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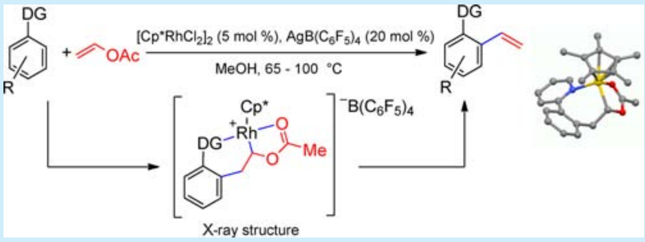
An Efficient Method for the Preparation of Styrene Derivatives via Rh(III)-Catalyzed Direct C−H Vinylation

Kate D. Otley and Jonathan A. Ellman*

Department of Chemistry, Yale University, 225 Prospect Street, New Haven, Connecticut 06520-8107, United States

S *Supporting Information*

ABSTRACT: The development of a method for the Rh(III)-catalyzed direct vinylation of an aromatic C−H bond to give functionalized styrenes in good yield, using vinyl acetate as a convenient and inexpensive vinyl source, is reported. High functional group tolerance is demonstrated for electronically distinct arenes as well as different directing groups. Mechanistic investigation resulted in the characterization of a novel rhodium−metallacycle, which represents the first X-ray structure of a [1,2]-Rh(III)-alkenyl addition adduct.



Styrenes are versatile and important synthetic intermediates due to the wide array of methods available for the rapid functionalization of the vinyl group such as cross-metathesis,[1] Mizoroki−Heck cross-coupling,[2] and asymmetric dihydroxylation, aminohydroxylation, and epoxidation.[3] In addition, styrenes are important inputs for the preparation of fine chemicals and polymers.[4]

Traditional methods for the preparation of functionalized styrene derivatives include dehydration of alcohols,[5] carbonyl olefination,[6] and the partial reduction of terminal alkynes.[7] More recently, efficient cross-coupling strategies have been developed to afford functionalized styrene products.[8] While significant effort has been invested into methods of direct C−H alkenylation through oxidative-Heck couplings,[9] the preparation of styrenes through direct coupling with ethylene gas is challenging. Examples of styrene synthesis by direct, oxidative C−H vinylation in the literature are limited by low yields, poor selectivity, and/or harsh reaction conditions.[10]

Herein, we report Rh(III)-catalyzed vinylation for the direct synthesis of styrenes without an external oxidant using vinyl acetate as a convenient and economical surrogate for ethylene.[11]

We began our exploration of the reaction conditions by coupling 2-phenylpyridine in the presence of an excess of inexpensive vinyl acetate with $[Cp^*RhCl_2]_2$ as a catalyst (Table 1, entry 1). The use of a cationic Rh(III) source resulted in a large increase in yield (entry 2). A variety of cosolvents were explored with MeOH proving to be optimal (entries 2−5). We further established that the noncoordinating $B(C_6F_5)_4^-$ counterion resulted in an increase in reaction yield (entries 6−7). With 2-phenylpyridine as a reaction substrate, we observed a mixture of single and double C−H activation products (**2** and **3**). Because meta-substituted substrate **1a** gave a comparable yield of vinylated product and effectively prevented over-vinylation (entry 8), we used this substrate for the remainder of our optimization efforts. Decreasing the reaction temperature to 100 °C gave the styrene **2a** in an improved 65% yield (entry 9).

After developing conditions for vinylation of the 2-phenylpyridine **1a** in good yield, we focused on expanding the directing group scope (Table 2). While reaction of amide substrate **1b** under the conditions developed for **1a** did not provide the styrene product (entry 1), decreasing the reaction temperature to 65 °C gave **2b** in 40% yield. NMR analysis revealed decomposition of the vinyl acetate under the reaction conditions, resulting in incomplete conversion of benzamide **1b**. A range of vinyl acetate/methanol ratios were therefore explored (entries 2,4−6), with a 1:1.5 ratio providing the vinylated product in 66% yield (entry 6). The commercially available preformed catalyst $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ provided a 46% yield (entry 7). Importantly, the reaction proved amenable to setup outside the glovebox to give styrene derivative **2b** in 61% yield (entry 8). Henceforward, all reactions were performed without use of a glovebox.

Directing group scope was next explored (Scheme 1). In addition to the vinylation of 2-phenylpyridine **1a** and pyrrolidine amide **1b**, vinylated acetanilide **2c** could also be obtained in moderate yield. Amide groups with a range of electronic and steric character (**2d−g**) were well-tolerated. Notably, the electronically deactivated morpholine benzamide **2e**, unhindered *N*,*N*-dimethyl benzamide (**2f**), and hindered *N*,*N*-diisopropyl benzamide (**2g**) all underwent vinylation in good yield.

After establishing good directing group scope, we investigated benzamides with a range of electronic and steric properties (Scheme 2). Benzamides without substitution on the arene could be monovinylated with high or complete selectivity and in excellent yield as demonstrated for the piperidine and diisopropyl benzamides **2h** and **2i**, respectively. Electron-

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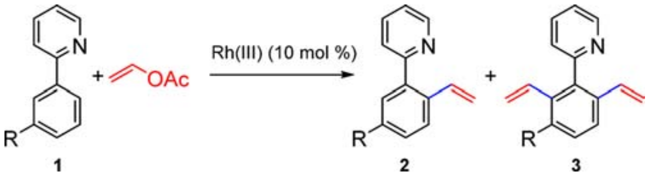
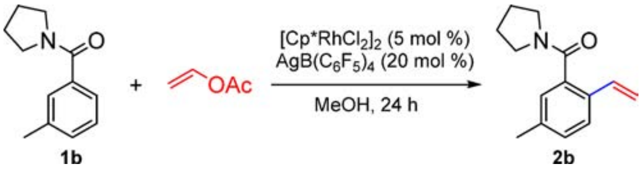
Table 1. Optimization of Reaction Conditions with 2-Phenylpyridine Substrate



entry[a]	R	Rh(III)-catalyst	silver salt	solvent	temperature (°C)	yield 2[b] (%)	yield 3[b] (%)
1	H	$[Cp^*RhCl_2]_2$	–	MeOH	120	25	0
2	H	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	–	MeOH	120	40	4
3	H	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	–	toluene	120	14	4
4	H	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	–	DCE	120	13	2
5	H	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	–	neat	120	0	37
6	H	$[Cp^*RhCl_2]_2$	$AgSbF_6$	MeOH	120	43	7
7	H	$[Cp^*RhCl_2]_2$	$AgB(C_6F_5)_4$	MeOH	120	50	8
8	Me	$[Cp^*RhCl_2]_2$	$AgB(C_6F_5)_4$	MeOH	120	45	0
9	Me	$[Cp^*RhCl_2]_2$	$AgB(C_6F_5)_4$	MeOH	100	65	0

[a] Conditions: 0.2 mmol scale, 2-phenylpydridine (1.0 equiv), Rh(III) (10 mol %), Ag salt (20 mol %), vinyl acetate (0.5 mL), solvent (0.5 mL), in glovebox, 24 h. [b] Yields determined by NMR relative to pentafluorobenzaldehyde external standard.

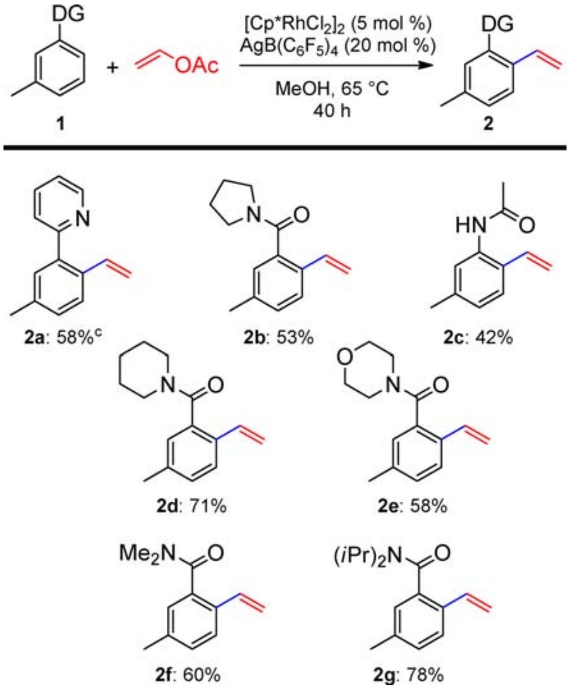
Table 2. Optimization with Benzamide Substrate



entry[a]	vinyl acetate/MeOH (mol/mol)	temperature (°C)	yield[b]
1	1:2.3	100	0
2	1:2.3	65	40
3	1:2.3	45	24
4	1:1	65	60
5	4:1	65	<5
6	1:1.5	65	66
7[c]	1:1.5	65	46
8[d]	1:1.5	65	61

[a] Conditions: 0.2 mmol scale, 0.2 M, in glovebox. [b] Yields determined by NMR relative to pentafluorobenzaldehyde external standard. [c] With $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$. [d] Outside glovebox, 40 h.

Scheme 1. Directing Group Scope[a,b]



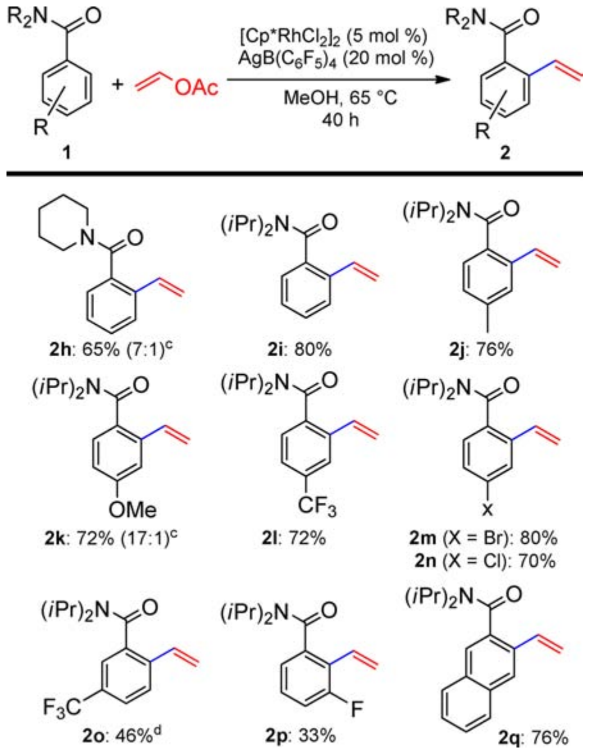
[a] Yields for isolated products. [b] Conditions: 0.4 mmol scale, vinyl acetate (1.2 mL), MeOH (0.8 mL), on benchtop. [c] Conditions: 0.4 mmol scale, 2-phenylpydridine (1.0 equiv), vinyl acetate (0.5 mL), solvent (0.5 mL), on benchtop, 100 °C, 24 h.

donating (**2k**), electron-withdrawing (**2l**), and halogen (**2m**, **2n**) substituents were well tolerated at the para position. While ortho substitution was incompatible with the developed conditions, a series of meta-substituted substrates was examined with the regioselectivity of vinylation depending largely on the nature of the meta substituent. Noncoordinating substituents promote vinylation at the more remote position, as is demonstrated by the regiospecific vinylation for substrates bearing meta-methyl (**2g**), trifluoromethyl (**2o**), and naphthyl (**2q**) functionality. On the other hand, small, coordinating groups at the meta position, such as fluoro (**2p**), resulted in selective vinylation at the proximal position. This observation is consistent with previous mechanistic studies on the regioselectivity of Rh(III)-catalyzed C−H activation conducted by Jones and co-workers.[12]

The vinyl acetate coupling partner is used in excess, which for practical considerations necessitates that it be both inexpensive and volatile. While isopropenyl acetate meets these specifications, coupling with *N*,*N*-diisopropyl benzamide **1a** was inefficient (<5%).

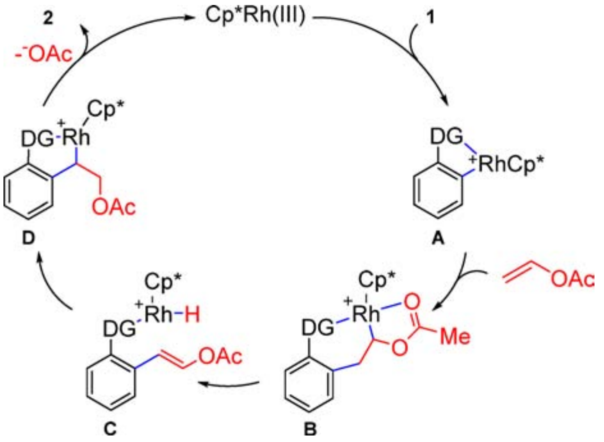
We depict a plausible mechanism for the observed transformation in Scheme 3. The pathway begins with C−H activation and formation of rhodacycle **A**, followed by [1,2]-insertion of the C−Rh bond into the alkene to generate the seven-membered metallacycle **B**. We propose that metallacycle **B** undergoes *β*-hydride elimination to give rhodium-hydride **C**. Reinsertion of the Rh−H bond gives the more stable six-membered metallacycle **D**,[13] which is poised to undergo elimination of acetate, resulting in styrene product **2**.[14] While we believe the proposed pathway to be most likely, an alternative pathway proceeding through elimination of acetate

Scheme 2. Arene Scope with Amide Directing Group[a,b]



[a] Yields for isolated products. [b] Conditions: 0.4 mmol scale, vinyl acetate (1.2 mL), MeOH (0.8 mL), on benchtop. [c] Isolated ratio of single to double C−H activation products. [d] 24 h reaction time.

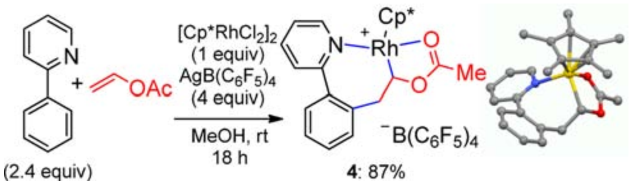
Scheme 3. Proposed Reaction Pathway



from B to give a rhodium-carbene intermediate cannot be completely ruled out.

To investigate the reaction mechanism, a room temperature reaction of 2-phenylpyridine with vinyl acetate was performed and resulted in isolation of rhodacycle **4** in 87% yield based upon Cp*$RhCl_2$ (Scheme 4). Single crystals of **4** were prepared, and the structure was determined by X-ray diffraction. For Rh(III)-catalyzed oxidative Heck reactions, similar seven-membered rhodacycle intermediates for the [1,2]-insertion of Rh−C bonds into alkenes have generally been proposed.[8,15] However, to the best of our knowledge, metallacycle **4** is the first such [1,2]-Rh(III)-alkenyl addition adduct to be isolated and characterized.

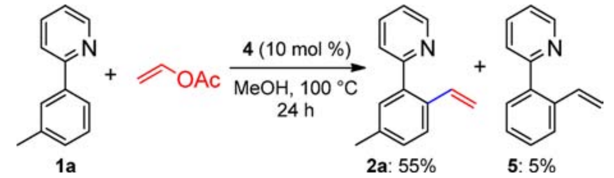
Scheme 4. Preparation of Proposed Metallacycle Intermediate[a,b]



[a] 0.06 mmol scale. [b] For clarity, hydrogens and $B(C_6F_5)_4^-$ counterion have been omitted from the ORTEP view of metallacycle **4**.

To establish the relevance of rhodacycle **4** in catalysis, we monitored by ^{1}H NMR a catalytic vinylation reaction of 2-phenylpyridine and observed that **4** is present throughout the reaction at a level comparable to Rh(III) loading (10 mol %). This result is consistent with **4** as a catalyst resting state. To further determine whether or not rhodacycle **4** is a catalytically competent species, the vinylation of 2-phenylpyridine **1a** with vinyl acetate in the presence of 10 mol % of **4** was next explored (Scheme 5). Vinylated product **2a** was obtained in 55% yield along with 5% of styrene **5**, which is derived from rhodacycle **4**. These results clearly establish that **4** is a competent vinylation catalyst.

Scheme 5. Reaction with 4 as Catalyst[a,b]



[a] Conditions: 0.2 mmol scale, vinyl acetate (0.5 mL), methanol (0.5 mL), on benchtop. [b] Yields determined by GC relative to tetradecane external standard.

In summary, the developed method enables rapid access to functionalized styrenes through direct, Rh(III)-catalyzed C−H vinylation. Vinyl acetate serves as a cost-effective and convenient vinyl source for a range of substrates. Mechanistic investigation resulted in the characterization of a seven-membered rhodacycle formed by [1,2]-insertion of the Rh−C bond into vinyl acetate. This type of alkene insertion intermediate has not previously been structurally characterized for other Rh(III)-catalyzed oxidative Heck reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details; characterization data; crystallographic data (CIF) for **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jonathan.ellman@yale.edu.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Lane, B. S.; Burgess, K. *Chem. Rev.* **2003**, *103*, 2457. (b) Xia, Q. H.; Ge, H. Q.; Ye, C. P.; Liu, Z. M.; Su, K. X. *Chem. Rev.* **2005**, *105*, 1603. (c) Howard, J. K.; Hyland, C. J. T. *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.* **2012**, *108*, 29.

(2) For reviews, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Whitcombe, N. J.; Hii, K. K. M.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449. (c) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (d) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533.

(3) For reviews, see: (a) Noe, M. C.; Letavic, M. A.; Snow, S. L. *Org. React.* **2005**, *66*, 109. (b) Xia, Q. H.; Ge, H. Q.; Ye, C. P.; Liu, Z. M.; Su, K. X. *Chem. Rev.* **2005**, *105*, 1603. (c) Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733.

(4) (a) Agbossou, F.; Carpentier, J.-F.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485. (b) Hirao, A.; Loykulnant, S.; Ishizone, T. *Prog. Polym. Sci.* **2002**, *27*, 1399. (c) Schellenberg, J.; Tomotsu, N. *Prog. Polym. Sci.* **2002**, *27*, 1925. (d) *Modern Styrenic Polymers: Polystyrenes and Styrenic Copolymers*; Scheirs, J., Priddy, D. B., Eds.; John Wiley & Sons: Chichester, UK, 2003. (d) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.

(5) Emerson, W. S. *Chem. Rev.* **1949**, *45*, 347.

(6) (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Ager, D. J. *Org. React.* **1990**, *38*, 1. (c) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563. (d) Bisceglia, J. A.; Orelli, L. R. *Curr. Org. Chem.* **2012**, *16*, 2206.

(7) For leading references, see: Cao, H.; Chen, T.; Zhou, Y.; Han, D.; Yin, S.-F.; Han, L.-B. *Adv. Synth. Catal.* **2014**, *356*, 765.

(8) (a) Denmark, S. E.; Butler, C. R. *J. Am. Chem. Soc.* **2008**, *130*, 3690. (b) Denmark, S. E.; Butler, C. R. *Chem. Commun.* **2008**, 20. (c) Kormos, C. M.; Leadbeater, N. E. *J. Org. Chem.* **2008**, *73*, 3854. (d) Lindh, J.; Sävmarker, J.; Nilsson, P.; Sjöberg, P. J. R.; Larhed, M. *Chem.—Eur. J.* **2009**, *15*, 4630.

(9) For reviews on the oxidative Heck reaction, see: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (b) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212. (c) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichimic Acta* **2012**, *45*, 31. (d) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (e) Odell, L. R.; Sävmarker, J.; Lindh, J.; Nilsson, P.; Larhed, M. In *Comprehensive Organic Synthesis*, 2nd ed.; Molander, G. A., Knochel, P., Eds.; Elsevier: Oxford, 2014; Vol. 7, 492−537.

(10) For vinylation of preformed palladacycles, see: (a) Horino, H.; Inoue, N. *J. Org. Chem.* **1981**, *46*, 4416. For direct C—H oxidative Heck coupling with ethylene, see: (b) Fujiwara, Y.; Noritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166. (c) Moritani, I.; Fujiwara, Y. *Synthesis* **1973**, *1973*, 524. (d) Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337. (e) Yamada, T.; Sakakura, A.; Sakaguchi, S.; Obora, Y.; Ishii, Y. *New J. Chem.* **2008**, *32*, 738. (f) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982. For vinylation using an oxidizing directing group see: (g) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. For a single example of the Ru-catalyzed vinylation of 2-phenylpyridine with vinyl butylate in 34% yield by GC see: (h) Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 9858. (i) Ogiwara, Y.; Tamura, M.; Kochi, T.; Matsuura, Y.; Chatani, N.; Kakiuchi, F. *Organometallics* **2014**, *33*, 402.

(11) Recently, vinyl esters have been used as acetylene surrogates in Rh(III)-couplings with *N*-(pivaloyloxy)-benzamides and benzoic acids to give 3,4-unsubstituted-isoquinolones and 3-substituted isocoumarins respectively, see: (a) Webb, N. J.; Marsden, S. P.; Raw, S. A. *Org. Lett.* **2014**, *16*, 4718. (b) Zhang, M.; Zhang, H.-J.; Han, T.; Ruan, W.; Wen, T.-B. *J. Org. Chem.* **2015**, *80*, 620.

(12) (a) Tsang, J. Y. K.; Buschhaus, M. S. A.; Legzdins, P.; Patrick, B. O. *Organometallics* **2006**, *25*, 4215. (b) Li, L.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2009**, *28*, 3492.

(13) A similar mechanistic pathway has been proposed by Jones and co-workers for the stoichiometric formation of a Rh(III)-[1,1]-insertion adduct formed by the coupling of 2-phenylpyridine and ethylene. Li, L.; Jiao, Y.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2010**, *29*, 4593.

(14) For examples of *β*-elimination of acetate/carbonate leaving groups, see: (a) Tsai, A. S.; Brasse, M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 540. (b) Wang, H.; Schröder, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 5386. (c) Feng, C.; Feng, D.; Loh, T.-P. *Org. Lett.* **2013**, *15*, 3670. (d) Wang, H.; Beiring, B.; Yu, D.-G.; Collins, K. D.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 12430. (e) Feng, C.; Feng, D.; Loh, T.-P. *Chem. Commun.* **2015**, *51*, 342. (f) Park, J.; Mishra, N. K.; Sharma, S.; Han, S.; Shin, Y.; Jeong, T.; Oh, J. S.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *J. Org. Chem.* **2015**, *80*, 1818.

(15) For leading references see: (a) Han, Y.-F.; Jin, G.-X. *Chem. Soc. Rev.* **2014**, *43*, 2799. (b) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443.