C–H Functionalization

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Rhodium(II)-Catalyzed Nondirected Oxidative Alkenylation of Arenes: Arene Loading at One Equivalent**

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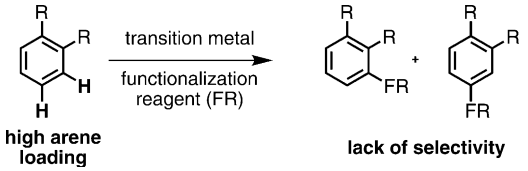
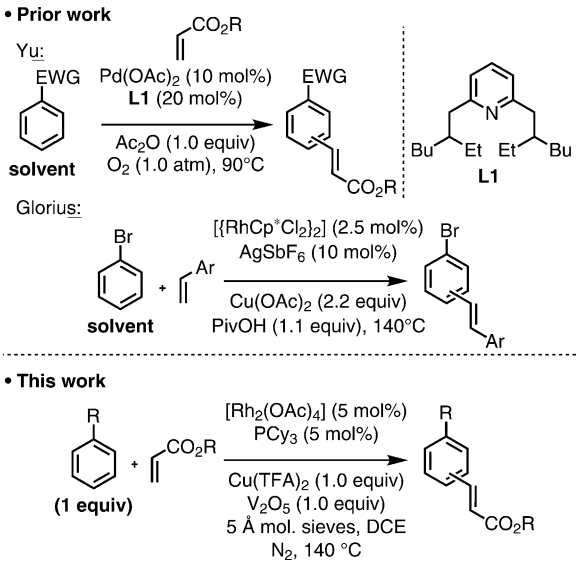
Abstract: *A bimetallic Rh^{II} catalyst promoted the C–H alkenylation of simple arenes at 1.0 equivalent without the use of a directing group. A phosphine ligand as well as cooperative reoxidation of Rh^{II} with $Cu(TFA)_2$ and V_2O_5 proved essential in providing monoalkenylated products in good yields and selectivities, especially with di- and trisubstituted arenes.*

The functionalization of C–H bonds holds great potential for the late-stage diversification of complex molecules.[1] A common strategy relies on the use of directing groups to overcome issues of selectivity and reactivity inherent to the targeting of C–H bonds.[2] Typically, these directing groups may be existing functionality; alternatively, they may be installed and then removed postfunctionalization.[3] In the absence of directing groups,[4] the functionalization of C–H bonds becomes considerably more challenging, as the requirement for high arene loadings and a lack of selectivity in the metallation step manifest themselves (Scheme 1).



Scheme 1. Challenges associated with nondirected functionalization.

The oxidative coupling between arenes and activated alkenes, as described by Fujiwara et al.,[5a] has been the standard against which catalytic systems with Pd,[5] Rh,[6] and Ru[7,8a] have been measured. Our research group has shown that electron-deficient arenes are suitable substrates for this process with palladium and a 2,6-dialkyl-substituted pyridine ligand under aerobic conditions.[8b] Similarly, Sanford and co-workers have shown that crotonic acid ester derivatives participate readily to afford β-disubstituted acrylates in good yield.[8c] Additionally, Glorius and co-workers were able to effect the alkenylation of bromobenzene under Rh^{III} catalysis.[8d] Although these studies showcase the ability of a wide range of metals to perform arene alkenylation, nondirected C–H functionalization reactions are still plagued by the need for very high arene loadings and a lack of selectivity in the metalation step (Scheme 2). We therefore directed our efforts toward the development of highly reactive catalysts that can activate C–H bonds when one equivalent of the arene is used, and investigated novel bimetallic Rh^{II} catalytic systems that would tolerate lower substrate loadings.



Scheme 2. Relevant examples of nondirected alkenylation.[8] Cp* = pentamethylcyclopentadienyl, Cy = cyclohexyl, DCE = 1,2-dichloroethane, EWG = electron-withdrawing group, Piv = pivaloyl.

Our interest in a Rh salt was predicated on the work of Grushin et al., who reported that an electrophilic $Rh(TFA)_3$ salt was a viable catalyst for the selective carboxylation of arenes with CO.[9] Subsequent investigations into the mechanism of this reaction revealed that the electrophilic catalyst is highly susceptible to a disproportionation event that renders the catalyst inactive. We hypothesized that a bimetallic Rh^{II} catalyst might provide an entrance point to an active Rh^{III} species through oxidation.[10] Cotton et al. also reported that Rh^{II} has an affinity for η^2 arene coordination, which could be beneficial in increasing effective molarity and promoting selectivity.[11] Moreover, the use of a bimetallic Rh^{II} catalyst in C–H bond functionalization was shown previously by Chang and co-workers, who demonstrated the arylation of quinoli-

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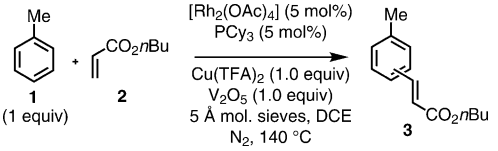
ne[12a] and benzo[*h*]quinoline.[12b] We thus sought to develop a nondirected alkenylation of simple arenes with a bimetallic Rh^{II} complex.

We found that the use of toluene (**1**; 1 equiv) as the model substrate with *n*-butyl acrylate (**2**; 1.0 equiv), $[Rh_2(OAc)_4]$ (5.0 mol%), PCy_3 (5.0 mol%), $Cu(TFA)_2$ (1.0 equiv), and V_2O_5 (1.0 equiv) provided the desired product **3** in 74% yield with 1:1 selectivity for the *meta* and *para* isomers (Table 1, entry 1). The use of V_2O_5 is crucial for this reaction. Other solvents gave significantly lower yields. An increase in the arene loading to 10 equivalents led to the formation of the product in 84% yield (Table 1, entry 2).

Table 1: Deviation from standard reaction conditions.

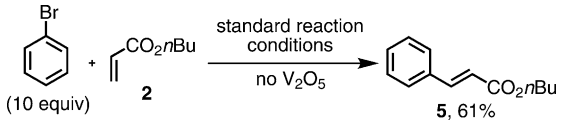


Entry	Deviation from standard reaction conditions	*T* [°C]	Yield [%][a]	Selectivity (*o*/*m*/*p*)
1	**none**	**140**	**74**	**0:1:1**
2	PhMe (10 equiv)	140	84	0:1:1
3	3 Å mol. sieves	140	55	0:1:1
4	temperature	130	45	0:1:1
5	**no $[Rh_2(OAc)_4]$**	**140**	**NR**	**NA**
6	$[Rh_2(OAc)_4]$ (2.5 mol%)	140	58	0:1:1
7	$[Rh_2(cap)_4]$ (5.0 mol%)	140	<5	NA
8	$[Rh_2(esp)_2]$ (5.0 mol%)	140	<5	NA
9	$[Rh_2(oct)_4]$ (5.0 mol%)	140	68	0:1:1
10	$[Rh_2(tfa)_4]$ (5.0 mol%)	140	14	0:1:1
11	$[\{Rh(cod)Cl\}_2]$ (5.0 mol%)	140	<5	NA
12	$[HRh(PPh_3)_3CO]$ (5.0 mol%)	140	14	0:1:1
13	$[(RhCp^*Cl_2)_2]$ (5.0 mol%)	140	<5	NA
14	$Rh(TFA)_3$ (5.0 mol%)	140	<5	NA
15	**no PCy_3**	**140**	**<5**	**NA**
16	$OPCy_3$ (5.0 mol%)	140	<10	0:1:1
17	PPh_3 (5.0 mol%)	140	58	0:1:1
18	P(*o*-tolyl)$_3$ (5.0 mol%)	140	58	0:1:1
19	$P(C_6F_5)_3$ (5.0 mol%)	140	15	0:1:1
20	**no $Cu(TFA)_2$**	**140**	**15**	**0:1:1**
21	$Cu(OAc)_2$	140	<5	NA
22	**no V_2O_5**	**140**	**<5**	**NA**

[a] The yield was determined by NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. cap = caprolactamate, cod = 1,5-cyclooctadiene, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate, oct = *n*-octyl, NA = not applicable, NR = no reaction.

We next focused our attention on the importance of molecular sieves in the reaction. Substitution of 3 Å for 5 Å molecular sieves led to a decrease in the yield to 55% with no change in selectivity (Table 1, entry 3).[13] A change in the temperature from 140 to 130°C provided **3** in 45% yield (Table 1, entry 4). In the absence of Rh^{II}, no product was obtained (Table 1, entry 5), whereas a reduction in the amount of $[Rh_2(OAc)_4]$ from 5 to 2.5 mol% provided **3** in 58% yield (entry 6). Moreover, the use of the alternative Rh^{II} catalysts $[Rh_2(cap)_4]$ and $[Rh_2(esp)_4]$ resulted in the formation of only small quantities of **3** (Table 1, entries 7 and 8), whereas $[Rh_2(oct)_4]$ provided **3** in 68% yield (entry 9). The use of $[Rh_2(tfa)_4]$ (tfa = trifluoroacetate) yielded **3** in 14% yield (Table 1, entry 10). Importantly, the use of either Rh^{I} or Rh^{III} catalysts resulted in negligible product yields (Table 1, entries 11–14). In the absence of tricyclohexyl phosphine or in the presence of its oxide, **3** was obtained in less than 10% yield (Table 1, entries 15 and 16). These results highlight one reason why rigorous exclusion of oxygen is necessary. In the presence of PPh_3 or P(*o*-tolyl)$_3$, **3** was obtained in 58% yield (Table 1, entries 17 and 18). Similarly, the use of more electron deficient $P(C_6F_5)_3$ provided **3** in only 15% yield (Table 1, entry 19). Arene-derived phosphines were not pursued further, as they are susceptible to competitive alkenylation.

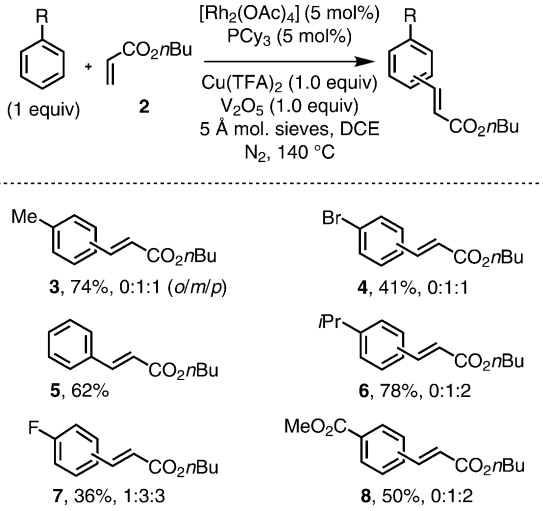
Next, we looked at the effect of the oxidants and the pivotal role they play. In the absence of $Cu(TFA)_2$ or when $Cu(TFA)_2$ was replaced with $Cu(OAc)_2$, the desired product **3** was obtained in low yield (Table 1, entries 20 and 21). When the alkenylation was carried out without vanadium oxide, a negligible amount of product **3** was generated (Table 1, entry 22). The important role of vanadium oxide in this transformation is attributed to its ability to oxidize low-valent rhodium and copper salts generated during the course of the reaction.[14] Interestingly, during the optimization of this reaction, we observed that the use of 10 equivalents of bromobenzene in the absence of V_2O_5 yielded the cinnamate **5** in 61% yield (Scheme 3). As the oxidative addition of aryl halides with Rh^{II} and Rh^{III} salts is thought to be difficult,[15] we



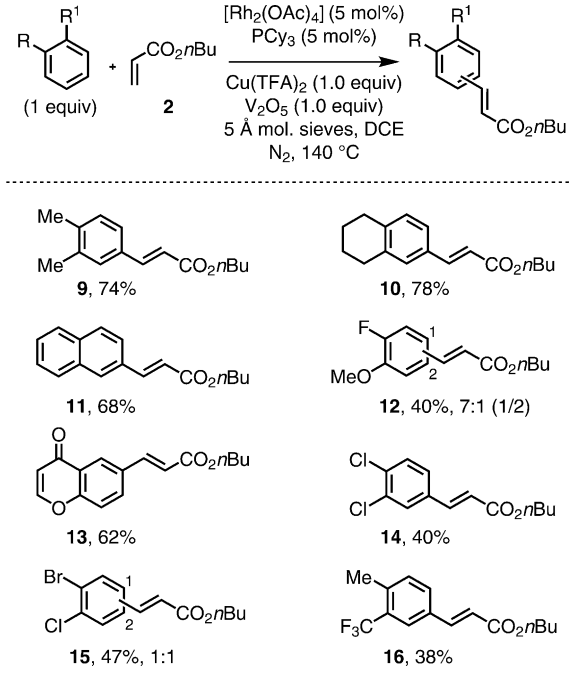
Scheme 3. Importance of vanadium oxide.

attribute the formation of **5** to a rhodium-catalyzed sequential C–H olefination and copper(I)-mediated proteo-debromination process. Presumably, the Cu^{I} generated can oxidatively insert into the aryl bromide and subsequently undergo protonolysis in the presence of exogenous TFA. We hypothesize that V_2O_5 plays a role in the oxidation of Cu^{I} to Cu^{II}, thus inhibiting proteo-dehalogenation.[16]

Having identified a set of optimized reaction conditions, we began our investigations into the scope of the reaction with respect to the Michael acceptor. After trying a variety of coupling partners, including vinyl phosphonates, acrylonitriles, substituted acrylates, crotonates, and vinyl ketones, we found that only simple acrylates were competent substrates.[17] When 1.0 equivalent of benzene was subjected to the reaction with **2**, **5** was obtained in 62% yield (Scheme 4). The use of cumene provided **6** in 78% yield and a 1:2 ratio of *meta* and *para* isomers. Halogenated arenes suffered from suppressed reactivity, and much lower yields were observed. We presume this lower reactivity to be a consequence of decreased arene electron density: less η^2 coordination and more Lewis basic coordination to the metal. Indeed, when bromobenzene and fluorobenzene were subjected to the



Scheme 4. Scope of the oxidative alkenylation of monosubstituted arenes. The yields given are for the isolated product as a mixture of regioisomers.



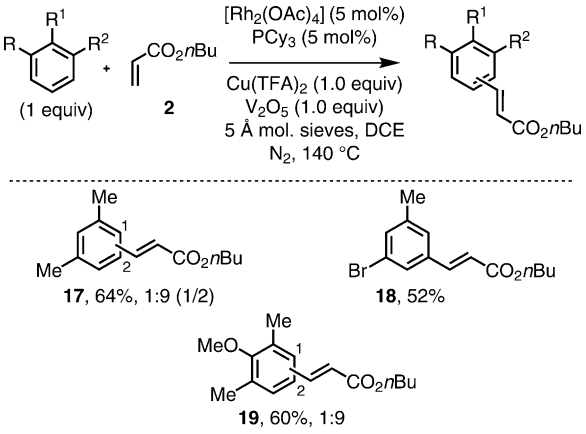
Scheme 5. Scope of the oxidative alkenylation of 1,2-disubstituted arenes. The yields given are for the isolated product as a mixture of regioisomers.

optimized reaction conditions, **4** and **7** were obtained in 41 and 36% yield, respectively, as mixtures of regioisomers. Similarly, the use of methylbenzoate provided **8** in 50% yield with functionalization occurring in a 1:2 ratio at the *meta* and *para* positions. The formation of *cis*-olefinated arenes in 2–10% yield was also observed (see the Supporting Information), the cause of which remains to be investigated.

We next surveyed symmetrical and nonsymmetrical 1,2-disubstituted arenes and their reactivity in this reaction (Scheme 5). The use of electron-rich arenes without Lewis basic functional groups provided the desired products **9**, **10**, and **11** in good yields (68–78%) as single regioisomers (Scheme 5). When substrates bearing Lewis basic groups were subjected to the reaction, lower yields were observed. When nonsymmetrical 2-fluoroanisole was used in the reaction, the desired product **12** was obtained in only 40% yield, with functionalization occurring primarily in the *para* position to the methoxy group. In the case of chromone, however, **13** could be obtained as a single regioisomer in satisfactory 62% yield. The use of dichlorobenzene, 2-bromochlorobenzene, and 2-(trifluoromethyl)toluene provided the respective products **14**, **15** and **16** in 40, 47, and 38% yield.

Having established the scope of the reaction with mono- and 1,2-disubstituted arenes at 1.0 equivalent, we next examined the scope of reaction with 1,3-disubstituted and 1,2,3-trisubstituted arenes (Scheme 6). When *meta*-xylene was subjected to the reaction conditions, **17** was obtained in 64% yield as predominantly a single regioisomer (1:9 *ortho*/*meta*). Similarly, the use of *m*-bromotoluene resulted in the formation of **18** in 52% yield as a single regioisomer. With 2,6-dimethylanisole, **19** was obtained as a mixture of regioisomers (1:9 *meta*/*para*) in 60% yield.

We put forth the following reasonable mechanistic proposal for the bimetallic Rh^{II} alkenylation: Initial coordination of tricyclohexylphosphane to dirhodium tetraacetate facilitates ligand exchange of the equatorial acetate groups



Scheme 6. Scope of the oxidative alkenylation of 1,3- and 1,2,3-substituted arenes. The yields given are for the isolated product as a mixture of regioisomers.

and affects the oxidation potential of the bimetallic complex.[18] Additionally, the exchange of the equatorial ligands generates a vacant site for acrylate coordination. Concurrent oxidation of the bimetallic complex, effected by $Cu(TFA)_2$ or V_2O_5, would generate a Rh^{III} species, C–H activation by which would generate the aryl rhodium species. Carbometalation of the acrylate, followed by β-hydride elimination, would yield the product and a rhodium hydride, which, after reductive elimination, would be reoxidized to generate the active catalyst.

In summary, we have developed a method for the alkenylation of arenes at 1.0 equivalent by utilizing a bimet-

allic Rh^{II} complex. In many cases involving 1,2- and 1,3-disubstituted arenes, products can be obtained in good yields and selectivities. Currently, effort towards elucidating the mechanism and developing this reaction to tolerate other nondirected functionalization reactions is ongoing in our laboratory.

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[1] For C–H functionalization in complex-molecule synthesis, see: a) K. Godula, D. Sames, *Science* **2006**, *312*, 67; b) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369; c) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem.* **2012**, *124*, 9092; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; for C–H functionalization in general, see: d) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507; e) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879.

[2] For directed C–H activation with Pd, see: a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; b) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; with Ru, see: c) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879; with Rh, see: d) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624.

[3] For a review on removable directing groups, see: G. Rousseau, B. Breit, *Angew. Chem.* **2011**, *123*, 2498; *Angew. Chem. Int. Ed.* **2011**, *50*, 2450.

[4] For a review on nondirected C–H bond functionalization of simple arenes, see: N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236.

[5] a) Y. Fujiwara, I. Moritani, S. Danno, R. Asano, S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166; b) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, *287*, 1992; c) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633; d) T. Matsumoto, H. Yoshida, *Chem. Lett.* **2000**, 1064; e) M. Dams, D. E. De Vos, S. Celen, P. A. Jacobs, *Angew. Chem.* **2003**, *115*, 3636; *Angew. Chem. Int. Ed.* **2003**, *42*, 3512; f) T. Yokota, M. Tani, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2003**, *125*, 1476; g) M. Tani, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2004**, *69*, 1221; h) T. Yamada, A. Sakakura, S. Sakaguchi, Y. Obora, Y. Ishii, *New J. Chem.* **2008**, *32*, 738; i) M. Ye, G.-L. Gao, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 6964; j) A. J. Hickman, M. S. Sanford, *ACS Catal.* **2011**, *1*, 170; k) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518.

[6] a) P. Hong, H. Yamazaki, *J. Mol. Catal.* **1984**, *26*, 297; b) K. Sasaki, T. Sakakura, Y. Tokunaga, K. Wada, M. Tanaka, *Chem. Lett.* **1988**, 685; c) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407; d) Z.-M. Sun, J. Zhang, R. Manan, P. Zhao, *J. Am. Chem. Soc.* **2010**, *132*, 6935; e) F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9982; f) F. W. Patureau, T. Besset, F. Glorius, *Angew. Chem.* **2011**, *123*, 1096; *Angew. Chem. Int. Ed.* **2011**, *50*, 1064; g) S. Rakshit, C. Grohmann, T. Besset, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2350; h) T. Besset, N. Kuhl, F. Patureau, F. Glorius, *Chem. Eur. J.* **2011**, *17*, 7167.

[7] a) C. S. Yi, D. W. Lee, *Organometallics* **2009**, *28*, 4266; b) K. H. Kwon, D. W. Lee, C. S. Yi, *Organometallics* **2010**, *29*, 5748; c) T. Ueyama, S. Mochida, T. Fukutani, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2011**, *13*, 706; d) P. B. Arockiam, C. Fischmeister, C. Bruneau, P. H. Dixneuf, *Green Chem.* **2011**, *13*, 3075; e) K. Padala, M. Jeganmohan, *Org. Lett.* **2011**, *13*, 6144; f) L. Ackermann, J. Pospech, *Org. Lett.* **2011**, *13*, 4153; g) L. Ackermann, L. Wang, R. Wolfram, A. V. Lygin, *Org. Lett.* **2012**, *14*, 728; h) B. Li, J. Ma, N. Wang, H. Feng, S. Xu, B. Wang, *Org. Lett.* **2012**, *14*, 736; i) K. Padala, M. Jeganmohan, *Org. Lett.* **2012**, *14*, 1134.

[8] a) H. Weissman, X. Song, D. Milstein, *J. Am. Chem. Soc.* **2001**, *123*, 337; b) Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 5072; c) A. Kubota, M. H. Emmert, M. S. Sanford, *Org. Lett.* **2012**, *14*, 1760; d) F. W. Patureau, C. Nimphius, F. Glorius, *Org. Lett.* **2011**, *13*, 6346.

[9] V. V. Grushin, W. J. Marshall, D. L. Thorn, *Adv. Synth. Catal.* **2001**, *343*, 161.

[10] a) D. N. Zalatan, J. Du Bois, *J. Am. Chem. Soc.* **2009**, *131*, 7558; b) J. M. Nichols, J. Wolf, P. Zavalij, B. Varughese, M. P. Doyle, *J. Am. Chem. Soc.* **2007**, *129*, 3504.

[11] F. A. Cotton, E. V. Dikarev, M. A. Petrukhina, *J. Am. Chem. Soc.* **2001**, *123*, 11655, and references therein.

[12] a) J. Kwak, M. Kim, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 3780; b) M. Kim, J. Kwak, S. Chang, *Angew. Chem.* **2009**, *121*, 9097; *Angew. Chem. Int. Ed.* **2009**, *48*, 8935.

[13] See the Supporting Information for additional details as to the need for molecular sieves.

[14] a) J. Zakzeski, A. T. Bell, *J. Mol. Catal. A* **2007**, *276*, 8; b) J. Zakzeski, A. Behn, M. H. Gordon, A. T. Bell, *J. Am. Chem. Soc.* **2009**, *131*, 11098.

[15] K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169.

[16] S. G. Bratsch, *J. Phys. Chem. Ref. Data* **1989**, *18*, 1. See the Supporting Information for additional details of relevant oxidation potentials.

[17] See the Supporting Information for additional details on the scope of the reaction with respect to the olefin coupling partner.

[18] a) "Rhodium Compounds": T. H. Chifotides, K. R. Dunbar in *Multiple Bonds between Metal Atoms*, 3rd ed. (Eds.: F. A. Cotton, C. A. Murillo, R. A. Walton), Springer, New York, **2005**; b) J. L. Bear, R. A. Howard, J. E. Korn, *Inorg. Chim. Acta* **1979**, *32*, 123.

