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Highly Enantioselective Catalytic Cross-Dehydrogenative Coupling of *N*-Carbamoyl Tetrahydroisoquinolines and Terminal Alkynes

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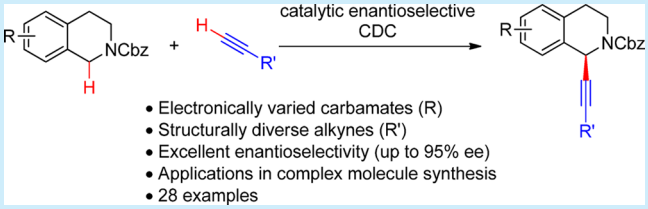
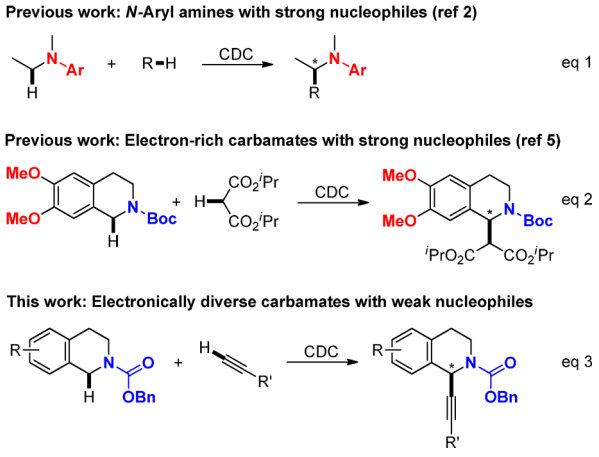
Supporting Information

ABSTRACT: The first catalytic asymmetric cross-dehydrogenative coupling of cyclic carbamates and terminal alkynes has been established. The reaction features high enantiocontrol and excellent functional group tolerance and displays a wide range of structurally and electronically diverse carbamates as well as terminal alkynes. *N*-Acyl hemiaminals were identified as the reactive intermediates through preliminary control experiments. Employing readily removable carbamates as substrates rather than traditionally adopted *N*-aryl amines allows applications in complex molecule synthesis and therefore advances the C−H functionalization strategy to a synthetically useful level.



The catalytic enantioselective cross-dehydrogenative coupling (CDC) reactions of readily accessible substrates represent a straightforward and effective strategy for the synthesis of numerous complex chiral molecules whereby the only loss is H_2 formally.[1] While impressive progress has recently been achieved for nitrogen-containing components, the scope is only limited to highly reactive *N*-aryl amines (Scheme 1, eq 1).[2]

Scheme 1. Catalytic Enantioselective CDC of *N*-Heterocycles



The aryl group linked to the nitrogen weakens the target C−H bond and stabilizes the resulting iminium intermediate, allowing the initial C−H cleavage and subsequent nucleophilic addition to occur at ambient conditions. Despite excellent enantioselectivity, removal of the aryl moiety in the presence of other functional groups proves to be difficult and thus limits the synthetic utility.[3a] Moreover, relatively strong nucleophiles such as enamines or 1,3-dicarbonyl compounds are always required for high enantioselectivity probably due to the poor electrophilicity of the stabilized iminium intermediate.[2,3b] Li and co-workers reported their efforts on the employment of relatively weak nucleophiles such as the arylacetylene.[2h,i] However, limited scope of both components was observed with modest enantiocontrol (36%−74% ee).

The direct C−H functionalization of carbamates rather than aryl amines provides an attractive solution for enhancing the scope and utility of the strategy through generating a more reactive acyliminium intermediate that can react with a broader range of nucleophiles and affords products that can be readily cleaved under mild conditions. While some progress in the racemic CDC of carbamates has been achieved, the existing methods usually required relative harsh conditions probably due to reduced substrate reactivities and stabilities of resulting *N*-acyliminium ions.[4] The art seriously hampers the design of catalytic enantioselective variants. So far, only one example of the catalytic enantioselective C−H functionalization of carbamates has been reported by Sodeoka (Scheme 1, eq 2).[5] Good enantiocontrol (up to 86% ee) was achieved by using a fastidious procedure for the oxidant addition over 10 h to avoid the decomposition of unstable acyliminium ions. However, the scope is still restricted to dimethoxy substituted electron-rich carbamates even when nucleophilic malonates are employed, leaving electron-neutral and -deficient ones intact. Herein, we report our recent efforts on the catalytic asymmetric CDC of electronically varied cyclic carbamates with weakly nucleophilic terminal alkynes and the applications in complex molecule synthesis (Scheme 1, eq 3).[6]

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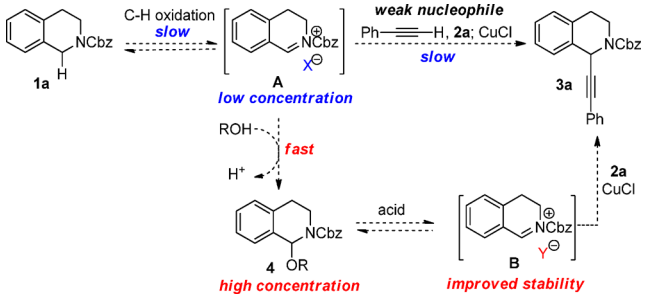
Initially, the racemic CDC of benzyl carbamate **1a** with phenylacetylene **2a** in the presence of CuCl was selected as the model reaction for optimization (Scheme 2). Oxidants including

Scheme 2. Strategy for CDC of Electron-Neutral Carbamate 1a and Terminal Alkyne 2a



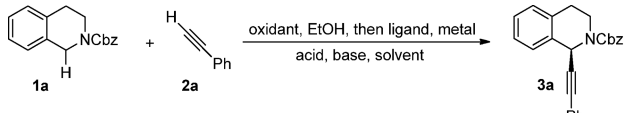
TBHP, DDQ, 2,2,6,6-tetramethylpiperidine *N*-oxide salt ($T^+BF_4^-$), and Ph_3CBF_4 did not promote the coupling, with all the **1a** recovery. The observation might be ascribed to the low reactivity of **1a** and poor stability of the resulting acyliminium **A**, making the C−H oxidation of **1a** thermodynamically unfavorable. Therefore, the low concentrations of the acyliminium ion **A** and copper acetylide would be insufficient to drive the coupling to the product. We envision that a protic additive that reacts quickly and thermodynamically favorably with **A** would drive the C−H oxidation to retain the oxidation state of the acyliminium ion in the form of *N*-acyl hemiaminal **4**. A suitable acid would promote the conversion of **4** to acyliminium **B** with a better counterion Y^- than X^- in **A** to stabilize the cation, and the coupling might be viable.

To test the hypothesis, one equivalent of ethanol was introduced. After all the carbamate **1a** was consumed, a variety of acids were explored. Delightedly, several Lewis acids bearing a triflate anion promoted the coupling when using $T^+BF_4^-$ as the oxidant (Table 1, entry 1, and Table S1 in the Supporting Information (SI)). Despite observed reactivity, racemic **3a** was always obtained in the presence of chiral ligand **L1** (Table 1, entry 2). After extensive studies of a series of additives, enantioselectivity was observed when KOH was used (Table 1, entry 3, and Table S2 in the SI). A systematic exploration of chiral ligands and copper salts identified **L3** with CuBr as the ideal combination (Table 1, entries 3−7, and Table S3 in the SI). The investigation on the Lewis acid effect on the enantioselectivity revealed that $Yb(OTf)_3$ proved to be the unique choice for the asymmetric reaction (Table 1, entries 7 and 8). The further study on the additive effect indicated that EtOH (1 equiv) together with H_2O (2 equiv) were beneficial to increasing the selectivity (Table 1, entries 7 and 9, and Table S4 in the SI). Extensive optimization of the solvent, carbamate, and oxidant identified a mixture of CH_2Cl_2/toluene (v/v, 1:4), Cbz moiety, and $T^+BF_4^-$ to be optimal (Table 1, entries 9 and 10, and Tables S5 and S6 in the SI).

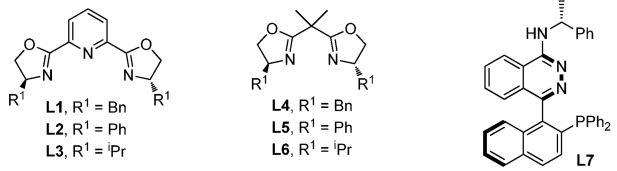
Under the optimized conditions, a variety of electronically varied aryl acetylenes with different substituent patterns were tolerated with the catalytic enantioselective CDC with carbamate **1a** efficiently (Scheme 3). Good to excellent enantioselectivities were observed for aryl acetylenes bearing both electron-withdrawing and -donating functionalities (**3a**−**3n**). Heteroaryl acetylenes like thiophen-2-yl ethyne (**3o**) and alkenyl acetylenes (**3p**) proved to be suitable substrates. Alkyl acetylene **2q** and methyl propiolate **2r** afforded desired products with compromised yields and ee, which might be ascribed to the reduced reactivity of alkynes.

The scope of carbamates was next explored (Scheme 4). As expected, the CDC of carbamates with electron-donating

Table 1. Reaction Condition Optimization[a]

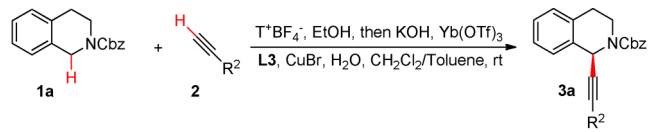


entry	ligand	metal	acid	base	yield (%)[b]	ee (%)[c]
1[d]	—	CuCl	LA	—	20-59	n.d.
2	**L1**	CuCl	$Yb(OTf)_3$	—	30	0
3	**L1**	CuCl	$Yb(OTf)_3$	KOH	44	41
4	**L2**	CuCl	$Yb(OTf)_3$	KOH	37	12
5	**L3**	CuCl	$Yb(OTf)_3$	KOH	43	49
6	**L4-L7**	CuCl	$Yb(OTf)_3$	KOH	< 5	n.d.
7	**L3**	CuBr	$Yb(OTf)_3$	KOH	49	56
8[e]	**L3**	CuBr	LA	KOH	n.d.	< 20
9[f]	**L3**	CuBr	$Yb(OTf)_3$	KOH	55	85
10[g]	**L3**	CuBr	$Yb(OTf)_3$	KOH	61	92



[a]Reaction condition: **1a** (0.1 mmol), **2a** (0.2 mmol), $T^+BF_4^-$ (0.1 mmol), ligand (0.015 mmol), metal (0.015 mmol), EtOH (0.1 mmol), acid (0.12 mmol), and base (0.19 mmol) in CH_2Cl_2 (1.0 mL) at rt for 48 h, unless otherwise specified. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Lewis acids including $Yb(OTf)_3$, $Sc(OTf)_3$, $In(OTf)_3$, and $Ga(OTf)_3$. [e]Lewis acid in footnote d except $Yb(OTf)_3$. [f]H_2O (0.2 mmol). [g]CH_2Cl_2/toluene (v/v, 1:4). LA = Lewis acid. n.d. = not determined.

Scheme 3. Scope of the Terminal Alkynes[a]



3a, R^2 = Ph (61%; ee = 92%)
3b, R^2 = 4-CF_3Ph (57%; ee = 90%)
3c, R^2 = 4-FPh (51%; ee = 91%)
3d, R^2 = 3-FPh (50%; ee = 85%)
3e, R^2 = 4-ClPh (53%; ee = 91%)
3f, R^2 = 3-ClPh (52%; ee = 88%)
3g, R^2 = 4-BrPh (60%; ee = 95%)
3h, R^2 = 4-CH_3Ph (64%; ee = 92%)
3i, R^2 = 3-CH_3Ph (62%; ee = 90%)
3j, R^2 = 3.4-MeOPh (55%; ee = 94%)
3k, R^2 = 4-MeOPh (61%; ee = 93%)
3l, R^2 = 3-MeOPh (57%; ee = 90%)
3m, R^2 =  (57%; ee = 91%)
3n, R^2 = 4-C_6H_5Ph (58%; ee = 90%)
3o, R^2 =  (70%; ee = 90%)
3p, R^2 =  (42%; ee = 70%)
3q R^2 = C_6H_{13} (23%; ee = 43%)
3r R^2 = CO_2CH_3 (15%; ee = 39%)

[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), $T^+BF_4^-$ (0.1 mmol), **L3** (0.015 mmol), CuBr (0.015 mmol), EtOH (0.1 mmol), $Yb(OTf)_3$ (0.12 mmol), KOH (0.19 mmol), and H_2O (0.2 mmol) in 1.0 mL of CH_2Cl_2/toluene (v/v, 1:4) at rt for 48 h.

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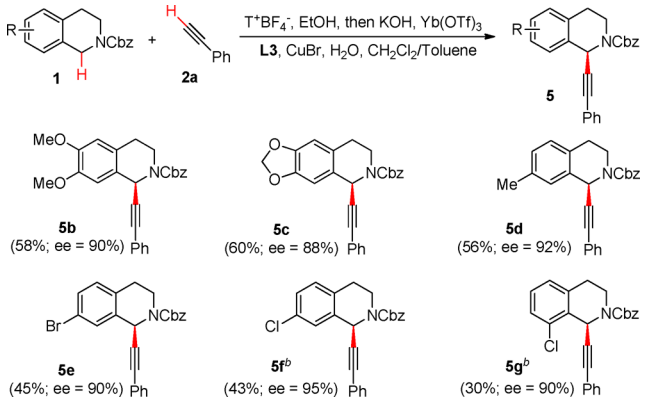
Scheme 4. Scope of Trityl Ion-Mediated CDC Reactions[a]

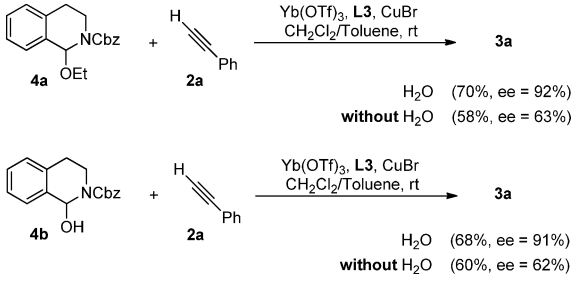


[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), $T^+BF_4^-$ (0.1 mmol), **L3** (0.015 mmol), CuBr (0.015 mmol), EtOH (0.1 mmol), $Yb(OTf)_3$ (0.12 mmol), KOH (0.19 mmol), and H_2O (0.2 mmol) in 1.0 mL of CH_2Cl_2/toluene at rt for 48 h. [b]NaOMe was used instead of EtOH.

substituents proceeded smoothly with high enantiocontrol (**5b**–**5d**). Notably, substrates bearing electron-withdrawing substituents such as chlorines and bromines were tolerated with excellent ee for further diversifications (**5e**-**5g**), albeit reduced yields probably due to reduced reactivities of the carbamate and stabilities of corresponding acyliminium intermediate.

In Scheme 2, *N*-acyl hemiaminal **4** was presumed as the precursor for subsequent alkynylation. Moreover, the CDC reaction required both EtOH and H_2O as the additives. To verify the identity of the intermediate for the asymmetric CDC reaction, *N*-acyl hemiaminal **4a** and **4b** were prepared and subjected respectively to the standard condition omitting $T^+BF_4^-$ and base (Scheme 5). In the presence of H_2O,

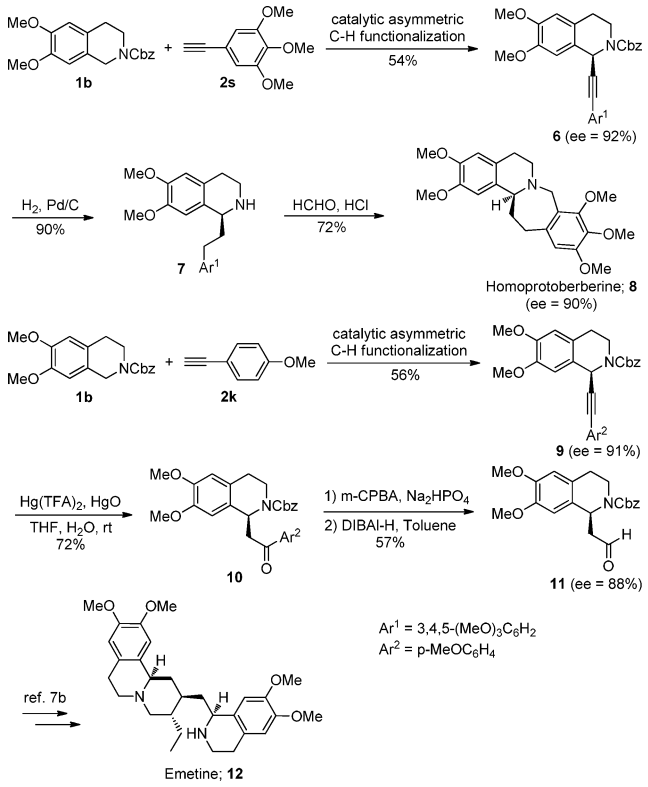
Scheme 5. *N*-Acyl Hemiaminals as Substrates



comparable enantioselectivities were observed for both substrates **4a** and **4b** as that of the CDC process. However, compromised enantiocontrol was observed for either **4a** or **4b** in the absence of H_2O. These experiments together with the observation that a considerable amount of **4a** and a small quantity of **4b** were detected on the TLC during the course of the reaction suggested that both *N*-acyl hemiaminals **4a** and **4b** should be the intermediates for the alkynylation process, though the exact role of H_2O remains unclear.

One of the greatest advantages for the C–H functionalization of carbamates over *N*-aryl amines is that the former can be readily cleavaged or functionalized, which would advance the strategy to complex molecule synthesis. 1-Arylethyl substituted tetrahydroisoquinolines (THIQs) represent ubiquitous structural motifs in numerous alkaloids exhibiting a range of pharmacological activities.[4e] The asymmetric CDC of carbamates with aryl acetylenes provides a straightforward approach to synthesize such scaffold, as demonstrated by the synthesis of homoprotoberberine **8** through asymmetric CDC of **1b** with **2s** followed by a hydrogenation and cyclization (Scheme 6). The synthesis also helps to assign the absolute configuration of products in this work.[7a]

Scheme 6. Synthetic Applications



In the majority of catalytic asymmetric reactions involving terminal alkynes, aryl acetylenes typically display better enantioselectivities than alkyl ones. Therefore, we designed a concise three-step sequence to enhance synthetic utilities of these methods by manipulating aryl acetylenes (Scheme 6). Aryl alkyne **9** generated through the asymmetric CDC of carbamate **1b** with **2k** was smoothly converted to aldehyde **10** through hydration, Baeyer–Villiger oxidation, and reduction with the ee highly conserved. Compound **11** was the intermediate for the total synthesis of biologically active natural product emetine (**12**), where 10 steps were conducted to prepare enantiopure **11**.[7b] The two examples demonstrate the method outlined herein has practicability in synthesizing structurally diverse complex molecules.

In conclusion, the first catalytic asymmetric CDC reaction of cyclic carbamates and terminal alkynes has been described. The reaction features high enantiocontrol and excellent functional group tolerance and displays a wide range of structurally and electronically diverse carbamates as well as terminal alkynes. Preliminary control experiments identified *N*-acyl hemiaminals as the reactive intermediates. Employing readily prepared and removable carbamates as substrates rather than traditionally adopted *N*-aryl amines allows applications in complex molecule synthesis and therefore advances the CDC reaction to a synthetically useful level. We envision that the strategy described

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herein would serve as a guide for future efforts in the catalytic asymmetric C−H functionalization of substrates in low reactivities with a broad range of nucleophiles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Rohlmann, R.; García Mancheño, O. *Synlett* **2013**, 6. (e) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (f) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497. (g) Boess, E.; Sureshkumar, D.; Sud, A.; Wirtz, C.; Farès, C.; Klussmann, M. *J. Am. Chem. Soc.* **2011**, *133*, 8106. (h) Murahashi, S. I.; Komiya, N.; Terai, H.; Nakae, T.; Komiya, N. *J. Am. Chem. Soc.* **2003**, *125*, 15312.

(2) (a) Guo, C.; Song, J.; Luo, S.-W.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 5558. (b) Zhang, G.; Zhang, Y.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 10429. (c) Zhang, J.; Tiwari, B.; Xing, C.; Chen, X.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 3649. (d) Zhang, G.; Ma, Y.; Wang, S.; Zhang, Y.; Wang, R. *J. Am. Chem. Soc.* **2012**, *134*, 12334. (e) Zhang, G.; Ma, Y.; Wang, S.; Kong, W.; Wang, R. *Chem. Sci.* **2013**, *4*, 2645. (f) Neel, A. J.; Hehn, J. P.; Tripet, P. F.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 14044. (g) Bergonzini, G.; Schindler, C. S.; Wallentin, C.-J.; Jacobsen, E. N.; Stephenson, C. R. J. *Chem. Sci.* **2014**, *5*, 112. (h) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997. (i) Li, Z.; MacLeod, P. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 590. (j) Wei, X.-H.; Wang, G.-W.; Yang, S.-D. *Chem. Commun.* **2015**, *51*, 832. (k) Liu, X.; Meng, Z.; Li, C.; Lou, H.; Liu, L. *Angew. Chem., Int. Ed.* **2015**, DOI: 10.1002/anie.201500703. (l) Meng, Z.; Sun, S.; Yuan, H.; Lou, H.; Liu, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 543.

(3) (a) Mengozzi, L.; Gualandi, A.; Cozzi, P. G. *Chem. Sci.* **2014**, *5*, 3915. (b) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

(4) (a) Ghobrial, M.; Harhammer, K.; Mihovilovic, M. D.; Schnürch, M. *Chem. Commun.* **2010**, *46*, 8836. (b) Richter, H.; García Mancheño, O. *Eur. J. Org. Chem.* **2010**, 4460. (c) Liu, X.; Sun, B.; Xie, Z.; Qin, X.; Liu, L.; Lou, H. *J. Org. Chem.* **2013**, *78*, 3104. (d) Richter, H.; Fröhlich, R.; Daniliuc, C.-G.; García Mancheño, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 8656. (e) Xie, Z.; Liu, L.; Chen, W.; Zheng, H.; Xu, Q.; Yuan, H.; Lou, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 3904. (f) Schweitzer-Chaput, B.; Sud, A.; Pintér, Á.; Dehn, S.; Schulze, P.; Klussmann, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 13228.

(5) (a) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2006**, *128*, 14010. (b) Christian, D.; Yoshitaka, H.; Naoki, S.; Seidel, T. M.; Suzuki, S.; Hashizume, D.; Sodeoka, M. *J. Org. Chem.* **2008**, *73*, 5859.

(6) (a) Taylor, A. M.; Schreiber, S. L. *Org. Lett.* **2006**, *8*, 143. (b) Hashimoto, T.; Omote, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 8952. (c) Lin, W.; Cao, T.; Fan, W.; Han, Y.; Kuang, J.; Luo, H.; Miao, B.; Tang, X.; Yu, Q.; Yuan, W.; Zhang, J.; Zhu, C.; Ma, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 277. (d) Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300. (e) Black, D. A.; Beveridge, R. E.; Arndtsen, B. A. *J. Org. Chem.* **2008**, *73*, 1906. (f) Maity, P.; Srinivas, H. D.; Watson, M. P. *J. Am. Chem. Soc.* **2011**, *133*, 17142.

(7) (a) Brossi, A.; Teitel, S. *Helv. Chim. Acta* **1969**, *52*, 1228. (b) Tietze, L. F.; Rackelmann, N.; Müller, I. *Chem.—Eur. J.* **2004**, *10*, 2722.

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Org. Lett. XXXX, XXX, XXX−XXX