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Dehydrative C−H Alkylation and Alkenylation of Phenols with Alcohols: Expedient Synthesis for Substituted Phenols and Benzofurans

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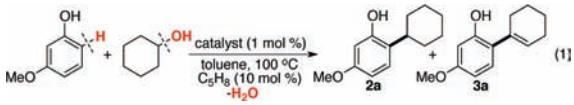
Supporting Information

ABSTRACT: A well-defined cationic Ru−H complex catalyzes the dehydrative C−H alkylation reaction of phenols with alcohols to form *ortho*-substituted phenol products. Benzofuran derivatives are efficiently synthesized from the dehydrative C−H alkenylation and annulation reaction of phenols with 1,2-diols. The catalytic C−H coupling method employs cheaply available phenols and alcohols, exhibits a broad substrate scope, tolerates carbonyl and amine functional groups, and liberates water as the only byproduct.

Transition-metal-catalyzed oxidative C−H coupling reactions constitute an expedient C−C bond formation protocol for arenes and related hydrocarbon substrates.[1] Recent seminal reports on the carbonyl-directed oxidative C−H arylation and alkenylation reactions have led to the development of a powerful synthetic methodology for producing both *bis*-arenes and vinylarenes.[2] A variety of nitrogen atom directing groups have also been successfully used for the oxidative C−C, C−O, and C−Si bond forming reactions of arenes.[3] Very recently, remarkably selective catalytic oxygenation and silylation reactions on aliphatic sp^3-C−H bonds have been achieved by using the heteroatom directing strategy.[4] The chelate-assisted catalytic oxidative C−H coupling methods have been utilized for intramolecular annulation of arene compounds in forming benzofurans[5] as well as for lactone and lactam products,[6] and for the synthesis of biologically active complex organic molecules.[7] While the oxidative C−H coupling methods allow the introduction of vinyl and aryl groups directly to unreactive hydrocarbon substrates, a relatively limited substrate scope and the requirement of stoichiometric metal oxidants and chelate directing groups still remain as major drawbacks in applying these methods to large-scale organic synthesis. In this regard, recent reports on the catalytic C−H oxidative coupling reactions under aerobic conditions represent a major advancement toward the development of practical catalytic C−C bond formation methods.[8]

Alcohols have been rarely employed as the substrate for the catalytic C−H coupling reactions because of their tendency for undergoing energetically more favorable alkoxylation and oxidation reactions over the respective C−O bond cleavage reaction. We recently discovered an exceptionally selective dehydrative C−H alkylation reaction of alkenes with alcohols that is catalyzed by a well-defined cationic ruthenium hydride complex $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ (**1**).[9] The catalytic C−H alkylation reaction utilizes cheaply available alcohols as the alkylating agent and tolerates a variety of oxygen and nitrogen functional groups in forming elaborated alkene products. We have also devised a number of catalytic oxidative C−H coupling reactions of arenes and alkenes by employing alkenes as both the substrate and the hydrogen acceptor.[10] Here we report a highly regioselective catalytic dehydrative C−H alkylation and alkenylation of phenols with alcohols to form substituted phenol and benzofuran products. The "green" features of the catalytic coupling method are that it employs readily available phenols and alcohols, tolerates a number of common heteroatom functional groups, uses cheaply available alkenes as the dehydrogenation agent, and generates water as the only byproduct in forming these coupling products.

We initially compared the catalytic activity of **1** with selected ruthenium and common acid catalysts for the coupling reaction of 3-methoxyphenol with cyclohexanol (eq 1). Among the



(1)

screened catalysts, complex **1** was found to exhibit distinctively high activity in forming the coupling product **2a** along with a trace amount of the alkenylation product **3a**, as analyzed by both GC and NMR spectroscopic methods (Table S1, Supporting Information (SI)). Addition of a substoichiometric amount of simple alkene (10 mol %) was found to promote the coupling reaction, and cyclopentene was most effective among several screened olefins. Protected phenols are typically used for the C−H coupling reactions to avoid side reactions, as exemplified by a recent report on the C−H insertion of silyl-protected phenols,[11] but in our case, complex **1** effectively promotes the alkylation reaction without using any protecting groups on either phenol or alcohol substrates.

The substrate scope of the C−H alkylation reaction was explored by using catalyst **1** (Table 1). In general, both primary and secondary alcohols were found to react smoothly with 3-methoxyphenol to give the alkylation products **2a**−**2i** at a relatively low catalyst loading (entries 1−9). Only linear C−H alkylation products were formed with primary alcohols without giving any branched alkylation products. Phenols with a *meta*-

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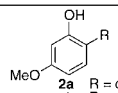
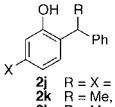
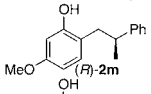
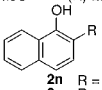
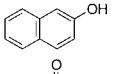
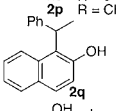
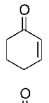
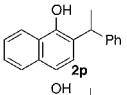
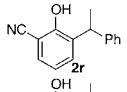
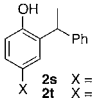
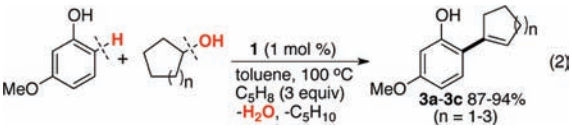
Table 1. Dehydrative *ortho*-C−H Alkylation of Phenols with Alcohols[a]

entry	arene	alcohol	product(s)		t (h)	yield (%)
1		cyclohexanol		**2a** R = c-C_6H_{11}	8	95
2		cyclopentanol		**2b** R = c-C_5H_9	8	93
3		methanol		**2c** R = Me	12	67
4		ethanol		**2d** R = Et	8	91
5		1-hexanol		**2e** R = n-C_6H_{13}	8	92
6		2-propanol		**2f** R = i-Pr	8	86
7		(*R*)-PhCH(CH$_3$)OH		(±)-**2g** R = CH(CH$_3$)Ph	6	91
8		4-Me-$C_6H_4CH_2OH$		**2h** R = $CH_2C_6H_4$-4-Me	6	92
9		tetrahydropyran-2-methanol		**2i** R = $CH_2C_5H_9O$	8	88
10		$PhCH_2OH$		**2j** R = X = H	6	92
11		PhCH(CH$_3$)OH		**2k** R = Me, X = H	8	90
12		PhCH(CH$_3$)OH		**2l** R = Me, X = Cl	10	88
13				(*R*)-**2m**	8	92
14		1-hexanol		**2n** R = n-C_6H_{11}	6	89
15		cyclopentanol		**2o** R = c-C_5H_9	6	91
16		PhCH(CH$_3$)OH		**2p** R = CH(CH$_3$)Ph	6	94
17		PhCH(CH$_3$)OH		**2q**	6	90
18		PhCH(CH$_3$)OH		**2k**	8	84
19		PhCH(CH$_3$)OH		**2p**	8	81
20		PhCH(CH$_3$)OH		**2r**	6	82
21		PhCH(CH$_3$)OH		**2s** X = OMe	8	92
22				**2t** X = Cl	8	87

[a]Reaction conditions: phenol (1.0 mmol), alcohol (1.2 mmol), cyclopentene (0.1 mmol), toluene (2 mL), **1** (1 mol %), 100 °C.

electron-donating group were found to promote the coupling reaction, but 3-chlorophenol and phenol also yielded the coupling products **2j**−**2l** with a slightly longer reaction time (entries 10−12). An optically pure chiral alcohol (*R*)-1-phenylethanol gave the racemic product (±)-**2g** (entry 7), while the reaction with (*R*)-2-phenyl-1-propanol afforded the coupling product (*R*)-**2m** without any racemization (entry 13). The alkylation of both 1- and 2-naphthols with alcohols led to the regioselective formation of the coupling products **2n**−**2q** (entries 14−17). The reaction of both cyclohexenone and α-tetralone with 1-phenylethanol yielded the arene coupling product **2k** and **2p**, apparently resulted from the dehydrogenation of the ketone substrate (entries 18 and 19).[12] Both *ortho*- and *para*-substituted phenols smoothly reacted with 1-phenylethanol to afford the alkylation products **2r**−**2t** (entries 20−22). In all cases, *ortho*-selective C−H coupling products are obtained predictably without giving any 1:2 coupling products or other byproducts.

The *ortho*-alkenylated phenols are a valuable class of synthetic precursor for a number of biologically active core structures.[13] We have been able to directly form the *ortho*-C−H alkenylation products **3** from the tandem alkylation and dehydrogenation protocol. Thus, the treatment of 3-methoxyphenol (1.0 mmol) with a cycloalkanol (1.2 mmol) and excess cyclopentene (3 equiv) in the presence of **1** (1 mol %) at 100 °C yielded the dehydrogenative coupling product **3a**−**3c** exclusively within 8 h of the reaction time (eq 2). The

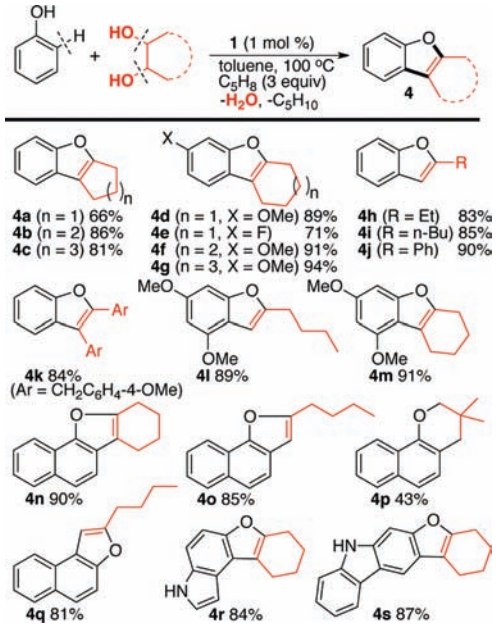


(2)

formation of **3** can be readily rationalized by invoking a chelate-directed *ortho*-C−H alkylation followed by the dehydrogenation steps, where cyclopentene is acting as the dehydrogenation agent.[12,14] The catalytic method achieves the regioselective C−H alkenylation without using any expensive and often toxic metal oxidants.

We have been able to extend the synthetic utility of the dehydrative C−H alkenylation method to form benzofuran derivatives. Thus, the treatment of phenol with 1,2-diols under similar conditions as specified in eq 2 cleanly led to the desired benzofuran products **4** (Table 2). Both substituted phenols and

Table 2. Dehydrative *ortho*-C−H Alkenylation and Cyclization of Phenols with Diols[a]



[a]Reaction conditions: phenol (1.0 mmol), diol (1.2 mmol), cyclopentene (3 mmol), toluene (2 mL), **1** (1 mol %), 100 °C, 8−12 h.

naphthols readily reacted with 1,2-diols to generate benzofuran products with a relatively low catalyst loading (1 mol %). Exclusive formation of the α-substituted benzofuran products resulted from the regioselective addition of the linear 1,2-diols to the *ortho*-arene position (**4h**−**4j**, **4l**, **4o**, **4q**). 1-Naphthol with 1,2-diols exclusively formed the corresponding naphthylfuran products **4n** and **4o**, while the analogous reaction with a 1,3-diol led to the hydropyran product **4p**. Both 5-hydroxyindole and 2-hydroxycarbazole with 1,2-cyclohexanediol led to the corresponding furan products **4r** and **4s**, respectively, tolerating an amine functional group. The catalytic method constitutes an effective *intermolecular* synthetic method for α-substituted benzofurans, as most catalytic methods rely on the *intramolecular* couplings to synthesize substituted benzofuran compounds.[5,15]

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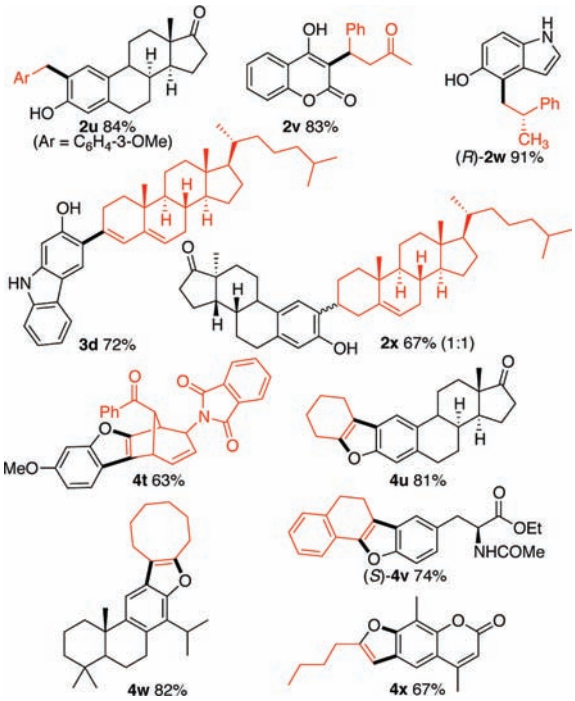
To further illustrate the synthetic versatility of the catalytic coupling method, we next surveyed the C−H alkylation and alkenylation reactions for a number of functionalized phenol and alcohol substrates of biological importance (Table 3). The

Table 3. Dehydrative C−H Alkylation and Alkenylation of Biologically Active Phenols with Alcohols and Diols[a]

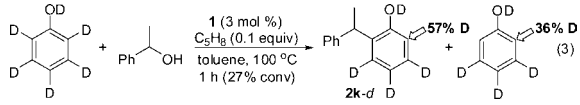


[a]General reaction conditions: phenol (1.0 mmol), alcohol (1.2 mmol), cyclopentene (0.1 mmol for the alkylation; 3.0 mmol for the alkenylation), solvent (2−3 mL), **1** (1−2 mol %), 100 °C. See SI for more specific reaction conditions for each product.

alkylation of estrone with 3-methoxybenzyl alcohol led to the alkylation product **2u** in 84% yield. The reaction of 4-hydroxycoumarin with 4-phenyl-4-hydroxy-2-butanone led to the warfarin product **2v** in a single step. Treatment of 5-hydroxyindole with (*R*)-2-phenyl-1-propanol led to the optically active coupling product (*R*)-**2w**, without any detectable racemization.

The analogous C−H alkenylation of 2-hydroxycarbazole with cholesterol led to the clean formation of the oxidative coupling product **3d**, while the C−H alkylation of estrone with cholesterol formed a 1:1 diastereomeric mixture of the coupling product **2x**. The C−H alkenylation/annulation of 3-methoxyphenol with an amide-substituted bicyclo[3.2.1]octendiol was found to occur in a regioselective manner in yielding the coupling product **4t**, while tolerating both amide and carbonyl functional groups. Highly regioselective formation of the product **4t** is apparently culminated from the alkylation of a sterically less hindered alcohol to the *ortho*-phenolic group, following the same regioselectivity pattern as the linear 1,2-diols. Cyclic 1,2-diols were predictively attached to estrone, tyrosine, and hydrophenanthrenol to form the corresponding benzofuran derivatives, **4u**−**4w**, without affecting any functional groups. The regioselective addition of 1,2-hexanediol to a coumarin derivative led to the α-substituted furanocoumarin compound **4x**. Synthetic furanocoumarin derivatives have been commonly used as photosensitizers for the treatment of psoriasis.[16]

The following kinetic experiments were performed to gain mechanistic insights into the catalytic C−H alkylation reaction. To examine the H/D exchange pattern on the phenol substrate, the reaction of phenol-d_6 (1.0 mmol) with 1-phenylethanol (1.2 mmol) in the presence of **1** (3 mol %) and cyclopentene (10 mol %) in toluene at 100 °C was stopped after 1 h (eq 3). The



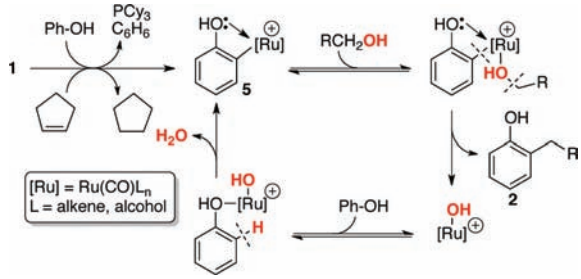
selective H/D exchange pattern on the *ortho*-arene positions of both the coupling product **2k** (57% D) and the phenol substrate (36% D) was observed at 27% product conversion (Figure S1, SI). Such an extensive H/D exchange pattern on the phenol substrate is consistent with a rapid and reversible *ortho*-C−H bond activation step. In support of this notion, a negligible isotope effect of k_H/k_D = 1.1 ± 0.1 was measured from the reaction of C_6H_5OH and C_6D_5OD with 1-phenylethanol at 100 °C (Figure S2, SI).

To discern the rate-limiting step of the alkylation reaction, the $^{12}C/^{13}C$ kinetic isotope effect was measured from the coupling reaction of 3-methoxyphenol and 1-phenylethanol by employing Singleton's NMR technique.[17] We observed the most pronounced carbon isotope effect on the *ortho*-carbon of **2g** when the ^{13}C ratio of the product **2g** at 90% conversion was compared to the ones obtained from three low conversions [(^{13}C at 90% conversion)/(average of ^{13}C at 10, 16 and 18% conversion) at C(6) = 1.038] (Table S2, SI). The result is consistent with the C−C bond formation rate-limiting step for the alkylation reaction, and is in-line with the carbon isotope effects observed in other ruthenium-catalyzed C−C bond formation reactions via C−H activation.[18]

To probe the electronic influence on the phenol substrate, we constructed a Hammett plot by comparing the rate of a series of *m*-X-C_6H_4OH with 1-phenylethanol (X = OCH_3, CH_3, H, F, Cl). A linear correlation from the relative rate vs Hammett σ_p led to a negative ρ value of −1.6 ± 0.2 (Figure S3, SI). A strong promotional effect by the electron-releasing group suggests a substantial cationic character on the transition state, which is promoted by an electrophilic Ru catalyst.

Though details are not clear at the present time, we present a putative mechanism of the C−H alkylation reaction on the basis of these results (Scheme 1). We propose that the cationic *ortho*-metalated Ru species **5** is initially generated from the *ortho*-C−H activation of phenol and dehydrogenation steps. As supporting evidence for the cationic Ru species **5**, we have been able to detect the formation of both cyclopentane and free benzene molecules from the crude reaction mixture. The

Scheme 1. Possible Mechanism for the Dehydrative C−H Alkylation Reaction of Phenol with an Alcohol



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observed H/D exchange pattern on both the coupling product and the recovered phenol substrate is consistent with a facile *ortho*-C−H activation step. Either an oxidative addition of the C−O bond followed by the C−C reductive elimination or a σ-bond metathesis coupling mechanism can explain the formation of the product **2**.[19] A few Ru-hydroxo complexes have been shown to mediate C−H activation reactions,[20] and our previous results from the catalytic C−H alkylation of alkenes with alcohols are inconsistent with either an S_N2 type of displacement or a Friedel−Crafts type electrophilic pathway.[9] The observation of a pronounced carbon isotope effect on the *ortho*-arene carbon of the product provides strong support for the C−C bond formation as the rate-determining step. The subsequent *ortho*-C−H activation of phenol and water elimination steps are envisaged for the regeneration of the *ortho*-metalated species **5**. The benzofuran formation can similarly be rationalized by invoking the *ortho*-alkylation of phenol followed by the dehydration and dehydrogenation steps.[21]

In summary, a highly regioselective catalytic C−H alkylation and alkenylation method of phenols with alcohols has been developed by using a well-defined ruthenium-hydride catalyst. The catalytic method employs environmentally benign and cheaply available phenols and alcohols and exhibits a broad substrate scope with high chemoselectivity in providing an expedient synthetic route to a library of substituted phenol and benzofuran compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and methods, Tables S1 and S2, Figures S1−S3, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Recent reviews on the catalytic oxidative C−H coupling reactions: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (b) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) You, S.-L.; Xia, J.-B. In *Topics in Current Chemistry*; Yu, J.-Q., Shi, Z., Eds.; Springer: Berlin, 2010; Vol. *292*, pp 165−194. (e) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215.

(2) (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (b) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (c) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (d) Xiao, B.; Fu, Y.; Xu, J.; Gong, T.-J.; Dai, J.-J.; Yi, J.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 468. (e) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982. (f) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1064. (g) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864.

(3) (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (b) Kalyani, D.; Sanford, M. S. In *Topics in Organometallic Chemistry*; Chatani, N., Ed.; Springer: Berlin, 2007; Vol. *24*, pp 85−116. (c) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (d) Beck, E. M.; Gaunt, M. J. In *Topics in Current Chemistry*; Yu, J.-Q., Shi, Z., Eds.; Springer: Berlin, 2010; Vol. *292*, pp 85−121.

(4) (a) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680. (b) Simmons, E. M.; Hartwig, J. F. *Nature* **2012**, *483*, 70.

(5) (a) Hayashi, T.; Yamasaki, K.; Miura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036. (b) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (c) Xiao, B.; Gong, T.-J.; Liu, Z.-J.; Liu, J.-H.; Luo, D.-F.; Xu, J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 9250. (d) Zhao, J.; Wang, Y.; He, Y.; Liu, L.; Zhu, Q. *Org. Lett.* **2012**, *14*, 1078.

(6) (a) Wang, F.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5430. (b) Ackermann, L.; Pospech, J. *Org. Lett.* **2011**, *13*, 4153. (c) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548. (d) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.* **2012**, *14*, 930.

(7) (a) Pintori, D. G.; Greaney, M. F. *J. Am. Chem. Soc.* **2011**, *133*, 1209. (b) Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 5767. (c) Mandal, D.; Yamaguchi, A. D.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2011**, *133*, 19660.

(8) (a) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, DOI: 10.1021/ar2002045. (b) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676. (c) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137.

(9) Lee, D.-H.; Kwon, K.-H.; Yi, C. S. *Science* **2011**, *333*, 1613.

(10) (a) Yi, C. S.; Lee, D. W. *Organometallics* **2009**, *28*, 4266. (b) Yi, C. S.; Lee, D. W. *Organometallics* **2010**, *29*, 1883. (c) Kwon, K.-H.; Lee, D. W.; Yi, C. S. *Organometallics* **2010**, *29*, 5748. (d) Kwon, K.-H.; Lee, D. W.; Yi, C. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 1692.

(11) Huang, C.; Chattopadhyay, B.; Gevorgyan, V. *J. Am. Chem. Soc.* **2011**, *133*, 12406.

(12) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681.

(13) (a) Gligorich, K. M.; Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2794. (b) Marsault, E.; Hoveyda, H. R.; Peterson, M. L.; Saint-Louis, C.; Landry, A.; Vézina, M.; Ouellet, L.; Wang, Z.; Ramaseshan, M.; Beaubien, S.; Benakli, K.; Beauchemin, S.; Déziel, R.; Peeters, T.; Fraser, G. L. *J. Med. Chem.* **2006**, *49*, 7190. (c) Pathak, T. P.; Sigman, M. S. *Org. Lett.* **2011**, *13*, 2774. (d) Majumdar, N.; Korthals, K. A.; Wulff, W. D. *J. Am. Chem. Soc.* **2012**, *134*, 1357.

(14) Yi, C. S.; Lee, D. W. *Organometallics* **2009**, *28*, 947.

(15) Selected recent examples: (a) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292. (b) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (c) Lockner, J. W.; Dixon, D. D.; Risgaard, R.; Baran, P. S. *Org. Lett.* **2011**, *13*, 5628. (d) Fischer, J.; Savage, G. P.; Coster, M. J. *Org. Lett.* **2011**, *13*, 3376. (e) Ye, S.; Liu, G.; Pu, S.; Wu, J. *Org. Lett.* **2012**, *14*, 70.

(16) (a) Koenigs, L. L.; Trager, W. F. *Biochemistry* **1998**, *37*, 10047. (b) Sardari, S.; Mori, Y.; Horita, K.; Micetich, R. G.; Nishibe, S.; Daneshtalab, M. *Bioorg. Med. Chem.* **1999**, *7*, 1933. (c) Conforti, F.; Marrelli, M.; Menichini, F.; Bonesi, M.; Statti, G.; Provenzano, E.; Menichini, F. *Curr. Drug Ther.* **2009**, *4*, 38.

(17) (a) Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357. (b) Frantz, D. E.; Singleton, D. A.; Snyder, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 3383.

(18) (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (b) Kakiuchi, F.; Kochi, T.; Mizushima, E.; Murai, S. *J. Am. Chem. Soc.* **2010**, *132*, 17741.

(19) Foley, N. A.; Lee, J. P.; Ke, Z.; Gunnoe, T. B.; Cundari, T. R. *Acc. Chem. Res.* **2009**, *42*, 585.

(20) (a) Feng, Y.; Lail, M.; Barakat, K. A.; Cundari, T. R.; Gunnoe, T. B.; Petersen, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 14174. (b) Matsumoto, T.; Nakaya, Y.; Itakura, N.; Tatsumi, K. *J. Am. Chem. Soc.* **2008**, *130*, 2458.

(21) Baxter, R. D.; Sale, D.; Engle, K. M.; Yu, J.-Q.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 4600.