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Nucleophilic β-Carbon Activation of Propionic Acid as a 3-Carbon Synthon by Carbene Organocatalysis

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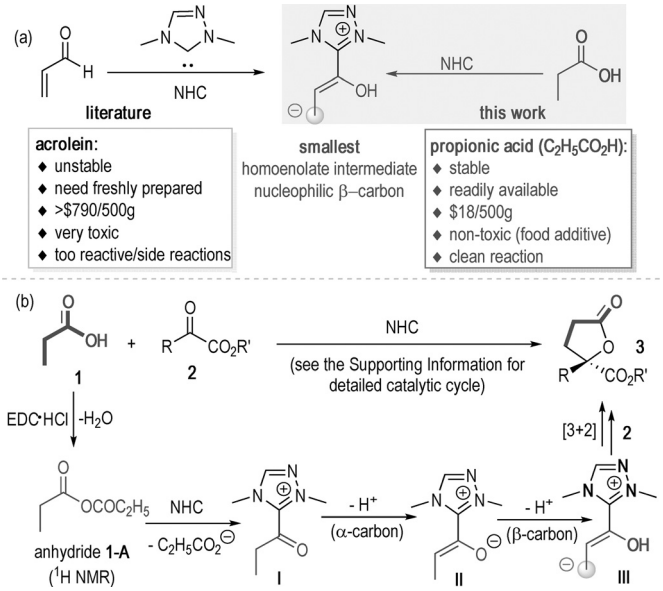
Abstract: Direct β-carbon activation of propionic acid ($C_2H_5CO_2H$) by carbene organocatalysis has been developed. This activation affords the smallest azolium homoenolate intermediate (without any substituent) as a 3-carbon nucleophile for enantioselective reactions. Propionic acid is an excellent raw material because it is cheap, stable, and safe. This approach provides a much better solution to azolium homoenolate synthesis than the previously established use of acrolein (enal without any substituent), which is expensive, unstable, and toxic.

N-heterocyclic carbene (NHC) organocatalysts provide unique opportunities in organic synthesis.[1] Raw materials widely explored under NHC organocatalysis include aldehydes and aldehyde derivatives such as α,β-unsaturated aldehydes (enals). In particular, reactions of NHC catalysts with enals form α,β-unsaturated Breslow intermediates (homoenolates) and convert the β-sp^2 carbon as a reactive nucleophilic carbon, as first disclosed in 2004 by the groups of Glorius[2] and Bode.[3] We are committed to developing new activation modes and effective synthetic methods that use readily available, easy to handle, and inexpensive substrates as starting materials. In the last few years, we have realized carbene-catalyzed activation of carboxylic esters and their derivatives.[4] We hope to offer complementary or better solutions that are not readily available with the catalytic approaches using aldehyde substrates. Studies from the groups of Romo,[5] Lectka,[6] Smith,[7] Lupton,[8] and others[9] have also shown that organocatalytic activation of carboxylic acids and their derivatives such as carboxylic esters and acetyl halides is a versatile strategy.

Herein we report a carbene-catalyzed β-sp^3 carbon activation of propionic acid ($CH_3CH_2CO_2H$) to generate the smallest homoenolate intermediate (bearing no substituent at the β-carbon) with a reactive nucleophilic β-carbon (Scheme 1 a).



Scheme 1. Carbene-catalyzed activation of $C_2H_5CO_2H$ as a 3-carbon nucleophile.

Mechanistically, condensation of propionic acid forms in situ a carboxylic anhydride that subsequently reacts with the NHC catalyst to initiate the catalytic cycle (Scheme 1 b). Urea additives were found to enhance reaction enantioselectivity consistently. In practical application, our approach should be very attractive when compared with the enal approach using acrolein (enal without β-substituent)[10] as the substrate. For instance, acrolein is unstable and usually needs to be prepared freshly from its acrolein diethyl acetal precursor that costs over $790 per 500 g (TCI). In contrast, propionic acid is stable and very inexpensive ($18 per 500 g, TCI). The high instability and reactivity of acrolein can also lead to undesired side reactions. In addition, acrolein is highly volatile and toxic.[11] Propionic acid is much safer: it can even be used as a food additive.

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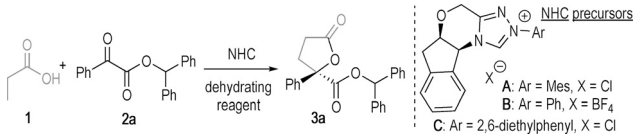
We started by using α-ketobenzhydryl ester[12] **2a** as a model electrophile substrate (Table 1). The indanol-derived triazolium catalyst **A**, first reported by Bode and co-workers,[13] could mediate the formation of proposed product **3a** in low

Table 1. Optimization of conditions.[a]



1 2a 3a

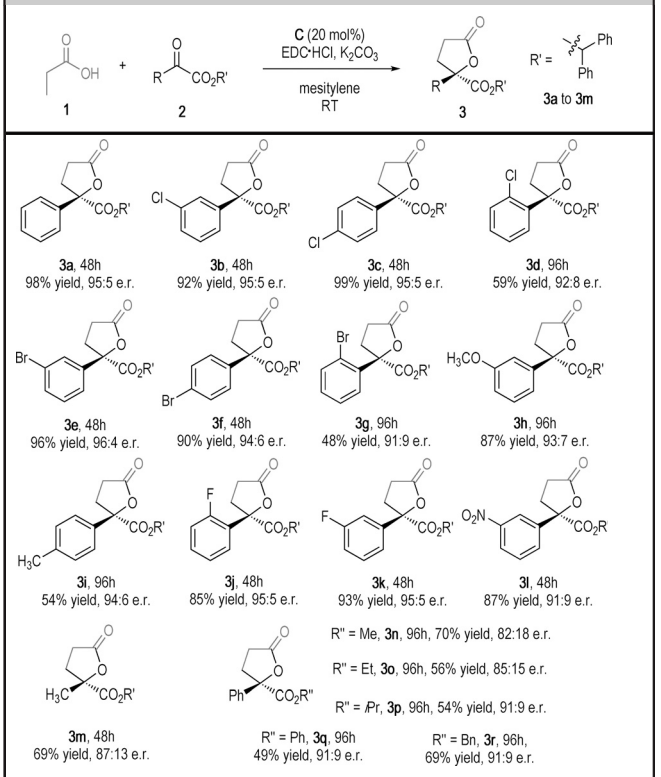
Entry	NHC	dehydrating reagent	solvent	base	Yield [%][b]	e.r.[c]
1	**A**	EDC·HCl	THF	DBU	28	79:21
2	**B**	EDC·HCl	THF	DBU	0	–
3	**C**	EDC·HCl	THF	DBU	35	80:20
4	**C**	DCC	THF	DBU	26	89:11
5	**C**	MsCl or CDI	THF	DBU	0	–
6	**C**	EDC·HCl	mesitylene	DBU	86	94:6
7	**C**	EDC·HCl	mesitylene	TEA	88	94:6
8	**C**	EDC·HCl	mesitylene	K_2CO_3	99	95:5
9[d]	**C**	EDC·HCl	mesitylene	K_2CO_3	98	95:5

[a] Reaction conditions, unless otherwise stated: **1** (5 equiv), **2a** (0.1 mmol, 1 equiv), NHC (20 mol%), base (2 equiv), dehydrating reagent (4 equiv), solvent (1 mL), RT (24 °C), 24 h; [b] yield of product isolated by column chromatography; [c] e.r. was determined by HPLC using a chiral stationary phase. [d] 4 Eq of **1** was used.

but encouraging 28% yield when using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) as a dehydrating reagent (to convert the propionic acid **1** into anhydride **1**–**A** in situ; Scheme 1b) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) as the base (Table 1, entry 1). NHC precatalyst **B**, with a *N*-phenyl substituent, first used by Rovis and co-workers,[14] was ineffective in our reaction (Table 1, entry 2). We then found that triazolium **C**, introduced by Scheidt and co-workers,[15] performed better in terms of both yield and e.r. (Table 1, entry 3). Evaluation of dehydrating reagents showed that EDC·HCl worked better than *N*,*N*′-dicyclohexylcarbodiimide (DCC), and the use of *N*,*N*′-carbonyldiimidazole (CDI) or methanesulfonyl chloride (MsCl) led to no formation of **3a** (Table 1, entries 3–5). We found mesitylene to be a much better solvent than THF, leading to **3a** in 86% yield and 94:6 e.r. (Table 1, entry 6). Last we found that by using K_2CO_3 as the base and 4 equivalent of propionic acid **1**, quantitative conversion of α-ketoester **2a** could be achieved with the formation of **3a** in exceptional 98% yield and 95:5 e.r. (Table 1, entry 9).

Having established acceptable conditions, we next examined the substrate scope of the reaction (Table 2). We first studied the substituents on the ketone moiety of the α-ketoesters **2**. Both aryl (**3a**–**l**) and alkyl (**3m**) groups on the ketone moiety worked well. The use of an electron-rich substituent (**3h**, **i**) on the aryl ring or placing a substituent at the *ortho*-position of the aromatic ketone (**3d**, **g**, **j**) slowed down the reaction, likely for electronic and steric reasons respectively. We then examined the ester moiety of the α-ketoesters **2**. Under the same conditions, various esters (**3n**–**r**) could be used, although the yields and enantioselectivities slightly varied.

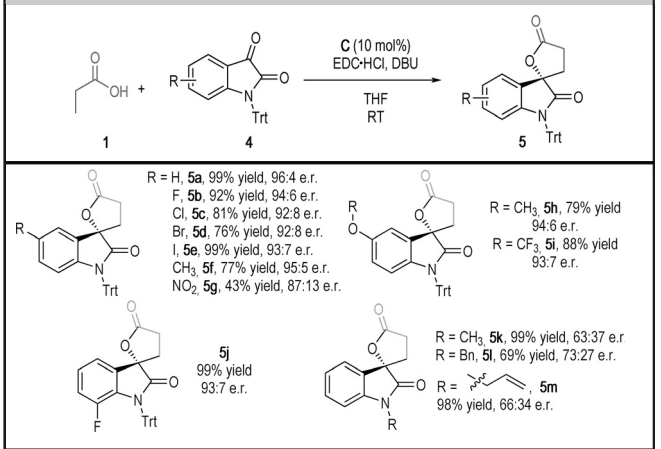
Table 2. Scope of α-ketoesters.[a]



[a] Reactions were carried out under the conditions outlined in Table 1, entry 9 for the indicated time; yields refer to product isolated by column chromatography; e.r. was determined by HPLC using a chiral stationary phase.

To further expand the utility of our method, we next demonstrated that isatins **4**[16] could be used as effective ketone electrophiles to react with the β-carbon of propionic acid **1** (Table 3). A search for conditions (see the Supporting Infor-

Table 3. Scope of isatins.[a]

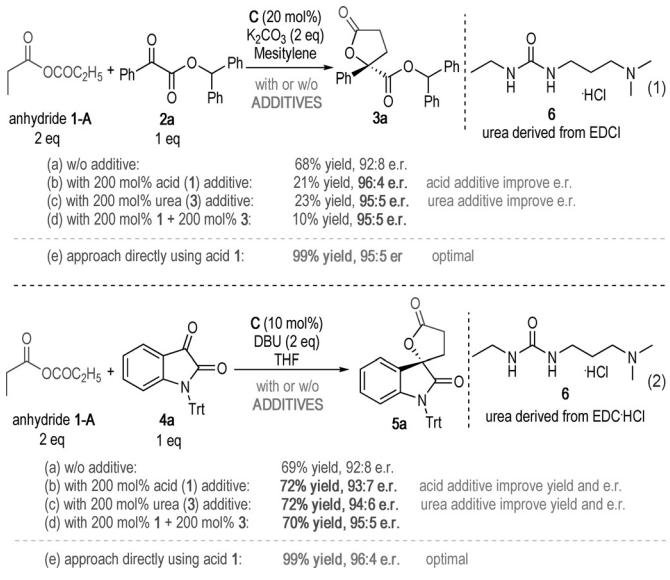


[a] **1** (5 equiv), **4** (0.1 mmol; 1 equiv), **C** (10 mol%), DBU (2 equiv), EDC·HCl (4 equiv), THF (1 mL), RT (24 °C), 12 h; yields refer to product isolated by column chromatography; e.r. was determined by HPLC using a chiral stationary phase.

mation for details) showed that by using 10 mol% of NHC pre-catalyst **C**, EDC·HCl as the dehydrating reagent, and DBU as the base in THF as the solvent, the desired lactone products **5** could be obtained in acceptable yields and enantioselectivities (**5a**–**j**). It is worth noting that the use of the electron-rich and sterically bulky trityl (Trt) unit as the *N*-protecting group was necessary to achieve high enantiomeric control. The use of other *N*-protecting groups for isatins led to products with good yields but unsatisfactory enantioselectivities (**5k**–**m**).

To understand the reaction mechanism, we monitored the catalytic reaction with ^{1}H NMR (see the Supporting Information for details). Our results showed that the acid substrate **1** was quickly converted into anhydride **1**–**A** (Scheme 1b) in less than 1 h. Anhydride **1**–**A** then reacted with the NHC catalyst via a β-activation process, as previously reported by our group,[4g,h,i] to form the smallest azolium homoenolate intermediate **III** (Scheme 1b), which subsequently underwent formal [3+2] cycloaddition reaction with the ketone electrophile to furnish the lactone product and regenerate the NHC catalyst.

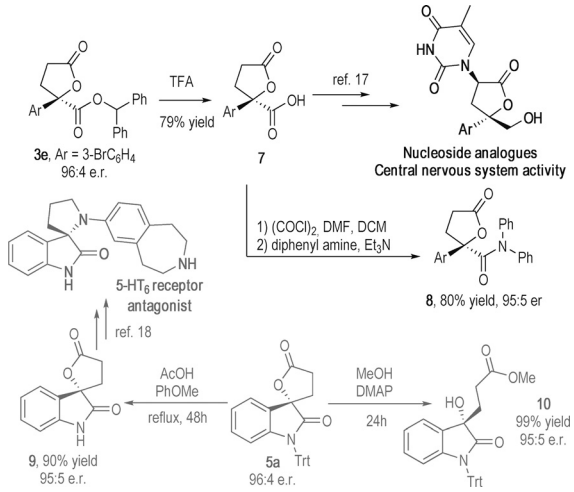
In addition to anhydride **1**–**A**, our reaction mixture contained carboxylic acid **1** and urea **6** formed from EDC·HCl during anhydride generation (Scheme 2). Acid and urea may



Scheme 2. Reaction starting with anhydride or acid as the substrate and effects of additives.

interact with the ketone substrate or other intermediates of our reaction. We therefore decided to study how the acid and urea affected the reaction outcome. We first found that reactions using pre-prepared anhydride **1**–**A** as the substrate gave **3a** and **5a** in around 70% yield with 92:8 e.r. (Scheme 2, **1a** and **2a**) that were much lower values than for the approach starting with acid **1** as the substrate (99% yield and >95:5 e.r.; **1e** and **2e**) under otherwise identical conditions. Acid **1** and urea **6** as additives were consistently found to improve the e.r. values of corresponding products, although they have different influences on the reaction yields with different electrophiles (**1b** to **1d**, **2b** to **2d**). We also found that the approach with a direct use of carboxylic acid as the starting material always performed better (**1e** and **2e**).

The products from our catalytic reactions (e.g., **3e**, **5a**) could be readily transformed into other synthetic building blocks or bioactive functional molecules (Scheme 3). For example, the ester moiety of **3e** could be easily removed by TFA (trifluoroacetic acid) to give the corresponding acid **7** without loss of e.r. The chiral acid product **7** could be converted into nucleoside analogues showing bioactivities on the central nervous system.[17] The *N*-trityl protecting group of catalytic product **5a** could be removed under mild conditions to give spirocyclic lactone **9**, which is the synthetic precursor for 5-HT$_6$ receptor antagonist.[18] Ester exchange of **5a** in methanol effectively afforded γ-hydroxyester **10** bearing a quaternary alcohol.



Scheme 3. Synthetic transformation of chiral products.

In summary, we have developed a direct β-carbon activation of propionic acid to generate the smallest azolium homoenolate intermediate. The majority of recent reaction developments have focused on substrates bearing various substituents. However, the synthetic potentials of many of the "smallest" substrates, such as CO, CO_2, HCHO, CH_3OH, or CH_3COOH, have not been well appreciated largely due to the lack of effective activation strategies for such "small" substrates. Our present study, with unusually cheap and safe 3-carbon carboxylic acid as the starting material, should encourage further investigation in this direction.

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Keywords: asymmetric synthesis · β-activation · N-heterocyclic carbenes · organocatalysis · propionic acid

[1] For selected reviews since 2010, see: a) J. L. Moore, T. Rovis, *Top. Curr. Chem.* **2009**, *291*, 77; b) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose, V. Sreekumar, *Chem. Soc. Rev.* **2011**, *40*, 5336; c) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2012**, *51*, 11686; *Angew. Chem.* **2012**, *124*, 11854; d) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511; e) J. Douglas, G. Churchill, A. D. Smith, *Synthesis* **2012**, *44*, 2295; f) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906; g) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696; h) P. Chauhan, D. Enders, *Angew. Chem. Int. Ed.* **2014**, *53*, 1485; *Angew. Chem.* **2014**, *126*, 1509; i) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485; j) S. R. Yetra, A. Patra, A. T. Biju, *Synthesis* **2015**, 1357.

[2] C. Burstein, F. Glorius, *Angew. Chem. Int. Ed.* **2004**, *43*, 6205; *Angew. Chem.* **2004**, *116*, 6331.

[3] S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370.

[4] a) L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao, Y. R. Chi, *Org. Lett.* **2012**, *14*, 2154; b) L. Hao, S. Chen, J. Xu, B. Tiwari, Z. Fu, T. Li, J. Lim, Y. R. Chi, *Org. Lett.* **2013**, *15*, 4956; c) L. Hao, W. C. Chan, R. Ganguly, Y. R. Chi, *Synlett* **2013**, 1197; d) S. Chen, L. Hao, Y. Zhang, B. Tiwari, Y. R. Chi, *Org. Lett.* **2013**, *15*, 5822; e) J. Xu, Z. Jin, Y. R. Chi, *Org. Lett.* **2013**, *15*, 5028; f) J. Cheng, Z. Huang, Y. R. Chi, *Angew. Chem. Int. Ed.* **2013**, *52*, 8592; *Angew. Chem.* **2013**, *125*, 8754; g) Z. Fu, J. Xu, T. Zhu, W. W. Y. Leong, Y. R. Chi, *Nat. Chem.* **2013**, *5*, 835; h) Z. Fu, K. Jiang, T. Zhu, J. Torres, Y. R. Chi, *Angew. Chem. Int. Ed.* **2014**, *53*, 6506; *Angew. Chem.* **2014**, *126*, 6624; i) Z. Jin, S. Chen, Y. Wang, P. Zheng, S. Yang, Y. R. Chi, *Angew. Chem. Int. Ed.* **2014**, *53*, 13506; *Angew. Chem.* **2014**, *126*, 13724.

[5] a) R. Tennyson, D. Romo, *J. Org. Chem.* **2000**, *65*, 7248; b) G. S. Cortez, R. L. Tennyson, D. Romo, *J. Am. Chem. Soc.* **2001**, *123*, 7945; c) V. C. Purohit, A. S. Matla, D. Romo, *J. Am. Chem. Soc.* **2008**, *130*, 10478; d) C. A. Leverett, V. C. Purohit, D. Romo, *Angew. Chem. Int. Ed.* **2010**, *49*, 9479; *Angew. Chem.* **2010**, *122*, 9669; e) S. Vellalath, K. N. Van, D. Romo, *Angew. Chem. Int. Ed.* **2013**, *52*, 13688; *Angew. Chem.* **2013**, *125*, 13933.

[6] a) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury, III, T. Lectka, *J. Am. Chem. Soc.* **2000**, *122*, 7831; b) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, D. Ferraris, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 6626; c) T. Bekele, M. H. Shah, J. Wolfer, C. J. Abraham, A. Weatherwax, T. Lectka, *J. Am. Chem. Soc.* **2006**, *128*, 1810; d) J. Wolfer, T. Bekele, C. J. Abraham, C. Dogo-Isonagie, T. Lectka, *Angew. Chem. Int. Ed.* **2006**, *45*, 7398; *Angew. Chem.* **2006**, *118*, 7558; e) C. J. Abraham, D. H. Pall, M. T. Scerba, J. W. Grebinski, T. Lectka, *J. Am. Chem. Soc.* **2006**, *128*, 13370.

[7] a) C. D. Campbell, D. K. A. Gallagher, J. E. Thomson, A. G. Lindsay, A. O'Donoghue, A. D. Smith, *Chem. Commun.* **2008**, 3528; b) C. Joannesse, C. P. Johnston, C. Concellon, C. Simal, D. Philp, A. D. Smith, *Angew. Chem. Int. Ed.* **2009**, *48*, 8914; *Angew. Chem.* **2009**, *121*, 9076; c) D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin, A. D. Smith, *J. Am. Chem. Soc.* **2011**, *133*, 2714; d) C. Simal, T. Lebl, A. M. Z. Slawin, A. D. Smith, *Angew. Chem. Int. Ed.* **2012**, *51*, 3653; *Angew. Chem.* **2012**, *124*, 3713; e) D. G. Stark, L. C. Morrill, P.-P. Yeh, A. M. Z. Slawin, T. J. C. O'Riordan, A. D. Smith, *Angew. Chem. Int. Ed.* **2013**, *52*, 11642; *Angew. Chem.* **2013**, *125*, 11856.

[8] a) S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2011**, *133*, 4694; b) L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2013**, *135*, 58; c) L. Candish, C. M. Forsyth, D. W. Lupton, *Angew. Chem. Int. Ed.* **2013**, *52*, 9149; *Angew. Chem.* **2013**, *125*, 9319; d) M. Kowalczyk, D. W. Lupton, *Angew. Chem. Int. Ed.* **2014**, *53*, 5314; *Angew. Chem.* **2014**, *126*, 5418; e) L. Candish, A. Levens, D. W. Lupton, *J. Am. Chem. Soc.* **2014**, *136*, 14397.

[9] For selected reviews, see: a) S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985; b) M. J. Gaunt, C. C. C. Johansson, *Chem. Rev.* **2007**, *107*, 5596; c) L. C. Morrill, A. D. Smith, *Chem. Soc. Rev.* **2014**, *43*, 6214. For selected recent examples, see: d) C. Zhu, X. Shen, S. G. Nelson, *J. Am. Chem. Soc.* **2004**, *126*, 5352; e) X. Shen, A. S. Wasmuth, J. Zhao, C. Zhu, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 7438; f) E. Bappert, P. Muller, G. C. Fu, *Chem. Commun.* **2006**, 2604; g) X. Xu, K. Wang, S. G. Nelson, *J. Am. Chem. Soc.* **2007**, *129*, 11690; h) L.-T. Shen, P.-L. Shao, S. Ye, *Adv. Synth. Catal.* **2011**, *353*, 1943; i) F. Manoni, C. Cornaggia, J. Murray, S. Tallon, S. J. Connon, *Chem. Commun.* **2012**, *48*, 6502; j) A. Lee, A. Younai, C. K. Price, J. Izquierdo, R. K. Mishra, K. A. Scheidt, *J. Am. Chem. Soc.* **2014**, *136*, 10589; k) X.-Y. Chen, Z.-H. Gao, C.-Y. Song, C.-L. Zhang, Z.-X. Wang, S. Ye, *Angew. Chem. Int. Ed.* **2014**, *53*, 11611; *Angew. Chem.* **2014**, *126*, 11795; l) L. Hesping, A. Biswas, C. G. Daniliuc, C. Muck-Lichtenfeld, A. Studer, *Chem. Sci.* **2015**, *6*, 1252; m) A. Lee, K. A. Scheidt, *Chem. Commun.* **2015**, *51*, 3407; n) Y. Xie, C. Yu, T. Li, S. Tu, C. Yao, *Chem. Eur. J.* **2015**, *21*, 5355.

[10] a) M. He, J. W. Bode, *J. Am. Chem. Soc.* **2008**, *130*, 418; b) M. Rommel, T. Fukuzumi, J. W. Bode, *J. Am. Chem. Soc.* **2008**, *130*, 17266; c) J. Kaeobamrung, M. C. Kozlowski, J. W. Bode, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20661; d) B. Maji, L. Ji, S. Wang, S. Vedachalam, R. Ganguly, X.-W. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 8276; *Angew. Chem.* **2012**, *124*, 8401.

[11] Z. Feng, W. Hu, M.-S. Tang, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 15404.

[12] a) Y. Wu, W. Yao, L. Pan, Y. Zhang, C. Ma, *Org. Lett.* **2010**, *12*, 640; b) J. Qi, X. Xie, R. Han, D. Ma, J. Yang, X. She, *Chem. Eur. J.* **2013**, *19*, 4146; c) K. P. Jang, G. E. Hutson, R. C. Johnston, E. O. McCusker, P. H.-Y. Cheong, K. A. Scheidt, *J. Am. Chem. Soc.* **2014**, *136*, 76; d) A. Lee, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2014**, *53*, 7594; *Angew. Chem.* **2014**, *126*, 7724; e) C. G. Goodman, M. M. Walker, J. S. Johnson, *J. Am. Chem. Soc.* **2015**, *137*, 122; f) C. T. Check, K. P. Jang, C. B. Schwamb, A. S. Wong, M. H. Wang, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2015**, *54*, 4264; *Angew. Chem.* **2015**, *127*, 4338.

[13] M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418.

[14] M. S. Kerr, J. R. Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 10298.

[15] D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766.

[16] a) B. Zhang, P. Feng, L. H. Sun, Y. X. Cui, S. Ye, N. Jiao, *Chem. Eur. J.* **2012**, *18*, 9198; b) J. Dugal-Tessier, E. A. O'Bayan, T. B. H. Schroeder, D. T. Cohen, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2012**, *51*, 4963; *Angew. Chem.* **2012**, *124*, 5047; c) J.-L. Li, B. Sahoo, C.-G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2014**, *53*, 10515; *Angew. Chem.* **2014**, *126*, 10683; d) R. Liu, C. Yu, T. Li, X. Wang, Y. Xie, C. Yao, *Org. Biomol. Chem.* **2014**, *12*, 1885.

[17] A. Jõgi, A. Paju, T. Pehk, T. Kailas, A.-M. Müürisepp, M. Lopp, *Tetrahedron* **2009**, *65*, 2959.

[18] G. Hostetler, D. Dunn, B. A. Mckenna, K. Kopec, S. Chatterjee, *Chem. Biol. Drug. Des.* **2014**, *83*, 149.

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