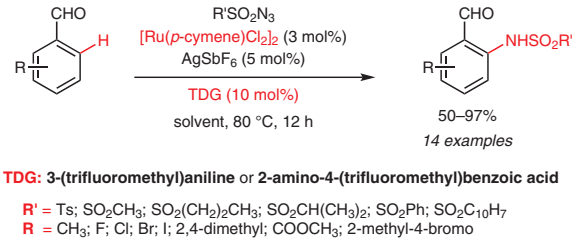
Synlett O. K. Rasheed, F.-l. Zhang Letter

Ruthenium-Catalyzed *Ortho* C(sp^2)–H Amidation of Benzaldehydes with Organic Azides

Omer K. Rasheed[*a,b]
Fang-lin Zhang[a]

[a] School of Chemistry, Chemical Engineering and Life Sciences, Wuhan University of Technology, Wuhan 430070, P. R. of China
[b] School of Chemistry, University of Montana, Missoula, MT 59812, USA
Omer.rasheed@mso.umt.edu



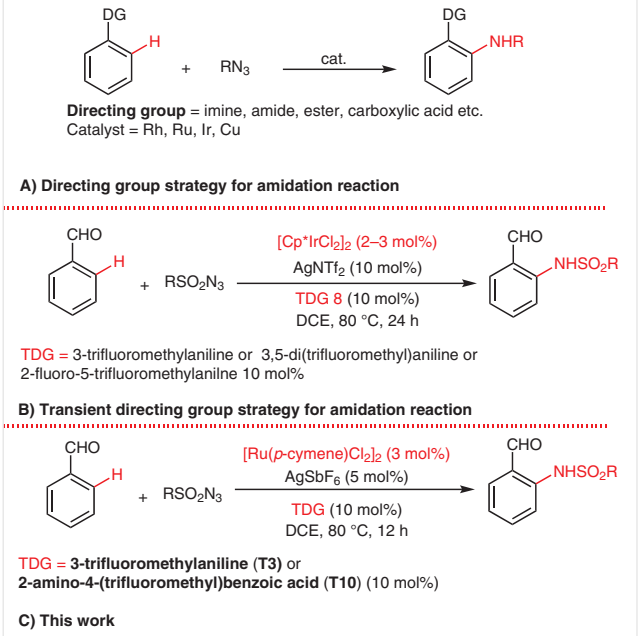
Received: 20.11.2017
Accepted after revision: 29.01.2018
Published online: 16.02.2018
DOI: 10.1055/s-0036-1591765; Art ID: st-2017-b0844-l

Abstract A ruthenium-catalyzed functionalization of benzaldehyde substrate with organic azides promoted by various transient directing groups has been developed. In this approach, C–H amination is achieved via a transient aldimine intermediate in good to excellent yields.

Key words C–H functionalization, directing groups, C–H activation, ruthenium catalysis, amidation

Catalytic C–H bond functionalization with formation of a C–C bond is attracting tremendous interest in synthesis, as it can maximize atom and step economy.[1] This method simplifies chemical synthesis and it has the potential to replace classical catalytic cross-coupling reactions and free-radical reactions.[2,3] A variety of metal catalysts have been reported to promote C–H bond activation and functionalization;[4] initially, catalysts based on palladium or rhodium were used, but more recently, catalysts based on iridium (which is significantly less expensive than ruthenium) or other metals have been used. In the past decade, a transition-metal-catalyzed *ortho* C(sp^2)–H amidation of benzaldehydes has emerged as a powerful tool for the synthesis of *ortho*-aminobenzaldehydes, which are important building blocks for the synthesis of natural products, pharmaceuticals, and organic materials.[5]

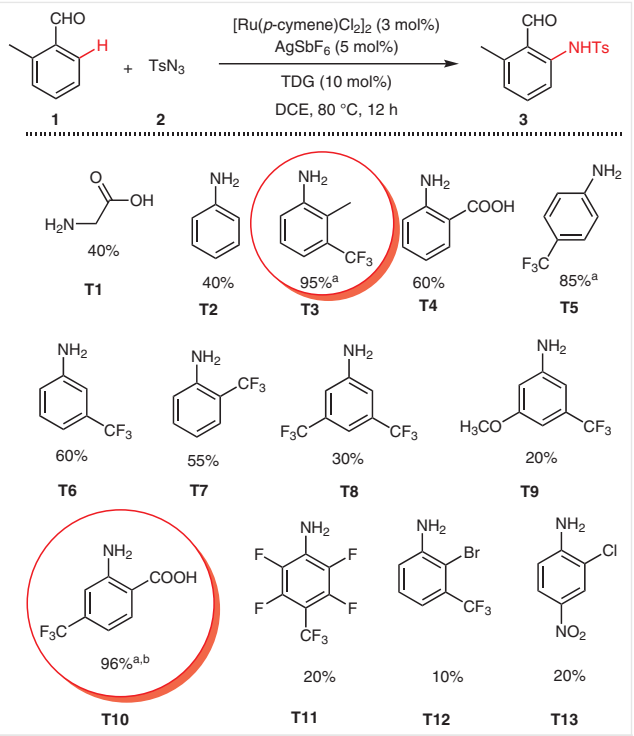
The groups of Chang,[6] Jio,[7] Bolm,[8] and others[9] have used organic azides as amidating reagents in transition-metal-catalyzed C–H amidation reactions. In this respect, many directing groups and metal catalysts have been examined for use in this amidation [Scheme 1(A)].[10] However, the direct *ortho* C–H amination of benzaldehydes remains challenging because of the weak coordinating ability and instability of the directing groups.[11] Recently, Shi and co-workers[12] and others[13,14] have reported an iridium-catalyzed *ortho* C(sp^2)–H amidation reaction of benzaldehydes with various anilines by using a stoichiometric or catalytic directing-group strategy [Scheme 1(B)]. Here, we report an efficient method for the synthesis of 2-(sulfonylamino)benzaldehydes by using an inexpensive ruthenium complex to catalyze the *ortho* C(sp^2)–H amidation of benzaldehydes with organic azides in the presence of catalytic amount of 3-(trifluoromethyl)aniline (**T3**) and 2-amino-4-(trifluoromethyl)benzoic acid (**T10**) as a transient directing group (TDG) (Scheme 1).



Scheme 1 Metal-catalyzed *ortho* C(sp^2)–H amination with organic azides

On the basis of previous observations,[12,13,15] we commenced our studies by treating 2-methylbenzaldehyde with tosyl azide under reported amidation conditions by using 5 mol% of [Ru(*p*-cymene)Cl_2]$_2$, 16 mol% of $AgNTf_2$, 30 mol% of AgTFA, and 10 mol% of the aniline derivative in 1,2-dichloroethane (DCE) as solvent at 80 °C. We were pleased to note that in a trial experiment, the desired C–H amidated product was obtained in 30% NMR yield. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture provided a baseline value for the catalytic activity of ruthenium catalyst in *ortho* C(sp^2)–H amidation of benzaldehydes with organic azides. In an exploratory investigation, after extensive screening, and from our previous studies on C–H activation of benzaldehydes by the TDG strategy,[15] we established that anilines can serve as effective TDGs for Ru-catalyzed amidation reactions with tosyl azide.

After extensive ligand screening (Scheme 2), **T3** and **T10** proved to be the most efficient TDGs, giving 95% and 96% isolated yields, respectively, of the amidated product.



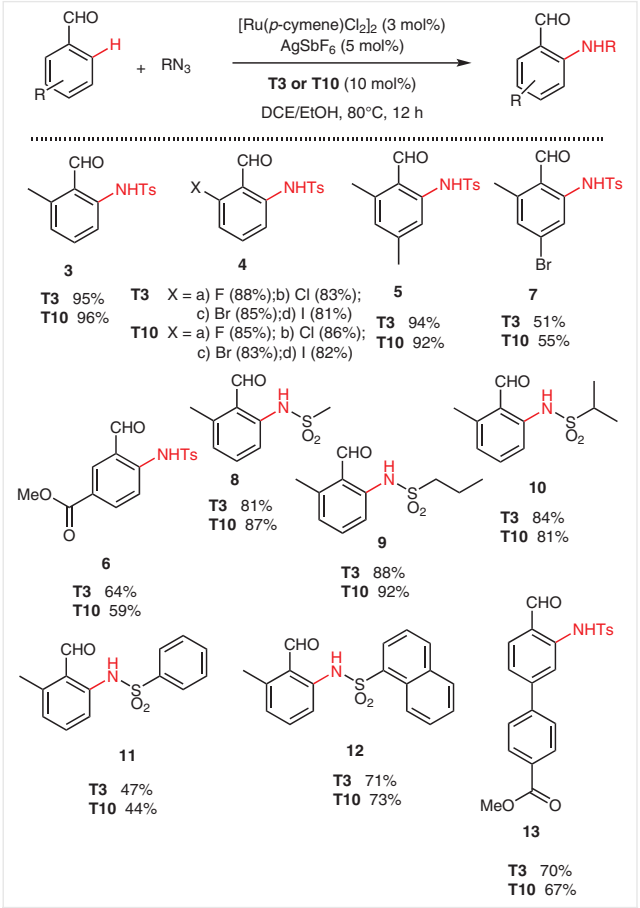
Scheme 2 Screening of TDGs for *ortho* C–H amidation of 2-methylbenzaldehyde with tosyl azide. Yields are based on ^{1}H NMR analysis except where otherwise stated.
[a] Isolated yield
[b] EtOH was used instead of DCE.

Next, we decided to optimize the reaction conditions to improve the yield of the amidated product by using 3 mol% of [Ru(*p*-cymene)Cl_2]$_2$ and 5 mol% of $AgSbF_6$ with 10 mol% of the aniline derivative as a TDG in DCE as solvent at 80 °C.

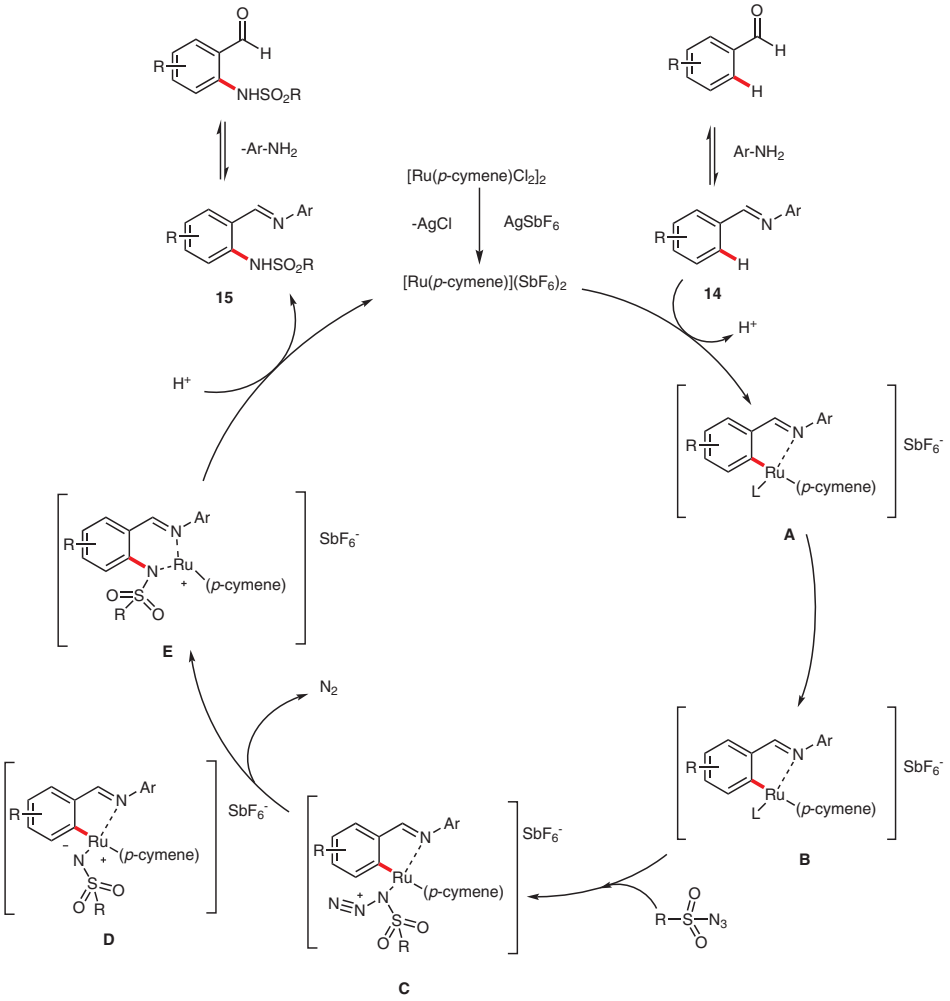
Control experiments showed that none of the desired product was obtained in the absence of a TDG. For example, when 2-methylbenzaldehyde was treated with tosyl azide under the reported conditions {[Ru(*p*-cymene)Cl_2]$_2$, (2 mol%), $AgSbF_6$ (0.3 equiv.), DCE, 80 °C, 12 h}[9b] in the absence of a TDG, none of the desired product was obtained. Solvent screening was also an important step in optimizing the reaction conditions; DCE, ethanol, and, in some cases, isopropyl alcohol proved to be the best solvents; other solvents tested gave significantly lower yields (see Supplementary Information).

Next, we examined the role of additives in this type of reaction. Interestingly, by addition of $AgSbF_6$ instead of $AgNTf_2$, the yield of the C–H amidation reactions was significantly improved and, in this reaction, $AgSbF_6$ proved to be the best chloride scavenger for generating active ruthenium species. Ag_2CO_3 and AgTFA showed little reactivity in the amidation reaction (see Supplementary Information).

With these optimized reaction conditions in hand, we next explored the generality of this ruthenium-catalyzed system by studying the substrate scope of various benz-



Scheme 3 Substrate scope of the Ru-catalyzed *ortho* C–H amination of benzaldehydes with organic azides under the optimized reaction conditions



Scheme 4 Proposed reaction pathway

aldehydes with tosyl azide (Scheme 3). The amidation of benzaldehydes with electron-donating or electron-withdrawing substituents proceeded well to provide the corresponding products in good to excellent yields (40–95%) with either TDG under the optimized reaction condition.[16] Furthermore, the reaction of 2-methylbenzaldehyde with various arylsulfonyl azides or alkylsulfonyl azides under the optimized reaction conditions gave the desired amidation products in good to excellent yields.

On the basis of the above experimental results and reports in the literature,[17,18] we propose the plausible reaction mechanism shown in Scheme 4. First, treatment of [Ru(*p*-cymene)Cl_2]$_2$ with $AgSbF_6$ generates a cationic Ru species that subsequently coordinates to substrate **14** to form complex **A**. Chelation-assisted C–H metalation then generates the ruthenacycle **B**. The azide coordinates to **B** to form complex **D** with release of nitrogen gas, and complex **D** then rearranges to afford the six-membered ruthenium intermediate **E**. Finally, **E** undergoes reductive elimination to form the final product.

In summary, we have developed a new protocol for the Ru-catalyzed *ortho* C–H amidation of benzaldehydes with organic azides by using a catalytic amount of TDG **T3** or **T10**. The reaction can be applied to a broad range of both benzaldehydes and sulfonyl azides and it offers a convenient method for the synthesis of various 2-(sulfonylamino)benzaldehydes in an economical manner without the use of iridium.

Funding Information

O.K.R. and F.-l.Z. thank the Wuhan University of Technology for financial support. Also, O.K.R. thanks the University of Montana for support.

Acknowledgment

O.K.R. wishes to dedicate this report to the late Muhammad Rashid Sheikh for his endless support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591765.

References and Notes

(1) For leading reviews, see: (a) Zhao, Q.; Poisson, T.; Pannecouke, X.; Besset, T. *Synthesis* **2017**, *49*, 4808. (b) Zhang, Z.; Tanka, K.; Yu, J.-Q. *Nature* **2017**, *543*, 538. (c) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (d) Topczewski, J. J.; Sanford, M. S. *Chem. Sci.* **2015**, *6*, 70. (e) Ros, A.; Fernández, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229.

(2) (a) Xu, G.-Q.; Li, C.-G.; Liu, M.-Q.; Cao, J.; Luo, Y.-C.; Xu, P.-F. *Chem. Commun.* **2016**, *52*, 1190. (b) Yang, Y.; Zhou, M.-B.; Ouyang, X.-H.; Pi, R.; Song, R.-J.; Li, J.-H. *Angew. Chem. Int. Ed.* **2015**, *54*, 6595. (c) Cambeiro, X. C.; Ahlsten, N.; Larrosa, I. *J. Am. Chem. Soc.* **2015**, *137*, 15636.

(3) (a) Davies, H. M. L.; Morton, D. *J. Org. Chem.* **2016**, *81*, 343. (b) Sun, H.; Guimond, N.; Huang, Y. *Org. Biomol. Chem.* **2016**, *14*, 8389. (c) Mousseau, J. J.; Charette, A. B. *Acc. Chem. Res.* **2013**, *46*, 412. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2009**, *110*, 624. (e) Breslow, R.; Heyer, D. *J. Am. Chem. Soc.* **1982**, *104*, 2045.

(4) For selected examples, see: (a) Wang, L.; Yang, Z.; Yang, M.; Zhang, R.; Kuai, C.; Cui, X. *Org. Biomol. Chem.* **2017**, *15*, 8302. (b) Chen, X.-Y.; Ozturk, S.; Sorensen, E. J. *Org. Lett.* **2017**, *19*, 6280. (c) Cheng, C.; Liu, S.; Lu, D.; Zhu, G. *Org. Lett.* **2016**, *18*, 2852. (d) Yang, F.; Rauch, K.; Kettelhoit, K.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 11285. (e) Kim, J.; Chang, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 2203. (f) Schröder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298. (g) Kakiuchi, F.; Kochi, T.; Mizushima, E.; Murai, S. *J. Am. Chem. Soc.* **2010**, *132*, 17741.

(5) Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Adv. Heterocycl. Chem.* **2011**, *102*, 139.

(6) For selected examples, see: (a) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110. (b) Ryu, J.; Shin, K.; Park, S. H.; Kim, J. Y.; Chang, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 9904; *Angew. Chem.* **2012**, *124*, 10042.

(7) Zheng, Q.-Z.; Liang, Y.-F.; Qin, C.; Jiao, N. *Chem. Commun.* **2013**, *49*, 5654.

(8) Hermann, N.; Becker, P.; Bolm, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 3781; *Angew. Chem.* **2016**, *128*, 3845.

(9) (a) Zhang, T.; Wang, Z.; Hu, X.; Yu, M.; Deng, T.; Li, G.; Lu, H. *J. Org. Chem.* **2016**, *81*, 4898. (b) Pi, C.; Cui, X.; Wu, Y. *J. Org. Chem.* **2015**, *80*, 7333.

(10) (a) Lanke, V.; Prabhu, K. R. *Chem. Commun.* **2017**, *53*, 5117. (b) Park, J.; Chang, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 14103.

(11) For selected examples of C(sp^2)–H functionalizations of benzaldehyde: (a) Santhoshkumar, R.; Mannathan, S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2015**, *137*, 16116. (b) Lanke, V.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 6262. (c) Padala, K.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 1134. (d) Gürbüz, N.; Özdemir, I.; Çetinkaya, B. *Tetrahedron Lett.* **2005**, *46*, 2273.

(12) Zhang, Y.-F.; Wu, B.; Shi, Z.-J. *Chem. Eur. J.* **2016**, *22*, 17808.

(13) (a) Liu, X.-H.; Park, H.; Hu, J.-H.; Hu, Y.; Zhang, Q.-L.; Wang, B.-L.; Sun, B.; Yeung, K.-S.; Zhang, F.-L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2017**, *139*, 888. (b) Hu, J.-H.; Xu, Y.-C.; Liu, D.-D.; Sun, B.; Yi, Y.; Zhang, F.-L. *RSC Adv.* **2017**, *7*, 38077.

(14) Mu, D.; Wang, X.; Chen, G.; He, G. *J. Org. Chem.* **2017**, *82*, 4497.

(15) (a) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. *Science* **2016**, *351*, 252. (b) Li, Y.; Feng, Y.; Xu, L.; Wang, L.; Cui, X. *Org. Lett.* **2016**, *18*, 4924.

(16) ***Ortho* Amidation of Benzaldehydes with Organic Azides; General Procedure**

A sealed tube equipped with a magnetic stirrer bar was charged with the appropriate benzaldehyde derivatives (0.5 mmol, 1.0 equiv.), organic azide (1 mmol, 2.0 equiv.), [Ru(*p*-cymene)Cl_2]$_2$ (3 mol%), $AgSbF_6$ (5 mol%), and **T3** or **T10** (10 mol%) at r.t. DCE or EtOH (2 mL) was added, and the mixture was stirred at 80 °C for 12 h. When the reaction was complete, the mixture was cooled to r.t., diluted with CH_2Cl_2, and filtered through a plug of silica gel. The filtrate was concentrated in vacuo, and the resulting residue was purified by flash chromatography [silica gel, hexane–EtOAc (4:1)].

***N*-(2-Formyl-3-methylphenyl)-4-methylbenzenesulfonamide** (**3**)

White solid; yield: 57.1 mg (96%); mp 95–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 2.57 (s, 3 H), 6.85 (d, *J* = 7.4 Hz, 1 H), 7.23 (d, *J* = 8.1 Hz, 2 H), 7.35–7.49 (m, 2 H), 7.75 (d, *J* = 8.1 Hz, 2 H), 10.32 (s, 1 H), 11.42 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0, 21.5, 116.1, 119.2, 125.6, 127.3, 129.8, 136.1, 136.5, 140.9, 143.8, 144.2, 194.0. MS (ES+): *m/z* = 290 [M + H]$^+$. HRMS (ES+): *m/z* [M + H]$^+$ calcd for $C_{15}H_{16}NO_3S$: 290.0845; found: 290.0849.

(17) (a) Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4534. (b) Zhou, T.; Guo, W.; Xia, Y. *Chem. Eur. J.* **2015**, *21*, 9209. (c) Figg, T. M.; Park, S.; Park, J.; Chang, S.; Musaev, D. G. *Organometallics* **2014**, *33*, 4076. (d) Zhang, L.-L.; Li, L.-H.; Wang, Y.-Q.; Yang, Y.-F.; Liu, X.-Y.; Liang, Y.-M. *Organometallics* **2014**, *33*, 1905. (e) Park, S. H.; Kwak, J.; Shin, K.; Ryu, J.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 2492. (f) Brasse, M.; Cámpora, J.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2013**, *135*, 6427. (g) Johnson, D. G.; Lynam, J. M.; Mistry, N. S.; Slattery, J. M.; Thatcher, R. J.; Whitwood, A. C. *J. Am. Chem. Soc.* **2013**, *135*, 2222.

(18) (a) Tauchert, M. E.; Incarvito, C. D.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 1482. (b) Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565. (c) Kwak, J.; Ohk, Y.; Jung, Y.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 17778. (d) Ke, Z.; Cundari, T. R. *Organometallics* **2010**, *29*, 821. (e) Dick, A. R.; Remy, M. S.; Kampf, J. W.; Sanford, M. S. *Organometallics* **2007**, *26*, 1365.