See also: D. H. G. Crout, D. L. Rathbone, *J. Chem. Soc. Chem. Commun*, **1987**, 290.

(6) a) J. V. Schloss, D. E. Van Dyk, J. F. Vasta, R. M. Kutny, *Biochemistry* **1985**, *24*, 4952; b) R. S. Chaleff, C. J. Mauvais, *Science* **1984**, *224*, 144.

(7) a) For a biomimetic (stoichiometric) artificial process, see: D. H. G. Crout, E. R. Lee, D. P. J. Pearson, *J. Chem. Soc. Chem. Commun*. **1990**, 331; b) for the enzymatic C-C bond formation using diketo substrates, see: P. P. Giovanninia, P. Pedrinia, V. Venturia, G. Fantin, A. Medicia, *J. Mol. Cat B:Enzym.* **2010**, *64*, 113.

(8) For the seminal work in this area see: a) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc*. **2006**, *128*, 4558; b) For an interesting study detailing how NHC catalysis (including the formation of acyl-azolium ions) can be influenced by the solvent see: B. E. Maki, E. V. Patterson, C. J. Cramer, K. A. Scheidt, *Org. Lett*. **2009**, *11*, 3942.

(9) M. Sreenivasulu, K. Arun Kumar, K. Sateesh Reddy, K. Siva Kumar, P. Rajender Kumar, K. B. Chandrasekhar, Manojit Pal, *Tetrahedron Lett*. **2011**, *52*, 727.

(10) For related NHC catalysed, but mechanistically distinct hydroacylations, see: a) K. Hirano, A. T. Biju, I. Piel, F. Glorius, *J. Am. Chem. Soc*. **2009**, *131*, 14190; b) A. T. Biju, N. E. Wurz, F. Glorius, *J. Am. Chem. Soc*. **2010**, *132*, 5970; c) A. T. Biju, F. Glorius, *Angew. Chem. Int. Ed*. **2010**, *49*, 9761.

(11) Recent reviews: a) P. -C. Chiang, J. W. Bode, *RSC Catalysis Series* **2010**, *6*, 399; b) C. D. Campbell, K. B. Ling, A. D. Smith in *Catalysis by Metal Complexes* **2010**, *32*, 263; c) J. L. Moore, T. Rovis, *Top. Curr. Chem.* **2009**, *291,* 77; d) E. M. Phillips, A. Chan, K. A. Scheidt, *Aldrichim. Acta* **2009**, *42*, 55; e) T. Rovis, *Chem. Lett*. **2008**, *37*, 1; f) K. Zeitler, *E. Schering Found. Symp. Proc.* **2007***, 2*, 183; g) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev*. **2007**, *107*, 5506; h) N. Marion, S. Diez-Gonzalez, S. P. Nolan, *Angew. Chem. Int. Ed*. **2007**, *46*, 2988; i) K. Zeitler, *Angew. Chem. Int. Ed*. **2005**, *44*, 7506.

(12) a) H. Stetter, G. Dämbkes, *Synthesis* **1977**, 403; b) H. Stetter, G. Dämbkes, *Synthesis*, **1980**, 309; c) R. Heck, A. P. Henderson, B. Köhler, J. Rétey, B. T. Golding, *Eur. J. Org. Chem.*

2001, 2623; d) S. M. Mennen, S. J. Miller, *J. Org. Chem*. **2007**, *72*, 5260; e) S. E. O'Toole, C. A. Rose, S. Gundala, K. Zeitler, S. J. Connon, *J. Org. Chem*. **2011**, *76*, 347; f) C. A. Rose, S. Gundala, S. J. Connon, K. Zeitler, *Synthesis* **2011**, 190; g) X. L. Huang, S. Ye, *Chinese Sci. Bull.* **2010**, *55*: 1753; h) N. Kuhl, F. Glorius, *Chem. Commun*. **2011**, *47*, 573; i) M. Y. Jin, S. M. Kim, H. Han, D. H. Ryu, J. W. Yang, *Org. Lett*. **2011**, *13*, 880.

(13) For representative examples of intramolecular variants see: a) D. Enders, O. Niemeier, T. Balensiefer, *Angew. Chem. Int. Ed*. **2006**, *45*, 1463; b) H. Takikawa, Y. Hachisu, J. W. Bode, K.Suzuki, *Angew. Chem. Int. Ed*. **2006**, *45*, 3492; c) D. Enders, O. Niemeier, G. Rabbe, *Synlett* **2006**, 2431; d) Y. Li, Z. Feng, S.–L. You, *Chem. Commun*. **2008**, 2263; e) T. Ema, Y. Oue, K. Akihara, Y. Miyazaki, T Sakai, *Org. Lett.* **2009**, *11*, 4866; f) For a sterically controlled example in the context of a multicatalytic cascade sequence: S. P. Lathrop, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13628; g) For a recent application in natural product synthesis: A. Takada, Y. Hashimoto, H. Takikawa, K. Hikita, K. Suzuki, *Angew. Chem. Int. Ed*. **2011**, *50*, 2297.

(14) a) D. Enders, A. Henseler, *Adv. Synth. Catal*. **2009**, *351*, 1749; b) D. Enders, A. Grossmann, J. Fronert, G. Raabe, *Chem. Commun*. **2010**, *46*, 6282; For cascade sequences involving an asymmetric intermolecular aldehyde-ketone crossed benzoin reaction: c) P. -C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc*. **2007**, *129*, 3520; J. Ma, Y. Huang, R. Chen, *Org. Biomol. Chem*. **2011**, *9*, 1791. d) For an example *via* an enzymatic carboligation reaction: P. Lehwald, M. Richter, C. Röhr, H.-W. Liu, M. Müller, *Angew. Chem. Int. Ed.* **2010**, *49*, 2389.

(15) a) M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Org. Chem*. **2005**, *70*, 5725; b) H. U. Vora, S. P. Lathrop, N. T. Reynolds, M. S. Kerr, J. Read de Alaniz, T. Rovis, *Org. Synth.* **2010**, *87*, 350.

(16) a) L. Baragwanath, C. A. Rose, K. Zeitler, S. J. Connon, *J. Org. Chem*. **2009**, *74*, 9214; b) S. E. O'Toole, S. J. Connon, *Org. Biomol. Chem*. **2009**, *7*, 3584.

(17) Importantly, mild conditions are required, as aldol reactions as a third undesired pathway also must be avoided. a) H. Takikawa, K. Suzuki, *Org. Lett.* **2007**, *9*, 2713; for selected NHC/aldol cascade reactions, see: b) E. Sánchez-Larios, J. M. Holmes, C. L. Daschner, M. Gravel, *Org. Lett.* **2010**, *12*, 5572; c) F. -G. Sun, X.-L. Huang, S. Ye, *J. Org. Chem.* **2010**, *75*, 273.

(18) Y. Li, Z. -A. Zhao, H. He, S. –L. You, *Adv. Synth. Catal*. **2008**, *350*, 1885.

(19) $CHCl_3$ as solvent allows for the preferential formation of cross benzoin products.

(20) Acetaldehyde is used in excess due to its high volatility – with heavier aldehyde partners stoichiometric loadings could be employed.

(21) Acylation is necessary to prevent the formation of two regioisomeric products α-hydroxy ketone products *via* keto-enol tautomerism during decarboxylation. Thus it is unlikely that – under the (at least slightly) basic conditions of NHC-catalysed AC processes – a high-yielding direct NHC-catalysed cross coupling reaction between two aliphatic aldehydes of similar characteristics (*i.e.* where the formation of one isomer would not be preferred thermodynamically over the other) will ever be possible. For a enzymatic kinetic resolution of related substrates, see: G. Scheid, W. Kuit, E. Ruijter, R. V. A. Orru, E. Henke, U. Bornscheuer, L. A. Wessjohann, *Eur. J. Org. Chem.* **2004**, 1063.

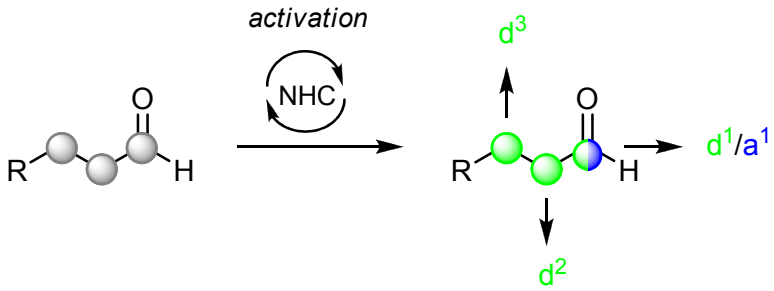
(22) For representative indirect methods of preparing crossed AC products see: *Acyl silanes*: a) X. Linghu, J. S. Johnson *Angew. Chem. Int. Ed.* **2003**, *42*, 2534; b) J. C. Tarr, J. S. Johnson, *Org. Lett.* **2009**, *11*, 3870; *Acyl phosphonates*: c) A. S. Demir, I. Esiringü, M. Göllü, Ö. Reis, *J. Org. Chem.* **2009**, *74*, 2197; d) C. C. Bausch, J. S. Johnson, *Adv. Synth. Catal.* **2005**, *347*, 1207; *Aldehyde-thiazolium carbene adducts*: e) A. K. Mathies, A. E. Mattson, K. A. Scheidt, *Synlett* **2009**, 377; f) A. E. Mattson, K. A. Scheidt, *J. Am. Chem. Soc*. **2007**, *129*, 4508.

2 Carbene Catalyzed C-O Bond Forming Reactions

2.1 Introduction

With respect to an increasing need for densely functionalized chemicals, such as pharmaceuticals or materials, the development of novel methods for carbon-heteroatom bond formation has been an important research goal for organic chemists. Owing to their unique reactivity, *N*-heterocyclic carbenes have proven to be valuable organic catalysts for such kind of transformations.

In general, NHCs can activate aldehydes – based on their corresponding structure[i] – either in the 1-, 2- or 3-position for functionalization processes (Scheme 1).



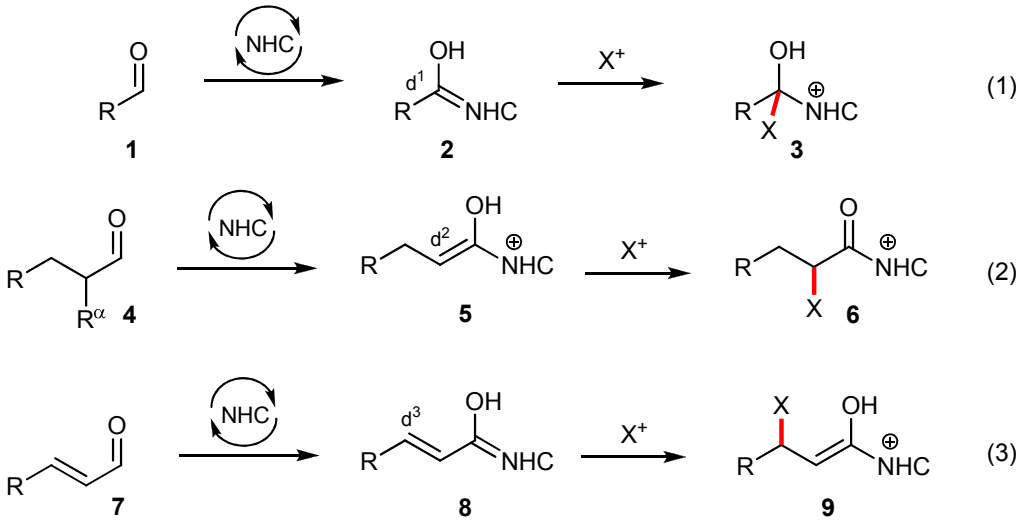
Scheme 1: General activation modes for aldehydes in NHC-catalyzed functionalization processes.

Positions 2 and 3 can exclusively be activated to react as a nucleophile (donor reactivity, d^n),[1] whereas the former carbonyl carbon (position 1) can either be transformed into an activated electrophilic species (acceptor reactivity, a^1) or a nucleophilic (d^1) reactive intermediate. Taking advantage of these activation modes, C–X bonds can be introduced into aldehydes.

[i] Please see Scheme 2 and Scheme 3 for details.

Carbene Catalyzed Nucleophilic C-X Bond Forming Reactions

Carbene organocatalysts are capable of transforming naturally electrophilic aldehydes into nucleophilic species *via* umpolung processes (Scheme 2). While the generation of d^1-compounds **2** ("classical umpolung", eq. 1) poses no special structural requirements to the aldehyde precursors, the formation of d^2- and d^3-species ("extended umpolung", eq. 2, 3), respectively, is generally limited to aldehydes bearing α-reducible functional groups.[2]



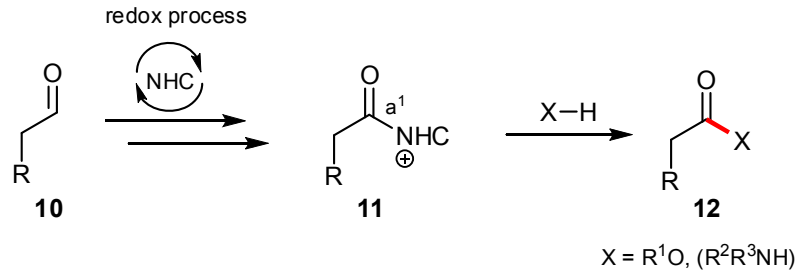
R^{α} = α-reducible group

Scheme 2: Generation of nucleophilic synthons *via* NHC-catalyzed umpolung processes.

Interestingly, compared to carbon-carbon bond forming reactions, the aforementioned synthons have only rarely been applied in analogous carbon-heteroatom couplings.[3]

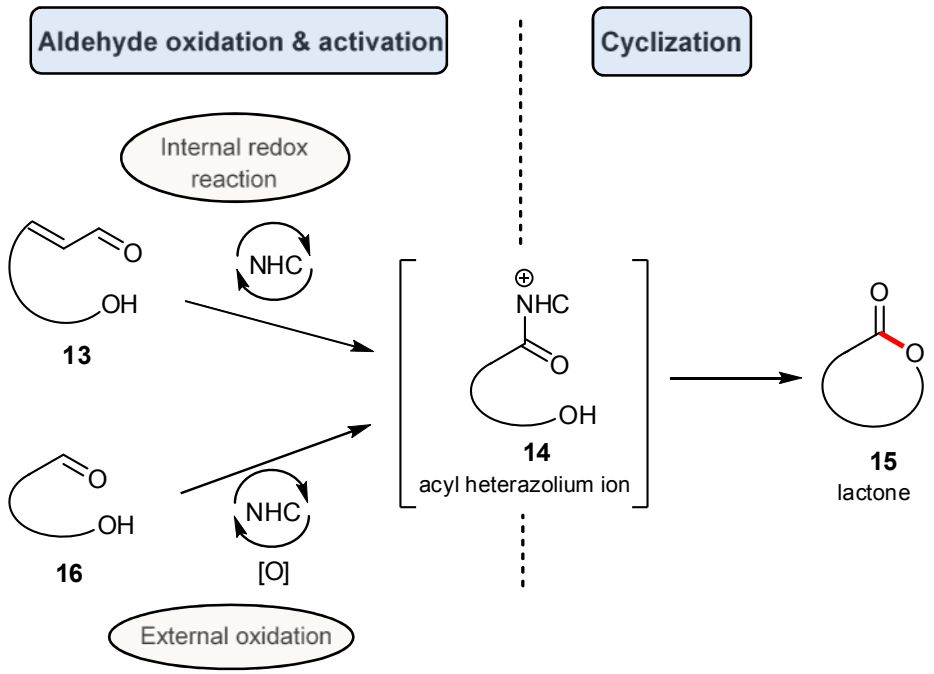
Carbene Catalyzed Electrophilic C-X Bond Forming Reactions

Electrophilic C-X bond forming reactions at the former carbonyl carbon (a^1- reactivity) proceed under retention of polarity (Scheme 3). The carbene catalyst produces acyl heterazolium ions **11** by mediating internal redox processes or external oxidation of aldehydes. Behaving like activated esters, these species can be intercepted by nucleophiles, such as alcohols.[4] The resulting esters are ubiquitous motifs in bioactive compounds and functional chemical materials.



Scheme 3: Generation of acyl heterazolium ions **11** *via* NHC-mediated redox processes.

In the following two chapters, novel carbene catalyzed approaches to benzolactones are disclosed. They take advantage of NHC`s ability to form acyl heterazolium species **14** *via* internal or external redox processes (Scheme 4). The catalyst fulfills a dual function: a) mediating the oxidation to the carboxyl species and b) concomitantly promoting the cyclization by activating the acid portion.

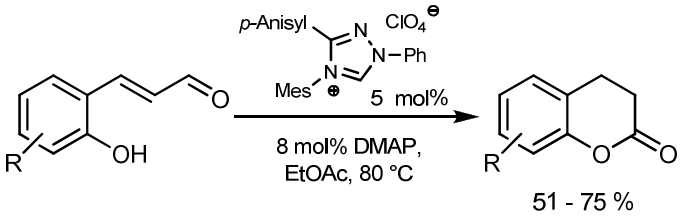


Scheme 4: Carbene catalyzed lactonization strategies taking advantage of the formation of acyl-heterazolium ions **14**.

References:

(1) D. Seebach, *Angew. Chem. Int. Ed.* **1979**, *18*, 239.
(2) K. Zeitler, *Angew. Chem. Int. Ed.* **2005**, *44*, 7506.
(3) a) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2008**, *130*, 2740; b) J. Seayad, P. K. Patra, Y. Zhang, J. Y. Ying, *Org. Lett.* **2008**, *10*, 953; c) F. T. Wong, P. K. Patra, J. Seayad, Y. Zhang, J. Y. Ying, *Org. Lett.* **2008**, *10*, 2333; d) Y. Wu, W. Yao, L. Pan, Y. Zhang, C. Ma, *Org. Lett.* **2010**, *12*, 640.
(4) For examples, see: J. W. Bode, P.-C. Chiang, in *RSC Catalysis Series No. 6* (Ed.: S. Díez-González), **2011** and references cited therein.

2.2 An Efficient Carbene-Catalyzed Access to 3,4-Dihydrocoumarins[i]



Dihydrocoumarins playing an important role as flavor and fragrance compounds can efficiently be prepared from *o*-hydroxycinnamaldehydes in a mild, atom-economic *N*-heterocyclic carbene catalyzed redox lactonization. Corresponding coumarins are accessible *via* a one-pot domino oxidation lactonization procedure in the presence of oxidants.[ii]

[i] Reproduced with permission from: K. Zeitler, C. A. Rose, *J. Org. Chem.* **2009**, *74*, 1759 – 1762. Copyright 2009 American Chemical Society.

[ii] All experiments were carried out by C. A. R.

2.2.1 Introduction

With respect to an increasing need of efficient and new catalytic synthetic methods, organocatalysis represents a powerful field and has found widespread application over the last decade.[1, 2] The rapidly growing interest in *N*–heterocyclic carbene (NHC) catalyzed processes might be attributed to the great versatility of these organocatalytic transformations,[3] but is also associated with the possibilities that arise from the NHC´s characteristic inversion of the classical reactivity, i. e. Umpolung.[4]
Inspired by nature´s ability to perform nucleophilic acylations within thiamine–dependent enzymes,[5] NHC catalysis merges two important strategic advantages for efficient synthetic methods. First, the high chemoselectivity of nucleophilic carbenes can be utilized for protecting group-free synthesis,[6] moreover, the potential to alter the practice of traditional retrosynthetic analysis is of particular interest.[7] Synthetic approaches to lactone derivatives that rely on the catalytic generation of activated carboxylates or enols *via N*-heterocyclic carbene-catalyzed reactions of α-functionalized aldehydes[3d] have witnessed impressive and rapid progress in the last few years.[8, 9] In connection with our work on NHC-mediated umpolung reactions[10] we considered to apply nucleophilic carbenes for a catalytic access to coumarin derivatives. Herein, we disclose that *o*-hydroxycinnamaldehydes cyclize efficiently in presence of triazolinylidene carbenes to form dihydrocoumarins or – under oxidative conditions – their unsaturated counterparts in moderate to high yield.

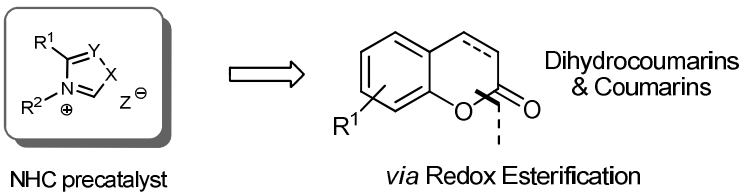


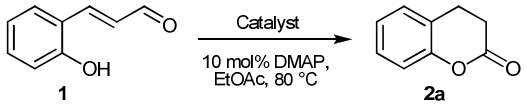
Figure 1: Dihydrocoumarins and coumarins by carbene-catalyzed extended umpolung lactonization.

Coumarins and dihydrocoumarins present a large class of natural products that have attracted considerable interest due to their various biological activities.[11] Moreover, coumarins play an important role as fluorescent material and as dyes in laser technology.[11c, 12] Hence, several conventional methods[13] are available to prepare coumarin derivatives, but most of these traditional approaches suffer from harsh reaction conditions and are only rarely catalytic.[14] Dihydrocoumarins (DHC), that play an important role as flavor and fragrance compounds in both food and cosmetics (perfumes), are traditionally prepared by transition metal catalyzed hydrogenations of coumarins or, more recently, biotechnologically.[15] Interestingly, despite the need for metal-free and enviromentally benign routes only very few organocatalytic examples have been reported.[16] A synthesis of 3-alkyl-coumarins using a “non-innocent” imidazolium ionic liquid as (super)stoichiometric mediator was recently described by Bräse and coworkers.[8i] We assumed that reaction of easy accessible

o-hydroxycinnamaldehydes with NHCs would result in the formation of 3,4-dihydrocoumarins *via* an intramolecular redox lactonization process. For exploratory studies, 2-hydroxy-cinnamaldehyde **1** was selected as model substrate.[17]

2.2.2 Results and Discussion

We started our experimental investigations with a survey of different heterazolium precatalysts. Notably, thiazolium **3**, benzimidazolium **4**, and imidazolium **5** salts – all known as potent precatalysts for internal redox reactions[18] – failed to give any conversion and proved to be ineffective for the desired ring closing transformation.[19]



entry	catalyst	mol %	yield (%)[a]
1[b]	3	10	no conv.
2[c]	4	10	no conv.
3	5	5	no conv.
4[c]	6a	10	41
5[d]	6b	10	42
6[c]	7a	10	34
7	7b	5	53
8	7c	5	22
9	7d	5	61

[a] Yield of isolated product after column chromatography. [b] 20 mol% of KOtBu was used as base instead of DMAP. [c] 20 mol% of base was used. [d] NEt_3 was used instead of DMAP (reaction was significantly slower with DMAP).

Table 1: Dihydrocoumarin synthesis with different heterazolium carbene precursors.

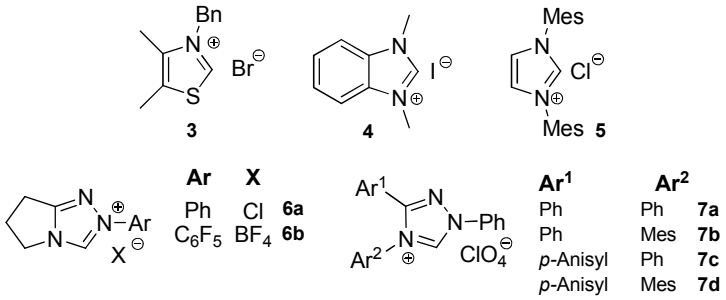
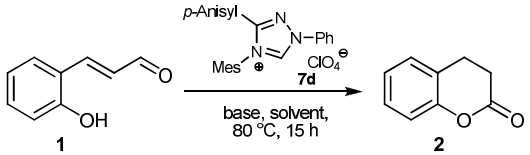


Figure 2: Evaluated heterazolium carbene precursors.

Systematic evaluation of a variety of triazolium salts revealed that both the sterically demanding mesityl *N*–substituent (entry 7, catalyst **7b**) and an electron-rich backbone *p*-methoxyphenyl substituent (entry 8, catalyst **7c**) were important to achieve useful reaction rates and yields (entry 9, catalyst **7d**). Moreover, the catalyst loading could be reduced to 5 mol%. The importance of the *N*-aryl substituents of triazolium salts was highlighted by Rovis[20] only recently and Bode et al. reported on the striking differences in reactivity between triazolium and imidazolium precursors for a number of different NHC-catalyzed processes.[21]



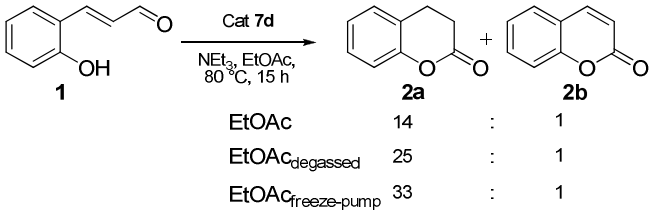
entry[a]	base/cocatalyst (mol %)		solvent	yield (%)[b]
1	K_3PO_4	20	EtOAc	51
2[c]	DMAP	8	EtOAc	61
3[c]	NEt_3	8	EtOAc	63 / 88[d]
4[c]	Pyridine	20	EtOAc	no conv.
5[c]	Imidazole	20	EtOAc	15
6[c]	PPY	20	EtOAc	56
7	DIPEA	20	THF	54
8	HOBt / DIPEA	10/20	THF	54
9	DMAP	20	CH_3CN	44
10	DMAP	20	*t*BuOH	50
11	DMAP	8	$EtOAc_{degassed}$	61

[a] Reaction conditions: 10 mol% of **7d** at 80 °C unless stated otherwise. [b] Yield of isolated product after column chromatography. [c] 5 mol% of catalyst **7d** was used. [d] Determined by ^1H NMR analysis of crude reaction mixture relative to an internal quantitative standard (octamethylcyclotetrasiloxane). PPY = 4-pyrrolidino pyridine, HOBt = hydroxy-benzotriazole, DIPEA=di*iso*-propylethylamine.

Table 2: Optimization of reaction conditions: influence of bases and solvents.

With the identification of **7d** as a suitable catalyst the reaction conditions were further optimized. A variety of inorganic and organic bases were examined (table 2) and showed comparable promising results for DMAP (entry 2) and triethylamine (entry 3). A screen of possible acylation cocatalysts (entries 4, 5, 6, 8), as described concurrently by Rovis and Bode in the context of relay catalysis for amide bond formation,[22] did not show a beneficial effect on further promoting the cyclization reaction. Remarkably, the reaction can be carried out in various apolar and polar (table 2, entries 7, 9), even protic solvents (entry 10) with comparable yields. The use of dry solvents is not mandatory, hence, single distilled technical grade solvents can be used. Interestingly, we noticed the formation of small amounts of the corresponding oxidized coumarin by-product **2b** (ratio 14:1; table 2, entry 2). But

simple degassing of the solvents by purging the solvent with argon or *via* a freeze-pump-thaw procedure significantly reduced these oxidized side products (ratio 25:1; table 2 entry 11 and scheme 1).

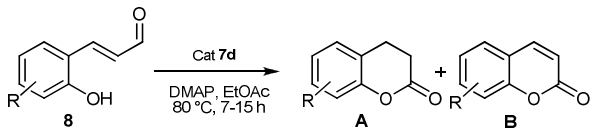


Scheme 1: Formation of minor amounts of oxidized coumarin byproduct (ratio determined by ^{1}H NMR).

A rational for this oxidative pathway of the reaction is provided by mechanistic considerations (scheme 2): upon initial nucleophilic attack of the nucleophilic carbene **I** to the aldehyde function, oxidation of the tetrahedral intermediate **II** is facilitated by this generation of a transient "benzylic" alcohol. Rapid oxidation of similar intermediates was observed by Scheidt and coworkers in the presence of oxidizing reagents.[23, 24]

NMR studies of the reaction progress revealed the straightforward, clean transformation of both *E*- and *Z*-isomers of the unsaturated starting material to yield 3,4-dihydrocoumarin **2a** in combination with only minor amounts of the oxidized coumarin product **2b** (ratio > 97:3). The yield of the model reaction was determined to be greater than 88 % by quantitative NMR analysis of the crude reaction mixture relative to OMS (octamethylcyclotetrasiloxane) as a quantitative internal standard (entry 3).[25] Both NMR experiments underline the efficiency of this intramolecular redox lactonization. Due to the high volatility of these fragrance compounds some product might be sacrificed during the work-up and purification procedures resulting in lower isolated yields. Consequently, we turned our attention to the improvement of the procedure for the product isolation and we were pleased to find an even simplified "column-free" purification method that allows for significantly higher isolated yields (75 % *vs*. 63 %).

Using these optimized conditions, we examined the scope of the new carbene-catalyzed dihydrocoumarin synthesis. A variety of different substituted *o*-hydroxycinnamaldehydes are suitable substrates for the redox lactonization. The reaction is tolerant to both electron-rich (table 3, entries 2, 3, 6, 7, 8) and electron-poor aldehyde derivatives (entries 4, 5).



entry[a]	product	yield (%)[b]	ratio **A**/**B**
1	**2a**	78	96 : 4
2	**9a**	60	93 : 7
3	**10a**	70	91 : 9
4	**11a**	61	93 : 7
5	**12a**	62	96 :4
6	**13a**	54	97 : 3
7[c, d]	**14a**	55	88 : 12
8	**15a**	58	93 : 7
9[c]	**16a**	19	>96 : 4

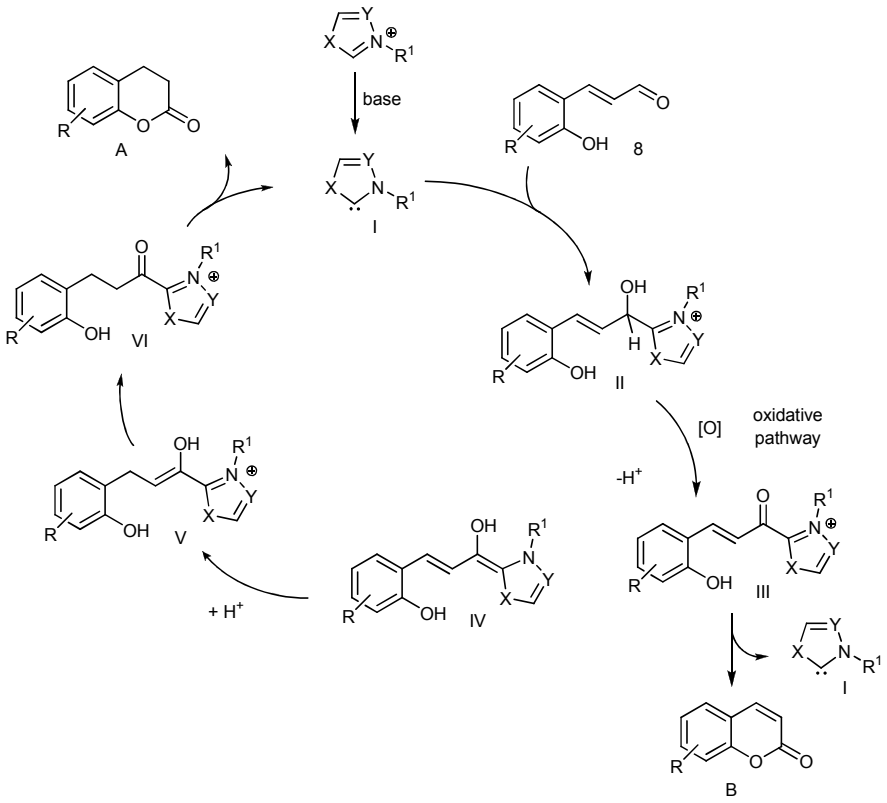
[a] Reaction conditions: 5 mol% of 7d with 8 mol% DMAP in EtOAc at 80 °C. [b] Yield of isolated product (mixture of A and B) after optimized aqueous work-up procedure. [c] 8 mol% of NEt_3 was used. [d] THF was used as solvent.

Table 3: Scope of the reaction.

Notably, the electron-rich substrates appeared to be more prone to the formation of oxidized coumarin side products. Comparison of the three regioisomeric methoxy substituted substrates (table 3, entries 6, 7, 8) with respect to the ratio of coumarin generation nicely displays its dependency on electronic effects where the *para*-derivative (entry 7) proves to be most easily oxidized. Only the strongly electron-deficient nitro derivative failed to undergo the cyclization with useful yield (entry 9), which might be due to the diminished nucleophilicity of the electron-poor phenolate.

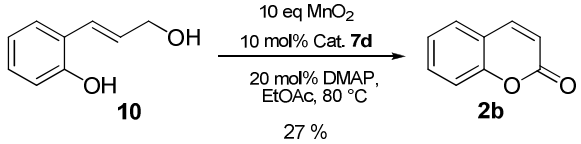
In addition to its robustness with regard to suitable solvents and reaction conditions one of the strengths of our catalytic protocol is also the atom-economic[26] preparation of the desired dihydrocoumarins.

The catalytic cycle is postulated to initiate upon generation of the carbene **I** which undergoes nucleophilic addition to the *o*-hydroxycinnamaldehyde **8** (scheme 2) forming the tetrahedral intermediate **II**. Deprotonation to furnish homoenolate equivalent **IV** and subsequent generation of the activated acyl azolium intermediate **VI** by tautomerization of the protonated species **V** allows for catalyst turnover by intramolecular acylation to yield the dihydrocoumarin **A**. Under oxidizing conditions the reaction can proceed *via* an alternative, oxidative pathway (vide supra and vide infra). Here, the crucial (unsaturated) acyl azolium species **III** that performs the intramolecular acyl transfer to produce coumarin derivatives **B** is generated upon an oxidation event.[24]



Scheme 2: Postulated mechanism for the carbene-catalyzed synthesis of dihydrocoumarins and coumarins.

Taking advantage of the functional group tolerance and the distinct chemoselectivity of both an allylic oxidation and the subsequent redox lactonization, coumarins can be accessed in a simple "one-pot" domino reaction[27] starting from *o*-hydroxycinnamyl alcohols.



Scheme 3: Domino reaction for the preparation of coumarins.

In the presence of an oxidizing agent, such as excess MnO_2,[23b, 28, 29] the coumarin derivatives can be generated directly from allyl alcohol precursors.[30]

2.2.3 Conclusion

In summary, we have developed a mild, carbene-catalyzed atom-economical access to 3,4-dihydrocoumarins that is virtually non-sensitive to solvent effects. Additionally, performance of the reaction in the presence of oxidizing reagents allows for the formation of coumarin derivatives in a one-pot domino oxidation-lactonization sequence starting from simple *o*-hydroxycinnamyl alcohols.

2.2.4 Experimental Section

General Methods

^{1}H NMR spectra were recorded on a 300 MHz spectrometer (300.13 MHz) using the solvent peak as internal reference ($CDCl_3$ δ H: 7.26; δ C: 77.0). Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants (*J*) are in Hz.

Infrared Spectra were obtained on FT-IR Spectrometer equipped with an ATR-System. All reactions were monitored by thin–layer chromatography (TLC) using silica gel aluminium plates 60 F_{254}; visualization was accomplished with UV–light and/or staining with appropriate stains (anisaldehyde, vaniline). Standard (flash) chromatography procedures were followed (particle size 40−63 μm). Solvent mixtures are understood as volume/volume.

All reactions were carried out under an atmosphere of Argon in flame–dried glassware with magnetic stirring. Solvents for the catalytic reactions were technical grade and distilled prior to use (EtOAc, THF) or purchased at absolute quality (^{t}BuOH, MeCN). Degassing was carried out by purging the solvent with Argon. Solvents for chromatography (EtOAc, hexanes, DCM) were technical grade and distilled prior to use. NEt_3 and DIPEA were stored over molecular sieves. Heterazolium salts were prepared according to reported protocols.[iii]

Ortho–hydroxy cinnamyl alcohol was prepared according to a previous literature procedure.[iv]

2–Hydroxy cinnamaldehydes were prepared according to a reported literature procedure *via* Wittig olefination[v] (please see ***general procedure 3)***.

[iii] a) M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Org. Chem.* **2005**, *70*, 5725–5728. b) D. Enders, K. Breuer, U. Kallfass, T. Balensiefer, *Synthesis* **2003**, 1292–1295.

[iv] N. S. S. Kumar, S. Varghese, G. Narayan, S. Das, *Angew. Chem. In. Ed.* **2006**, *45*, 6317–6321.

[v] R. A. Bunce, C. L. Schilling III, *Tetrahedron* **1997**, *53*, 9477–9486.

General Procedures

General Procedure 1: Preparation of dihydrocoumarins from 2–hydroxy cinnamaldehydes

An oven-dried screw-capped test tube equipped with a magnetic stirring bar was charged with the corresponding 2-hydroxy cinnamaldehyde **8** (0.40 mmol, 1 equiv.) which was then dissolved in ethyl acetate. After the addition of triazolium salt **7d** (0.02 mmol, 5 mol %) the vial was set under positive pressure of Argon. Finally, the indicated appropriate base (0.032 mmol, 8 mol%) was added and the reaction mixture was stirred at 80° C for 15 hours (TLC-control).

Workup procedure A

The reaction mixture was concentrated under reduced pressure and purified by column chromatography yielding pure chroman-2-one **A**.

Workup procedure B

The reaction mixture was cooled to ambient temperature, diluted with 3 mL ethyl acetate and washed four times with saturated NH_4Cl solution (2 mL portions). The organic layer was then washed four times with saturated $NaHCO_3$ solution (2 mL portions), whereupon a bathochromic shift was observed. Removal of polar compounds was accomplished by recurrent addition of petroleum ether (1–2 mL portions) and successive aqueous extraction (2 mL portions). This procedure was repeated until TLC indicated the complete removal of undesired compounds. Finally, the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, yielding δ-lactone **A** as major and the unsaturated δ-lactone **B** as minor constituent (for the respective ratios please, refer to table 3).

General Procedure 2: Preparation of chromen-2-one starting from 2-hydroxy cinnamyl alcohol

An oven–dried screw–capped test tube equipped with a magnetic stirring bar was charged with 2-hydroxy cinnamyl alcohol **10** (0.40 mmol, 1 equiv.) which was then dissolved in ethyl acetate. The vial was set under a positive pressure of Argon. After sequential addition of triazoliumsalt **7d** (0.04 mmol, 10 mol %), MnO_2 (4 mmol, 10 equiv.) and DMAP (0.032 mmol, 8 mol %) the reaction vessel was heated to 80 °C for 24 hours. The reaction mixture was diluted with DCM, filtered over a small pad of Celite and concentrated under reduced pressure. The residual red-brown liquid was purified by column chromatography using 10:1→7:1 hexanes/ethyl acetate mixtures as eluents.

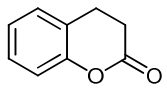
General Procedure 3: Preparation of 2-hydroxy cinnamaldehydes

In a round-bottom flask, 0.85 mL (1000 mg, 8.2 mmol, 1 equiv.) salicylaldehyde was dissolved in 60 mL benzene. After the addition of 3.738 g (12.2 mmol, 1.5 equiv.) (formylmethylene)triphenylphosphorane the mixture was heated to 110° C (reflux-condenser) under magnetic stirring for 7 hours. The reaction mixture was concentrated under reduced pressure and purified by column chromatography, yielding the desired 2-hydroxy cinnamaldehydes in 55% to 100%.[vi]

Experimental Data

Chroman-2-one [vii] (**2a**) according to **general procedure 1:**

Purified according to workup procedure **A** using hexanes/ethyl acetate 7:1 yielding 63% yellowish to brown oil. Yields for workup procedure **B** are given in table 3**.**

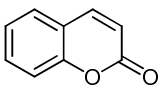


$C_9H_8O_2$
148.16

^{1}H NMR (300 MHz, $CDCl_3$) δ =7.26–7.10 (m, 2H), 7.10–6.95 (m, 2H), 3.01–2.89 (m, 2H), 2.78–2.69 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ =168.6, 152.0, 128.3, 128.0, 124.4, 122.6, 117.0, 29.3, 23.7; MS (EI) m/z (%) 148 (100) $[M]^+$, 120 (73) $[M–CO]^+$, 91 (65) $[M\text{-}CHO]^+$; IR (ATR-IR) 3042 , 2918, 1682, 1595, 1505; R_f = 0.34 (hexanes/ethyl acetate 3:1).

2*H*-Chromen-2-one[viii] (**2b**) according to **general procedure 2**:

Yield: 27 % (two steps) almost colourless solid.



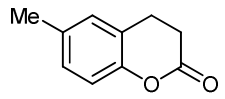
$C_9H_6O_2$
146.14

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.71 (d, J = 9.61 Hz, 1H), 7.58–7.44 (m, 2H), 7.38–7.22 (m, 2H), 6.42 (d, J = 9.61 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 160.8, 154.1, 143.5, 131.9, 127.9, 124.5, 118.9, 116.9, 116.7; MS (EI) m/z (%) 146 (70) $[M]^+$, 118 (100) $[M–CO]^+$, 90 (51) $[M\text{-}C_2O_2]^+$; IR (ATR-IR) 3075, 1699, 1677, 1619, 1602, 1562 ; R_f = 0.25 (hexanes/ethyl acetate 3:1).

[vi] Alternatively, the desired compounds can be prepared by aldol type reactions.
[vii] J. R. Hwu, Y. S. Wein, Y.-J. Leu, *J. Org. Chem*. **1996**, 61, 1493-1499.
[viii] R. S. Mali, V. J. Yadav, *Synthesis* **1977**, 464-465.

6-Methylchroman-2-one[ix] (**9a**) according to **general procedure 1:**

Purified according to workup procedure **A** using hexanes/ethyl acetate 7:1 yielding 54% brownish crystals. Yields for workup procedure **B** are given in table 3**.**

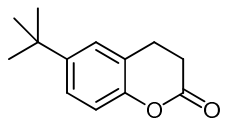


$C_{10}H_{10}O_2$
162.19

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.10–6.88 (m, 3H), 3.20–2.89 (m, 2H), 2.81–2.70 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 168.9, 149.9, 134.0, 128.7, 128.5, 122.3, 116.7, 29.3, 23.7, 20.7; MS (EI) m/z (%) 162 (100) $[M]^+$, 134 (86) $[M–CO]^+$, 91 (76) $[C_7H_7]^+$; HRMS (EI) calcd for $C_{10}H_{10}O_2$ $[M]^+$: 162.0681; found 162.0681; IR (ATR-IR) 3032, 2925, 2863, 1740, 1616, 1499; m.p. = 74 °C (lit.[x] 77 °C); R_f = 0.35 (hexanes/ethyl acetate 3:1).

6-*tert*-Butylchroman-2-one (**10a**) according to **general procedure 1**:

Purified according to workup procedure **A** using hexanes/ethyl acetate 10:1 yielding 52% yellow to brown oil. Yields for workup procedure **B** are given in table 3**.**



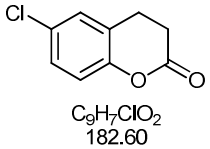
$C_{13}H_{16}O_2$
204.26

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33–7.22 (m, 1H), 7.22–7.15 (m, 1H), 6.98 (d, *J* = 8.51 Hz, 1H), 3.05–2.94 (m, 2H), 2.83–2.73 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 168.9, 149.8, 147.5, 125.2, 124.9, 121.8, 116.4, 34.4, 31.4, 29.4, 24.0; MS (EI) m/z (%) 204 (22) $[M]^+$, 189 (100) $[M\text{-}CH_3]^+$, 161 (30) $[M\text{-}CH_3\text{-}CO]^+$ oder $[M\text{-}C_2H_4]^+$; HRMS (EI) calcd for $C_{13}H_{16}O_2$ $[M]^+$: 204.1150. Found 204.1155; IR (ATR-IR) 2961, 2905, 2869, 1745, 1707, 1612, 1503 ; R_f = 0.41 (hexanes/ethyl acetate 3:1).

6-Chlorochroman-2-one (**11a**) according to **general procedure 1**:

Purified according to workup procedure **A** using hexanes/ethyl acetate 6:1 yielding 51% almost colourless crystals. Yields for workup procedure **B** are given in table 3**.**

[ix] P. Cannone, D. Belanger, G. Lemay, *Synthesis* **1980**, 301-303.
[x] K. Sato, T. Amakasu, S. Abe, *J. Org. Chem.* **1964**; *29*, 2971-2972.

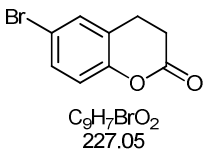


$C_9H_7ClO_2$
182.60

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25–7.17 (m, 2H), 6.99 (d, *J* = 8.51 Hz, 1H), 3.05–2.94 (m, 2H), 2.84–2.74 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 167.8, 150.6, 129.4, 128.3, 127.9, 124.3, 118.3, 28.8, 23.6; MS (EI) m/z (%) 182 (65) $[M]^+$, 156 (34) $[M\text{-}C_2H_2]^+$, 154 (100) $[M–CO]^+$, 91 (92) $[C_7H_7]^+$; HRMS (EI) calcd for $C_9H_7ClO_2$ $[M]^+$: 182.0135; found 182.0133.; IR (ATR-IR) 2960, 1734, 1611, 1480 ; m.p. = 105 °C (lit.[xi] 107–110 °C); R_f = 0.35 (hexanes/ethyl acetate 3:1).

6-Bromochroman-2-one (**12a**) according to **general procedure 1**:

Purified according to workup procedure **A** using hexanes/ethyl acetate 7:1 yielding 53% beige crystals. Yields for workup procedure **B** are given in table 3**.**

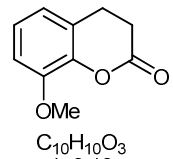


$C_9H_7BrO_2$
227.05

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.42–7.31 (m, 2H), 6.93 (d, *J* = 8.23 Hz, 1H), 3.05–2.94 (m, 2H), 2.83–2.73 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 167.7, 159.1, 131.3, 130.9, 124.7, 118.7, 116.9, 28.8, 23.6; MS (EI) m/z (%) 228 (80) $[M]^+$, 226 (73) $[M]^+$, 200 (75) $[M–CO]^+$ bzw. $[M\text{-}C_2H_4]^+$, 198 (79), 91 (100) $[C_7H_7]^+$, 77 (57) $[C_6H_5]^+$, 51 (46) [C4H3+]; HRMS (EI) calcd for $C_9H_7{}^{79}BrO_2$ $[M]^+$: 225.9630; found 225.9624; IR (ATR-IR) 2849, 1761, 1725, 1602, 1559, 1476 ; m.p. = 98 °C (lit.[xii] 97–98 °C); R_f = 0.37 (hexanes/ethyl acetate 3:1).

8-Methoxychroman-2-one (**13a**) according to **general procedure 1**:

Purified according to workup procedure **A** using hexanes/ethyl acetate 5:1 yielding 54% beige solid. Yields for workup procedure **B** are given in table 3**.**



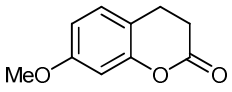
$C_{10}H_{10}O_3$
178.18

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.03 (t, *J* = 7.96 Hz, 1H), 6.85 (d, *J* = 8.23 Hz, 1H), 6.81–6.72 (m, 1H), 3.88 (s, 3H), 3.05–2.94 (m, 2H), 2.82–2.72 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 166.9, 146.6, 140.2, 123.3, 122.8, 118.5, 110.0, 55.0, 28.1, 22.9; MS (EI) m/z (%) 178 (100) $[M]^+$, 150 (43) $[M\text{-}CO]^+$, 136 (40) $[M\text{-}C_2H_2O]^+$, 135 (56) $[M\text{-}CO\text{-}CH_3]^+$; HRMS (EI) calcd for $C_{10}H_{10}O_3$ $[M]^+$: 178.0630; found 178.0632.; IR (ATR-IR) 2961, 2936, 2842, 1746, 1694, 1619, 1601, 1479 ; m.p. = 75 °C (lit.[xiii] 77 °C); R_f = 0.20 (hexanes/ethyl acetate 3:1).

[xi] J. C. Westfahl, T. L. Gresham, *J. Am. Chem. Soc.* **1954**, *76*, 1076-1080.
[xii] X. Verdaguer, M. C. Hansen, S. C. Berk, S. L. Buchwald, *J. Org. Chem.* **1997**, *62*, 8522-8528.
[xiii] N. Kretchmer, R. Taylor, *J. Am. Chem. Soc.* **1950**, *72*, 3291-3292.

7-Methoxychroman-2-one (**14a**) according to **general procedure 1**:

Purified according to workup procedure **A** using hexanes/ethyl acetate 5:1 yielding 25% slightly red oil. Yields for workup procedure **B** are given in table 3**.**

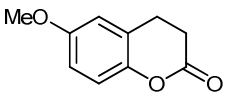


$C_{10}H_{10}O_3$
178.18

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.07 (d, *J* = 8.23 Hz, 1H), 6.69–6.58 (m, 2H), 3.00–2.88 (m, 2H), 2.81–2.72 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 168.6, 159.7, 152.7, 128.5, 114.4, 110.4, 102.5, 55.6, 29.5, 23.0; MS (EI) m/z (%) 178 (100) $[M]^+$, 150 (41) $[M–CO]^+$, 136 (36) $[M\text{-}C_2H_2O]^+$, 135 (8) $[M\text{-}CO\text{-}CH_3]^+$; HRMS (EI) calcd for $C_{10}H_{10}O_3$ $[M]^+$: 178.0630; found 178.0628.; IR (ATR-IR) 2911, 2838, 1764, 1625, 1588, 1508; R_f = 0.30 (hexanes/ethyl acetate 3:1).

6-Methoxychroman-2-one (**15a**) according to **general procedure 1**:

Purified according to workup procedure **A** using hexanes/ethyl acetate 5:1 yielding 48% brown oil. Yields for workup procedure **B** are given in table 3**.**

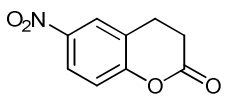


$C_{10}H_{10}O_3$
178.18

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.96 (d, *J* = 8.78 Hz, 1H), 6.81–6.65 (m, 2H), 3.10–2.89 (m, 2H), 2.81–2.69 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 168.8, 156.1, 145.9, 123.6, 117.6, 113.3, 113.1, 55.7, 29.2, 24.0; MS (EI) m/z (%) 178 (100) $[M]^+$, 150 (40) $[M–CO]^+$, 136 (71) $[M\text{-}C_2H_2O]^+$, 135 (56) $[M\text{-}CO\text{-}CH_3]^+$; HRMS (EI) calcd for $C_{10}H_{10}O_3$ $[M]^+$: 178.0630; found 178.0630.; IR (ATR-IR) 2938, 2839, 1734, 1708, 1595, 1494 ; R_f = 0.22 (hexanes/ethyl acetate 3:1).

6-Nitrochroman-2-one (**16a**) according to **general procedure 1**:

Purified according to workup procedure **A** using hexanes/ethyl acetate 7:1 yielding 18% almost colourless crystals. Yields for workup procedure **B** are given in table 3**.**



$C_9H_7NO_4$
193.16

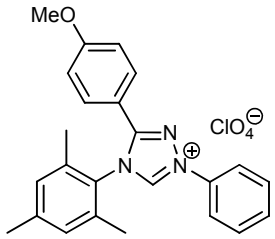
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.24–8.12 (m, 2H), 7.18 (d, *J* = 8.51 Hz, 1H), 3.21–3.07 (m, 2H), 2.94–2.81 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 166.4, 156.4, 144.1, 124.4, 124.0, 123.7, 117.9, 28.4, 23.7; MS (EI) m/z (%) 193 (100) $[M]^+$, 165 (45) $[M–CO]^+$, 135 (34) $[M\text{-}CO\text{-}NO]^+$; HRMS (EI) calcd for $C_9H_7NO_4$

$[M]^+$: 193.0375; found 193.0379.; IR (ATR-IR) 3110, 2923, 2854, 1779, 1728, 1694, 1610, 1515 ; m.p. = 126 °C (lit.[xiv] 130–136 °C); R_f = 0.21 (hexanes/ethyl acetate 3:1).

Experimental Data for Triazolium-Precatalyst 7d

4-Mesityl-3-(4-methoxyphenyl)-1-phenyl-4*H*-1,2,4-triazol-1-ium perchlorate (7d)

Prepared according to reported protocols:[iib] colorless solid.



^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.67 (s, 1H), 8.25–8.15 (m, 2H), 7.72–7.55 (m, 3H), 7.50–7.41 (m, 2H), 7.09 (s, 2H), 6.95–6.88 (m, 2H), 3.84 (s, 3H), 2.40 (s, 3H), 2.08 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 163.3, 154.0, 142.6, 141.5, 134.6, 134.5, 131.3, 130.7, 130.5, 129.6, 127.8, 120.7, 115.1, 114.2, 55.6, 21.4, 17.9; HRMS (EI) calcd for $C_{24}H_{24}N_3O$ $[M]^+$: 370.1919; found 370.1910; IR (ATR-IR) 3049, 2934, 1702, 1610, 1486, 1464; m.p. = 205 °C.

→Please find supporting information including **^{1}H- and ^{13}C-NMR spectra** on the enclosed CD.

2.2.5 References

(1) (a) Berkessel, A; Gröger, H. *Asymmetric Organocatalysis*, WILEY-VCH: Weinheim 2005. (b) Dalko, P. I. *Enantioselective Organocatalysis*, WILEY-VCH: Weinheim, 2007.

(2) For some recent reviews on organocatalysis, see: (a) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660. (b) special issue on organocatalysis: *Chem. Rev.* **2007**, *107* (12), 5413–5883. (c) special issue on organocatalysis: *Acc. Chem. Res.* **2004**, *37* (8), 487–631. (d) special issue on organocatalysis: *Adv. Synth. Catal.* **2004,** *346* (9/10), 1007–1249. (e) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175. (f) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724.

(3) For recent reviews on NHC-catalyzed reactions, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655. (b) Zeitler, K. *E. Schering Found. Symp. Proc.* **2007***, 2*, 183–206. (c) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988–3000. (d) Zeitler, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 7506–7510. (e) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534–541.

(4) Seebach, D. *Angew. Chem. Int. Ed.* **1979**, *18*, 239–258.

[xiv] T. M. Kitson, G. H: Freeman, *Bioorg. Chem.* **1993**, *21*, 354-365.

(5) (a) Kluger, R.; Tittman, K. *Chem. Rev.* **2008**, *108*, 1797–1833. (b) Frank, R. A. W.; Leeper, F. J.; Luisi, B. F. *Cell. Mol. Life Sci* **2007**, *64*, 892–905. (c) Müller, M.; Sprenger, G. A. in *Oxidative Stress and Diseases – Thiamine: Catalytic Mechanisms and Disease States* (Eds: F. Jordan, M. S. Patel), Marcel Dekker: New York, 2004, pp. 77–90.

(6) (a) Hoffmann, R. W. *Synthesis* **2006**, 3531–3541. (b) Gademann, K.; Bonazzi, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 5656–5658. For two recent examples, please see: (c) Enquist Jr., J. A.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231. (d) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404–408.

(7) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*, Wiley: New York, 1995.

(8) For examples of NHC–catalyzed preparation of lactones, see: β-lactones: (a) Burstein, C.; Tschan, S.; Xie, X.; Glorius, F. *Synthesis* **2006**, 2418–2439. (b) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098–10099. γ-butyrolactones: (c) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371. (d) Glorius, F.; Burstein, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6205–6208. (e) Ye, W.; Cai, G.; Zhuang, Z.; Jia, X.; Zhai, H. *Org. Lett.* **2005**, *7*, 3769–3771. (f) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507–509. (g) Li, Y.; Zhao, Z.-A.; He, H.; You, S.-L. *Adv. Synth. Cat.* **2008**, *350*, 1885–1890. δ-lactones (in combination with Michael reaction): (h) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3107–3110. δ-lactones (in combination with Aldol reaction): (i) Toräng, J.; Vanderheiden, S.; Nieger, M.; Bräse, S. *Eur. J. Org. Chem.* **2007**, 943–947. δ-lactones *via* Hetero-Diels-Alder reaction: (j) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088–15089. (k) He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817–3820.

(9) For a different NHC-catalyzed approach to δ-butyrolactones *via* ketene derived zwitterionic enolates, see: Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S. *Chem. Eur. J.* **2008**, *14*, 8473–8476.

(10) (a) Zeitler, K. *Org. Lett.* **2006**, *8*, 637–640. (b) Zeitler, K.; Mager, I. *Adv. Synth. Catal.* **2007**, *349*, 1851–1857.

(11) (a) Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriate, E. *Curr. Med. Chem.* **2005**, *12*, 887–916. (b) Estévez-Braun, A.; González, A. G. *Nat. Prod. Rep.* **1997**, *14*, 465–475. (c) O´Kennedy, R.; Thornes, R. D. *Coumarins: Biology, Applications and Mode of Action*, Wiley: Chichester, 1997.

(12) Katerinopoulos, H. E. *Curr. Pharm. Des.* **2004**, *10*, 3835–3852.

(13) (a) Hepworth, J. D. in *Comprehensive Heterocyclic Chemistry* Vol. 3 (Eds. A. Katritzky, C. W. Rees, A. J. Boulton, A. McKillop), Pergamon: Oxford, 1984, pp 799–810. (b) see also references cited in 14a.

(14) For some recent transition metal catalyzed reactions, please see: (a) Gabriele, B.; Mancuso, R.; Salerno, G.; Plastina, P. *J. Org. Chem.* **2008**, *73*, 756–759. (b) Kotani, M.; Yamamoto, K.; Oyamada, J.; Fujiwara, Y.; Kitamura, T. *Synthesis* **2004**, 1466–1470. (c) Kadnikov, D. V.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3643–3646. (d) Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc.* **2003**, *125*, 4518–4526.

(15) (a) Kuhn, W.; Funk, H.-U.; Senft G. (Haarmann & Reimer GmbH), WO2002018360, **2002**. (b) Zhang, Z.; Ma, Y.; Zhao, Y. *Synlett* **2008**, 1091–1095. (c) Häser, K.; Wenk, H. H.; Schwab, W. *J. Agric. Food Chem.* **2006**, *54*, 6236–6240.

(16) For an elegant phosphine catalyzed exception, please see: (a) Henry, C. E.; Kwon, O. *Org. Lett.* **2007**, *9*, 3069–3072. For the preparation of furo-coumarins using an enamine approach, see: (b) Rueping, M.; Merino, E.; Sugiono, E. *Adv. Synth.Catal.* **2008**, *350*, 2127–2131. (c) For a concurrent related NHC-catalyzed access, see: Du, D.; Wang, Z. *Eur. J. Org. Chem.* **2008**, 4949-4954.

(17) Substrates could be prepared in good yields *via* Wittig olefination of the corresponding salicylaldehydes and (formylmethylene)triphenylphosphorane: Bunce, R. A.; Schilling III, C. L. *Tetrahedron* **1996**, *53*, 9477–9486. For a general procedure, please see supporting information.

(18) Thiazolium: (a) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518–9519. (b) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126–8127.

Benzimidazolium: (c) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905–908. Imidazolium, e. g.: ref. 8c, d.

(19) Application of reaction conditions as reported by Scheidt et. al. (ref. 18c) for a related intermolecular reaction did not yield the desired product.

(20) Rovis, T. *Chem. Lett.* **2008**, *37*, 2–7.

(21) Struble, J. R.; Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 957–960.

(22) (a) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797. (b) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799.

(23) For a detailed study of this benzylic activation of aldehyde precursors, please refer to: (a) Maki, B. E.; Scheidt, K. A. *Org. Lett*. **2008**, *10*, 4331–4334. For a MnO_2 tandem oxidation approach, see: (b) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371–374. (c) Guin, J; De Sarkar, S.; Grimme, S.; Studer, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 8727–8730.

(24) The residual amount of oxidized by-product (3%) could be assigned to an alternative hydride transfer mechanism. As described by Scheidt et al. in the context of stereoselective protonation attempts of homoenolates, alternatively, intermediate **III** could be formed in a Cannizzaro-type fashion *via* intermolecular hydride transfer, but at the cost of the reduction of an equimolar amount of the starting material: Maki, B. E.; Chan, A.; Scheidt, K. A. *Synthesis* **2008**, 1306–1315.

(25) For details, please see supporting information on enclosed CD.

(26) Trost, B. M. *Science* **1991**, *254*, 1471–1477.

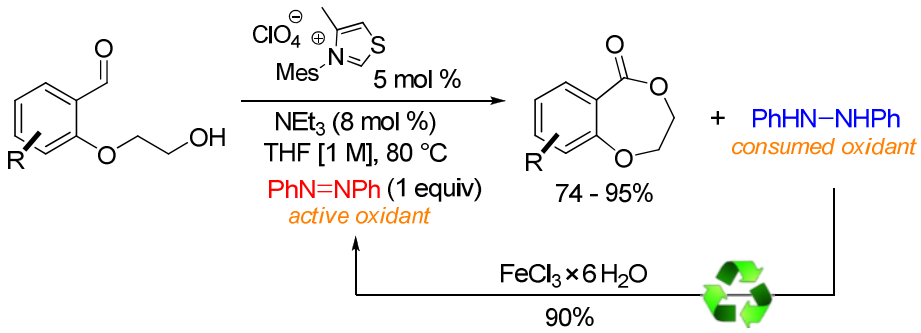
(27) For excellent reviews on domino reactions, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (c) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*, WILEY-VCH: Weinheim, 2006.

(28) (a) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616–5617. (b) Foot, J. D; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. *Synthesis* **2003**, 1055–1064.

(29) For a recent application of azobenzene as organic oxidizer, please see: Noonan, C.; Baragwanath, L:; Connon, S. J. *Tetrahedron Lett.* **2008**, *49*, 4003–4006.

(30) In the presence of bases like DMAP, coumarins can also be formed *via* an alternative hemiacetal pathway[28b] while solely MnO_2 showed only incomplete conversion suggesting a possible promotion of double bond isomerization and consequent acetalization by nucleophilic catalysts.

2.3 Efficient Catalytic, Oxidative Lactonization for the Synthesis of Benzodioxepinones Using Thiazolium Derived Carbene Catalysts[i]



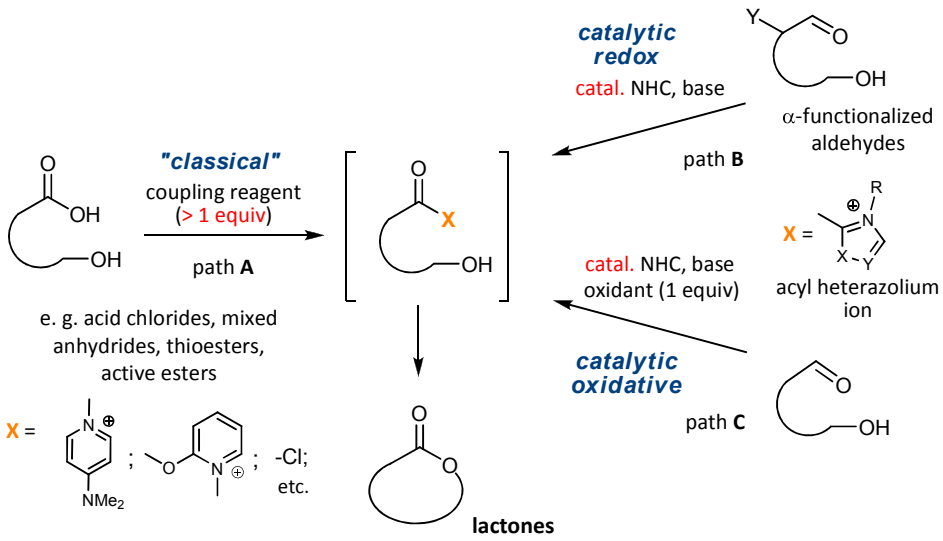
An efficient, oxidative carbene-catalyzed lactonization reaction has been developed. Using thiazolium precatalysts a variety of benzodioxepinone products is accessible in good to excellent yields under mild and operationally simple conditions. The reaction does not require high dilution conditions and proceeds *via* mild and selective oxidation with azobenzene, which can easily be recovered and reused applying inexpensive $FeCl_3$ as formal terminal oxidant.[ii]

[i] Reproduced with permission from: C. A. Rose, K. Zeitler, *Org. Lett*. **2010**, *12*, 4552 – 4555. Copyright 2010 American Chemical Society.

[ii] All experiments were carried out by C. A. R.

2.3.1 Introduction

Lactones are ubiquitous motifs in organic chemistry and constitute the core of many biologically active compounds and natural products. As a consequence the mild and efficient preparation of these cyclic systems, particularly *via* new strategies, remains an important objective. Thus, a variety of powerful methods for the "carbonyl centered"[1] ring closure has been developed, including numerous approaches of coupling pre-formed or *in situ* activated acyl species, such as mixed anhydrides, thioesters, acyl halides or activated esters, amenable for the subsequent C-O bond formation with the nucleophilic alcohol species.[2] However, such classical lactonization protocols starting from the parent acid (Scheme 1, path A) require the (super)stoichiometric use of an activation reagent and often depend on non "step-economical"[3] protection/deprotection sequences to ensure chemoselectivity and to avoid potential side reactions. In contrast, there are only few catalytic reactions to achieve the desired ring closure. Based on Cannizzaro-, respectively Tishchenko-type disproportionation of dialdehydes only recently a number of elegant transition-metal catalyzed intramolecular ketone hydroacylation processes[4, 5] have been developed; general organocatalytic lactonization approaches are rather rare.[6] Additionally, in the context of valuable alternative transformations oxidative lactonization reactions[7] have recently attracted a revived interest.[8]

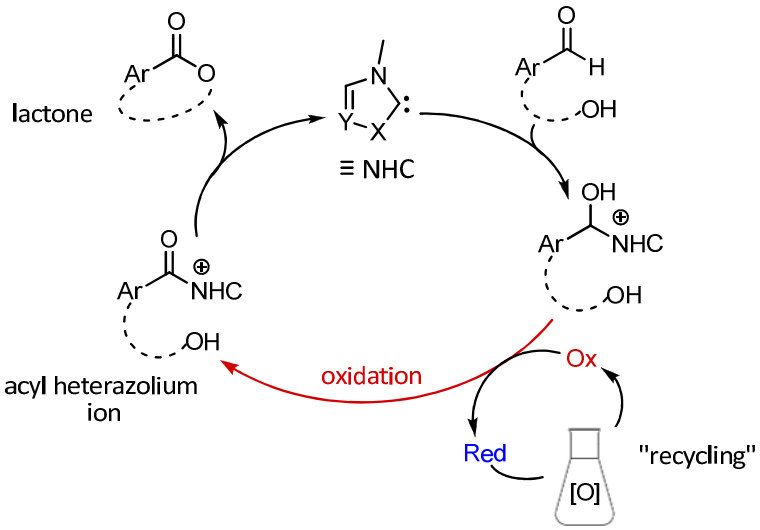


Scheme 1: Overview of stoichiometric and (NHC) catalytic lactonization approaches *via* activated acyl species.

Apart from the versatile chemistry of *N*-heterocyclic carbene (NHC) catalyzed C-C bond formations[9] NHCs also allow for the catalytic generation of activated acyl azolium species which can undergo subsequent C-O or C-N bond formation.[10] In general, these activated carboxylates are not only accessible *via internal* redox reactions employing α–functionalized aldehyde precursors (Scheme 1,

path B),[11] but can, in principle, also be obtained from unfunctionalized aldehydes upon carbene attack *via external* oxidation (Scheme 1, path C)[12, 13] of the corresponding initial intermediate.

Recently, we reported on the NHC-mediated synthesis of 3,4-dihydrocoumarins following the intramolecular redox strategy starting from *o*-hydroxycinnamaldehydes.[14]



Scheme 2: Catalytic oxidative lactonization using NHCs.

The obvious benefits of a related oxidation/ esterification sequence using heterazolium derived carbenes as *catalytic acyl transfer agents* for the synthesis of lactones and the significant potential of merging this approach with a operationally trivial recycling method for the oxidant prompted us to evaluate the feasibility of this concept (Scheme 2). Herein, we disclose the successful development of a simple carbene-catalyzed oxidative lactonization protocol for the efficient synthesis of benzodioxepinone derivatives.

Macrocyclic benzolactones such as the marine salicylihalamides and structurally related salicylic acid lactones exhibit attractive biological properties;[15] also the lichen and endophytic fungi derived class of depsidones with their characteristic 7-membered benzo[*e*]1,4-dioxepan-5-one core shows a broad range of interesting biological activities.[16] Moreover, in perfumery so-called marine notes mainly stem from benzodioxepinone compounds.[17]

2.3.2 Results and Discussion

Our initial experiments began with simple test substrates, such as **6**, which could be conveniently prepared from salicylaldehyde derivatives.[18] At the outset of our study we investigated the efficacy and selectivity of various heterazolium salt/base combinations (table 1). As we envisioned the "reactivation" of the oxidizing agent, we focused on mild organic oxidants, such as azobenzene,[13c,g,i] which previously had proven to also work successfully without the general requirement of being applied in excess.

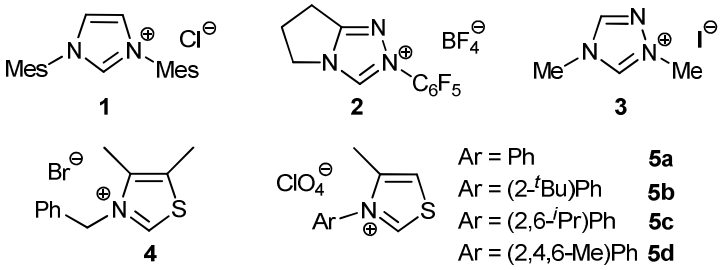
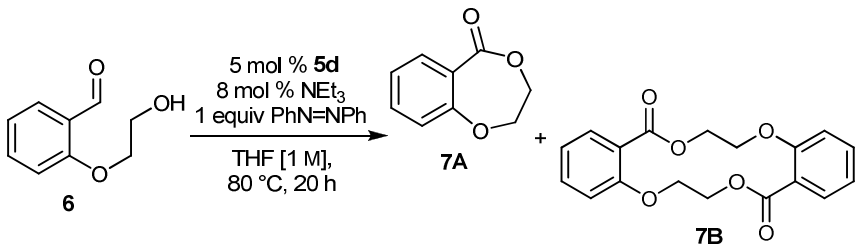


Figure 1: Evaluated heterazolium derived carbene precursors.

After examining a number of common NHC precursors (figure 1 and table 1) we found that sterically hindered Mes-substituted thiazolium perchlorate **5d** in combination with NEt_3 and azobenzene indeed promotes the desired cyclization providing lactone **7A** in excellent yield (94%, entry 1).[19] Gratifyingly, our initial concerns centered on a potential concurrent competing dimerization[2a] of the starting material were not confirmed as even at 1 M substrate concentration we could only detect traces of the 14-membered diolide **7B**.[20] In a brief solvent screen toluene and dichloromethane in addition to THF gave best yields while the use of chloroform and acetonitrile showed some limitations and ethyl acetate proved ineffective. Changing the oxidant to MnO_2 resulted in diminished, but still very good yield. (entry 2).[21]



entry	variation of standard condition	yield[a] **A** [%]	yield[a] **B** [%]
1	none	95 (94)[b]	< 5
2	1 equiv of MnO_2 instead of azobenzene	84	< 5
3[c]	**1** instead of **5d**, 5 mol % DMAP instead of NEt_3, toluene [0.5 M] instead of THF	10	< 5
4	**2** instead of **5d**	49	< 5
5[d]	**3** instead of **5d**, 1.2 equiv DBU instead of NEt_3, 5 equiv MnO_2 instead of azobenzene, toluene[c]	41	< 5
6	**4** instead of **5d**	93	7
7	**5a** instead of **5d**	27	< 5
8	**5b** instead of **5d**	91	< 5
9	**5c** instead of **5d**	93	< 5
10	0 mol % **5d**	0	0
11	0 mol % **5d**; 1 equiv MnO_2 instead of azobenzene	0	0

[a] Yields determined by ^{1}H NMR using 1,1,2-trichloroethylene as internal standard. [b] Isolated yield. [c] Reaction conditions according to ref 11f .[d] Reaction conditions related to ref 12a. [e] c = 0.2 M

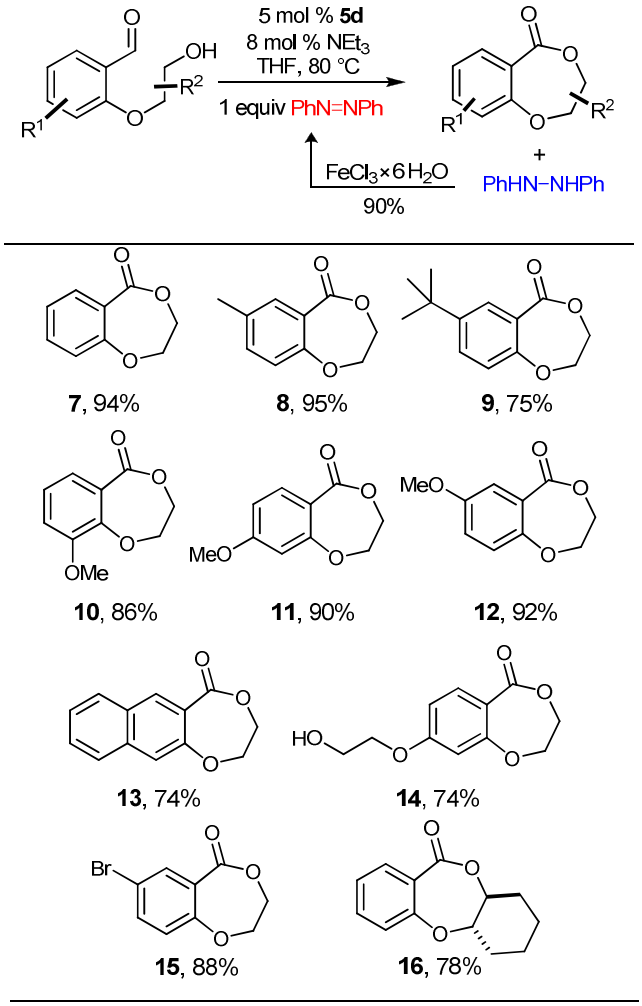
Table 1: Optimization of reaction conditions for oxidative lactonization.

This study also revealed marked effects on reactivity and performance of the heterazolium carbene precursors emphasizing the importance of the employment of thiazolium derived carbenes for this process (entries 6-9 *vs*. entries 3-5). In the presence of imidazolium precatalyst **1** lactone **7A** was obtained in poor yield while triazolium salts **2** and **3** only showed moderate activity for the desired conversion (including versatile conditions developed by Scheidt et al.; entry 5). Within the group of thiazolium precatalysts simple, commercially available benzyl-substituted precatalyst **4** demonstrated an excellent performance for this transformation, albeit with a slightly diminished selectivity (entry 6). However, *N*-phenyl thiazolium catalyst **5a** only displayed minor lactonization reactivity providing further evidence for the need of a distinct steric environment. We also performed control experiments in order to verify the essential catalytic role of the NHCs for this transformation and to exclude a conceivable hemiacetal oxidation/lactonization process.[22] In the absence of a NHC catalyst no conversion could be observed (entries 10 and 11).

In an effort to further improve our conditions with respect to the terminal oxidant, also being aware of the potential drawbacks of the stoichiometric use of azobenzene, which could significantly curtail the attractivity of our method, we turned our attention to finding a useful, operationally trivial recycling

procedure. After separation of the reduced hydrazobenzene from the product *via* simple filtration over SiO_2 it was treated with $FeCl_3 \times 6H_2O$ in aqueous acetone under reflux.[23] After 5 min, the reoxidized, active oxidant azobenzene can be isolated by filtration, thus rendering this process more attractive by employing $FeCl_3$ as an inexpensive formal oxidant.[24]

Having developed optimal conditions for the oxidative lactonization we next examined the substrate scope of this transformation. As shown in Scheme 3 a wide range of differently substituted electron-rich as well as electron-deficient aromatic hydroxyaldehydes can undergo catalytic lactonization with good to excellent yields.

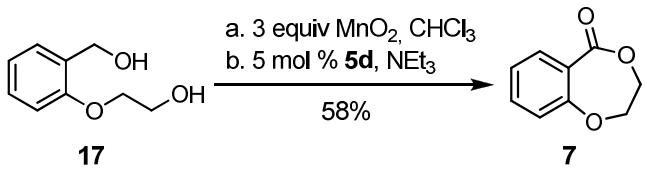


Scheme 3: Substrate Scope of the Catalytic Lactonization.

Due to the mild reaction conditions and the chemoselective oxidant additional hydroxy groups are tolerated without further protection (**14**, 74% yield). This method is also applicable to secondary alcohol precursors, e. g. pro-viding access to tricyclic lactone **16** with 78% isolated yield. Interestingly, an illustrative survey of the olfactory properties of lactones **8**, **9** and **10** evidenced their

quite remarkable high intensity as odorants (threshold values: 250 ng/L air, 0.050 ng/L air resp. 0.99 ng/L air).

Taking advantage of MnO_2´s[12] ability to effectively oxidize allylic and benzylic alcohols and having its usability as alternative oxidant for the oxidative lactonization in mind we envisioned its application for a tandem sequence combining benzylic oxidation with subsequent oxidative lactonization.



Scheme 4:Tandem One-Pot Oxidation/Lactonization Process.

As depicted in Scheme 4 this two-step transformation could be performed as a single-flask procedure without the need of intermediate purification providing lactone **7** in an overall isolated yield of 58%.

2.3.3 Conclusion

In conclusion, we have developed an NHC-catalyzed mild oxidative lactonization protocol under non high-dilution conditions. Application of $FeCl_3$ as recycling agent and thus as formal terminal oxidant, provides an efficient access to interesting benzodioxepinones derivatives. Future studies will explore the full scope of this method[25] and its application.

2.3.4 Experimental Section

General Methods

NMR spectra were recorded on a Bruker Avance 300 (300.13 MHz) spectrometer using the solvent peak as internal reference ($CDCl_3$: δ H 7.26; δ C: 77.0; d^6-Acetone δ H 2.05; δ C 29.84, 206.26). Multiplicities are indicated, s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet); coupling constants (*J*) are in Hertz (Hz).

Mass spectra (MS ESI) were recorded with a Finnigan MAT 95 or Varian MAT 311A. All reactions were monitored by thin–layer chromatography (TLC) using Merck silica gel plates 60 F_{254}; visualization was accomplished with UV light and/or staining with appropriate stains (anisaldehyde, vanillin). Standard chromatography procedures were followed (particle size 63 – 200 μm). Solvent mixtures are understood as volume/volume. Infrared Spectra were obtained using samples on a Biorad Excalibur FTS 3000 FT IR spectrometer equipped with a universal ATR sampling accessory (Specac Golden Gate Diamond Single Reflection ATR system); wave numbers $\tilde{\nu}$ are reported in cm^{-1}.

All reactions were carried out under an atmosphere of Argon in oven-dried glassware with magnetic stirring. THF was distilled from sodium/benzophenone. $CHCl_3$, MeCN and toluene were purchased at absolute quality and stored over molecular sieves. DCM and EtOAc were technical grade and distilled prior to use. Solvents for column-chromatography (EtOAc, hexanes) were technical grade and distilled prior to use.

NEt_3 was stored over molecular sieves. Other chemicals (azobenzene, MnO_2, DBU, DMAP) were used as purchased from the supplier provided without further purification. Heterazolium salts were prepared according to reported protocols.[26, 27, 28, 29, 30] A synthetic procedure for catalyst **5d** including its full experimental characterization has been reported by Glorius and coworkers.[31]

Ortho-hydroxyethoxy benzaldehydes **S6a-S6i** were synthesized from the corresponding salicylaldehyde derivative and 2-chloroethanol according to a known literature procedure;[32,33] 2-(2-hydroxycyclohexyloxy)benzaldehyde **S6j** was prepared from salicylaldehyde and cyclohexene oxide according to a known literature procedure.[34] 2-(2-(Hydroxymethyl)phenoxy)ethanol **S6k** was synthesized according to a slightly modified known procedure by reduction of the corresponding aldehyde with $NaBH_4$ in THF instead of MeOH.[35]

General Procedures

General Procedure 1 (Oxidative NHC-Catalyzed Lactonization)

An oven dried screw-capped test-tube equipped with a magnetic stirring bar was charged with corresponding hydroxyethoxy arylcarbaldehyde **S6** (0.6 mmol) and 0.6 mL of THF. After the resulting solution has been stirred for 5 minutes, thiazolium perchlorate **5d** (10 mg, 0.03 mmol) and azobenzene (109 mg, 0.6 mmol) were added. Now NEt_3 (7 µL, 0.048 mmol) was added *via* syringe and the vial was flushed with Argon. After having sealed the reaction vessel with a screw-cap, the mixture was stirred and heated to 80° C for 20h. After cooling to ambient temperature, the crude reaction mixture was concentrated *in vacuo* and purified by filtration over SiO_2 resp. chromatography (separation from hydrazobenzene).

General Procedure 2 (One Pot Oxidation/Oxidative NHC-Catalyzed Lactonization)

An oven dried screw-capped test-tube equipped with a magnetic stirring bar was charged with 2-(2-(hydroxymethyl)phenoxy)ethanol (**S6k**) (168 mg, 1 mmol) and 1 mL of $CHCl_3$. After addition of MnO_2 (261 mg, 3 mmol) the vial was sealed with a screw-cap and heated to 80° C. After full conversion to the aldehyde (20 h, indicated by TLC), the mixture was allowed to cool to ambient temperature. Now thiazolium perchlorate **5d** (16 mg, 0.05 mmol) and NEt_3 (11 µL, 0.08 mmol) were added. The vial was flushed with Ar, sealed with a screw-cap and heated to 80 °C for 24h under magnetic stirring. After cooling to ambient temperature, the mixture was filtered over a pad of celite and rinsed with a solution of 10 % MeOH in DCM (total amount 50 mL). The filtrate was concentrated *in vacuo* and purified by column chromatography yielding 96 mg (58%) of benzodioxepinone **7** as pale yellow oil.

General Procedure 3 (Sample Preparation for Quantitative NMR Experiments using Trichloroethylene)

The reaction mixture was allowed to cool to ambient temperature. Subsequently, trichloroethylene (54 µL, 0.6 mmol) was added *via* syringe and the solution was stirred for 5 minutes. Now a sufficient amount of the mixture (ca. 0.05 mL) was transferred into an NMR-tube (using a Pasteur pipet), diluted with $CDCl_3$ and submitted to NMR analysis.

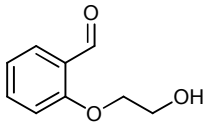
General Procedure 4 ("Recycling" of Azobenzene)

After isolation of hydrazobenzene (110 mg, 0.6 mmol) from the reaction mixture *via* filtration of the crude reaction mixture over SiO_2, it was dissolved in 5 mL of acetone and heated to 75°C. To the orange mixture was added a solution of $FeCl_3$ hexahydrate (324 mg, 1.2 mmol) in 1.5 mL H_2O and the resulting darker orange mixture was stirred at 75 °C for 5 min. Upon cooling in an ice-bath the azobenzene precipitates and can be collected by filtration.

For *small scale reactions* the following alternative extraction procedure sometimes is more convenient: After heating the mixture was allowed to cool to ambient temperature and 15 mL H_2O were added. Extraction with DCM (4×20 mL) followed by washing of the combined organic layers with sat. NaCl-solution and finally evaporation of the solvent affords azobenzene (98 mg, 90% recovery) as orange crystals.

Experimental Data for Substrates

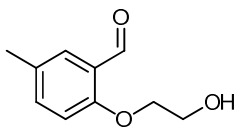
2-(2-Hydroxyethoxy)benzaldehyde (S6a)



$C_9H_{10}O_3$
166.17

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.42 (d, *J* = 0.6 Hz, 1H), 7.79 (dd, *J* = 7.7 Hz, 1.7 Hz, 1H), 7.57 – 7.47 (m, 1H), 7.08 – 6.94 (m, 2H), 4.20 (t, *J* = 4.5 Hz, 2H), 4.02 (t, *J* = 4.5 Hz, 2H), 2.99 (br s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 190.1, 160.9, 136.1, 129.7 125.0, 121.1, 113.0, 70.2, 61.1. HRMS (EI) calcd for $C_9H_{10}O_3$ $[M]^+$: 166.0630 Found 166.0631.

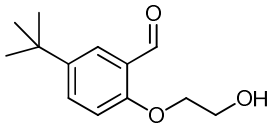
2-(2-Hydroxyethoxy)-5-methylbenzaldehyde (S6b)



$C_{10}H_{12}O_3$
180.20

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.40 (s, 1H), 7.59 (d, *J* = 2.2 Hz, 1H), 7.34 (dd, *J* = 8.5 Hz, 1.9 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 4.17 (t, *J* = 4.5 Hz, 2H), 4.01 (t, *J* = 4.3 Hz, 2H), 2.75 (s, 1H), 2.31 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 190.4, 159.0, 136.7, 130.6, 129.6, 124.7, 113.0, 70.3, 61.1, 20.3. HRMS (EI) calcd for $C_{10}H_{12}O_3$ $[M]^+$: 180.0786 Found 180.0784.

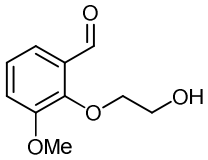
5-*tert*-Butyl-2-(2-hydroxyethoxy)benzaldehyde (S6c)



$C_{13}H_{18}O_3$
222.28

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.40 (s, 1H), 7.83 (d, *J* = 2.7 Hz, 1H), 7.58 (dd, *J* = 8.6 Hz, 2.6 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 4.20 (t, *J* = 4.5 Hz, 2H), 4.02 (t, *J* = 4.5 Hz, 2H), 2.49 (br s, 1H), 1.31 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 190.1, 158.8, 144.2, 133.2, 126.1, 124.5, 112.9, 70.3, 61.3, 34.3, 31.3 (3C).

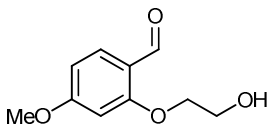
2-(2-Hdroxyethoxy)-3-methoxybenzaldehyde (S6d)



$C_{10}H_{12}O_4$
196.20

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.31 (s, 1H), 7.40 – 7.32 (m, 1H), 7.18 – 7.11 (m, 2H), 4.23 (t, *J* = 4.7 Hz, 2H), 3.91 – 3.83 (m, 5H), 3.31 (br s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 190.8, 152.9, 150.5, 129.8, 124.4, 121.4, 118.0, 76.7, 61.7, 56.1. HRMS (EI) calcd for $C_{10}H_{12}O_4$ $[M]^+$: 196.0736 Found 196.0732.

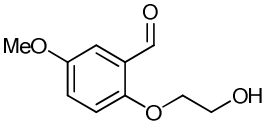
2-(2-Hydroxyethoxy)-4-methoxybenzaldehyde (S6e)



$C_{10}H_{12}O_4$
196.20

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.25 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 6.58 (dd, *J* = 8.6 Hz, 2.1 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 1H), 4.17 (t, *J* = 4.5 Hz, 2H), 4.06 – 3.98 (m, 2H), 3.87 (s, 3H), 2.66 (t, *J* = 6.2 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 188.5, 166.1, 162.6, 131.9, 119.3, 106.3, 99.3, 70.2, 61.1, 55.7. HRMS (EI) calcd for $C_{10}H_{12}O_4$ $[M]^+$: 196.0736 Found 196.0736.

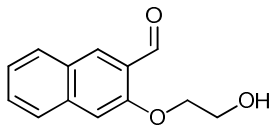
2-(2-Hydroxyethoxy)-5-methoxybenzaldehyde (S6f)



$C_{10}H_{12}O_4$
196.20

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.31 (s, 1H), 7.17 (d, *J* = 3.0 Hz, 1H), 7.00 (dd, *J* = 9.0 Hz, 3.3 Hz, 1H), 6.83 (d, *J* = 9.1 Hz, 1H), 4.08 – 4.02 (m, 2H), 3.93 – 3.87 (m, 2H), 3.69 (s, 3H), 3.40 (br s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 190.0, 155.8, 153.8, 125.1, 123.4, 114.8, 111.0, 70.9, 61.1, 55.7. HRMS (EI) calcd for $C_{10}H_{12}O_4$ $[M]^+$: 196.0736 Found 196.0738.

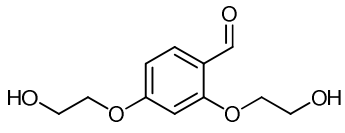
3-(2-Hydroxyethoxy)-2-naphthaldehyde (S6g)



$C_{13}H_{12}O_3$
216.23

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.97, (s, 1H), 9.22 (d, *J* = 9.1 Hz, 1H), 8.07 (d, *J* = 9.3 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.68 – 7.60 (m, 1H), 7.49 – 7.41 (m, 1H), 7.31 (d, *J* = 9.3 Hz, 1H), 4.37 (t, *J* = 4.67 Hz, 2H), 4.10 (br t, *J* = 4.3 Hz, 2H), 2.10 (br s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 192.5, 164.8, 138.4, 132.2, 130.4, 129.6, 129.3, 125.5, 125.4, 117.5, 115.5, 72.7, 61.4. HRMS (EI) calcd for $C_{13}H_{12}O_3$ $[M]^+$: 216.0786 Found 216.0785.

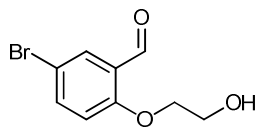
2,4-Bis(2-hydroxyethoxy)benzaldehyde (S6h)



$C_{11}H_{14}O_5$
226.23

^{1}H NMR (300 MHz, d^6-Acetone): δ = 10.34 (s, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 6.71 (d, *J* = 2.2 Hz, 1H), 6.65 (dd, *J* = 8.5 Hz, 1.92 Hz, 1H), 4.27 – 4.14 (m, 5H), 4.12 – 4.02 (m, 1H), 4.00 – 3.84 (m, 4H). ^{13}C NMR (75.5 MHz, d^6-Acetone): δ = 188.2, 166.7, 164.3, 130.2, 119.9, 108.1, 100.1, 71.6, 71.1, 61.2, 61.0.

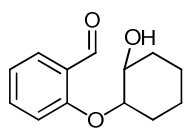
5-Bromo-2-(2-hydroxyethoxy)benzaldehyde (S6i)



$C_9H_9BrO_3$
245.07

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.32 (s, 1H), 7.84 (d, *J* = 2.7 Hz, 1H), 7.58 (dd, *J* = 8.9 Hz, 2.6 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 4.16 (t, *J* = 4.5 Hz, 2H), 4.00 (br t, *J* = 4.3 Hz, 2H), 3.07 (br s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 188.8, 159.9, 138.4, 131.8, 126.2, 114.9, 113.8, 70.5, 61.0. HRMS (EI) calcd for $C_9H_9O_3Br$ $[M]^+$: 243.9735 Found 243.9740.

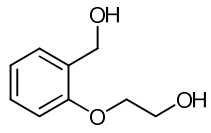
2-(2-Hydroxycyclohexyloxy)benzaldehyde (S6j)



$C_{13}H_{16}O_3$
220.26

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.44 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.57 – 7.47 (m, 1H), 7.13 – 7.00 (m, 2H), 4.21 – 4.08 (m, 1H), 3.88 – 3.76 (m, 1H), 2.80 (s, 1H), 2.27 – 2.07 (m, 2H), 1.85-1.69 (m, 2H), 1.53 – 1.28 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 190.1, 160.6, 135.8, 129.4, 126.2, 121.3, 115.2, 83.6, 73.1, 32.2, 29.5, 23.9, 23.7. MS (CI) m/z (%) 238 (100) $[MNH_4]^+$, 221 (41) $[MH]^+$, 203 (11) $[MH^+ - H_2O]$.

2-(2-Hydroxycyclohexyloxy)benzaldehyde (S6k)

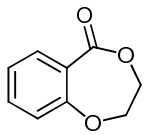


$C_9H_{12}O_3$
168.19

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 – 7.21 (m, 2H), 6.94 (td, *J* = 7.4 Hz, 1.1 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 4.65 (s, 2H), 4.14 – 4.08 (m, 2H), 3.92 – 3.87 (m, 2H), 3.30 (br s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.3, 129.8, 129.4, 129.4, 121.1, 112.5, 70.1, 61.9, 61.0. HRMS (EI) calcd for $C_9H_{12}O_3$ $[M]^+$: 168.0786 Found 168.0785

Experimental Data for Benzodioxepinones

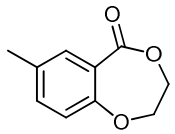
2*H*-Benzo[*e*][1,4]dioxepin-5(3*H*)-one (7)



$C_9H_8O_3$
164.16

according to the **general procedure 1**: yield 94 %, yellowish oil. R_f (hexanes/ethyl acetate 2/1) 0.29. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (dd, *J* = 7.9 Hz, 1.65 Hz, 1H), 7.55 – 7.45 (m, 1H), 7.17 – 7.07 (m, 1H), 7.01 (dd, *J* = 8.4 Hz, 1.0 Hz, 1H), 4.57 – 4.42 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 169.2, 154.7, 135.0, 133.7, 122.7, 121.0, 119.3, 70.9, 65.6. MS (EI) m/z (%) 164 (100) $[M]^+$, 134 (30) $[M\text{-}C_2H_6]^+$, 105 (92) $[M\text{-}C_2H_3O_2]^+$ or $[PhCO]^+$. HRMS (EI) calcd for $C_9H_8O_3$ $[M]^+$: 164.0473 Found 164.0475. IR: $\tilde{\nu}$ = 3072, 2925, 2885, 1703, 1604, 1479, 1451, 1376, 1296, 1220, 1113, 1021, 754, 633, 532.

7-Methyl-2*H*-benzo[*e*][1,4]dioxepin-5(3*H*)-one (8)



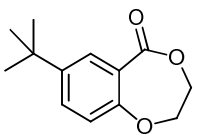
$C_{10}H_{10}O_3$
178.18

according to the **general procedure 1**: yield 95 %, pale yellow oil crystallizing at 5 °C. R_f (hexanes/ethyl acetate 2/1) 0.32. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 2.2 Hz, 1H), 7.33 – 7.27 (m, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 4.52 – 4.40 (m, 4H), 2.32 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 169.5, 152.5, 135.9, 133.3, 132.5, 120.9, 119.3, 70.8, 65.5, 20.3. MS (EI) m/z (%) 178 (100) $[M]^+$, 148 (21), $[M\text{-}C_2H_6]^+$, 119 (76) $[M\text{-}C_2H_3O_2]^+$, 91 (23) $[M\text{-}C_4H_7O_2]^+$ or $[PhCH_2]^+$. HRMS (EI) calcd for $C_{10}H_{10}O_3$ $[M]^+$: 178.0630 Found 178.0626. IR: $\tilde{\nu}$ = 3039, 2958, 2924, 1693, 1617, 1564, 1490, 1458, 1407, 1300, 1280, 1238, 1209, 1186, 1140, 1118, 1044, 977, 879, 827, 777, 745, 643, 529.

Odor Description: very weak citrusy, green-floral odor with sweet fruity aspects.

Odor Threshold: 250 ng/L air.

7-*tert*-Butyl-2*H*-benzo[*e*][1,4]dioxepin-5(3*H*)-one (9)



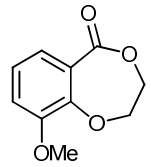
$C_{13}H_{16}O_3$
220.26

according to the **general procedure 1**:yield 75 %, yellowish oil crystallizing at 5 °C. R_f (hexanes/ethyl acetate 3/1) 0.28. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 2.7 Hz, 1H), 7.52 (dd, *J* = 8.6 Hz, 2.61 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 4.51 – 4.41 (m, 4H), 1.30 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 169.7, 152.5, 145.7, 132.5, 129.8, 120.7, 118.7, 70.8, 65.5, 34.3, 31.2. MS (EI) m/z (%) 220 (18) $[M]^+$, 205 (100) $[M\text{-}CH_3]^+$, 161 (32) $[M\text{-}C_2H_3O_2]^+$. HRMS (EI) calcd for $C_{13}H_{16}O_3$ $[M]^+$: 220.1099 Found 220.1098. IR: $\tilde{\nu}$ = 2961, 2870, 1707, 1611, 1566, 1492, 1461, 1409, 1301, 1247, 1144, 1086, 1045, 1023, 874, 836, 774, 675, 580, 548.

Odor Description: intense and powerful leathery-woody odor with green and somewhat chemical nuances.

Odor Threshold: 0.050 ng/L air.

9-Methoxy-2*H*-benzo[*e*][1,4]dioxepin-5(3*H*)-one (10)



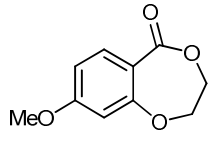
$C_{10}H_{10}O_4$
194.18

according to the **general procedure 1**: yield 86 %, almost colorless needles. m.p. 103 °C. R_f (hexanes/ethyl acetate 2/1) 0.12. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 – 7.36 (m, 1H), 7.13 – 7.04 (m, 2H), 4.61 – 4.52 (m, 2H), 4.50 – 4.40 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 169.2, 151.3, 143.9, 124.1, 123.2, 121.8, 116.2, 71.1, 65.2, 56.4. MS (EI) m/z (%) 194 (100) $[M]^+$. HRMS (EI) calcd for $C_{10}H_{10}O_4$ $[M]^+$: 194.0579 Found 194.0581. IR: $\tilde{\nu}$ = 2961, 1692, 1617, 1565, 1490, 1459, 1408, 1378, 1303, 1282, 1210, 1188, 1044, 978, 879, 828, 776, 744, 645, 529.

Odor Description: phenolic, indolic odor with a chemical, rubbery connotation.

Odor Threshold: 0.99 ng/L air.

8-Methoxy-2*H*-benzo[*e*][1,4]dioxepin-5(3*H*)-one (11)

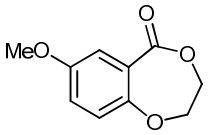


$C_{10}H_{10}O_4$
194.18

according to the **general procedure 1**: yield 90 %, yellowish crystals. m.p. 88 °C. R_f (hexanes/ethyl acetate 3/1) 0.14. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 9.1 Hz, 1H), 6.64 (dd, *J* = 8.9 Hz, 2.61 Hz, 1H), 6.44 (d, *J* = 2.5 Hz, 1H), 4.56 – 4.42 (m, 4H), 3.82 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.7, 165.1, 157.1,

136.0, 110.5, 110.1, 104.0, 70.8, 65.8, 55.6. MS (EI) m/z (%) 194 (67) $[M]^+$, 163 (18) $[M\text{-}CH_3O]^+$, 151 (22) $[M\text{-}CH_3\text{-}CO]^+$, 135 (100) $[M\text{-}C_2H_3O_2]^+$, 107 (38) $[M\text{-}C_4H_7O_2]^+$. HRMS (EI) calcd for $C_{10}H_{10}O_4$ $[M]^+$: 194.0579 Found 194.0580. IR: $\tilde{\nu}$ = 3085, 2980, 2937, 1681, 1614, 1566, 1456, 1439, 1421, 1380, 1344, 1299, 1229, 1198, 1177, 1115, 1039, 1015, 933, 837, 763, 685, 598.

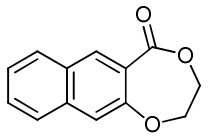
7-Methoxy-2*H*-benzo[*e*][1,4]dioxepin-5(3*H*)-one (12)



$C_{10}H_{10}O_4$
194.18

according to the **general procedure 1**: yield 92 %, slightly orange oil. R_f (hexanes/ethyl acetate 2/1) 0.24. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 3.0 Hz, 1H), 7.07 (dd, *J* = 8.9 Hz, 3.16 Hz, 1H), 6.95 (d, *J* = 9.1 Hz, 1H), 4.44 (s, 4H), 3.81 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 169.3, 155.1, 148.4, 122.7, 122.5, 120.7, 115.0, 70.8, 65.4, 55.8. MS (EI) m/z (%) 194 (100) $[M]^+$, 135 (32) $[M\text{-}C_2H_3O_2]^+$, 107 (20) $[M\text{-}C_4H_7O_2]^+$. HRMS (EI) calcd for $C_{10}H_{10}O_4$ $[M]^+$: 194.0579 Found 194.0577. IR: $\tilde{\nu}$ = 2942, 1718, 1618, 1575, 1482, 1460, 1417, 1280, 1218, 1175, 1133, 1084, 1022, 873, 827, 773, 688, 542

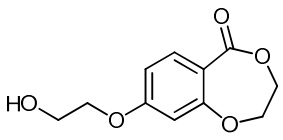
2*H*-Naphtho[2,3-*e*][1,4]dioxepin-5(3*H*)-one (13)



$C_{13}H_{10}O_3$
214.22

according to the **general procedure 1**: yield 74 %, orange to brown oil. R_f (hexanes/ethyl acetate 2/1) 0.30. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 9.1 Hz, 1H), 7.96 (d, *J* = 9.1 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.63 – 7.53 (m, 1H), 7.51 – 7.42 (m, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 4.53 – 4.36 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.6, 152.3, 134.8, 131.8, 130.9, 128.3, 128.3, 125.7, 125.1, 121.2, 117.9, 71.4, 63.8. MS (EI) m/z (%) 214 (100) $[M]^+$, 184 (15) $[M\text{-}C_2H_6]^+$, 155 (66) $[M\text{-}C_2H_3O_2]^+$. HRMS (EI) calcd for $C_{13}H_{10}O_3$ $[M]^+$: 214.0630 Found 214.0627. IR: $\tilde{\nu}$ = 2966, 2881, 1716, 1592, 1509,1469, 1433, 1343, 1284, 1227, 1189, 1110, 1078, 832, 755, 636, 582, 450.

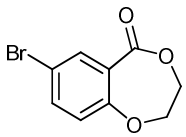
8-(2-Hydroxyethoxy)-2*H*-benzo[*e*][1,4]dioxepin-5(3*H*)-one (14)



$C_{11}H_{12}O_5$
224.21

according to the **general procedure 1**: yield 74 %, colorless crystals. m.p. 110 °C R_f (hexanes/ethyl acetate 1/1) 0.08. ^{1}H NMR (300 MHz, d^6-Acetone): δ = 7.78 (d, *J* = 8.8 Hz, 1H), 6.72 (dd, *J* = 9.1 Hz, 2.5 Hz, 1H), 6.52 (d, *J* = 2.5 Hz, 1H), 4.65 – 4.41 (m, 4H), 4.14 (t, *J* = 4.8 Hz, 2H), 4.06 (t, *J* = 5.9 Hz, 1H), 3.94 – 3.81 (m, 2H). ^{13}C NMR (75.5 MHz, d^6-Acetone): δ = 168.8, 165.3, 157.9, 136.2, 112.4, 111.1, 105.5, 71.9, 71.1, 66.4, 61.1. MS (EI) m/z (%) 224 (31) $[M]^+$, 137 (44) $[M\text{-}C_4H_7O_2]^+$, 121 (100) $[C_7H_5O_2]^+$. HRMS (EI) calcd for $C_{11}H_{12}O_5$ $[M]^+$: 224.0685 Found 224.0682. IR: $\tilde{\nu}$ = 3371, 2929, 1659, 1612, 1561, 1455, 1432, 1387, 1308, 1242, 1179, 1138, 1078, 1054, 1026, 902, 835, 759, 616, 565.

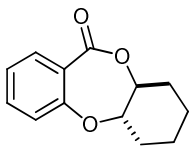
7-Brom-2*H*-benzo[*e*][1,4]dioxepin-5(3*H*)-one (15)



$C_9H_7BrO_3$
243.05

according to the **general procedure 1**: yield 88 %, cream colored crystals. m.p. 101 °C. R_f (hexanes/ethyl acetate 2/1) 0.26. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 2.7 Hz, 1H), 7.57 (dd, *J* = 8.8 Hz, 2.7 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 4.59 – 4.43 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 167.6, 154.0, 137.9, 136.0, 122.9, 120.4, 114.9, 70.9, 65.7. MS (EI) m/z (%) 242 (95) $[M]^+$, 244 (100) $[M]^+$, 200 (28) $[M\text{-}CO]^+$, 185 (39) $[M\text{-}C_2H_3O_2]^+$, 183 (44) $[M\text{-}C_2H_3O_2]^+$. HRMS (EI) calcd for $C_9H_7O_3Br$ $[M]^+$: 241.9579 Found 241.9580. IR: $\tilde{\nu}$ = 3107, 3008, 2942, 2894, 1694, 1597, 1471, 1405, 1382, 1318, 1271, 1237, 1191, 1135, 1041, 983, 819, 769, 657, 542.

7,8,9,9a-Tetrahydro-5a*H*-dibenzo[*b,e*][1,4]dioxepin-11(6*H*)-one (16)



$C_{13}H_{14}O_3$
218.25

according to the **general procedure 1**: yield 78 %, orange oil. R_f (hexanes/ethyl acetate 2/1) 0.36. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (dd, *J* = 7.7 Hz, 1.9 Hz, 1H), 7.53 – 7.42 (m, 1H), 7.16 (td, *J* = 7.55 Hz, 1.10 Hz, 1H), 6.97 (dd, *J* = 8.1 Hz, 1.0 Hz, 1H), 4.41 – 4.27 (m, 1H), 4.25 – 4.12 (m, 1H), 2.27 – 2.12 (m, 2H), 1.85 – 1.53 (m, 3H), 1.50 – 1.06 (m, 3H) . ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 169.4, 153.6, 134.5, 132.0, 123.7, 123.4, 122.5, 84.7, 77.7, 31.2, 30.5, 23.6 (2C). MS (EI) m/z (%) 218 (30) $[M]^+$, 120 (100) $[C_7H_4O_2]^+$, 92 (22) $[C_7H_4O_2\text{-}CO]^+$. HRMS (EI) calcd for $C_{13}H_{14}O_3$ $[M]^+$: 218.0943 Found

218.0942. IR: $\tilde{\nu}$ = 2941, 2865, 1720, 1602, 1476, 1452, 1288, 1215, 1113, 1084, 1041, 941, 767, 651, 511, 494.

→Please find supporting information including **^{1}H- and ^{13}C-NMR spectra** on the enclosed CD.

2.3.5 References

(1) Especially for the synthesis of macrolides alternative methods targeting other positions to achieve ring closure, such as ring closing metathesis or (Suzuki) cross coupling have gained in importance during the last years; for corresponding reviews, see: RCM (a) Rouge dos Santos, A.; Kaiser, C. R.; Férézou, J.-P. *Quim. Nova* **2008**, *31*, 655. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. Cross coupling (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.

(2) (a) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911. (b) Shiina, I.; Fukui, H.; Sasaki, A. *Nat. Protoc.* **2007**, *2*, 2312 and references cited therein.

(3) (a) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (b) Young, I. S.; Baran, P. S. *Nature Chem.* **2009**, *1*, 193. (c) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.

(4) For selected examples, see: aldehyde C-H activation with Rh cat: (a) Phan, D. H. T.; Kim, B.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 15608. (b) Shen, Z.; Khan, H. A.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2916. (c) Shen, Z.; Dornan, P. K.; Khan, H. A.; Woo, T. K.; Dong, V M. *J. Am. Chem. Soc.* **2009**, *131*, 1077. Rh-catalyzed oxidative process: (d) Ye, Z.; Lv, G.; Wang, W.; Zhang, M.; Cheng, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3671. Pd cat: (e) Ye, Z.; Qian, P.; Lv, G.; Luo, F.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 6043. (f) Li, Y.; Jardine, K. J.; Tan, R.; Song, D.; Dong, V. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9690. (g) Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032. Ru cat: (h) Omura, S.; Fukuyama, T.; Murakami, Y.; Okamoto, H.; Ryu, I. *Chem. Commun.* **2009**, 6741 and references cited therein.

(5) For a NHC-catalyzed intramolecular hydroacylation yielding a phthalide scaffold, see: Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4558.

(6) For selected recent examples: (a) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298. (b) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664. (c) Zhang, H.; Zhang, S.; Liu, L.; Luo, G.; Duan, W.; Wang, W. *J. Org. Chem.* **2010**, *75*, 368.

(7) Potential complications arise from over-oxidation especially in the case of electron rich substrates and as well from missing selectivity if non-*meso*-diols are used. For a general review on oxidative esterifications: Ekoue-Kove, K.; Wolf, C. *Chem. Eur. J.* **2008**, *14*, 6302.

(8) Representative recent examples: (a) Ebine, M.; Suga, Y.; Fuwa, H.; Sasaki, M. Org. Biomol. Chem. 2010, 8, 39. (b) Ito, M.; Osaku, A.; Shiibashi, A.; Ikariya, T. Org. Lett. 2007, 9, 1821. (c) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57. (d) Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *Org. Lett.* **2002**, *4*, 2361.

(9) For recent reviews, see: (a) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichim. Acta* **2010**, *42*, 55. (b) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2010**, *291*, 77. (c) Zeitler, K. *E. Schering Found. Symp. Proc.* **2007**, *2*, 183. (d) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (e) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506.

(10) For selected related, recent preparations of lactones *via* NHC-catalysis, see (a) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810. (b) Ryan S. J.; Candish L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176. (c) Phillips, E. M.; Wadamoto, M.; Roth, H. S.; Ott, A. W.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 105. (d) Wang, L.; Thai, K.; Gravel, M. *Org. Lett.* **2009**, *11*, 891. (e) Wang, X.-N.; Shao, P.-L.; Lv H.; Ye, S. *Org. Lett.* **2009**, *11*, 4029. (f) Li, G.-Q.; Dai, L.-X.;You, S.-L. *Org. Lett.* **2009**, *11*, 1623. (g) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (h) Glorius, F.; Burstein, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6205. (i) See also references cited in ref 14.

(11) Representative recent examples: (a) Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518.(b) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126. (c) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905. (d) Sohn, S. S.; Bode, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6021. (e) Vora, H. U.; Rovis, T *J. Am. Chem. Soc.* **2010**, *132*, 2860.(f) Zeitler, K. *Org. Lett.* **2006**, *8*, 637.

(12) Representative recent examples using MnO_2: (a) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Tetrahedron* **2009**, *65*, 3102. (b) Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331. (c) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371.

(13) Representative examples using organic oxidants: (a) De Sarkar, S.; Studer, A. *Org. Lett.* **2010**, *12*, 1992. (b) De Sarkar, S.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190. (c) Noonan, C.; Baragwanath, L.; Connon, S. J. *Tetrahedron Lett.* **2008**, *49*, 4003. (d) Guin, J.; De Sarkar, S.; Grimme, S.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727. (e) Miyashita, A.; Suzuki, Y.; Nagasaki, I.; Ishiguro, C.; Iwamoto, K.-I.; Higashino, T. *Chem. Pharm. Bull.* **1997**, *45*, 1254. (f) Tam, S. W.; Jimenez, L.; Diederich, F. *J. Am. Chem. Soc.* **1992**, *114*, 1503. (g) Inoue, H.; Higashiura, K. *J. Chem. Soc., Chem. Commun.* **1980**, 549. (h) Shinkai, S.; Yamashita, T.; Kusano, Y.; Manabe, O. *J. Org. Chem.* **1980**, *45*, 4947. (i) Castells, J.; Pujol, F.; Llitjós, H.; Moreno-Mañas, M. *Tetrahedron* **1982**, *38*, 337. (j) Castells, J.; Llitjós, H.; Moreno-Mañas, M. *Tetrahedron Lett.* **1977**, *18*, 205 and references cited therein.

(14) Zeitler, K.; Rose, C. A. *J. Org. Chem.* **2009**, *74*, 1759.

(15) Yet, L. *Chem. Rev.* **2003**, *103*, 4283.

(16) (a) Pittayakhajonwut, P.; Dramae, A.; Madla, S.; Lartpornmatulee, N.; Boonyuen, N.; Tanticharoen, M. *J. Nat. Prod.* **2006**, *69*, 1361. (b) Khumkomkhet, P.; Kanokmedhakul, S.; Kanokmedhakul, K.; Hahnvajanawong, C.; Soytong, K. *J. Nat. Prod.* **2009**, *72*, 1487. (c) Zheng, Y.; Zhao, B.; Lu, C.; Lin, X.; Zvheng, Z.; Su, W. *Nat. Prod. Commun.* **2009**, *4*, 501.

(17) Kraft, P.; Popaj, K.; Müller, P.; Schär, M. *Synthesis* **2010**, 3029. (b) Hügel, H. M.; Drevermann, B.; Lingham, A. R.; Marriott, P. J. *Chem. Biodiv.* **2008**, *5*, 1034.

(18) He, J.; Zheng, J.; Liu, J.; She, X; Pan, X. *Org. Lett.* **2006**, *8*, 4637

(19) In addition, benzimidazolium and *N*-Mes triazolium salts were evaluated, but provided much lower yields than **5d**.

(20) We could observe a concentration effect: at 3 M the ratio of **7A** to **7B** was determined to be ca. 9:1.

(21) Attempts to use air or O_2 (balloon) as terminal oxidant did not provide satisfactory yields (11% resp. 21%); however, for reports on strongly electron deficient substrates that could be converted to their corresponding esters/acids without additional oxidant: (a) Goswami, S.; Hazra, A. *Chem. Lett.*, **2009**, *38*, 484. (b) Yoshida, M.; Katagiri, Y.; Zhu, W.-B.; Shishido, K. *Org, Biomol. Chem.* **2009**, *7*, 4062.

(22) Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. *Synthesis* **2003**, 1055.

(23) See experimental section for details: Wang, C.-L.; Wang, X.-X.; Wang, X.-Y.; Xiao, J.-P.; Wang, Y.-L. *Synth. Commun.* **1999**, *29*, 3435. Efforts to the concurrent use of $FeCl_3$ for an *in situ* recycling process of azobenzene have not proven successful so far.

(24) For a recent application of NHC-Fe complexes for an aerobic esterification with boronic acids: Rosa, J. N.; Reddy, R. S.; Candeias, N. R.; Cal, P. M. S. D.; Gois, P. M. P. *Org. Lett.* **2010**, *12*, 2686.

(25) Initial attempts to apply this methodology to the synthesis of the most challenging 8-membered ring system[2a] affords the desired lactone in only 14% yield. However, this is remarkable as a related Ru-catalyzed approach only yielded 7% of the envisaged 8-ring, see ref 4h.
(26) J. L. Belletire, R. A. Bills, S. A. Shackelford, *Synth. Commun.* **2008**, *38*, 738.
(27) M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Org. Chem.* **2005**, *70*, 5725.
(28) J. Pesch, K. Harms, T. Bach, *Eur. J. Org. Chem.* **2004**, 2025.
(29) A J. Arduengo, III, R. Krafczyk, R. Schmutzler, H. A. Craig, J. R. Goerlich, W. J. Marshall, M. Unverzagt, *Tetrahedron* **1999**, *55*, 14523.
(30) K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126.
(31) K. Hirano, I. Piel, F. Glorius, *Adv. Synth. Cat.* **2008**, *350*, 984.
(32) J. Almog, J. E. Baldwin, M. J. Crossley, J. F. Debernardis, R. L. Dyer, J. R. Huff, M. K. Peters, *Tetrahedron* **1981**, *37*, 3589.
(33) J. He, J. Zheng, J. Liu, X. She, X. Pan, *Org. Lett.* **2006**, *8*, 4637.
(34) E. Baciocchi, M. Bietti, M. F. Gerini, O. Lanzalunga, S. Mancinelli, *Perkin Trans. 2* **2001**, 1506.
(35) B. Sur, M. M. Adak, T. Pathak, B. Hazra, A. Banerjee, *Synthesis* 1985, 652.

3 List of abbreviations

abs.	absolute
Ac	acetyl
Ad	adamantyl
aliph.	aliphatic
app.	apparent
ATR	attenuated total reflectance
Ar	aryl
Bn	benzyl
br	broad
Bu	butyl
calcd.	calculated
cat.	catalytic
CI	chemical ionization
CSP	chiral stationary phase
d	doublet, day(s)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
decomp.	decomposition
DIPEA	di*iso*propylethylamine
DMAP	4-(*N, N*-dimethylamino) pyridine
DMSO	dimethylsulfoxide
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EE	ethyl acetate
EI	electron impact
equiv.	equivalents
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardement
FT	fourier-transform
h	hour
HMDS	hexamethyldisilazane
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectroscopy
IMes	1,3-dimesityl-2,3-dihydro-1*H*-imidazole
i-Pr	*iso*propyl
IR	infrared
LSI	liquid secondary ion
m	multiplet
Me	methyl
MeCN	acetonitrile
MeOH	methanol
Mes	2,4,6-trimethylphenyl (= mesityl)
min	minute
m.p.	melting point
MS	mass spectroscopy
n.d.	not determined
NHC	*N*- heterocyclic carbene
NMR	nuclear magnetic resonance
Nu	arbitrary nucleophile
PE	petroleum ether
Ph	phenyl
ppm	parts per million
q	quartet
R	arbitrary residue
rac.	racemic
R_f	retention factor
r.t.	room temperature
s	singlet, seconds
t	triplet
TBDMS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
t-BuOH	*tert*-butanol
tert	tertiary
Tf	trifluoromethanesulfonate
THF	tetrahydrofurane
TLC	thin layer chromatography
TMS	tetramethylsilane or trimethylsilyl
TOF	time of flight
Ts	*p*-toluenesulfonate
UV	ultraviolett
KO*t*Bu	potassium-*tert*-butylate

4 Curriculum Vitae

Christopher Rose

Dr. Gesslerstraße 11a
D–93051 Regensburg, Germany
Phone: +49 (0)941 2005879
Email: christopher.rose@chemie.uni-regensburg.de
Born: 18.09.1981 in Forchheim, Germany
Nationality: German

Fakultät für Chemie und Pharmazie

Institut für Organische Chemie
Universität Regensburg
Universitätsstraße 31
D–93053 Regensburg, Germany
Phone: +49 (0)941 943 4071

Education and Training

Since 01/01/2008	**Doctoral Studies**, Institute of Organic Chemistry, University of Regensburg
October 2007	**Scientific Associate**, Institute of Organic Chemistry, University of Regensburg (Dr. Kirsten Zeitler)
January 2007 – October 2007	**Diploma Thesis**, Institute of Organic Chemistry, University of Regensburg (Dr. Kirsten Zeitler): "Development and Application of Novel Carbene Mediated Umpolung-Type Transformations in Organocatalysis"
October 2002 – December 2006	**Studies in Chemistry** (Diplom, i.e. Masters Program), University of Regensburg, Germany
October 2004	**B. S. in Chemistry**, University of Regensburg, Germany

Professional Experience

since 01/01/2008	**Research Assistant**, Institute of Organic Chemistry, University of Regensburg **Supervision of undergraduate students** in advanced lab courses
January 2005 – February 2005	**Undergraduate Research Assistant**, Institute of Organic Chemistry, University of Regensburg

School Education and Civil Service

July 2001 – April 2002	Civil Service, Bavarian Red Cross, Forchheim
September 1992 – June 2001	Ehrenbürg-Gymnasium-Forchheim, Germany, Abitur
September 1988 – August 1992	Elementary School, Mittelehrenbach/Bavaria, Germany

Poster Contributions

- CATAFLU.OR Symposium 2011, Bologna, Italy: “New Organocatalytic Methods for C–C and C–O Bond Formation”

- ORCHEM 2010, Weimar, Germany: “C-C and C-O Bond Formations Catalyzed by *N*-Heterocyclic Carbenes”

- EuCheMS 2010, Nürnberg, Germany: “The Versatility of NHC Catalysis: Organocatalytic C-C and C-O Bond Formations”

- International Symposium on Organocatalysis (ISO μ) 2010, Mülheim, Germany: “The Versatility of NHC Catalysis: Organocatalytic C-C and C-O Bond Formations”

- Hochschule trifft Industrie 2009, Bad Dürkheim, Germany: “Carbenkatalysierte Lactonisierungen“

- Synthesefest 2009, München, Germany: “Carbene Catalyzed Lactonization Reactions“

Oral Communications

- Meeting of the DFG research group “Diversity of Asymmetric Thiamine Catalysis“ (FOR 1296), March 2011, Freiburg, Germany: “Crossed Acyloin Condensations Catalyzed by *N*-Heterocyclic Carbenes”

- Christmas colloquium, December 2008, University of Regensburg: “An Efficient Carbene-Catalyzed Access to 3,4-Dihydrocoumarins”

List of Publications

- "Hydroacylation Avoided: NHC-Catalyzed, Completely Chemoselective Crossed-Acyloin Reactions"
  C. A. Rose, S. Gundala, S. J. Connon, K. Zeitler, *manuscript submitted for publication*.

- "Chemoselective Crossed Acyloin Condensations: Catalyst and Substrate Control"
  C. A. Rose, S. Gundala, S. J. Connon, K. Zeitler, *Synthesis* **2011**, *2*, 190 – 198 (feature article).

- "Highly Chemoselective Direct Crossed Aliphatic-Aromatic Acyloin Condensations with Triazolium-Derived Carbene Catalysts"
  S. E. O`Toole, C. A. Rose, S. Gundala, K. Zeitler, S. J. Connon, *J. Org. Chem* **2011**, *76*, 347 – 357.
  - publication as featured article
  - invitation for cover design

- "Efficient Catalytic, Oxidative Lactonization for the Synthesis of Benzodioxepinones using Thiazolium Derived Carbene Catalysts"
  C. A. Rose, K. Zeitler, *Org. Lett.* **2010**, *12*, 4552 – 4555.

- "Highly Enantioselective Benzoin Condensation Reactions Involving a Bifunctional Protic Pentafluorophenyl-Substituted Triazolium Precatalyst"
  L. Baragwanath, C. A. Rose, K. Zeitler, S. J. Connon, *J. Org. Chem.* **2009**, *74*, 9214 – 9217.

- "An Efficient Carbene-Catalyzed Access to 3,4-Dihydrocoumarins"
  K. Zeitler, C. A. Rose, *J. Org. Chem.* **2009**, *74*, 1759 – 1762.

Academic Referees

Dr. Kirsten Zeitler
Institut für Organische Chemie
Universität Regensburg
Universitätsstraße 31
D–93053 Regensburg
e-Mail: kirsten.zeitler@chemie.uni-regensburg.de
phone: +499419434627

Prof. Dr. Oliver Reiser
Institut für Organische Chemie
Universität Regensburg
Universitätsstraße 31
D–93053 Regensburg
e-Mail: oliver.reiser@chemie.uni-regensburg.de
phone: +499419434631

Prof. Dr. Stephen Connon
Centre for Synthesis and Chemical Biology
School of Chemistry
The University of Dublin, Trinity College
Dublin 2, Ireland
e-Mail: connons@tcd.ie
phone: +35318961306

5 Acknowledgement

I am indebted to my supervisor Dr. Kirsten Zeitler for an exciting, motivating and open research project, for excellent support, “24 hour” availability in case of requests, for lots of fruitful discussions, for having the opportunity to participate in a number of inspiring conferences and for allowing me to follow the “call of the mountains”, whenever I asked her.

Special thanks go to Prof. Dr. Stephen Connon from Trinity College, Dublin, for the excellent and very productive collaboration over the past years and for acting as one of my academic referees.

I thank Prof. Dr. Oliver Reiser for financial support, for providing access to different solvents, consumables and office material, for the opportunity to present my work within the group seminar and for acting as my 2nd examiner.

I would like to thank Prof. Dr. Henri Brunner (3rd examiner) and Prof. Dr. Joachim Wegener (chairman) for completing the board of examiners in my PhD defense.

I owe my thanks to Luise Baragwanath, Sarah O`Toole and Sivaji Gundala from the group of Prof. Dr. Stephen Connon for their contributions to our good work on benzoin- and acyloin couplings.

I very much enjoyed the years in the Zeitler group. Thanks to current group members Clément Padié, Matthias Neumann, Johannes Franz and Beatriz López-Sánchez for the good working atmosphere and for the great times we had on various kitchen- or rooftop-parties and conferences. Special thanks go to my former labmate Ina Mager, for introducing me to carbene chemistry during a student research internship and for enjoyable days in lab 23.2.20.

Furthermore, I thank Mario Weist, Natascha Kuzmanović, Sebastian Heinl, Sebastian Barrois, Jan-Philip Meyer and Carina Koch for their engaged and skillful work during student research internships.

Sincere thanks go to all co-workers of the central analytical departement. In particular, I thank Dr. Thomas Burgemeister, Fritz Kastner, Georgine Stühler and Annette Schramm for providing excellent NMR service, as well as Josef Kiermaier and Wolfgang Söllner for recording mass spectra.

I owe my thanks to Dr. Peter Kreitmeier for his kind help especially in case of technical problems.

Special thanks to Georg Adolin, Helena Konkel and Klaus Döring for providing an excellent service regarding consumables, chemical waste disposal, solvents and for accepting shippings of new chemicals.

Many thanks to Dr. Philip Kraft (Givaudan AG, Switzerland) for analyzing a selection of our benzodioxepinones with respect to their properties as odorants.

Funding by the DFG Priority Program "Organocatalysis" is gratefully acknowledged.

Timeout is essential to stay motivated and re-charge the inner batteries. In this regard, I would like to express my deep gratitude to my friends for the good times we have had going out in the evenings, having barbecues anywhere and for great moments we shared on numerous (bigger and smaller) climbing- and mountaineering excursions and playing music together. Special thanks go to Caro Russ, Caro Fischer and Dominik "Gregor" Grögel – the "mensa-team" – for enjoying daily lunch and exchanging current news and gossip.

I would not have made it to this point without my parents Katharina and Wolfgang and my sister Judith, who have been supporting me in many ways during all the years. At this point, I would like to thank them with all my heart.