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Lewis Acid Catalyzed Cyclopropane Ring-Opening-Cyclization Cascade Using Thioureas as a N,N-bisnucleophile: Synthesis of Bicyclic Furo-, Pyrano-, and Pyrrololactams *via* a Formal [4+1]-Addition

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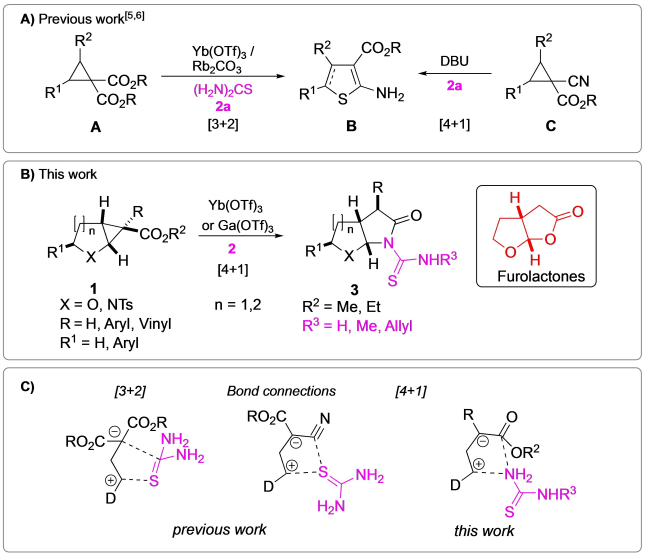
In memoriam of Ulf Diederichsen

Fused bicyclic cyclopropanes were converted by Lewis acid-catalysis with thioureas to furo-, pyrano, and pyrrololactams with yields of up to 99% and high diastereoselectivity. The formation of the title compounds, representing a formal [4+1]-cycloaddition to a donor-acceptor substituted cyclopropane, follows a cascade reaction involving S_N1-type ring-opening addition and cyclization. Thiourea, being a cost-effective and odorless reagent, acts as an *N,N*-bis-nucleophile to generate bicyclic compounds containing an *N*-substituted γ-lactam moiety.

Introduction

Donor-acceptor (D–A) cyclopropanes offer great value as versatile and readily prepared three-carbon building blocks in organic synthesis.[1] When activated by Lewis acids, these cyclopropanes readily undergo ring-opening followed by [3+2]-cycloaddition reactions with a wide array of dipolarophiles,[2] enabling the generation of cyclic and, related to our study, bicyclic heterocyclic ring systems[2g] that are valuable from a synthetic and biological point of view. Alternatively, but less explored are formal [4+1]-cycloadditions, in which a bis-nucleophile interacts both with the electrophilic center adjacent to the donor and the acceptor group of the D–A cyclopropane (Scheme 1C).

The functionalization of thiocarbonyl compounds in combination with D–A cyclopropanes has been scarcely explored.[3] Notably, thiourea, an odorless, cost-effective, and manageable sulfur source,[4] has been employed in only two examples for this purpose (Scheme 1A): Guo *et al.* reported in 2019 the $Yb(OTf)_3$-catalyzed [3+2]-cycloaddition of cyclopropane-1,1-dicarboxylic acid esters **A** (Scheme 1A),[5] which resulted in the formation of 2-amino-4,5-dihydrothiophene derivatives **B**. Wang *et al.* disclosed a DBU-mediated [4+1]-annulation of D–A cyclopropanes **C** with thiourea for the synthesis of 2-amino-thiophene-3-carboxylates.[6] Both reactions proceeded *via* an S-nucleophilic attack of thiourea, producing similar 2-amino-thiophene products, albeit through different reaction pathways (Scheme 1C). Inspired by these results and building upon our ongoing interest in ring opening chemistry of cyclopropanated furans and pyrroles,[7] we sought to explore the potential of this reaction with bicyclic systems **1**, assuming an analogous reaction outcome. In contrast to our expectations, this combination led to a formal [4+1]-cycloaddition through a cascade ring opening/cyclization reaction (Scheme 1B), representing to the best of our knowledge the first example of thiourea acting as an *N,N*-bisnucleophile in D–A cyclopropane ring openings. This way, bicyclic pyrrolidinones **3** become accessible being



Scheme 1. Cyclizations between D–A cyclopropanes and thiourea: **A)** [3+2]-cycloaddition by Guo[5] and [4+1]-annulation by Wang[6] **B)** Formal [4+1]-cycloaddition. **C)** Different reaction modes of thiourea.

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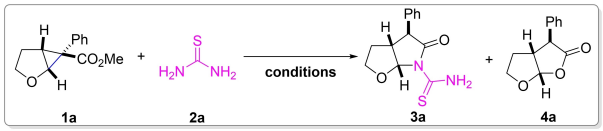
attractive scaffolds given the relevance of furolactones and furofuranes in drug development.[8]

Results and Discussion

Treating fused cyclopropane **1a** and thiourea **2a** (Table 1, Entry 1) under the conditions reported by Guo *et al.*[5] (Scheme 1A) and Wang *et al.*[6] This resulted in a full conversion of the starting materials but yielded a complex product mixture that was not followed up on further. A solvent screen revealed a dramatic effect on the course of the reaction, allowing the identification of furolactam **3a** as the product, along with the known lactonization to furolacton **4a**.[9] Best results were obtained in polar aprotic solvents (Table 1, Entries 4–7), and employment of Rb_2CO_3 as base is disadvantageous, presumably promoting the hydrolysis of the methyl ester moiety that leads to the byproduct **4a** (Table 1, Entry 8). Furthermore, $Yb(OTf)_3$ is superior to other Lewis acids such as $Sc(OTf)_3$, $Zn(OTf)_2$, $Y(OTf)_3$, $Fe(OTf)_3$ or $Cu(OTf)_2$ (see SI, Table S4). Besides a decrease in yield, also increasing amounts of the side product **4a** are observed as a result of an Brønstedt acid-catalyzed rearrangement of **1a**, which might also explain the superior performance of triflates compared to chlorides.

Table 1. Screening and optimization of the reaction conditions[a] for the formation of furolactam **3a**. For complete screening, see SI.

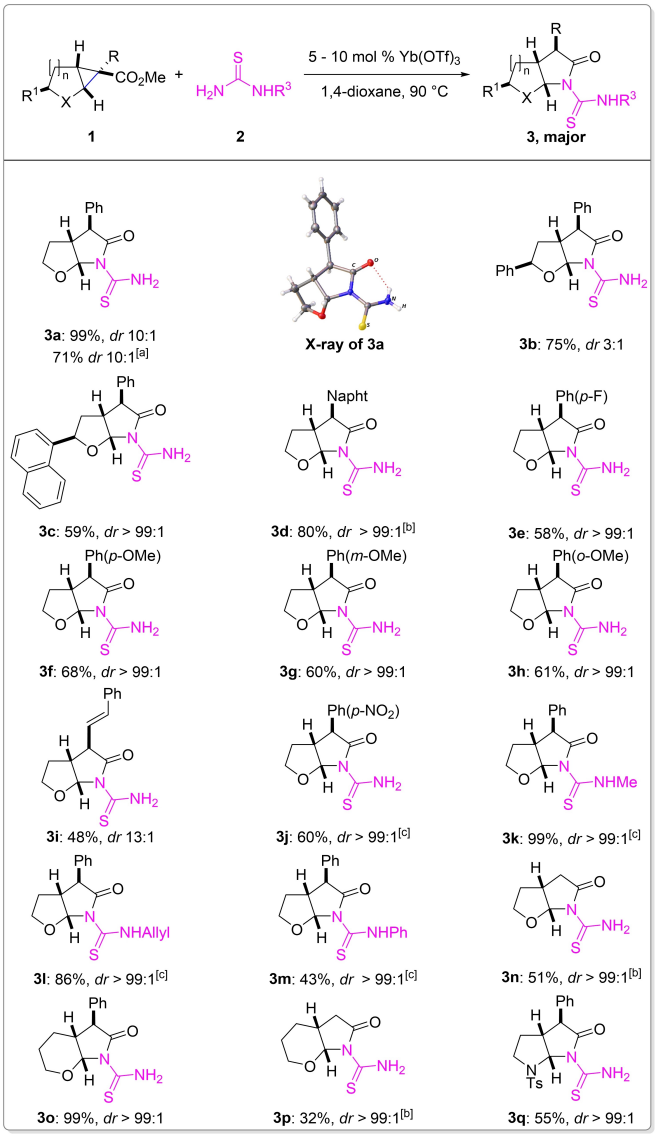


Entry	Solvent	$Yb(OTf)_3$ [mol%]	Result[c]
1	DCE	10	Complex Mixture
2	Toluene	10	**3a**: 21%, *dr* 3:1 **4a**: 16%, *dr* 3:1
3	I-Propanol	10	**3a**: 7%, *dr* 7:1 **4a**: 11%, *dr* 1:1
4	DMF	10	**3a**: traces **4a**: 34%, *dr* 4:1
5	MeCN	10	**3a**: 62%, *dr* 7:1 **4a**: 12%, *dr* 3:1
6	THF	10	**3a**: 56%, *dr* 11:1 **4a**: 11%, *dr* 2:1
7	1,4-Dioxane	10	**3a**: 72%, *dr* 8:1 **4a**: 5%, *dr* 1:1
8[b]	1,4-Dioxane	10	**3a**: 99%, *dr* 10:1 **4a**: –
9[b]	1,4-Dioxane	5	**3a**: 99%, *dr* 10:1 **4a**: –
10	1,4-Dioxane	1	**3a**: 74%, *dr* 6:1 **4a**: –

[a] Reactions were carried out in closed vessels. Oil bath temperature 90–120 °C. Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Rb_2CO_3 (20 mol%), solvent. (3 mL), 18 h. [b] Without Rb_2CO_3. [c] Yields given are NMR yields determined by using 1,1,2,2-tetrachloroethane as internal standard.

Thus, optimal conditions were found with the combination of $Yb(OTf)_3$ (5 mol%) in dioxane at 90 °C, giving rise to **3a** in quantitative yield and high (10:1) diastereoselectivity, orienting the phenyl group on the convex face of the bicycle (Table 1, Entry 9). Decreasing the catalyst loading further (1 mol%, entry 10) resulted in a drop in yield. All reactions were run in closed vessels with oil bath temperatures of 90–120 °C, which did not affect the outcome, while lower temperatures resulted in complex product mixtures or incomplete conversions.

With optimized conditions, we examined the scope of this formal [4+1]-cycloaddition (Scheme 2). Cyclopropanated dihydrofurans **1a–h** gave the desired bicyclic products **3a–h** in good yields and diastereoselectivities, tolerating aryl substitution at the 3-position of the dihydrofuran ring as well as a range of electronically differentiated aryl substituents in the arene



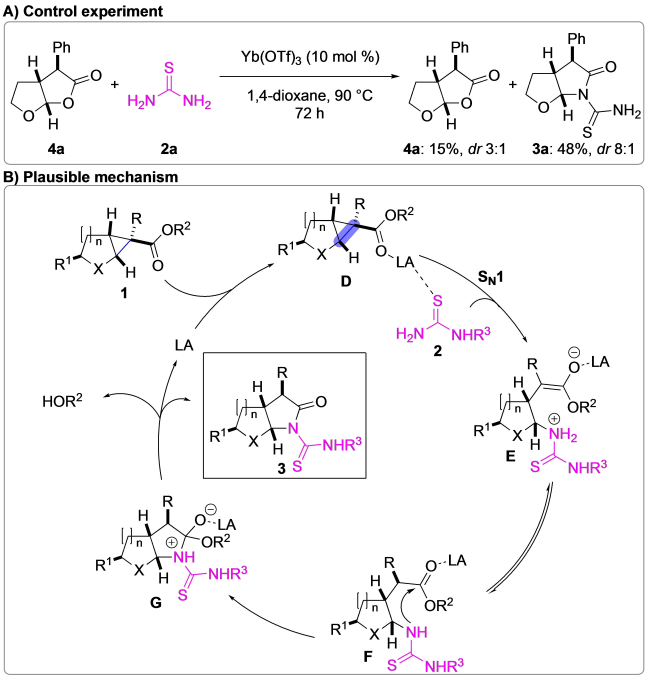
Scheme 2. Reaction conditions: **1** (0.4–0.5 mmol), 2 (2 equiv), 1,4-dioxane, $Yb(OTf)_3$ (5 mol%; 10 mol% for **3q**), 90 °C, 24 h; the major diastereomer is shown [a] 7.0 mmol scale. [b] The ethyl ester of **1** was used instead of methyl ester. [c] Reaction conditions: $Ga(OTf)_3$ (10 mol%) instead of $Yb(OTf)_3$, MeCN, 90 °C, 18 h.

moiety. Styryl substitution on the cyclopropane was suitable as well, delivering compound **3i** albeit in a moderate yield of 48%. Monosubstituted thioureas did not react under catalysis with $Yb(OTf)_3$, but a short screening (see SI for more information) revealed $Ga(OTf)_3$ (10 mol%) in MeCN to be effective, allowing the synthesis of methyl-, allyl-, and phenyl-substituted thiourea products **3k–m** (43–99%, >99:1 dr). This way, also **3j** with a strong electron-deficient aryl group could be synthesized, whereas the protocol utilizing $Yb(OTf)_3$ as a Lewis acid catalyst failed. Furthermore, the reaction is also possible without an aryl group on the cyclopropane ring, although **3n** was obtained in a comparatively lower yield of 51%. Other heterocyclic ring systems were also compatible, providing **3o–q** (32–99%). Scale-up for the lactam anellation was demonstrated on a 7 mmol scale, affording **3a** in 71% yield (1.3 g) and 10:1 *dr*.

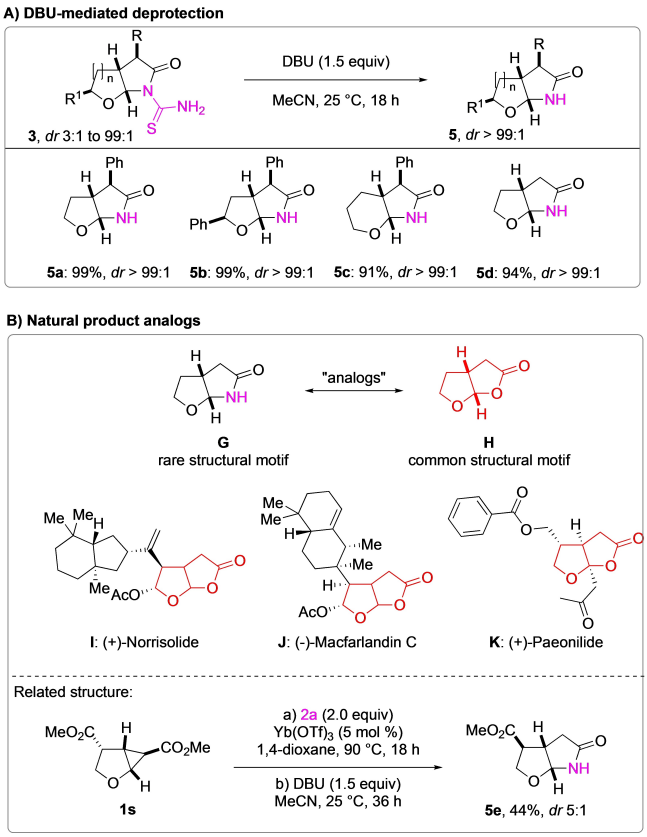
To gain insight into the mechanism, we subjected compound **4a**, observed as a byproduct in some cases (*cf.* Table 1), to the reaction conditions (Scheme 3A). Indeed, product **3a** is formed after an extended period (72 h) in a moderate yield (48%; *dr* 8:1). Thus, while bicyclic furolactone **4a** could be en route towards **3a**,[10] considering reaction time, conversion, and yield this pathway appears to be unlikely.

Hence, we propose (Scheme 3B) the Lewis acid activation of the ester moiety in **1**, resulting in the S_N1-type ring opening along the D–A-cyclopropane bond in **D** (marked in blue) to give rise to **E**. Protonation of the enolate sets the stage for a second *N*-nucleophilic attack of the thiourea moiety, favoring a 5-*exo* over a 7-*exo* cyclization in which the substituent R is oriented on the convex face of the bicyclic system.

Unmasking the pyrrolidine moiety readily occurs upon simple stirring of **3** with DBU in acetonitrile, giving rise to **5** in high yields (>90%) (Scheme 4A). As an additional benefit of this deprotection, the selectivity towards the sterically favored *exo*-diastereomer is further increased *via* a deprotonation/protonation sequence.



Scheme 3. A) Control experiment. B) Plausible mechanism for the reaction of fused D–A cyclopropanes with thioureas.



Scheme 4. A) Scope of the DBU-mediated elimination. B) Furolactone natural products.

Noteworthy, compounds **5** exhibit an unexplored structural motif distinguished by a fused γ-lactam-furan ring system **G**. This core bears structural similarity to the prevalent furo-γ-lactone ring system, which is found in various natural products (Scheme 4B).

Notably, these compounds contain a substitution on the 3-position of the dihydrofuran ring. Therefore, compound **5e** was synthesized in good overall yield (44%, *dr* 5:1) from **1s**, having a versatile methyl ester in this position, which should allow further modification towards analogs of such natural products, e.g. Norrisolide **I**, Macfarlandin C **J**, and Paeonilide **K** (Scheme 4B) that display significant bioactive properties.[9,11]

Conclusions

In summary, we have developed a strategy for a formal [4+1]-cycloaddition of D–A cyclopropanes and thioureas, leading to a broad spectrum of bicyclic furolactams **3** through a cascade reaction involving S_N1-type ring-opening addition and cyclization. Thiourea reacts here as an *N,N*-bis-nucleophile, contrasting previous reports that demonstrated cycloadditions via the C=S group or nucleophilic reactions via the sulfur group. This

unprecedented reaction mode might result from a weak interaction between thiourea and $Yb(OTf)_3$,[12] allowing for sufficient nucleophilicity of the nitrogen moiety. In contrast, employing urea, coordinating more strongly to rare earth Lewis-acids, instead of thiourea could not be engaged in the title reaction. After deprotection, the parent furolactams **5** are readily obtained, promising to target analogs of furolactone natural products.

Supporting Information Summary

The authors have cited additional references within the Supporting Information.[13–26]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Cycloaddition · Cyclopropanes · Thiourea · Lewis acids · Furolactam

[1] a) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151; b) M. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321; c) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.* **2009**, *38*, 3051; d) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2014**, *53*, 5504; e) F. de Nanteuil, F. de Simone, R. Frei, F. Benfatti, E. Serrano, J. Waser, *Chem. Comm.* **2014**, *50*, 10912; f) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.* **2014**, *43*, 804;g) H. K. Grover, M. R. Emmett, M. A. Kerr, *Org. Biomol. Chem.* **2015**, *13*, 655; h) P. Singh, R. K. Varshnaya, R. Dey, P. Banerjee, *Adv. Synth. Catal.* **2020**, *362*, 1447; i) K. Strunk, O. Reiser, *Top. Heterocyclic Chem.* **2023**, *59*, 157.

[2] a) F. Doraghi, S. Karimian, O. H. Qareaghaj, M. J. Karimi, B. Larijani, M. Mahdavi, *J. Organomet. Chem.* **2024**, *1005*, 122963; b) M. Bao, M. P. Doyle, *ChemCatChem* **2023**, *15*; c) A. U. Augustin, D. B. Werz, *Acc. Chem. Res.* **2021**, *54*, 1528; d) O. A. Ivanova, I. V. Trushkov, *Chem. Rec. (New York, N. Y.)* **2019**, *19*, 2189; e) I. Kumar, *RSC Adv.* **2014**, *4*, 16397; f) L. Jiao, Z.-X. Yu, *J. Org. Chem.* **2013**, *78*, 6842; g) T. P. Lebold, M. A. Kerr, *Org. Lett.* **2009**, *11*, 4354–4357.

[3] a) A. U. Augustin, M. Sensse, P. G. Jones, D. B. Werz, *Angew. Chem. Int. Ed.* **2017**, *56*, 14293; b) A. U. Augustin, M. Busse, P. G. Jones, D. B. Werz, *Org. Lett.* **2018**, *20*, 820; c) A. Kreft, P. G. Jones, D. B. Werz, *Org. Lett.* **2018**, *20*, 2059; d) Y. Matsumoto, D. Nakatake, R. Yazaki, T. Ohshima, *Chem. Eur. J.* **2018**, *24*, 6062.

[4] a) G. Lu, F. Chen, C. Cai, *J. Chem. Educ.* **2017**, *94*, 244; b) J. Wang, Q.-Y. Zhang, M.-S. Xie, D.-C. Wang, G.-R. Qu, H.-M. Guo, *Org. Lett.* **2018**, *20*, 6578.

[5] M.-S. Xie, G.-F. Zhao, T. Qin, Y.-B. Suo, G.-R. Qu, H.-M. Guo, *Chem. Comm.* **2019**, *55*, 1580.

[6] Z. Su, S. Qian, S. Xue, C. Wang, *Org. Biomol. Chem.* **2017**, *15*, 7878.

[7] a) S. Budde, F. Goerdeler, J. Floß, P. Kreitmeier, E. F. Hicks, O. Moscovitz, P. H. Seeberger, H. M. L. Davies, O. Reiser, *Org. Chem. Front.* **2020**, *7*, 1789; b) C. M. Sonnleitner, S. Park, R. Eckl, T. Ertl, O. Reiser, *Angew. Chem. Int. Ed.* **2020**, *59*, 18110; c) N. Wurzer, U. Klimczak, T. Babl, S. Fischer, R. A. Angnes, D. Kreutzer, A. Pattanaik, J. Rehbein, O. Reiser, *ACS Catal.* **2021**, *11*, 12019; d) R. Eckl, S. Fischer, C. M. Sonnleitner, D. Schmidhuber, J. Rehbein, O. Reiser, *ACS Org. Inorg. Au* **2022**, *2*, 169; e) T. Babl, O. Reiser, *J. Org. Chem.* **2022**, *87*, 6410; f) S. Fischer, T.-T. H. Nguyen, A. Ratzenboeck, H. M. L. Davies, O. Reiser, *Org. Lett.* **2023**, *25*, 4411.

[8] B. A. Bhat, S. Rashid, G. Mehta, *Asian J. Org. Chem.* **2020**, *9*, 1726.

[9] K. Harrar, O. Reiser, *Chem. Comm.* **2012**, *48*, 3457.

[10] a) G. Etornam Adukpo, T. Borrmann, R. Manski, R. I. Sáez Díaz, W.-D. Stohrer, F.-P. Montforts, *Eur. J. Org. Chem.* **2007**, *2007*, 249; b) D. D. Tien, B. Panek-Bryla, E. Gögüs, D. Leupold, E. L. A, F.-P. Montforts, *Arkivoc* **2022**, *2021*, 41.

[11] a) T. P. Brady, S. H. Kim, K. Wen, E. A. Theodorakis, *Angew. Chem.* **2004**, *116*, 757; b) T. K. Allred, A. P. Dieskau, P. Zhao, G. L. Lackner, L. E. Overman, *Angew. Chem. Int. Ed. Engl.* **2020**, *59*, 6268.

[12] F. Berny, G. Wipff, *J. Chem. Soc. Perk. Trans.* **2001**, *2*, 73.

[13] W. L. F. Armarego, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Kidlington, Oxford, United Kingdom, Cambridge, MA **2017**.

[14] H. M. L. Davies, T. Hansen, M. R. Churchill, *J. Am. Chem. Soc.* **2000**, *122*, 3063.

[15] G. Chen, J. Song, Y. Yu, X. Luo, C. Li, X. Huang, *Chem. Sci.* **2016**, *7*, 1786.

[16] W.-W. Chan, S.-H. Yeung, Z. Zhou, A. S. C. Chan, W.-Y. Yu, *Org. Lett.* **2010**, *12*, 604.

[17] Y. Zhang, Y. Yao, L. He, Y. Liu, L. Shi, *Adv. Synth. Catal.* **2017**, *359*, 2754.

[18] H. M. Davies, M. V. Grazini, E. Aouad, *Org. Lett.* **2001**, *3*, 1475.

[19] N. E. Searle, *Org. Synth.* **1956**, *36*, 25.

[20] H. M. Davies, C. Oldenburg, M. J. McAfee, J. Nordahl, J. P. Henretta, K. R. Romines, *R. Tetrahedron Lett.* **1988**, *29*, 975.

[21] H. M. L. Davies, P. R. Bruzinski, D. H. Lake, N. Kong, M. J. Fall, *J. Am. Chem. Soc.* **1996**, *118*, 6897.

[22] P. Hewawasam, O. D. Lopez, Y. Tu, A. X. Wang, N. Xu, J. F. Kadow, N. A. Meanwell, S. V. S. A. K. Gupta, I. J. G. Kumar, S. K. Ponugupati et al., US2015/0023913 A1 **2015**.

[23] V. Klöpfer, R. Eckl, J. Floß, P. M. C. Roth, O. Reiser, J. P. Barham, *Green Chem.* **2021**, *23*, 6366.

[24] M. P. Doyle, D. van Leusen, *J. Org. Chem.* **1982**, *47*, 5326.

[25] I. D. Jurberg, H. M. L. Davies, *Chem. Sci.* **2018**, *9*, 5112.

[26] S. Gratia, K. Mosesohn, S. T. Diver, *Org. Lett.* **2016**, *18*, 5320.

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