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Zn-Mediated Hydrodeoxygenation of Tertiary Alkyl Oxalates

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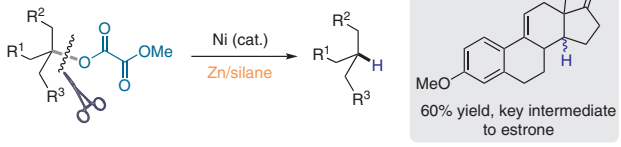

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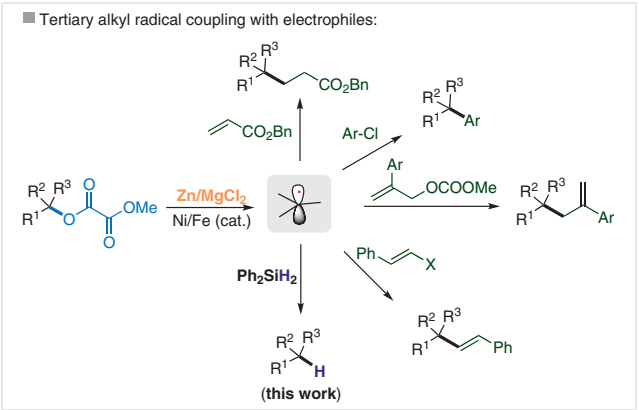
Abstract Herein we describe a general, mild, and scalable method for hydrodeoxygenation of readily accessible tertiary alkyl oxalates by Zn/silane under Ni-catalyzed conditions. The reduction method is suitable for an array of structural motifs derived from tertiary alcohols that bear diverse functional groups, including the synthesis of a key intermediate en route to estrone.

Key words Zn, silane, hydrodeoxygenation, C–O bonds, oxalates

The abundance of alcohols and their derivatives in nature constitutes an important part of our chemical feedstocks. Thus, direct manipulation of C(sp^3)–O bond transformations is sustainably desirable.[1–3] In this context, Barton alkyl C–O bond radical fragmentation has recently experienced rejuvenation. The traditional Barton homolytic scission of C(sp^3)–O bonds oftentimes requires forcing conditions such as UV irradiation and/or toxic radical inducing reagents, e.g., Bu_3SnH as radical initiators that add to thionyl- and carbonyl-modified alcohols.[4,5] This conventional strategy has been widely used in the total synthesis of bioactive natural occurring compounds, e.g., (–)-rhodomollanol A,[6] (–)-conidiogenone B,[7] (–)-sculponin R, and (–)-isodocarpin.[8] Recently, a visible-light-induced Barton C–O bond-scission protocol has been developed that allows alkyl (primary, secondary, and tertiary) oxalate salts and tertiary alkyl *N*-phthalimidoyl (NP) oxalyl esters to generate alkyl radicals under Ir-catalyzed oxidative and Ru-catalyzed reductive conditions, respectively.[5] We, on the other hand, disclosed a Zn/$MgCl_2$-mediated and Ni-promoted C–O bond-fragmentation strategy that permits readily accessible dialkyl oxalates to generate alkyl radical intermediates.[9] Such a process enabled us to develop effective Ni- and Fe-catalyzed cross-electrophile coupling of dialkyl oxalates with aryl/vinyl halides or activated alkenes to afford all carbon quaternary stereogenic centers (Scheme 1).[9–12]



Scheme 1 Zn/$MgCl_2$-mediated C(sp^3)–O fragmentation of tertiary alkyl oxalates[9a,11,14]

Given the importance of hydrodeoxygenative Barton reaction in the synthesis of valuable compounds, we quest whether the Zn/$MgCl_2$-mediated C–O bond radical scission process can be extended to deoxylative C–H bond-forming reactions when silanes are used as hydrogen donors to terminate the radical reactions.[13]

Herein, we depict an efficient Zn-mediated and Ni-promoted reductive hydrodeoxygenation of unactivated tertiary alkyl oxalates with diphenylsilane as the hydrogen source (Scheme 1), which avoids use of toxic tin hydride. The utility of this strategy was showcased in the formal total synthesis of estrone.[15a]

We first examined the hydrodeoxygenation of a tertiary alkyl methyl oxalate **1a** in the presence of diphenylsilane as hydrogen donor. The previous conditions[9a,11a] of Ni- and Fe-catalyzed cross-coupling of dialkyl oxalates with electro-

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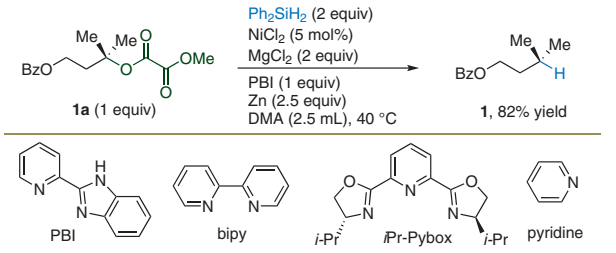
philes in *N*,*N*-dimethylacetamide (DMA) gave **1** in low yields (Table 1, entries 7 and 8). An extensive survey of the reaction conditions led us to identify that a combination of $NiCl_2$ (5 mol%), 2-(pyridin-2-yl)-1*H*-benzo[*d*]imidazole (PBI, 1 equiv) with Zn and $MgCl_2$ in DMA at mild temperature provided the hydrodeoxygenated product **1** in an optimal 82% yield (entry 1). The control experiments indicated the necessity of Zn and $MgCl_2$ (entries 2 and 3). However, without PBI, a reasonably good yield was detected (entry 5), which was consistent with our previous reports.[9a] With DMA as the solvent, the use of Co salts to replace Ni as the promoter also generated **1** in 37% yield (entry 9), wherein the reaction efficiency is not high.[16] By contrast, copper salts were incompetent (entry 10).[17] Replacement of PBI with other pyridine-containing additives did not improve the results (entries 11–13). While other independent hydrogen sources such as H_2, BH_3, and H_2O, were not suitable (entries 14–16 and Supporting Information, Table S2). However, in the absence of Ph_2SiH_2, **1** was detected in 32% yield (entry 6). Using 10 μL of H_2O instead of Ph_2SiH_2, the yield of **1** was up to 38%, while more H_2O almost killed the reaction (entries 16 and 17). Taken together, these results suggest that the existence of small amount of water did not affect the reaction (Supporting Information, Table S1, entries 14 and 15). Finally, the reaction run on a gram scale gave **1** in 78% yield (entry 18).

This hydrodeoxygenation method displayed excellent compatibility for a broad range of unactivated tertiary alkyl oxalates when treated with diphenylsilane (Scheme 2). The tertiary alkyl oxalates containing geminal dimethyl groups delivered **2**–**15** in good to excellent yields. Comparing to **7** and **8**, the free hydroxyl substrate allowed the formation of **6** in 40% yield, indicated that the relatively acidic proton may not affect the hydrodeoxygenation efficiency to an appreciable extent. The N-containing heterocycle compound **15** could give 58% yield. Excellent yield was obtained for sclareol-derived **16**. The reaction also exhibited moderate to excellent results for tertiary alkyl substrates within closed rings, as evident in **18** and **19** including 3- and 6-membered ones. The bicyclic cyclotryptamine product **20** was obtained in 64% yield. Interestingly, this reaction has high hydrodeoxygenation efficiency for oxalates derived from α-hydroxyl carbonyl compounds as exemplified by **21** and **22**. To our delight, the quantitative conversion was obtained for citric acid derived **23**. In addition, the simultaneous hydrodeoxygenation of the dioxalates successfully generated **24**. The more sterically demanding tertiary alkyl oxalates contained ethyl and propyl groups proved to be compatible, as evident in the products of **25** and **26**. The more complex steroid-tethered tertiary alcohol can be converted into **27** and **28** in good yields. Finally, moderate to excellent yields were obtained for cholesterol and cholic acid derived **29**–**32**, these examples showcased the utility of this work in the preparation of sophisticated structures. A wide range of functional groups were tolerated, and the notable ones include ester, silyl ether, aryl polycyclic and heterocyclic, and acidic amide proton.

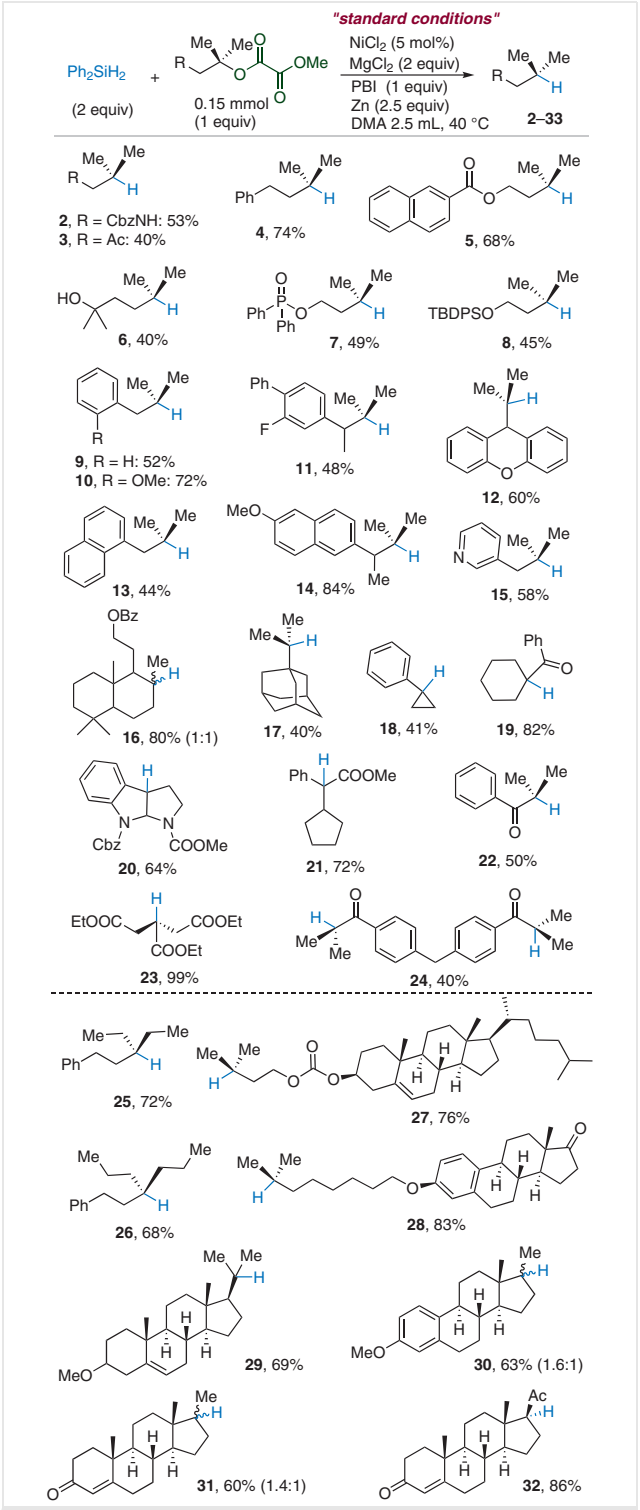
Table 1 Optimization of Hydrodeoxygenation of **1a** with Diphenylsilane



Entry	Variation from the standard conditions	Yield (%)[a]
1	none	82[b]
2	without $MgCl_2$	no reaction
3	without Zn	no reaction
4	without $NiCl_2$	38
5	without PBI	42
6	without Ph_2SiH_2	32
7	$NiCl_2(py)_4$	30
8	$Fe(acac)_3$	19
9	$Co(acac)_2$	37
10	CuI	26
11	pyridine instead of PBI	35
12	bipy instead of PBI	30
13	*i*-Pr-Pybox instead of PBI	no reaction
14	H_2 instead of Ph_2SiH_2	12
15	BH_3 instead of Ph_2SiH_2	18
16	H_2O (10 μL) instead of Ph_2SiH_2	38
17	H_2O (0.5 mL) instead of Ph_2SiH_2	5
18	5.0 mmol of **1a**	78[b]

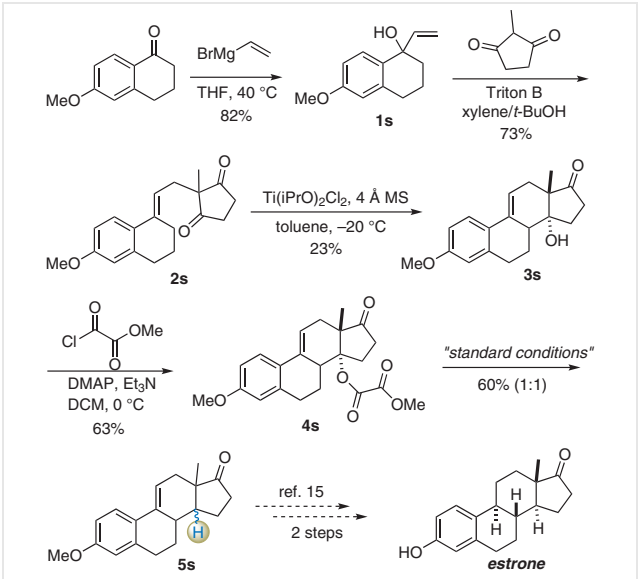
[a] NMR yield using 2,5-dimethyl furan as the internal standard from a mixture containing other impurities after a quick flash column chromatography.
[b] Isolated yield (average of 2 independent runs).

To illustrate the practical utility of our method, a Torgov cyclization and the concise synthesis of estrone were realized (Scheme 3).[18] Accordingly, diketone **2s** (obtained in two steps from commercially available 6-methoxy-1-tetralone) was subjected to slightly modified asymmetric Torgov cyclization conditions (see the Supporting Information) to furnish 23% yield of the tertiary alcohol **3s**,[19] whereas tertiary alkyl oxalate **4s** was prepared according to a general procedure. It is worth noting that our method was highly effective for hydrodeoxygenation of the oxalate **4s** with diphenylsilane, furnished product **5s** in 60% yield as a 1:1 *cis*/*trans* mixture. Product **5s** is a key intermediate en route to estrone through two-step transformations.[15] This result further indicated that dialkyl oxalates derived from tertiary alcohols undergo Barton-type homolytic scission of

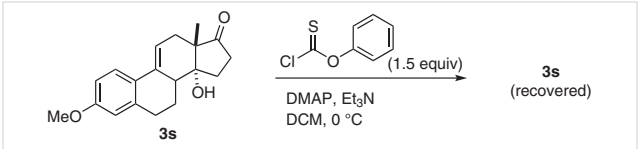


Scheme 2 Scope of hydrodeoxygenation of tertiary alkyl oxalates

C(sp^3)–O bonds to afford tertiary alkyl radicals when treated with Zn and $MgCl_2$ in the presence of Ni catalysts. By comparison, we tried to obtain the thioacyl derivatives from tertiary alcohol **3s** but failed to obtain the thiocarbonate; only **3s** was recovered (Scheme 4), showing the advantage of activation of tertiary alkyl alcohols with oxalates.[4]

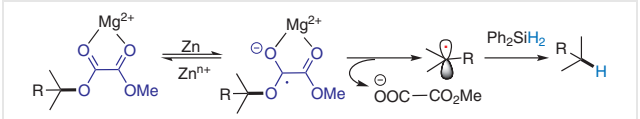


Scheme 3 Total synthesis of estrone in seven steps



Scheme 4 The synthesis of thiocarbonate from tertiary alcohols.

According to our previous studies on the Zn/$MgCl_2$-mediated and Ni-promoted radical C–O bond scission of tertiary alkyl oxalates,[9a] we proposed that this C–O bond hydrogenation process undergoes a similar reaction mechanism, wherein activation of oxalate with $MgCl_2$ is key. Upon single-electron reduction by Zn or low-valent Ni, the resulting radical anion species decomposes to give a tertiary alkyl radical which can abstract hydride from silanes (Scheme 5).



Scheme 5 A mechanistic proposal of this hydroreduction work

In summary, an efficient hydrodeoxygenation protocol for the reductive cleavage of C–O bonds followed by C–H bond formation has been developed. The method involves generation of tertiary alkyl radical intermediates that are invoked by single-electron reduction by Zn, wherein $MgCl_2$ serves as the indispensable additive and Ni as the promoter. The reaction displays excellent functional group tolerance

and broad substrate scope. The methodology has been successfully applied to the concise synthesis of a key intermediate en route to estrone. It thus may find useful applications in the synthesis of natural products and pharmaceuticals.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1328-0352.

References and Notes

(1) (a) Cornella, J.; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081. (b) Su, B.; Cao, Z.-C.; Shi, Z.-J. *Acc. Chem. Res.* **2015**, *48*, 886. (c) Pound, S. M.; Watson, M. P. *Chem. Commun.* **2018**, *54*, 12286. (d) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A. M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (e) Tollefson, E. J.; Hanna, L. E.; Jarvo, E. R. *Acc. Chem. Res.* **2015**, *48*, 2344.

(2) (a) Bisz, E.; Szostak, M. *ChemSusChem* **2017**, *10*, 3964. (b) Sundararaju, B.; Achard, M.; Bruneau, C. *Chem. Soc. Rev.* **2012**, *41*, 4467. (c) Liu, J.; Ye, Y.; Sessler, J. L.; Gong, H. *Acc. Chem. Res.* **2020**, *53*, 1833. (d) Lu, X.; Zhang, Z.-Q.; Lu, Y.; Zhang, B.; Wang, B.; Gong, T.-J.; Tian, C.-L.; Xiao, B.; Fu, Y. *Chin. J. Chem.* **2019**, *37*, 11.

(3) For reviews on aryl–O couplings, see: (a) Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717. (b) Zeng, H.; Qiu, Z.; Domínguez-Huerta, A.; Hearne, Z.; Chen, Z.; Li, C.-J. *ACS Catal.* **2017**, *7*, 510.

(4) (a) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413. (b) McCombie, S. W.; Motherwell, W. B.; Tozer, M. J. *Org. React.* **2012**, *77*, 161. (c) Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588.

(5) (a) Jamison, C. R.; Overman, L. E. *Acc. Chem. Res.* **2016**, *49*, 1578. (b) Nawrat, C. C.; Jamison, C. R.; Slutskyy, Y.; MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 11270. (c) Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 15342. (d) Gao, C.; Li, J.; Yu, J.; Yang, H.; Fu, H. *Chem. Commun.* **2016**, *52*, 7292. (e) Zhang, X.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 13862. (f) Rackl, D.; Kais, V.; Lutsker, E.; Reiser, O. *Eur. J. Org. Chem.* **2017**, 2130.

(6) Gao, J.; Rao, P.; Xu, K.; Wang, S.; Wu, Y.; He, C.; Ding, H. *J. Am. Chem. Soc.* **2020**, *142*, 4592.

(7) Xu, B.; Xun, W.; Su, S.; Zhai, H. *Angew. Chem. Int. Ed.* **2020**, *59*, 16475.

(8) Pan, S.; Chen, S.; Dong, G. *Angew. Chem. Int. Ed.* **2018**, *57*, 6333.

(9) (a) Ye, Y.; Chen, H.; Sessler, J. L.; Gong, H. *J. Am. Chem. Soc.* **2019**, *141*, 820. (b) Gao, M.; Sun, D.; Gong, H. *Org. Lett.* **2019**, *21*, 1645. (c) Pan, Y.; Gong, Y.; Song, Y.; Tong, W.; Gong, H. *Org. Biomol. Chem.* **2019**, *17*, 4230.

(10) (a) Álvarez-Bercedo, P.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 17352. (b) Tobisu, M.; Yamakawa, K.; Shimasaki, T.; Chatani, N. *Chem. Commun.* **2011**, *47*, 2946. (c) Speckmeier, E.; Padié, C.; Zeitler, K. *Org. Lett.* **2015**, *17*, 4818. (d) Qin, T.; Malins, L. R.; Edwards, J. T.; Merchant, R. R.; Novak, A. J. E.; Zhong, J. Z.; Mille, R. B.; Yan, M.; Yuan, C.; Eastgate, M. D.; Baran, P. S. *Angew. Chem. Int. Ed.* **2017**, *56*, 260. (e) Sergeev, A. G.; Hartwig, J. F. *Science* **2011**, *332*, 439.

(11) (a) Ye, Y.; Chen, H.; Yao, K.; Gong, H. *Org. Lett.* **2020**, *22*, 2070. (b) Chen, H.; Ye, Y.; Tong, W.; Fang, J.; Gong, H. *Chem. Commun.* **2020**, *56*, 454.

(12) For more examples on reductive formation of all-carbon quaternary centers, see: (a) Wang, X.; Ma, G.; Peng, Y.; Pitsch, C. E.; Moll, B. J.; Ly, T. D.; Wang, X.; Gong, H. *J. Am. Chem. Soc.* **2018**, *140*, 14490. (b) Chen, H.; Jia, X.; Yu, Y.; Qian, Q.; Gong, H. *Angew. Chem. Int. Ed.* **2017**, *56*, 13103. (c) Wang, X.; Wang, S.; Xue, W.; Gong, H. *J. Am. Chem. Soc.* **2015**, *137*, 11562. (d) Zhao, C.; Jia, X.; Wang, X.; Gong, H. *J. Am. Chem. Soc.* **2014**, *136*, 17645. (e) Primer, D. N.; Molander, G. A. *J. Am. Chem. Soc.* **2017**, *139*, 9847. (f) Green, S. A.; Vásquez-Céspedes, S.; Shenvi, R. A. *J. Am. Chem. Soc.* **2018**, *140*, 11317. (g) Green, S. A.; Huffman, T. R.; McCourt, R. O.; Puyl, V.; Shenvi, R. A. *J. Am. Chem. Soc.* **2019**, *141*, 7709. (h) García-Domínguez, A.; Li, Z.; Nevado, C. *J. Am. Chem. Soc.* **2017**, *139*, 6835. (i) Lu, X.; Wang, Y.; Zhang, B.; Pi, J.-J.; Wang, X.-X.; Gong, T.-J.; Xiao, B.; Fu, Y. *J. Am. Chem. Soc.* **2017**, *139*, 12632.

(13) (a) Breitenfeld, J.; Scopelliti, R.; Hu, X. *Organometallics* **2012**, *31*, 2128. (b) Cornella, J.; Gómez-Bengoa, E.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997.

(14) For reviews on cross-electrophile couplings, see: (a) Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Wangelin, A. J. *Chem. Eur. J.* **2014**, *20*, 6828. (b) Moragas, T.; Correa, A.; Martin, R. *Chem. Eur. J.* **2014**, *20*, 8242. (c) Weix, D. J. *Acc. Chem. Res.* **2015**, *48*, 1767. (d) Gu, J.; Wang, X.; Xue, W.; Gong, H. *Org. Chem. Front.* **2015**, *3*, 1411.

(15) (a) Prévost, S.; Dupré, N.; Leutzsch, M.; Wang, Q.; Wakchaure, V.; List, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 8770. (b) Gong, Q.; Wen, J.; Zhang, X. *Chem. Sci.* **2019**, *10*, 6350.

(16) Reddy, B. R. P.; Chowdhury, S.; Auffrant, A.; Gosmini, C. *Adv. Synth. Catal.* **2018**, *360*, 3026.

(17) Zhang, J.; Li, Z.; Zhuo, J.; Cui, Y.; Han, T.; Li, C. *J. Am. Chem. Soc.* **2019**, *141*, 8372.

(18) See the Supporting Information for details.

(19) Enev, V. S.; Harre, J. M.; Nickisch, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2693.