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Bidentate Directing-Enabled, Traceless Heterocycle Synthesis: Cobalt-Catalyzed Access to Isoquinolines

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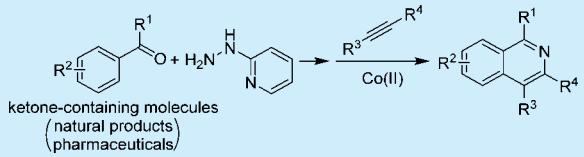
Supporting Information

ABSTRACT: Traceless heterocycle synthesis based on transition-metal-catalyzed C−H functionalization is synthetically appealing but has been realized only in monodentate directing systems. Bidentate directing systems allow for the achievement of high catalytic reactivity without the need for a high-cost privileged ligand. The first bidentate directing-enabled, traceless heterocycle synthesis is demonstrated in the cobalt-catalyzed synthesis of isoquinolines via 2-hydrazinylpyridine-directed C−H coupling/cyclization with alkynes. Convenient directing group installation through a ubiquitously present ketone group allows synthetic elaboration for complex molecules.



Transition-metal-catalyzed directed C−H functionalization represents a promising strategy for the synthesis of diverse organic structures.[1] Key to the successful reaction development is the achievement of electronic and steric activation of the catalytic center via an appropriate coordination environment.[2] In this regard, electronic and steric control can be implemented in two modalities depending on the directing group: through a combination of ligand on the catalyst precursor and the directing group on the substrate,[3] and solely through the directing group on the substrate.[4] The former modality is typically in use when the directing group is monodentate (Scheme 1).[5] This modality has witnessed tremendous success for both the attachment of appendages and synthesis of heterocycles via the involvement of a high-cost privileged ligand (e.g., tightly bound Cp*) on the metal center.[6] The latter modality alleviates the electronic and steric constraints of the catalyst system through the use of a bidentate directing group (Scheme 1). The relaxation of requirement for a privileged ligand enables the achievement of high catalytic activity for a diverse set of catalyst precursors, especially low-cost metal salts.[7] In addition, an important advantage for the bidentate directing systems is the overriding of otherwise interfering coordination of competing monodentate binding sites when synthetic elaboration of complex molecules is in demand.[4e,8] However, despite the high reactivity, the bidentate directing strategy is primarily used for appendage attachment, and method development in heterocycle synthesis is largely lagging behind, in part due to the limited available choice of directing groups.[9] Most importantly, mechanistically distinct, traceless heterocycle synthesis, an approach featuring in situ elimination of an unwanted portion of a directing group along the catalytic process and important for improving step economy as well as functional group compatibility, remains elusive for this supposedly versatile strategy. Indeed, the undesired auxiliary is removed thus far exclusively as a separate step, many through harsh conditions, following the heterocycle formation process.[10]

Herein we report on the first demonstration of bidentate directing-enabled, traceless synthesis of heterocycles (Scheme 1). In particular, isoquinolines have been efficiently synthesized through cobalt-catalyzed, 2-hydrazinylpyridine-directed coupling with both terminal and internal alkynes. Key to the traceless synthesis reported herein is the use of the N−N bond in the readily available hydrazone derivative (conveniently synthesized through reaction between 2-hydrazinylpyridine and a ubiquitously present ketone group) as a labile synthetic handle. Significantly, the reaction protocol allows the performance of synthesis in air (no need for an inert atmosphere protection) with a low-cost commercially available salt and ready synthetic elaboration for ketone-containing molecules, including natural products and pharmaceutically important compounds.

Our synthetic efforts began with the examination of a reaction between (*E*)-2-(2-(1-phenylethylidene)hydrazinyl) pyridine (**1a**) and phenylacetylene (**2a**). Initial screening of the catalytic systems showed the effectiveness of a variety of Cp*-free cobalt salts in promoting the target transformation, demonstrating the advantage of using a bidentate directing system. An isoquinoline derivative **3a** could be obtained, by using $Co(acac)_2$ (10 mol %) as the catalyst precursor and NaOAc (2 equiv) as the additive, in a promising 26% yield when reacting in DCE at 80 °C, under air, for 24 h. A change of solvent proved to be futile in boosting the catalytic performance. Instead, a switch from NaOAc to an acidic additive, PivOH, allowed an increase in yield to 67%. The yield could be improved to 71% with the reduction of the PivOH quantity to 1 equiv. Further tuning of the reaction temperature revealed the highest yield of 78% at 70 °C. A control experiment under nitrogen identifies only a trace amount of **3a**, indicating that air is crucial for maintaining an effective catalytic cycle.

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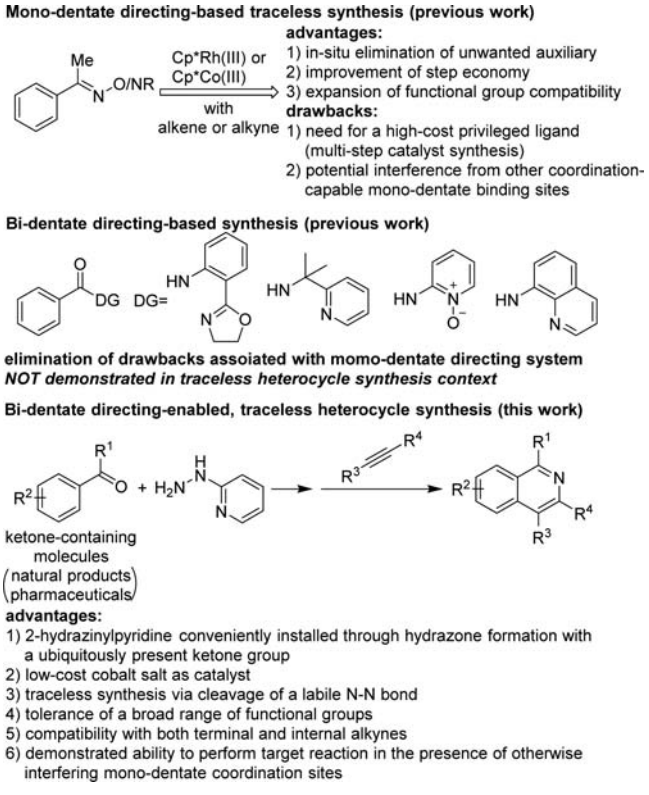
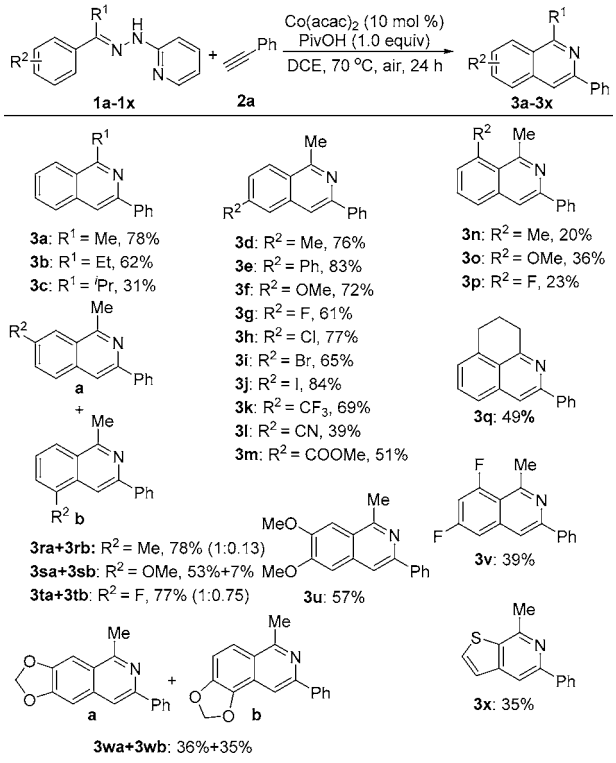
Scheme 1. C−H Activation-Based Synthetic Strategies for the Generation of Heterocycles



Oxygen is the working component of air, as a comparable yield (81%) was observed under this atmosphere.

The optimized synthetic conditions allowed us to explore the substrate scope for (*E*)-2-(2-(1-arylalkylidene)hydrazinyl)-pyridines by employing **2a** as the reacting partner (Scheme 2). The synthetic efficiency is inversely correlated with the bulkiness of the alkylidene group. Thus, variation from ethylidene (**1a**) to propylidene (**1b**) and *iso*-butylidene (**1c**) leads to a decrease in the yield to 62% and 31%, respectively. The synthetic versatility is highlighted by the compatibility of a diverse set of electron-donating (Me, **1d**; Ph, **1e**; OMe, **1f**) and electron-withdrawing (F, **1g**; Cl, **1h**; Br, **1i**; I, **1j**; CF_3, **1k**; CN, **1l**; COOMe, **1m**) groups as a *para*-substituent on the phenyl ring. The *ortho* substitution, irrespective of the electronic character (Me, **1n**; OMe, **1o**; F, **1p**), invariably affords a relatively low yield. This phenomenon most likely derives from disfavored C−H activation due to steric interaction-engendered placement of the cobalt catalytic center in a nonideal geometry. In support of this, the reactivity can be partially recovered by linking the *ortho*-substituent and alkylidene group into a steric interaction-free cyclic moiety (**1q**). The reaction proceeds smoothly for *meta*-substituted substrates (Me, **1r**; OMe, **1s**; F, **1t**), with regioselectivity favoring C−H activation at the less hindered site. Disubstitution poses no significant synthetic hurdle for the delivery of the target product (**1u**−**1w**). A noteworthy observation is that regioselectivity is primarily dictated by the steric factor, as electronically similar substituents (**1u**, **1w**) exhibit distinct preferred reaction sites in C−H coupling. (*E*)-2-(2-(1-(Thiophen-2-yl)ethylidene)-hydrazinyl)pyridine (**1x**) is also sufficiently reactive for the transformation, yielding a fused bicyclic heterocycle as the target product.

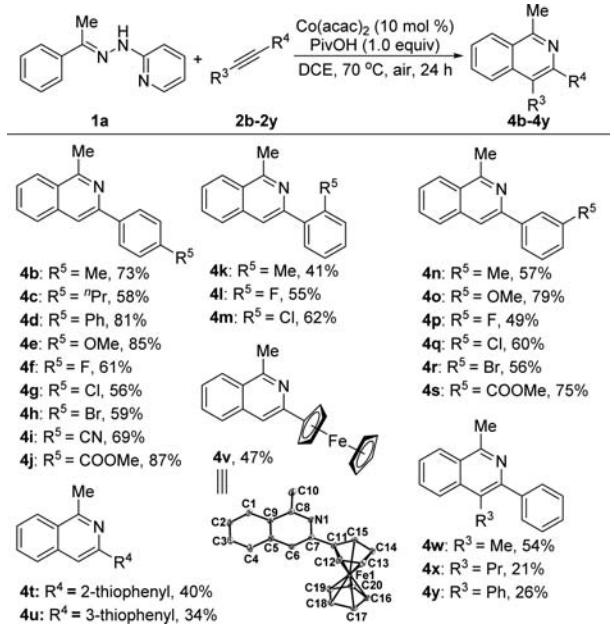
Scheme 2. Substrate Scope for (*E*)-2-(2-(1-Arylalkylidene)hydrazinyl)pyridines[a,b]



[a]Conditions: (*E*)-2-(2-(1-arylalkylidene)hydrazinyl)pyridine (0.5 mmol), **2a** (0.75 mmol), DCE (2 mL). [b]Isolated yields.

The broad substrate scope for (*E*)-2-(2-(1-arylalkylidene)-hydrazinyl)pyridine prompted us to further examine the substrate scope for alkynes (Scheme 3), with **1a** used as the coupling partner. Similarly observed was the compatibility of a

Scheme 3. Substrate Scope for Alkynes[a,b]



[a]Conditions: **1a** (0.5 mmol), alkyne (0.75 mmol), DCE (2 mL). [b]Isolated yields.

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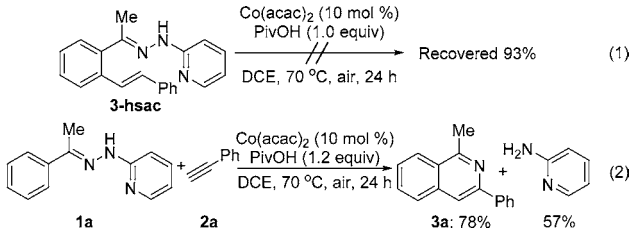
broad range of electron-donating (Me, **2b**; ^{n}Pr, **2c**; Ph, **2d**; OMe, **2e**) and electron-withdrawing (F, **2f**; Cl, **2g**; Br, **2h**; CN, **2i**; COOMe, **2j**) functional groups at the *para* position of arylacetylene. The shift of substituent position from *para* to *ortho* witnesses different consequences for different groups. The negative impact for a methyl substituent (**2k**) is apparent, but the effect for the fluoro (**2l**) and chloro (**2m**) substituents is not noticeable. The reaction proceeds well in general for a *meta*-substituted arylacetylene (Me, **2n**; OMe, **2o**; F, **2p**; Cl, **2q**; Br, **2r**; COOMe, **2s**). In addition, 2- and 3-thiophenylacetylene (**2t**, **2u**) are compatible with the synthetic system reported herein. The bulky ferrocenylacetylene (**2v**) is also a viable substrate for the transformation, generating a readily crystallizable product for structure confirmation with single-crystal X-ray diffraction analysis. Gratifyingly, further experimental survey revealed the synthetic compatibility of both unsymmetrically (**2w**, **2x**) and symmetrically (**2y**) substituted internal alkynes.

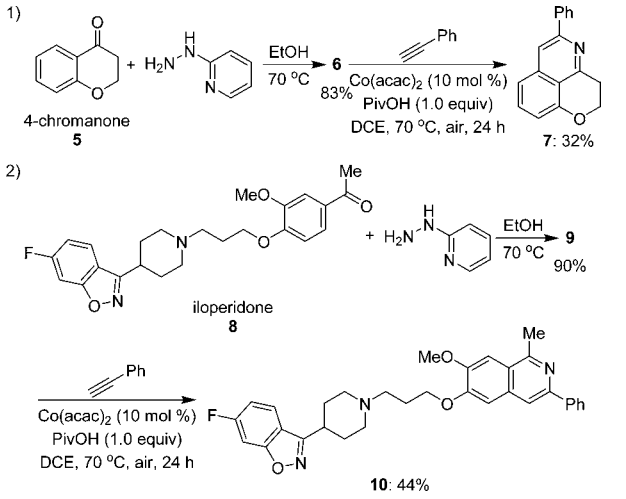
With the broad substrate scope demonstrated, a series of experiments were then performed to gain mechanistic insight into this versatile reaction system. A high kinetic isotope effect value (k_H/k_D = 2.45) was observed for a reaction between **1a**/**1a**-d_3 and **2a**. Two competition experiments, one involving **1f**/**1m** and **2a** and the other involving **1a** and **2e**/**2j**, identified the preferred reaction for electron-rich **1f** (**1f**/**1m** = 1.33) and virtually no electronic preference in the case of alkyne (**2e**/**2j** = 0.98). These results support that C−H activation is the turnover-limiting step and proceeds through an electrophlic aromatic substitution pathway. An attempt at the cyclization of a formal alkenylation product (**3-hsac**, from **1a** and **2a** assuming the occurrence of proto-demetalation after C−H activation and migratory insertion steps) under standard catalytic conditions yielded no target product **3a** (eq 1), ruling out the detachment of



the cobalt center prior to the cyclization process. Key evidence for the internal oxidation mechanism (based on the use of an N−N bond) came from the identification of 2-aminopyridine as a side product (eq 2). Importantly, this side product does not significantly inhibit the catalytic reactivity for the cobalt center even though it is supposed to be strongly coordinating, which highlights the unique synthetic advantage conferred by the bidentate directing systems. A systematic study of catalytic and stoichiometric reactivity for $Co(acac)_2$ and $Co(acac)_3$ under nitrogen suggests that oxygen most likely changes the coordination environment for the generation of a more reactive cobalt catalytic center (instead of simple oxidation of Co(II) to Co(III)) at an early stage of the catalytic cycle (prior to the C−H activation step): (1) catalytic amount of both $Co(acac)_2$ and $Co(acac)_3$ exhibits minimal reactivity under nitrogen; (2) addition of a stoichiometric amount of either $Co(acac)_2$ or $Co(acac)_3$ under nitrogen does not allow the achievement of a similar reactivity for the catalytic amount of respective salt under oxygen; (3) preliminary oxygen uptake experiments reveal the consumption of the catalytic amount of oxygen during the reaction. A noteworthy phenomenon for the synthetic transformation reported herein is that the reaction is negatively impacted by an excessive amount of $Co(acac)_2$ (e.g., 1 or 2 equiv), reflecting partial trapping of catalytically active species into an inert state under this condition. Taken together, the above data are consistent with the following mechanistic proposal: reaction of oxygen with $Co(acac)_2$ to generate a catalytically active species, coordination of catalytically active species with (*E*)-2-(2-(1-arylalkylidene)hydrazinyl)pyridine, turnover-limiting *ortho*−C-H cobaltation and release of proton, migratory insertion of alkyne to generate an alkenylcobalt intermediate, simultaneous nucleophilic attack of alkenylcobalt on a N atom (linked to the C atom via a double bond), N−N bond cleavage, electrophilic attack of a N atom (linked to the 2-pyridinyl group) on the released proton, and regeneration of the cobalt catalyst.

As a demonstration of the synthetic utility of the reaction protocol developed herein, synthetic transformations of ketone-containing molecules were performed (Scheme 4). The ketone

Scheme 4. Synthetic Transformations for Natural Product (Chromanone) and Pharmaceutically Important Compound (Iloperidone) Using the Synthetic Protocol Developed Herein



group is a ubiquitously present moiety in natural products and pharmaceutically important compounds. Chromanones are naturally present in many different plants, and tremendous efforts have been devoted to their synthetic elaboration for medicinal purposes.[11] With 4-chromanone as the model substrate, the 2-hydrazinylpyridine directing group could be efficiently installed as expected and provided the desired cyclized product **7**. A second example used for synthetic potential validation is a structurally more complex, pharmaceutically active compound, iloperidone.[12] Significantly, the directing bidentate allowed overriding of otherwise interfering coordination of two competing N atom sites and furnished target product **10** in an efficient manner.

In conclusion, a bidentate directing-enabled, traceless heterocycle synthesis protocol has been developed. The protocol features convenient installation of a 2-hydrazinylpyridine directing group through hydrazone formation with a ubiquitously existing ketone group and a low-cost cobalt salt-catalyzed C−H coupling with both terminal and internal alkynes, allowing the generation of isoquinolines with a diverse set of substitution patterns. The synthetic utility of the bidentate

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directing system reported herein is manifested by the ability to perform target transformation in the presence of otherwise interfering monodentate coordination sites.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02870.

Experimental procedure, characterization of the products (PDF)

Copies of the ^{1}H and ^{13}C NMR spectra of selected products (PDF)

Crystallographic data for complex **4v** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Koschker, P.; Breit, B. *Acc. Chem. Res.* **2016**, *49*, 1524. (b) Jamison, C. R.; Overman, L. E. *Acc. Chem. Res.* **2016**, *49*, 1578. (c) Kacprzak, K.; Skiera, I.; Piasecka, M.; Paryzek, Z. *Chem. Rev.* **2016**, *116*, 5689. (d) Zeng, X.; Liu, S.; Shi, Z.; Liu, G.; Xu, B. *Angew. Chem., Int. Ed.* **2016**, *55*, 10032. (e) Zhou, S.; Wang, J.; Wang, L.; Song, C.; Chen, K.; Zhu, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 9384. (f) Kawaguchi, Y.; Yasuda, S.; Mukai, C. *Angew. Chem., Int. Ed.* **2016**, *55*, 10473. (g) Deng, Y.; Yglesias, M. V.; Arman, H.; Doyle, M. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 10108. (h) Hua, Y.; Asgari, P.; Avullala, T.; Jeon, J. *J. Am. Chem. Soc.* **2016**, *138*, 7982. (i) Nandakumar, A.; Midya, S. P.; Landge, V. G.; Balaraman, E. *Angew. Chem., Int. Ed.* **2015**, *54*, 11022. (j) Odom, A. L.; McDaniel, T. J. *Acc. Chem. Res.* **2015**, *48*, 2822. (k) Hummel, J. R.; Ellman, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 490.

(2) (a) Zhang, F.; Hong, K.; Li, T.; Park, H.; Yu, J.-Q. *Science* **2016**, *351*, 1484. (b) Tian, P.; Feng, C.; Loh, T. P. *Nat. Commun.* **2015**, *6*, 7472. (c) Wang, X.; Gong, W.; Fang, L.; Zhu, R.; Li, S.; Engle, K. M.; Yu, J.-Q. *Nature* **2015**, *519*, 334. (d) Liu, Y.; Xu, H.; Kong, W.; Shang, M.; Dai, H.; Yu, J.-Q. *Nature* **2014**, *515*, 389. (e) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (f) Minami, Y.; Hiyama, T. *Acc. Chem. Res.* **2016**, *49*, 67.

(3) (a) Kumar, N. Y. P.; Bechtoldt, A.; Raghuvanshi, K.; Ackermann, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 6929. (b) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. *Chem. Soc. Rev.* **2015**, *44*, 7764. (c) Sun, B.; Yoshino, T.; Kanai, M.; Matsunaga, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 12968. (d) Wang, X.; Yu, D.-G.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 10280. (e) Fu, L.; Guptill, D. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2016**, *138*, 5761. (f) Zhou, S.; Wang, J.; Zhang, F.; Song, C.; Zhu, J. *Org. Lett.* **2016**, *18*, 2427. (g) Zhou, S.; Wang, J.; Chen, P.; Chen, K.; Zhu, J. *Chem. - Eur. J.* **2016**, *22*, 14508. (h) Kornhaaß, C.; Li, J.; Ackermann, L. *J. Org. Chem.* **2012**, *77*, 9190.

(4) (a) He, G.; Wang, B.; Nack, W. A.; Chen, G. *Acc. Chem. Res.* **2016**, *49*, 635. (b) Topczewski, J. J.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S. *Nature* **2016**, *531*, 220. (c) Zhang, L.; Hao, X.; Zhang, S.; Liu, Z.; Zheng, X.; Gong, J.; Niu, J.; Song, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 272. (d) Shang, M.; Wang, H.; Sun, S.; Dai, H.; Yu, J. *J. Am. Chem. Soc.* **2014**, *136*, 11590. (e) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O. *ACS Catal.* **2016**, *6*, 551. (f) Yan, Q.; Chen, Z.; Yu, W.; Yin, H.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 2482. (g) Liang, H.; Ding, W.; Jiang, K.; Shuai, L.; Yuan, Y.; Wei, Y.; Chen, Y. *Org. Lett.* **2015**, *17*, 2764. (h) Mei, R.; Wang, H.; Warratz, S.; Macgregor, S. A.; Ackermann, L. *Chem. - Eur. J.* **2016**, *22*, 6759.

(5) (a) Yu, S.; Liu, S.; Lan, Y.; Wan, B.; Li, X. *J. Am. Chem. Soc.* **2015**, *137*, 1623. (b) Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. *J. Am. Chem. Soc.* **2014**, *136*, 5424. (c) Zeng, R.; Fu, C.; Ma, S. *J. Am. Chem. Soc.* **2012**, *134*, 9597. (d) Huang, X.; Huang, J.; Du, C.; Zhang, X.; Song, F.; You, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12970. (e) Liu, G.; Shen, Y.; Zhou, Z.; Lu, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6033. (f) Wang, H.; Moselage, M.; González, M. J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 2705. (g) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 498. (h) Lu, Q.; Vásquez-Céspedes, S.; Gensch, T.; Glorius, F. *ACS Catal.* **2016**, *6*, 2352. (i) Mei, R.; Loup, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 793. (j) Nobushige, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 1188. (k) Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 3032.

(6) (a) Kim, J. H.; Greßies, S.; Glorius, F. *Angew. Chem., Int. Ed.* **2016**, *55*, 5577. (b) Liang, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 4035. (c) Sun, B.; Yoshino, T.; Kanai, M.; Matsunaga, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 12968. (d) Yang, Y.; Zhou, M.; Ouyang, X.; Pi, R.; Song, R.; Li, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 6595. (e) Hummel, J. R.; Ellman, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 490. (f) Liu, B.; Song, C.; Sun, C.; Zhou, S.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 16625. (g) Zhou, S.; Wang, J.; Wang, L.; Chen, K.; Song, C.; Zhu, J. *Org. Lett.* **2016**, *18*, 3806. (h) Wang, J.; Wang, M.; Chen, K.; Zha, S.; Song, C.; Zhu, J. *Org. Lett.* **2016**, *18*, 1178. (i) Mo, J.; Wang, L.; Cui, X. *Org. Lett.* **2015**, *17*, 4960. (j) Chu, H.; Sun, S.; Yu, J.; Cheng, J. *Chem. Commun.* **2015**, *51*, 13327. (k) Song, C.; Yang, C.; Zhang, F.; Wang, J.; Zhu, J. *Org. Lett.* **2016**, *18*, 4510.

(7) (a) Zhang, J.; Chen, H.; Lin, C.; Liu, Z.; Wang, C.; Zhang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 12990. (b) Shang, M.; Sun, S.; Dai, H.; Yu, J. *J. Am. Chem. Soc.* **2014**, *136*, 3354. (c) Fruchey, E.; Monks, R. B. M.; Cook, S. P. *J. Am. Chem. Soc.* **2014**, *136*, 13130. (d) Zhou, Y.; Zhu, J.; Li, B.; Zhang, Y.; Feng, J.; Hall, A.; Shi, J.; Zhu, W. *Org. Lett.* **2016**, *18*, 380. (e) Ma, W.; Ackermann, L. *ACS Catal.* **2015**, *5*, 2822. (f) Takamatsu, K.; Hirano, K.; Miura, M. *Org. Lett.* **2015**, *17*, 4066. (g) Dong, J.; Wang, F.; You, J. *Org. Lett.* **2014**, *16*, 2884. (h) Liang, H.; Jiang, K.; Ding, W.; Yuan, Y.; Shuai, L.; Chen, Y.; Wei, Y. *Chem. Commun.* **2015**, *51*, 16928.

(8) (a) Tan, G.; He, S.; Huang, X.; Liao, X.; Cheng, Y.; You, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 10414. (c) Zhang, Q.; Yin, X.; Chen, K.; Zhang, S.; Shi, B. *J. Am. Chem. Soc.* **2015**, *137*, 8219.

(9) (a) Gandeepan, P.; Rajamalli, P.; Cheng, C. *Angew. Chem., Int. Ed.* **2016**, *55*, 4308. (b) Grigorjeva, L.; Daugulis, O. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209. (c) Shang, M.; Wang, H.; Sun, S.; Dai, H.; Yu, J. *J. Am. Chem. Soc.* **2014**, *136*, 11590. (d) Liu, Y.; Yin, X.; Gu, W.; Shi, B. *Chem. - Eur. J.* **2015**, *21*, 205. (e) Zheng, X.; Du, C.; Zhao, X.; Zhu, X.; Suo, J.; Hao, X.; Niu, J.; Song, M. *J. Org. Chem.* **2016**, *81*, 4002.

(10) Zhang, L.; Hao, X.; Liu, Z.; Zheng, X.; Zhang, S.; Niu, J.; Song, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 10012−10015.

(11) (a) Yang, J.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 2870. (b) Wen, G.; Su, Y.; Zhang, G.; Lin, Q.; Zhu, Y.; Zhang, Q.; Fang, X. *Org. Lett.* **2016**, *18*, 3980. (c) Shimizu, M.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem. - Asian J.* **2008**, *3*, 881. (d) Feng, L.; Maddox, M. M.; Alam, M. Z.; Tsutsumi, L. S.; Narula, G.; Bruhn, D. F.; Wu, X.; Sandhaus, S.; Lee, R. B.; Simmons, C. J.; Tse-Dinh, Y.-C.; Hurdle, J. G.; Lee, R. E.; Sun, D. *J. Med. Chem.* **2014**, *57*, 8398.

(12) (a) Hartwig, J.; Kirschning, A. *Chem. - Eur. J.* **2016**, *22*, 3044. (b) Zhang, A.; Neumeyer, J. L.; Baldessarini, R. J. *Chem. Rev.* **2007**, *107*, 274. (c) Zhang, T.; Yang, Y.; Wang, H.; Sun, F.; Zhao, X.; Jia, J.; Liu, J.; Guo, W.; Cui, X.; Gu, J.; Zhu, G. *Cryst. Growth Des.* **2013**, *13*, 5261. (d) Solanki, P. V.; Uppelli, S. B.; Pandit, B. S.; Mathad, V. T. *Org. Process Res. Dev.* **2014**, *18*, 342. (e) Sheridan, R. P.; Korzekwa, K. R.; Torres, R. A.; Walker, M. J. *J. Med. Chem.* **2007**, *50*, 3173.

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Org. Lett. 2016, 18, 5632−5635