Organic LETTERS
Letter
pubs.acs.org/OrgLett

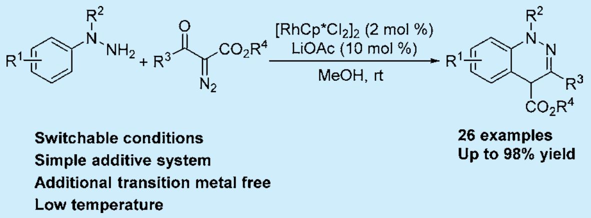
Access to the Cinnoline Scaffold via Rhodium-Catalyzed Intermolecular Cyclization under Mild Conditions

Chao Song, Chen Yang, Feifei Zhang, Jinhu Wang, and Jin Zhu*

Department of Polymer Science and Engineering, School of Chemistry and Chemical Engineering, State Key Laboratory of Coordination Chemistry, Nanjing National Laboratory of Microstructures, Collaborative Innovation Center of Chemistry for Life Sciences, Nanjing University, Nanjing 210093, China

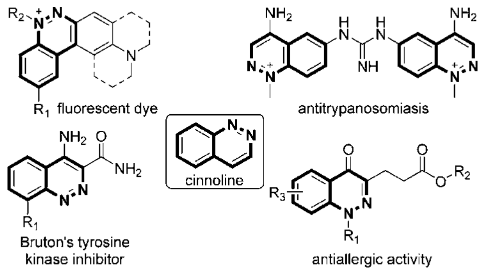
Supporting Information

ABSTRACT: Herein, we report Rh(III)-catalyzed, *N*-amino (hydrazine)-directed C−H functionalization with *α*-diazo-*β*-ketoesters for access to the cinnoline scaffold. A diverse set of nondiscriminating conditions obtained for a highly efficient test transformation prompted use of a substrate-replacement technique for an in-depth search of experimental parameter space and pinpointing of the optimized conditions. A successive C−H activation/C−C coupling/intramolecular dehydration mechanistic sequence is proposed. The ability to perform gram-scale synthesis proves the synthetic utility of this simple, yet efficient, method.



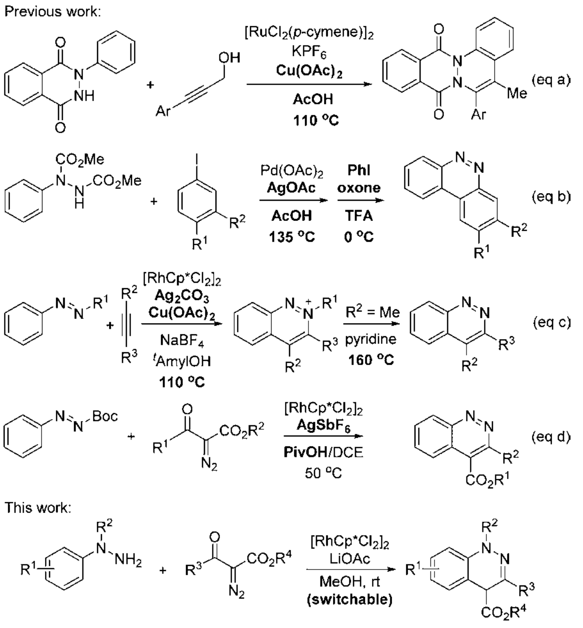
The cinnoline skeleton is common in fluorescent chemicals and biologically active and other functional molecules.[1−5] For example, some of its derivatives (Scheme 1) exhibit fluorescent properties for cell-based imaging,[2] antitrypanosomiasis activity,[3] inhibitory activity toward Bruton's tyrosine kinase,[4] and antiallergic activities.[5] Various synthetic methods have been developed for such a two nitrogen atom bearing heterocycle that primarily include diazonium-based annulation[6] and aryl−halogen-based C−C and C−N coupling reactions,[7] etc.[8] However, their synthetic utility is restricted due to various drawbacks: (1) extra preparation steps for the installation of multiple functionalities undermining the step economy, (2) harsh reaction conditions limiting the substrate scope, and (3) demands for nitrogen protection compromising the atom efficiency. In addition, 1-substituted cinnoline derivatives, which are also important bioactive molecules,[2,3,5] cannot be generated by direct modification of cinnoline, and very few synthetic methods were reported on this kind of cinnoline derivatives.[7b,9]

Scheme 1. Functional Molecules Containing the Cinnoline Skeleton



Transition-metal-catalyzed C−H functionalization has emerged as a useful tool for heterocycle synthesis,[10−15] including chromenes,[11] isoquinolines,[12] furans,[13] indazoles,[14] and cinnolines,[15] etc. Despite synthetic advances achieved for cinnoline scaffold, various bulky protecting groups were adopted for initial protection of one or both of the nitrogen atoms and subsequent removal along with the formation of C−N bond (Scheme 2, eqs b[15b] and d[15d]) or retained in the products requiring additional

Scheme 2. Schematic of Transition-Metal-Catalyzed C−H Functionalization Reactions for Cinnoline Synthesis



Received: July 18, 2016
Published: September 1, 2016

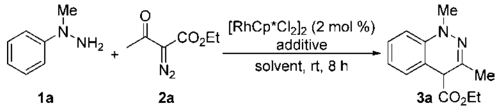
DOI: 10.1021/acs.orglett.6b02103
Org. Lett. 2016, 18, 4510−4513

deprotection steps (Scheme 2, eqs a[15a] and c[15c]). In addition, large amount of acids (Scheme 2, eqs a, b, and d), multiple additional transition metal salts (Scheme 2, eqs a−d), and high temperature (Scheme 2, eqs a−c) were necessary for the transformations. The end products of these methods are limited in substitution patterns, and therefore, further development of C−H functionalization-based methods for expansion of the cinnoline structural diversity is warranted.

Recently, we have initiated a program for *N*-amino group (hydrazine)-directed C−H bond functionalization reactions. The amino group functioned as an internal oxidant for the access of indole and *ortho*-alkenylated aniline derivatives.[16] The remarkable reactivity of the directing system translates into mild reaction conditions for the synthesis of nitrogen-containing compounds. We envisioned that that N−N bond would remain intact after coupling with redox-neutral partners and the retained amino group could be further used for the formation of a heterocycle when an intramolecular cyclization reaction can proceed. Herein, we report on the synthesis of the cinnoline scaffold through the use of C−H activation of 1-alkyl-1-phenylhydrazines and α-diazo-β-ketoesters as the redox-neutral coupling partners. After the formation of the C−C bond, a formal dehydration reaction occurs between amino and keto groups and allows the generation of 1-alkyl-1,4-dihydrocinnolines. This synthetic protocol features an atom- and step-economic intermolecular cyclization of simple substrates under mild conditions, with water and nitrogen gas as the only side products, furnishing the target products in high yields.

We initiated our investigations by examining $[RhCp^*Cl_2]_2$-catalyzed reactions of 1-methyl-1-phenylhydrazine (**1a**) and ethyl 2-diazo-3-oxobutanoate (**2a**). According to our previous work[16a] and the screen of solvents (Table 1, entries 1−6), we selected 2 mol % of $[RhCp^*Cl_2]_2$ as the catalyst and MeOH as the solvent. Acetic acid and acetates were used to improve the catalytic performance (Table 1, entries 6−10). To our satisfaction, HOAc, NaOAc, and KOAc conditions all offered excellent >80% yields (termed primary validation on the original test substrate). Since there were only slight differences between the yields under these conditions (termed primary conditions), we used the substrate-replacement (SURE) technique for identifying a broadly applicable condition. The SURE technique basically involves a replacement of substrate, further optimization of reaction conditions (termed secondary conditions), and a secondary validation on the original substrate. Additional rounds of substrate replacement, reaction condition optimization, and back validation can be solicited when desired. The idea is to perform an in-depth search in the experimental parameter space and eliminate the selection of a randomly obtained reaction condition as the so-called "optimized" condition for all substrates. As a proof-of-concept demonstration of the synthetic utility of our proposed SURE technique, we replaced the test substrate from **1a** with a supposedly less reactive *p*-cyano-substituted substrate, **1g**. When the aforementioned conditions were examined (Table S1, entries 1−5), the yields significantly dropped to below 60%. Then different amounts of additives were examined (Table S1, entries 6−10), and the yield eventually reached 89% yield when 10 mol % of LiOAc was used as the sole additive. We then applied these optimized conditions to the reaction of **1a** and **2a** for secondary validation (Table 1, entry 12), and an excellent 94% yield was obtained. In addition, a reduction in catalyst loading could also provide a satisfactory 97% yield for **1a** (Table 1, entry 13). However, under these conditions, the yield decreased to 77% for **1g** (Table S1, entry 11). Finally, a control experiment omitting the rhodium catalyst proved it to be essential in this reaction (Table 1, entry 14). Overall, the reaction conditions were quite switchable for moderately reactive substrates as **1a**, exhibiting great performance under acidic (Table 1, entry 6), basic (Table 1, entries 8 and 9), and near-neutral (Table 1, entries 12 and 13) conditions.

Table 1. Optimization of Reaction Conditions[a,b]

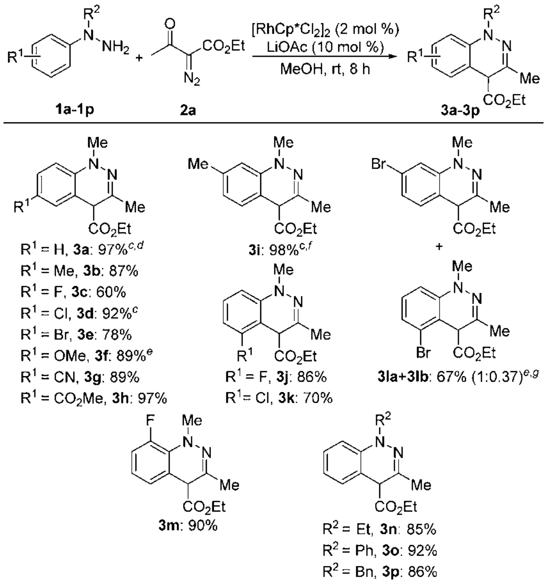


entry	solvent	additive (mol %)	yield (%)
1	DCE	HOAc (100)	46
2	CH_3CN	HOAc (100)	0
3	THF	HOAc (100)	0
4	toluene	HOAc (100)	0
5	1,4-dioxane	HOAc (100)	0
6	MeOH	HOAc (100)	92
7	MeOH	LiOAc (100)	62
8	MeOH	NaOAc (100)	84
9	MeOH	KOAc (100)	89
10	MeOH	CsOAc (100)	67
11	MeOH		0
12	MeOH	LiOAc (10)	94
13[c]	MeOH	LiOAc (10)	97
14[d]	MeOH	LiOAc (10)	0

[a] Conditions: **1a** (0.25 mmol, 1 equiv), **2a** (1.1 equiv), solvent (1 mL). [b] Isolated yields. [c] With 1 mol % of $[RhCp^*Cl_2]_2$. [d] Without $[RhCp^*Cl_2]_2$.

With the SURE-delivered optimized conditions in hand, we commenced to explore the scope of 1-alkyl-1-phenylhydrazine substrates. We employed **2a** as the coupling partner and examined various substituents (Scheme 3). For *para* substituents, both electron-donating groups (**1b** and **1f**) and electron-withdrawing groups (**1c−e** and **1g,h**) participated in the reaction, affording good to excellent yields in 8 h. Impressive were the substrates **1a** and **1d**, both of which reached high yields above 90% under a lower catalyst loading of 1 mol %. For a highly reactive substrate **1f**, the expected product **3f** could be obtained in 89% yield in 4 h. The *meta*-substituted substrates were also effective in this reaction, and regiospecificity was observed in almost all of the products. For methyl substitution, only the *para*-position of the methyl group was reactive, and we gained **3i** in 98% yield using 1 mol % of catalyst in 16 h. In comparison, for fluoro and chloro substituents, single products reacting at their *ortho*-position were isolated. However, the bromo substituent offered a product mixture of *ortho*/*para* regioisomers at higher temperature in 67% yield (trace product at room temperature). The regioselectivity can be rationalized by the inherent higher reactivity at the *ortho* position, but steric effects take control (reactive site at *para* position) when the substituent is too bulky. *Ortho* substitution was also compatible, as proved by 1-(*o*-fluorophenyl)-1-methylhydrazine, which provided a 90% yield of **3m**. A change of substituent on the aryl-linked nitrogen (defined as 1-nitrogen) was then investigated. Both 1-alkyl (**1a,n,p**) and 1-aryl (**1o**) phenylhydrazines participated well in the reaction, offering ∼90% yields. For 1-benzyl-1-phenylhydrazine (**1p**), a substrate bearing highly reactive benzyl C−H bonds, no reaction was observed on this position, and the expected product **3p** was obtained in 86% yield. Furthermore, we carried out a gram-scale

Scheme 3. Substrate Scope of 1-Alkyl-1-phenylhydrazines[a,b]

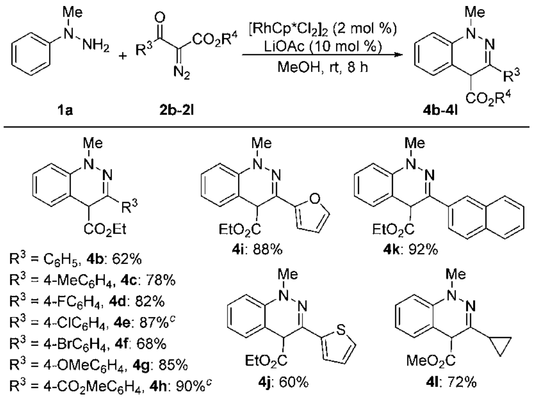


[a]Conditions: **1a**−**p** (0.25 mmol, 1 equiv), **2a** (1.1 equiv), MeOH (1 mL). [b]Isolated yields. [c]With 1 mol % of $[RhCp^*Cl_2]_2$. [d]75% yield at 10 mmol scale. [e]Reaction time: 4 h. [f]Reaction time: 16 h. [g]Temperature: 50 °C.

reaction of **1a** and **2a** under standard conditions, and **3a** was isolated in 75% yield, which promised this synthetic method as a useful tool in practical synthetic contexts.

We then examined an array of *α*-diazo-*β*-ketoester coupling partners (Scheme 4). 1-Methyl-1-phenylhydrazine (**1a**) was adopted as the C−H activation substrate. Phenyl substitutions on the keto group were first studied. *p*-Methyl (**2c**), *p*-fluoro (**2d**), and *p*-methoxy (**2g**) substituents invariably gave a ∼80% yield. Simple phenyl (**2b**) and *p*-bromo (**2f**) phenyl substitutions also achieved good yields above 60%. However, with the change of substituent to either *p*-chloro (**2e**) or *p*-methoxycarbonyl (**2h**), the yield dropped to below 60%. Fortunately, with the adjustment of temperature to 50 °C, these coupling reactants attained excellent yields up to 90%. Other aromatic substitutions, including furyl (**2i**), thienyl (**2j**), and naphthyl (**2k**), were also compatible in this reaction. The furyl and naphthyl ones offered excellent ∼90% yields. However, likely due to the strong coordination of thienyl sulfur atom to rhodium catalyst, **2j** showed a lower 60% yield. Additionally, with the derivatization of a cyclopropyl group (**2l**) on the coupling partner, 72% yield was obtained, and no ring-opening product was observed.

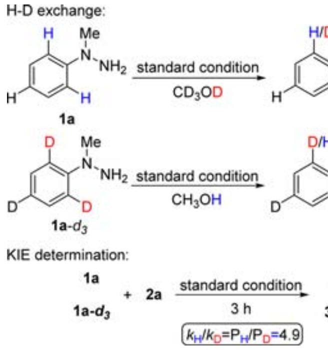
Scheme 4. Substrate Scope of *α*-Diazo-*β*-ketoesters[a,b]



[a]Conditions: **1a** (0.25 mmol, 1 equiv), **2b**−**l** (1.1 equiv), MeOH (1 mL). [b]Isolated yields. [c]Temperature: 50 °C.

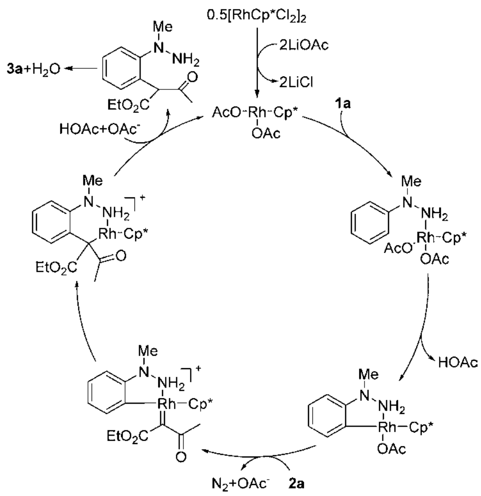
Furthermore, the mechanism of this reaction system was examined by hydrogen−deuterium exchange experiments and kinetic isotope effect (KIE) studies (Scheme 5). Treating **1a** under standard conditions in CD_3OD solvent resulted in an approximately 2% deuterium substitution in the *ortho* position of the substrate, and the reversal test using **1a-*d*$_3$** as the starting material in CH_3OH gave almost the same ratio of exchange. This low efficiency of H−D exchange revealed the C−H activation step in this reaction to be close to irreversible. We then carried out a KIE test through intermolecular competition between **1a** and **1a-*d*$_3$** with **2a** under standard conditions.[17] The KIE value was determined as 4.9 by the calculation of the yield ratio of **3a** to **3a-*d*$_2$** through ^{1}H NMR analysis. This high KIE value indicated that the C−H activation step was likely rate-determining in the catalytic process.

Scheme 5. Mechanistic Studies



In our previous work, the mechanism of C−H activation step of 1-alkyl-1-phenylhydrazine substrates was well investigated.[16a] Based on this understanding and the observations in the mechanism studies, we proposed a mechanism of this reaction in Scheme 6 using **1a** and **2a** as the model reactants. Initially, the rhodium catalyst dimer experienced a ligand exchange to form a reactive acetate rhodium species. It then coordinated the amino group of the substrate **1a** and activated the *ortho* C−H bond of

Scheme 6. Proposed Mechanism



the directing group to generate the rhodacycle complex, a species already identified in our previous report.[16a] Then the diazo compound **2a** formed a carbene species, bound to rhodium atom, and inserted into the Rh−C bond. Through ligand exchange with acetate compounds, the catalytic cycle was completed, and a C−C coupling product was formed leading to the end product by an easy dehydration process.

In summary, we have developed a simple, atom- and step-economic method for the synthesis of 1-alkyl-1,4-dihydrocinnoline derivatives via intermolecular cyclization between 1-alkyl-1-phenylhydrazines and α-diazo-β-ketoesters. The reaction condition is quite switchable, and a broad range of substituents can be tolerated in this reaction. All of the products were obtained in good to excellent yields, and a synthetically useful ester group is introduced into the 4-position of the cinnoline skeleton and amenable for further transformations and applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02103.

Experimental procedure, characterization of the products (PDF)

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jinz@nju.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge support from the National Natural Science Foundation of China (21425415, 21274058) and the National Basic Research Program of China (2015CB856303).

■ REFERENCES

(1) (a) Lewgowd, W.; Stanczak, A. *Arch. Pharm.* **2007**, *340*, 65. (b) Tonk, R. K.; Bawa, S.; Chawla, G.; Deora, G. S.; Kumar, S.; Rathore, V.; Mulakayala, N.; Rajaram, A.; Kalle, A. M.; Afzal, O. *Eur. J. Med. Chem.* **2012**, *57*, 176. (c) Hu, E.; Kunz, R. K.; Rumfelt, S.; Chen, N.; Bürli, R.; Li, C.; Andrews, K. L.; Zhang, J.; Chmait, S.; Kogan, J.; Lindstrom, M.; Hitchcock, S. A.; Treanor, J. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2262. (d) Garofalo, A. W.; Adler, M.; Aubele, D. L.; Bowers, S.; Franzini, M.; Goldbach, E.; Lorentzen, C.; Neitz, R. J.; Probst, G. D.; Quinn, K. P.; Santiago, P.; Sham, H. L.; Tam, D.; Truong, A. P.; Ye, X. M.; Ren, Z. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 71. (e) Parrino, B.; Carbone, A.; Muscarella, M.; Spano, V.; Montalbano, A.; Barraja, P.; Salvador, A.; Vedaldi, D.; Cirrincione, G.; Diana, P. *J. Med. Chem.* **2014**, *57*, 9495. (f) Yang, H.; Murigi, F. N.; Wang, Z.; Li, J.; Jin, H.; Tu, Z. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 919. (g) Giovannoni, M. P.; Schepetkin, I. A.; Crocetti, L.; Ciciani, G.; Cilibrizzi, A.; Guerrini, G.; Khlebnikov, A. I.; Quinn, M. T.; Vergelli, C. *J. Enzyme Inhib. Med. Chem.* **2016**, *31*, 628. (h) Çelik, G. K.; Üzdürmez, A. F.; Erkal, A.; Kılıç, E.; Solak, A. O.; Üstündağ, Z. *Electrocatalysis* **2016**, *7*, 207.

(2) Shen, Y.; Shang, Z.; Yang, Y.; Zhu, S.; Qian, X.; Shi, P.; Zheng, J.; Yang, Y. *J. Org. Chem.* **2015**, *80*, 5906.

(3) Lourie, E. M.; Morley, J. S.; Simpson, J. C. E.; Walker, J. M. *Br. J. Pharmacol. Chemother.* **1951**, *6*, 643.

(4) Smith, C. R.; Dougan, D. R.; Komandla, M.; Kanouni, T.; Knight, B.; Lawson, J. D.; Sabat, M.; Taylor, E. R.; Vu, P.; Wyrick, C. *J. Med. Chem.* **2015**, *58*, 5437.

(5) Holland, D.; Jones, G. *J. Med. Chem.* **1976**, *19*, 1225.

(6) (a) Richter, V. v. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 677. (b) Vasilevsky, S. F.; Tretyakov, E. V.; Verkruijsse, H. D. *Synth. Commun.* **1994**, *24*, 1733. (c) Senadi, G. C.; Gore, B. S.; Hu, W.-P.; Wang, J.-J. *Org. Lett.* **2016**, *18*, 2890.

(7) (a) Zhang, G.; Miao, J.; Zhao, Y.; Ge, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 8318. (b) Hasegawa, K.; Kimura, N.; Arai, S.; Nishida, A. *J. Org. Chem.* **2008**, *73*, 6363. (c) Ball, C. J.; Gilmore, J.; Willis, M. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 5718. (d) Zhu, C.; Yamane, M. *Tetrahedron* **2011**, *67*, 4933.

(8) (a) Kiselyov, A. S.; Dominguez, C. *Tetrahedron Lett.* **1999**, *40*, 5111. (b) Gomaa, A.-M. M. *Tetrahedron Lett.* **2003**, *44*, 3493. (c) Kaur, J.; Pal, B. *Chem. Commun.* **2015**, *51*, 8500. (d) Yan, J.; Tay, G. L.; Neo, C.; Lee, B. R.; Chan, P. W. H. *Org. Lett.* **2015**, *17*, 4176. (e) Shu, W. M.; Ma, J. R.; Zheng, K. L.; Wu, A. X. *Org. Lett.* **2016**, *18*, 196.

(9) Wang, S. F.; Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* **1988**, *110*, 7235.

(10) (a) Cui, S.; Zhang, Y.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3421. (b) Cui, S.; Zhang, Y.; Wang, D.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3912. (c) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364. (d) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364. (e) Lian, Y.; Hummel, J. R.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 12548. (f) Seoane, A.; Casanova, N.; Quiñones, N.; Mascareñas, J. L.; Gulías, M. *J. Am. Chem. Soc.* **2014**, *136*, 834. (g) Chen, Y.; Wang, D.; Duan, P.; Ben, R.; Dai, L.; Shao, X.; Hong, M.; Zhao, J.; Huang, Y. *Nat. Commun.* **2014**, *5*, 4610. (h) Sun, H.; Wang, C.; Yang, Y.-F.; Chen, P.; Wu, Y.-D.; Zhang, X.; Huang, Y. *J. Org. Chem.* **2014**, *79*, 11863. (i) Zhao, D.; Kim, J. H.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 4508.

(11) (a) Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, *72*, 5362. (b) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.* **2012**, *14*, 930. (c) Deponti, M.; Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Biomol. Chem.* **2013**, *11*, 142. (d) Thirunavukkarasu, V. S.; Donati, M.; Ackermann, L. *Org. Lett.* **2012**, *14*, 3416.

(12) (a) Karthikeyan, J.; Haridharan, R.; Cheng, C. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 12343. (b) Hyster, T. K.; Rovis, T. *Synlett* **2013**, *24*, 1842. (c) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem.* **2011**, *123*, 6503. (d) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2011**, *13*, 3332. (e) Wang, H.; Koeller, J.; Liu, W.; Ackermann, L. *Chem. - Eur. J.* **2015**, *21*, 15525. (f) Sen, M.; Kalsi, D.; Sundararaju, B. *Chem. - Eur. J.* **2015**, *21*, 15529. (g) Sun, B.; Yoshino, T.; Kanai, M.; Matsunaga, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 12968. (h) Yu, D.-G.; de Azambuja, F.; Glorius, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 2754. (i) Huang, X.-C.; Yang, X.-H.; Song, R.-J.; Li, J.-H. *J. Org. Chem.* **2014**, *79*, 1025.

(13) (a) Hummel, J. R.; Ellman, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 490. (b) Lian, Y.; Huber, T.; Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 629.

(14) (a) Chen, J.; Chen, P.; Song, C.; Zhu, J. *Chem. - Eur. J.* **2014**, *20*, 14245. (b) Yu, D.-G.; Suri, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 8802. (c) Lian, Y.; Bergman, R. G.; Lavis, L. D.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 7122.

(15) (a) Rajkumar, S.; Savarimuthu, S. A.; Kumaran, R. S.; Nagaraja, C. M.; Gandhi, T. *Chem. Commun.* **2016**, *52*, 2509. (b) Reddy, B. V. S.; Reddy, C. R.; Reddy, M. R.; Yarlagadda, S.; Sridhar, B. *Org. Lett.* **2015**, *17*, 3730. (c) Zhao, D.; Wu, Q.; Huang, X.; Song, F.; Lv, T.; You, J. *Chem. - Eur. J.* **2013**, *19*, 6239. (d) Sun, P.; Wu, Y.; Huang, Y.; Wu, X.; Xu, J.; Yao, H.; Lin, A. *Org. Chem. Front.* **2016**, *3*, 91.

(16) (a) Zhou, S.; Wang, J.; Zhang, F.; Song, C.; Zhu, J. *Org. Lett.* **2016**, *18*, 2427. (b) Zhou, S.; Wang, J.; Wang, L.; Chen, K.; Song, C.; Zhu, J. *Org. Lett.* **2016**, *18*, 3806.

(17) (a) Gómez-Gallego, M.; Sierra, M. A. *Chem. Rev.* **2011**, *111*, 4857. (b) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.