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Enantioselective Synthesis of 1,2-Dihydronaphthalenes via Oxidative N-Heterocyclic Carbene Catalysis

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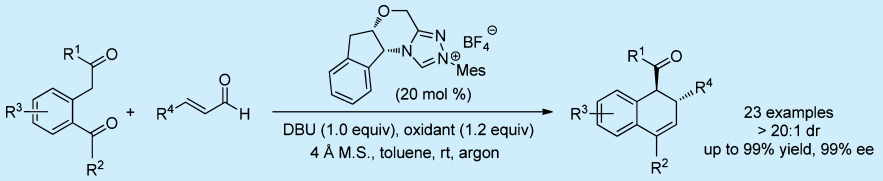
Supporting Information

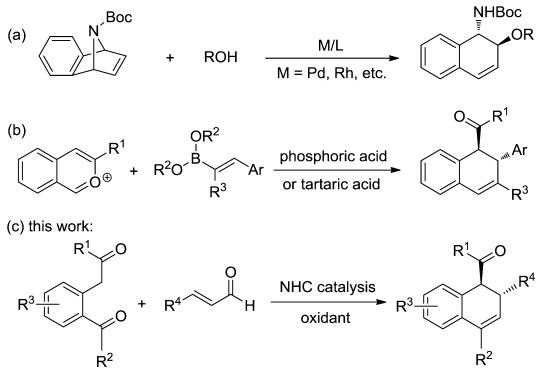


ABSTRACT: 1,2-Dihydronaphthalenes are important molecules in both medicinal and synthetic chemistry, but methods for the catalytic asymmetric construction of this class of molecules are limited. The diastereo- and enantioselective N-heterocyclic carbene-catalyzed cascade annulation reactions using benzodiketones and enals under oxidative conditions, which afford a variety of 1,2-dihydronaphthalenes with two adjacent stereocenters in up to 99% yield, with >20:1 dr, and up to 99% ee, are reported. Furthermore, the product can be easily transformed to a series of useful compounds such as alcohol, amide, and epoxide.

1,2-Dihydronaphthalenes are key structural motifs that widely exist in a variety of natural products and biologically active molecules, such as cannabisin C, negundin B, phyltetralin, podophyllic aldehyde, and pycnanthulignenes A–B, etc.[1] They are also important intermediates in organic synthesis and have been used to access tetrahydronaphthalene-related natural products such as podophyllotoxin and epipodophyllotoxin.[2] Consequently, development of a concise and efficient synthetic method for the assembly of enantioenriched 1,2-dihydronaphthalenes is in high demand. However, conventional methods mostly rely on the nucleophilic attack of electron-deficient naphthalenes with the aid of either chiral auxiliary groups or stoichiometric chiral ligands.[3] To date, very limited catalytic enantioselective approaches have been developed to realize the rapid access of 1,2-dihydronaphthalenes. Among them, transition-metal-catalyzed desymmetrization of oxabenzonorbornadienes is probably the most explored one (Scheme 1a).[4a−c] A copper-catalyzed non-asymmetric [4 + 2] cycloaddition of *o*-alkynyl(oxo)benzenes with alkenes has also been disclosed by Yamamoto et al.[4d] Recently, Sun and Schaus reported the elegant synthesis of the title compounds from isobenzopyrilium and styrylboronic acids using chiral phosphoric acid or tartaric acid as catalysts (Scheme 1b).[5] Considering the vital importance of 1,2-dihydronaphthalenes, new approaches that can rapidly assemble them are still highly desirable.

Oxidative N-heterocyclic carbene (NHC) catalysis via an α,β-unsaturated acyl azolium intermediate has been recently accepted as a valuable strategy for the construction of enantioenriched cyclic compounds.[6] For example, Studer, Bode, Ye, You, Chi, Biju, Wang, and other groups have realized the synthesis of dihydropyranones, dihydropyridinones, 1,2,3-trisubstituted indane derivatives, cyclopropanes, pyrazoles, pyrazolidinones, cyclopentenes, spirocyclohexadienones, and β-lactones.[7] Furthermore, Lupton and co-workers have developed the NHC-catalyzed synthesis of cyclohexenes or cyclohexadienes via a Michael–aldol–lactonization sequence.[8] Studer and Biju independently demonstrated the synthesis of highly substituted β-lactones or cyclopetenes via the similar process.[9] We proposed that an oxidative NHC catalysis-mediated Michael addition–aldol reaction–lactone formation–decarboxylation cascade from benzodiketones and enals could be used as an alternative method to provide 3,4-disubstituted-1,2-dihydronaphthalenes (Scheme 1c). Herein we report our results.

Scheme 1. Catalytic Asymmetric Synthesis of 1,2-Dihydronaphthalenes



At the initial stage, we selected diketone **1a**, cinnamaldehyde **2a**, and triazolium **A**[10] for the optimization of reaction

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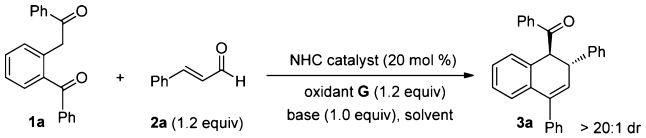
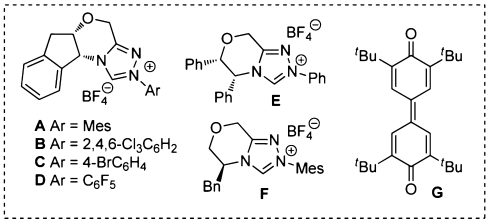
conditions. To our delight, 1,2-dihydronaphthalene **3a** was obtained in 59% yield with 93% ee when DBU was used as the base, toluene as the solvent, and **G** as the oxidant, and only one diastereoisomer was observed from the ^{1}H NMR analysis of the reaction mixture (Table 1, entry 1). However, the replacement

Table 1. Optimization of Reaction Conditions[a]





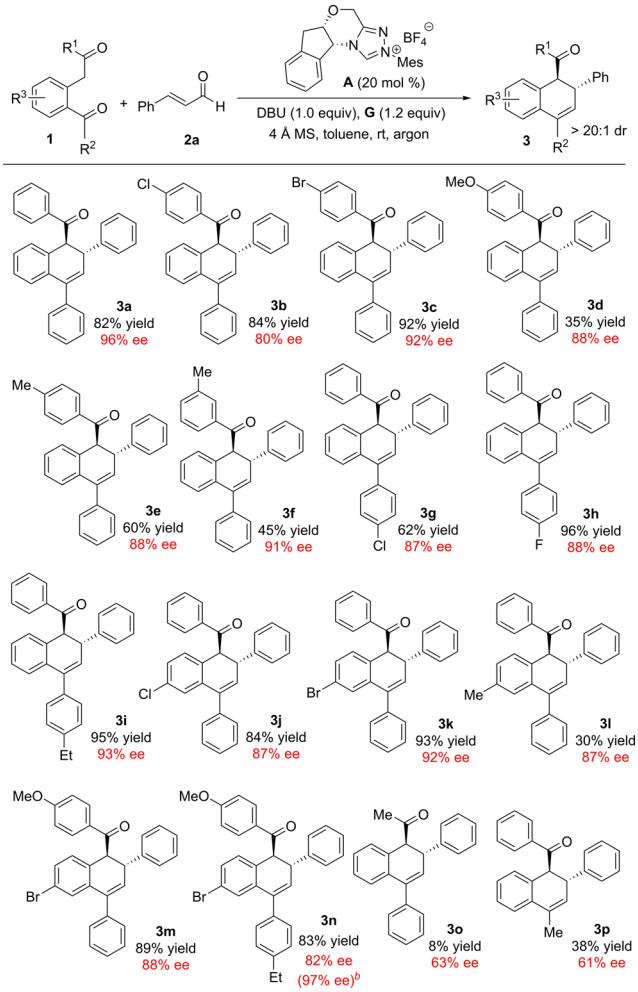
entry	catalyst	base	solvent	yield[b] (%)	ee[c] (%)
1	**A**	DBU	toluene	59	93
2	**A**	Et_3N	toluene	trace	
3	**A**	$^iPr_2NEt$	toluene	trace	
4	**A**	K_2CO_3	toluene	trace	
5	**A**	DBU	THF	60	89
6	**A**	DBU	CH_2Cl_2	11	74
7[d]	**A**	**DBU**	**toluene**	**82**	**96**
8[d]	**B**	DBU	toluene	32	71
9[d]	**C**	DBU	toluene	trace	
10[d]	**D**	DBU	toluene	18	63
11[d]	**E**	DBU	toluene	13	63
12[d]	**F**	DBU	toluene	88	71

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), NHC (0.02 mmol), toluene (1 mL), argon protection, rt. [b]Isolated yields based on **1a**. [c]Determined via HPLC analysis on a chiral stationary phase. The absolute configuration was determined via the single-crystal X-ray structure analysis of **3n** (Figure 1). [d]**2a** (0.2 mmol) and 4 Å MS (400 mg) were added.

of DBU with other bases such as Et_3N, $^iPr_2NEt$, and K_2CO_3 resulted in very low conversion of the substrates (Table 1, entries 2–4). We then tested different solvents (i.e., THF and CH_2Cl_2) while keeping DBU as the base, but no better results than that in toluene were detected (Table 1, entries 5 and 6). After a series of further screening of the reaction parameters, we found that the desired product **3a** can be isolated in 82% yield and with an excellent 96% ee through the introduction of 4 Å MS and increasing the amount of **2a** (Table 1, entry 7). Under these conditions, other NHC catalysts such as **B**–**F**[11] were also evaluated, but the annulation product **3a** was obtained with decreased ee in all cases (Table 1, entries 10–12).

Having established the optimal conditions (Table 1, entry 7), we then investigated the substrate scope of benzodiketone **1**. As shown in Scheme 2, when the R^1 group is electron-withdrawing 4-Cl- or 4-Br-substituted phenyl rings, the corresponding dihydronaphthalenes were formed in high yields and with good to excellent enantioselectivities (Scheme 2, **3b** and **3c**). Introduction of electron-rich 4-OMe, 4-Me, or 3-Me groups was also tolerated, with 88–91% ee observed, albeit in low to moderate yields (Scheme 2, **3d**–**3f**). Then various R^2 groups were examined, and the electronic properties showed little

Scheme 2. Substrate Scope of Benzodiketones[a]



[a]All reactions were run on a 0.1 mmol scale; all yields were of isolated products; ee values were determined via HPLC analysis on a chiral stationary phase. [b]After recrystallization.

effect on the outcomes (Scheme 2, **3g**–**3i**). Furthermore, the R^3 group on the phenyl ring of substrate **1** can be Cl, Br, or Me (Scheme 2, **3j**–**3l**). We were also pleased to find that the introduction of two or three substituents into different moieties of substrate **1** was also possible, with good yields and good ee values perceived (Scheme 2, **3m** and **3n**). Moreover, we studied substrates with methyl ketone units and found that the reaction was retarded probably owing to the low reactivities of the substrates, and the corresponding annulation products were released in low yields with moderate enantioselectivities (Scheme 2, **3o** and **3p**). It is worthwhile to mention that in all the above cases, only one diastereoisomer was detected. The absolute configuration of product **3n** was determined via single-crystal X-ray structure analysis (Figure 1),[12] and other products were assigned by analogy.

Having evaluated the substrate scope and limitations of benzodiketones, we then transferred our focus to enals. To our delight, a variety of enals with differently substituted phenyl groups were all tolerated. For instance, the introduction of an electron-rich 4-OMe or 2-Me group proved successful, allowing the access to products **4a** and **4b** in high yields and with excellent 95 and 97% ee, respectively (Scheme 3, **4a** and **4b**). Moreover, enals with electron-withdrawing 4-Cl-, 4-Br-, or 4-F-

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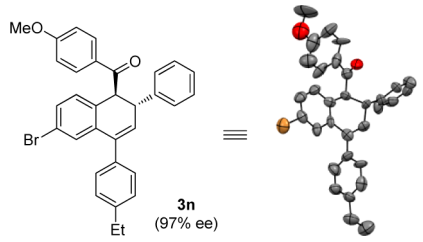
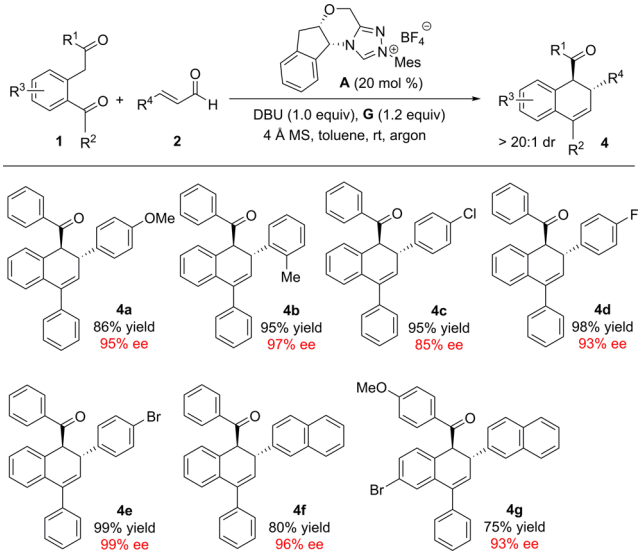


Figure 1. Single-crystal X-ray structure analysis of **3n**.

Scheme 3. Substrate Scope of Enals[a]

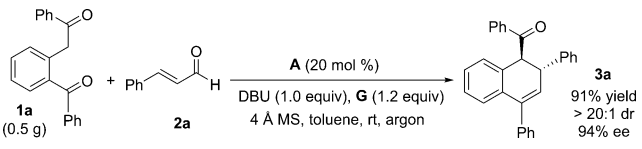


[a]All reactions were run on a 0.2 mmol scale; all yields were of isolated products; ee values were determined via HPLC analysis on a chiral stationary phase.

substituted phenyl rings were also tolerated, furnishing the dihydronaphthalenes in excellent yields and with high to excellent ee values (Scheme 3, **4c**–**4e**). It is also noteworthy that the reactions of 2-naphthyl-substituted enal could afford the annulation products in excellent 96 and 93% ee (Scheme 3, **4f** and **4g**, respectively). Unfortunately, reactions using aliphatic-group-substituted enals such as methacrylaldehyde failed to give the desired product.

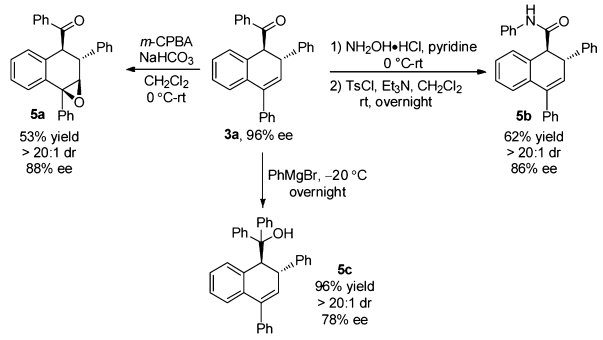
A scale-up reaction was also conducted using 0.5 g of the staring material **1a**. As shown in Scheme 4, the yield and diastereoselectivity of **3a** were both excellent, and only a slight decrease of the enantioselectivity was detected.

Scheme 4. Scale-up Reaction



A diverse set of further transformations based on product **3a** can be readily accomplished (Scheme 5). For instance, oxidation of the double bond in **3a** resulted in epoxide **5a** in moderate yield, with good stereoselectivities.[13] The Beckmann rearrangement of **3a** can afford chiral amide **5b** in good yield and with good ee.[14] Furthermore, we found that the product can tolerate some harsh conditions such as the nucleophilic

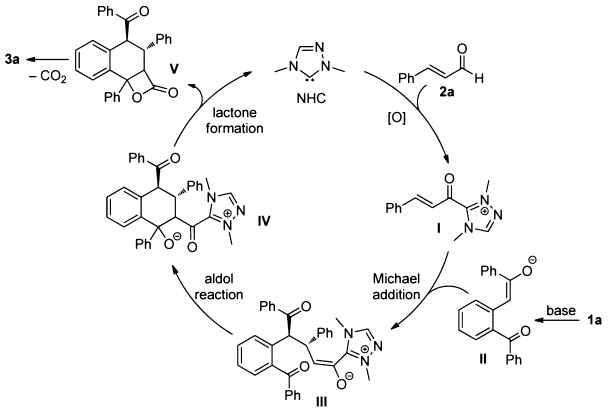
Scheme 5. Derivatizations of Product 3a



attack of **3a** with phenyl Grignard reagent, and the reaction provided alcohol **5c** in high yield, albeit with a decreased ee value.

A plausible mechanism was proposed based on the experimental results and literature reports. As outlined in Scheme 6, reaction of NHC catalyst with enal **2a** under

Scheme 6. Proposed Reaction Mechanism



oxidative conditions leads to the α,β-unsaturated acyl azolium intermediate **I**. Meanwhile, deprotonation of **1a** under basic conditions affords enolate **II**, which will subsequently undergo Michael addition with **I** to release a new enolate **III**. The aldol reaction within **III** can provide intermediate **IV**, which will form lactone **V** and at the same time realize the regeneration of NHC catalyst. Product **3a** is finally obtained after a spontaneous decarboxylation process.

In summary, oxidative NHC catalysis was employed to achieve the diastereo- and enantioselective synthesis of a variety of 1,2-dihydronaphthalenes. The products were obtained in up to 99% yield, with >20:1 dr, and up to 99% ee. Furthermore, the product can be easily converted to a series of value-added molecules. A cascade process involving Michael addition–aldol reaction–lactone formation–decarboxylation was proposed to demonstrate the reaction mechanism. Further work based on the oxidative NHC catalysis is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00555.

X-ray structure of **3n** (CIF)

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Experimental procedures, optimization details, data for all new compounds, NMR and HPLC spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Stevenson, R.; Williams, J. R. *Tetrahedron* **1977**, *33*, 2913. (b) Sakakibara, I.; Ikeya, Y.; Hayashi, K.; Mitsuhashi, H. *Phytochemistry* **1992**, *31*, 3219. (c) Ward, R. S. *Nat. Prod. Rep.* **1997**, *14*, 43. (d) Azhar-Ul-Haq; Malik, A.; Anis, I.; Khan, S. B.; Ahmed, E.; Ahmed, Z.; Nawaz, S. A.; Choudhary, M. I. *Chem. Pharm. Bull.* **2004**, *52*, 1269. (e) Castro, M. A.; Miguel del Corral, J. M.; Gordaliza, M.; García, P. A.; Gómez-Zurita, M. A.; García-Gràvalos, M. D.; de la Iglesia-Vicente, J.; Gajate, C.; An, F.; Mollinedo, F.; San Feliciano, A. *J. Med. Chem.* **2004**, *47*, 1214. (f) Nono, E. C. N.; Mkounga, P.; Kuete, V.; Marat, K.; Hultin, P. G.; Nkengfack, A. E. *J. Nat. Prod.* **2010**, *73*, 213.

(2) (a) Sainsbury, M.; Williams, C. S. *Tetrahedron Lett.* **1990**, *31*, 2763. (b) Maeda, K.; Farrington, E. J.; Galardon, E.; John, B. D.; Brown, J. M. *Adv. Synth. Catal.* **2002**, *344*, 104. (c) Andrews, R. C.; Teague, S. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7854. (d) Engelhardt, U.; Sarkar, A.; Linker, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2487.

(3) (a) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266. (b) Rawson, D. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2292. (c) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351. (d) Engelhardt, U.; Sarkar, A.; Linker, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2487.

(4) (a) Cho, Y.-H.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837. (b) Webster, R.; Boing, C.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131*, 444. (c) Yang, F.; Chen, J.; Xu, J.; Ma, F.; Zhou, Y.; Shinde, M. V.; Fan, B. *Org. Lett.* **2016**, *18*, 4832. (d) Asao, N.; Kasahara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3504.

(5) (a) Qian, H.; Zhao, W.; Wang, Z.; Sun, J. *J. Am. Chem. Soc.* **2015**, *137*, 560. (b) Luan, Y.; Barbato, K. S.; Moquist, P. N.; Kodama, T.; Schaus, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 3233.

(6) For selected reviews involving α,β-unsaturated acyl azolium intermediate, see: (a) Zhang, C.; Hooper, J. F.; Lupton, D. W. *ACS Catal.* **2017**, *7*, 2583. (b) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696. (c) Levens, A.; Lupton, D. W. *Synlett* **2017**, *28*, 415. (d) De Sarkar, S.; Biswas, A.; Samanta, R. C.; Studer, A. *Chem. - Eur. J.* **2013**, *19*, 4664. (e) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (f) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906. (g) Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Synthesis* **2017**, *49*, 451.

(7) For selected reports, see: (a) De Sarkar, S.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266. (b) Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 4080. (c) Zhu, Z.-Q.; Zheng, X.-L.; Jiang, N.-F.; Wan, X.; Xiao, J.-C. *Chem. Commun.* **2011**, *47*, 8670. (d) Wanner, B.; Mahatthananchai, J.; Bode, J. W. *Org. Lett.* **2011**, *13*, 5378. (e) Biswas, A.; De Sarkar, S.; Frohlich, R.; Studer, A. *Org. Lett.* **2011**, *13*, 4966. (f) Kravina, A. G.; Mahatthananchai, J.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9433. (g) Biswas, A.; De Sarkar, S.; Tebben, L.; Studer, A. *Chem. Commun.* **2012**, *48*, 5190. (h) Mahatthananchai, J.; Kaeobamrung, J.; Bode, J. W. *ACS Catal.* **2012**, *2*, 494. (i) Bera, S.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2015**, *17*, 4940. (j) Yetra, S. R.; Mondal, S.; Mukherjee, S.; Gonnade, R. G.; Biju, A. T. *Angew. Chem., Int. Ed.* **2016**, *55*, 268. (k) Yetra, S. R.; Mondal, S.; Suresh, E.; Biju, A. T. *Org. Lett.* **2015**, *17*, 1417. (l) Li, G.-T.; Gu, Q.; You, S.-L. *Chem. Sci.* **2015**, *6*, 4273. (m) Liang, Z.-Q.; Wang, D.-L.; Zhang, H.-M.; Ye, S. *Org. Lett.* **2015**, *17*, 5140. (n) Wu, X.; Liu, B.; Zhang, Y.; Jeret, M.; Wang, H.; Zheng, P.; Yang, S.; Song, B.-A.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2016**, *55*, 12280. (o) Jia, Q.; Wang, J. *Org. Lett.* **2016**, *18*, 2212. (p) Zhang, C.-L.; Gao, Z.-H.; Liang, Z.-Q.; Ye, S. *Adv. Synth. Catal.* **2016**, *358*, 2862. (q) Bera, S.; Studer, A. *Synthesis* **2016**, *49*, 121. (r) Wu, X.; Liu, B.; Zhang, Y.; Jeret, M.; Wang, H.; Zheng, P.; Yang, S.; Song, B.-A.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2016**, *55*, 12280. (s) Wu, X.; Hao, L.; Zhang, Y.; Rakesh, M.; Reddi, R. N.; Yang, S.; Song, B.-A.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2017**, *56*, 4201. (t) Li, G.-T.; Li, Z.-K.; Gu, Q.; You, S.-L. *Org. Lett.* **2017**, *19*, 1318.

(8) (a) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2011**, *133*, 4694. (b) Ryan, S. J.; Stasch, A.; Paddon-Row, M. N.; Lupton, D. W. *J. Org. Chem.* **2012**, *77*, 1113. (c) Candish, L.; Levens, A.; Lupton, D. W. *J. Am. Chem. Soc.* **2014**, *136*, 14397. (d) Levens, A.; Zhang, C.; Candish, L.; Forsyth, C. M.; Lupton, D. W. *Org. Lett.* **2015**, *17*, 5332.

(9) (a) Bera, S.; Samanta, R. C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 9622. (b) Mondal, S.; Yetra, S. R.; Patra, A.; Kunte, S. S.; Gonnade, R. G.; Biju, A. T. *Chem. Commun.* **2014**, *50*, 14539.

(10) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088.

(11) (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (b) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (c) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094.

(12) CCDC 1533319 (**3n**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) The relative configuration of the product was assigned by analogy to a known report: Toselli, N.; Martin, D.; Achard, M.; Tenaglia, A.; Buono, G. *J. Org. Chem.* **2009**, *74*, 3783.

(14) For a similar report, see: Kenwright, J. L.; Galloway, W. R. J. D.; Wortmann, L.; Spring, D. R. *Synth. Commun.* **2013**, *43*, 1508.

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