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# Rh(III)-Catalyzed Tandem Oxidative Olefination−Michael Reactions between Aryl Carboxamides and Alkenes

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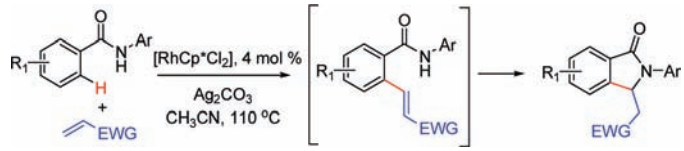
## ABSTRACT




**Rh(III)-catalyzed oxidative coupling reactions between benzamides or heteroaryl carboxamides and olefins have been developed. The vinylation product can further undergo a Michael reaction leading to γ-lactam in the case of electron-withdrawing olefins.**

Pioneered by Fujiwara and Moritani, oxidative olefination of arenes using alkenes (the oxidative Heck reaction) represents an atom-economic strategy to directly functionalize arenes (eq 1).[1] This process is highly attractive in that no prior functionalization of the arene is necessary.[2] A survey of recent reports on oxidative Heck reactions reveals that palladium catalysts are most commonly used, as in the seminal work of Yu[3] and others.[4,5] Significantly, Yu and co-workers even discovered the oxidative C($sp^3$)−H olefination of *N*-aryl carboxamides.[3a] Nevertheless, the *N*-aryl groups are limited to highly electron-withdrawing ones in this case.

Rhodium catalysts stand out in the area of C−C coupling reactions that proceed via a C−H activation pathway for their high functional group tolerance and wide range of synthetic utility.[7] However, rhodium-catalyzed oxidative C−H functionalization has been less well-studied. Matsumoto and Yoshida achieved an oxidative Heck reaction between benzene and ethylene using cyclometalated Rh(III) catalysts.[8] More recently, Miura and Satoh[9] and Glorius[6] reported important Rh(III)-catalyzed oxidative Heck reactions with Cu(II) oxidants (eq 2−4).[9]

[†] These authors contributed equally to this work.

(1) (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.

(2) For the applications of oxidative Heck reactions in natural product synthesis, see: (a) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856. (b) Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6316.

(3) (a) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680. (b) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886. (c) Lu, Y.; Wang, D.-H.; Engle, K.-M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916. (d) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460. (e) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (f) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452.

(4) (a) Song, C. X.; Cai, G.-X.; Farrell, T. R.; Jiang, Z. P.; Li, H.; Gan, L. B.; Shi, Z.-J. *Chem. Commun.* **2009**, 6002. (b) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666. (c) Boele, M. D. K.; van Strijdonck, G. P. F.; der Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (d) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (e) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009**, *131*, 13888. (f) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (g) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476. (h) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230.

(5) (a) Ma, S.; Yu, S. *Tetrahedron Lett.* **2004**, *45*, 8419. (b) Liu, C.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 10250. (c) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (d) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 1972.

(6) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982.

(7) For a recent review, see: Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624.

(8) Matsumoto, T.; Periana, R. A.; Taube, D. J.; Yoshida, H. *J. Catal.* **2002**, *206*, 272.

(9) (a) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7094. (b) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407.

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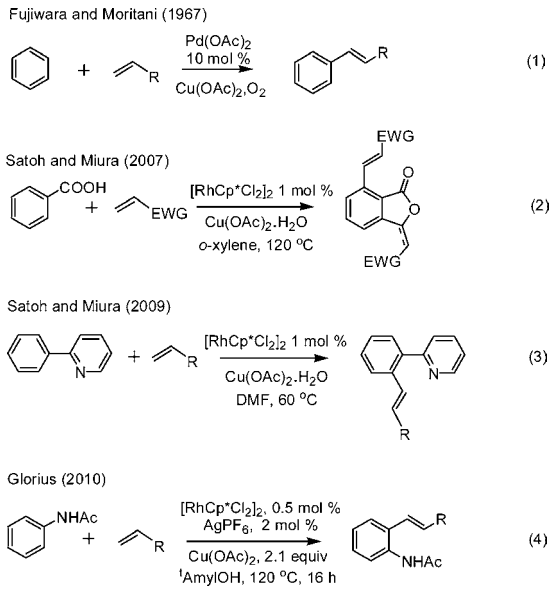
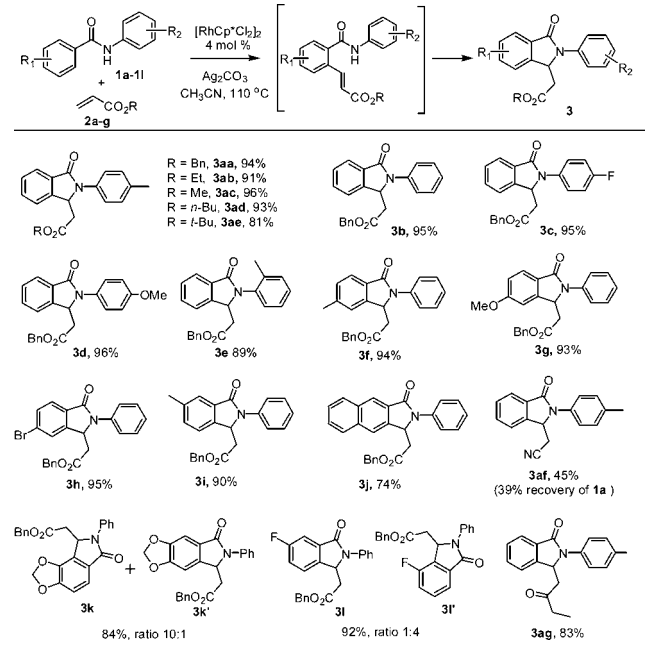
Recent studies on Rh(III)-catalyzed oxidative C−C, C−N, and C−O coupling reactions by Satoh and Miura, Fagnou, Jones, Glorius, and Zhang has revealed that in most cases proximal heteroatom-directing groups such as amide,[6,10] pyridyl,[9a,11] imine,[12] hydroxyl,[13] and carboxyl[9b,14] are important both to facilitate the activation of C($sp^2$)-H bonds and to direct the selectivity to the *ortho* position. Considering that amides are readily available and amide functionality offers sufficient assistance, oxidative functionalization of acetanilides has been well studied.[5d,6,10a,15] In contrast to the specific selectivity of C−H functionalization in acetanilides, C−H functionalization of *N*-aryl benzamides may be complicated by chemoselectivity in terms of which arene undergoes C−H cleavage, and this substrate was not studied until very recently by us[16] and others in Rh catalysis,[10d,e] although Pd-catalyzed C−H activation of *N*-aryl amides has been reported to occur at the carboxylic acid unit.[17] As a continuation of our studies, we now report C−H olefination of such benzamides at the *C*-aryl ring. More importantly, when electron-poor olefins are utilized, the coupled products may further undergo in situ Michael addition to give $\gamma$-lactams.




We initiated our investigation with the coupling between benzamide **1a** and benzyl acrylate. Gratifyingly, the use of $[Cp^*RhCl_2]_2$ as the single catalyst and $Ag_2CO_3$ as the oxidant in MeCN or acetone yielded lactam **3aa** (110 °C, sealed tube, 12 h) in 94% yield (Scheme 1). Reactions performed at

**Scheme 1.** Rh(III)-Catalyzed Tandem Oxidative Olefination−Michael Reactions between Benzamides and Alkenes[a,b]




[a] Reaction conditions: benzamide, olefin (2 equiv), $Ag_2CO_3$ (2 equiv), $[RhCp^*Cl_2]_2$ (4 mol %), MeCN (5 mL), sealed tube under nitrogen, 110 °C, 12 h. [b] **2a** = benzyl acrylate; **2b** = ethyl acrylate; **2c** = methyl acrylate; **2d** = butyl acrylate; **2e** = *tert*-butyl acrylate; **2f** = acrylonitrile; **2g** = ethyl vinyl ketone.

higher temperatures (125 °C) but with lower catalyst loading (2 mol %) only gave lower yields (64%). This reaction is proposed to go by the oxidative olefination of the *ortho* C−H bond in the *C*-aryl ring, followed by intramolecular hydroamination (Michael addition).[3a,f,9b] The scope of this reaction is outlined in Scheme 1. Benzamides with electron-donating or -withdrawing groups afforded lactams in high isolated yield. Furthermore, *N*-*o*-tolyl benzamide (**1e**) also reacts to give the coupled product in 89% isolated yield, indicating tolerance of the steric bulk in the *N*-aryl group. It is noteworthy that the halide substituent (**1h**) can be tolerated without any Heck coupling byproduct being detected, which highlights an advantage of rhodium catalysis compared to palladium catalysis. To examine the regioselectivity of this reaction, substrates **1i** and **1j** were allowed to react under the standard conditions to give **3i** and **3j**, respectively, where C−H functionalization occurred at the less sterically hindered

(10) (a) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474. (b) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (c) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (d) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (e) Mochida, S.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 744.

(11) (a) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019. (b) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414. (c) Guan, Z.-H.; Spinella, S. M.; Yu, S.; Liang, Y.-M.; Zhang, X. *J. Am. Chem. Soc.* **2009**, *131*, 729. (d) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2068.

(12) (a) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050. (b) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141.

(13) Uto, T.; Shimizu, M.; Ueura, K.; Tsurugi, H.; Satoh, T.; Miura, M. *J. Org. Chem.* **2008**, *73*, 298.

(14) (a) Shimizu, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 3478. For a recent review, see: (b) Satoh., T.; Ueura, K.; Miura, M. *Pure Appl. Chem.* **2008**, *80*, 1127.

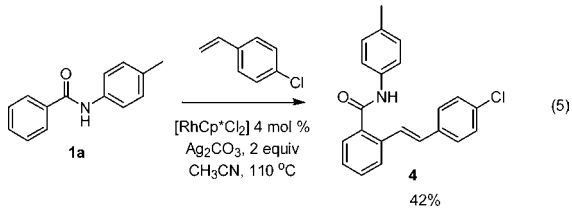
(15) (a) Phipps, R. J.; Gaunt, M. *Science* **2009**, *323*, 1593. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066. (d) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156.

(16) Song, G.; Chen, D.; Pan, C.-L.; Crabtree, R. H.; Li, X. *J. Org. Chem.* DOI: 10.1021/jo101596d.

(17) (a) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (b) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275.

site, although (reversible) C−H activation may take place at both positions *ortho* to the amide directing group.[10a] In sharp contrast, the olefination of **1k** gave a mixture of two regioisomers **3k** and **3k′** in 10:1 ratio, with the major product being derived from the *ortho* C−H activation at the more hindered position. Similar results were also observed for amide **1l**, where **3l** and **3l′** were isolated in 1:4 ratio as analytically pure compounds. This observed selectivity is most plausibly ascribed to the directing effect of the *meta* heteroatom and/or the electronic effect of the aryl ring. The range of olefin substrates can also be extended to other acrylates, an enone, and acrylonitrile (Scheme 1). In all cases, only monovinylation products can be detected, in contrast to the divinylation of benzoic acids observed by Satoh and Miura.[9b] This result also indicates that the amide functionality in the product cannot function as an efficient directing group to achieve further *ortho* C−H activation. Thus, the observed single lactam product might be ascribed to the fast Michael reaction that traps the olefination intermediate (vide infra).

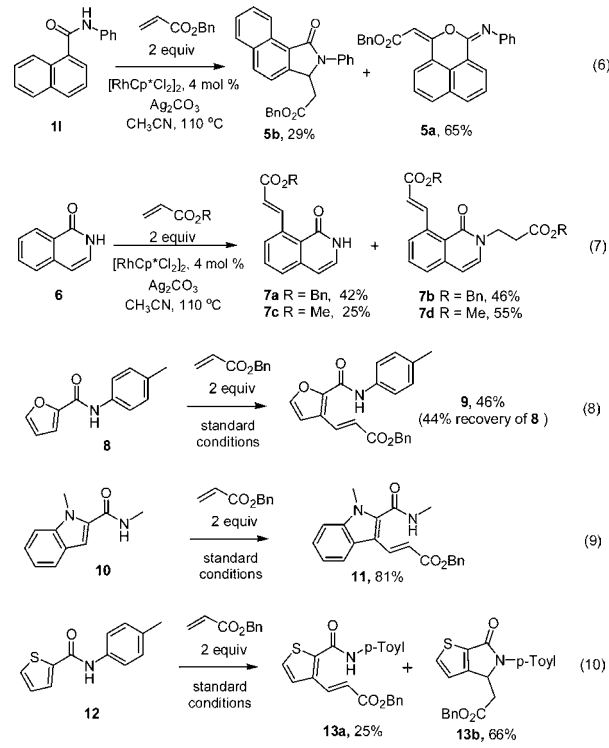
We reasoned that when using electron-neutral or electron-rich olefins this reaction should stop after the olefination stage. Indeed, when **1a** was allowed to react with styrene under the same conditions, the corresponding stilbene products could be detected (GC-MS). However, they cannot be isolated in analytically pure form using column chromatography. Fortunately, switching from styrene to *p*-chlorostyrene (1 equiv) leads to the successful isolation of stilbene **4** (62% GC yield and 42% isolated yield, eq 5), together with the recovery of the starting benzamide (30%).



(5)

To better define the substrate scope, 1-naphthamide **1l** was subjected to the same reaction conditions. Surprisingly, although the expected lactam **5b** can still be obtained, the major product is an imidoester (**5a**), resulting from a double oxidative coupling reaction which involves sequential C−H olefination and intramolecular oxidative C−O formation (eq 6). Optimization of the reaction conditions by simply providing an access of $Ag_2CO_3$ leads to the isolation of **5a** and **5b** in 65% and 29% yield, respectively. The structure of **5a** was elucidated using NMR ($^1$H and $^{13}$C) and IR spectroscopy and HRMS (see Supporting Information for the characterization of **5a**). We noted that directed activation of the C−H bond at the 8-position of 1-substituted naphthalenes is rare.[18]

The scope of this reaction can be further extended to 1-hydroxyisoquinoline **6**, which is essentially an isoquinolone, where two products have been isolated and fully characterized (eq 7). In the reaction of **6** and benzyl acrylate, a monovinylation product (**7a**) and an *N*-alkyl product (**7b**) were isolated in 42% and 46% yield, respectively. In both products, the C−H activation takes place at the 8-position, facilitated by the proximal O atom of the amide moiety. No further intramolecular oxidative $C_{olefin}-O_{amide}$ coupling was observed for product **7a**, even though an excess of $Ag_2CO_3$ was provided. When isolated **7a** was allowed to react (MeCN, 110 °C) with benzyl acrylate under the same reaction conditions ($[Cp^*RhCl_2]_2$, 4 mol %, and $Ag_2CO_3$, 2 equiv), product **7b** was isolated in 35% yield, together with the complete recovery of **7a**. These results indicate that product **7a** can be an intermediate leading to the *N*-alkyl product **7b**. However, the alternative Michael reaction−oxidative olefination sequence is also possible.




Extension of this reaction to heteroaryl carboxamides turned out to be successful under the standard conditions. Furyl-2-carboxamide (**8**) undergoes a somewhat sluggish reaction with benzyl acrylate to give an olefin product **9** in 46% yield (eq 8); however, this reaction is clean, and the unreacted substrate **8** can be recovered (44%). Indolyl-3-carboxamide (**10**) readily reacts with benzyl acrylate to give **11** in high isolated yield (eq 9), and here even the *N*-methyl amide is reactive enough. In neither case did further Michael reaction take place. It should be noted that the amide-directing group in **10** is necessary as evidenced by the absence of any reaction when simple *N*-methyl indole was allowed to react with acrylates under these conditions. This is in contrast to the observed Pd(II)-catalyzed oxidative coupling between *N*-methyl indole and butyl acrylate at the 3-position using $Cu(OAc)_2$ as oxidant.[19] Thiophenyl-2-carboxamide (**12**) readily reacted with benzyl acrylate, and both olefin (**13a**) and Michael reaction products (**13b**) were

(18) (a) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78. (b) Kaïm, L. E.; Gamez-Montaño, R.; Grimaud, L.; Ibarra-Riverab, T. *Chem. Commun.* **2008**, 1350. (c) Harayama, T.; Sato, T.; Hori, A.; Abe, H.; Takeuchi., Y. *Synthesis* **2004**, *9*, 1446.

isolated (eq 10). The differences observed for these heteroaryl carboxamides and benzamides with respect to Michael reactions are likely caused by the differences of the stereoelectronic effects of the olefin intermediate/product.

To probe the reaction mechanism, competitive reactions have been carried out. An equimolar amount of *p*-$MeOC_6H_4C(O)NHPh$, *p*-$BrC_6H_4C(O)NHPh$, and benzyl acrylate was allowed to react under the standard conditions. Benzamides with electron-poor groups in the *C*-aryl ring tend to react in slight preference (Supporting Information). Likewise, the competitive reaction between $PhC(O)NH(p\text{-}FC_6H_4)$ and $PhC(O)NH(p\text{-}OMeC_6H_4)$ also leads to the conclusion that this coupling reaction is favored for benzamides with electron-poor *N*-aryl groups (see the Supporting Information).[20] The fact that benzamides with electron-poor *N*-aryl groups react at a higher rate also suggests that the Michael reaction cannot be the turnover limiting step for the catalytic cycle.

Although there is no formal N−H cleavage (prior to the Michael reaction) in the olefination of benzamides, (reversible) metalation seems to take place on the nitrogen rather than on oxygen.[21] This hypothesis is consistent with the facts that (1) withdrawing *N*-aryls (and *C*-aryls) and hence more acidic NH give a higher rate and (2) essentially no reaction was observed for PhC(O)NHMe, PhC(O)NH(Mes), and PhC(O)N(Me)Ph. The strong influence of the N-substituent on the reaction rate, particularly the poor reactivity of PhC(O)NHMe, seems inconsistent with oxygen coordination.[22]

In conclusion, we have successfully developed a Rh(III)-catalyzed synthesis of $\gamma$-lactams from oxidative coupling of benzamides or heteroaryl carboxamides with electron-poor olefins. In these reactions, the *ortho* C−H bonds in the *C*-aryl rings undergo selective activation to give the vinylation products, followed by intramolecular Michael reactions. 2-Heteroaryl carboxamides can undergo oxidative coupling with or without subsequent Michael addition. The oxidative coupling between benzamides and styrenes gives olefination products. The simplicity of this catalyst system and the high regio- and chemoselectivity of the synthesis of lactams should find broader applications, especially in natural product synthesis.

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**Supporting Information Available:** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102241F

(19) Maehara, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1159.

(20) We would have liked to obtain information on the cleavage of the *ortho* C−H bond from kinetic isotope effect (KIE) experiments. However, KIE data could not be obtained from inter- or intramolecular competition since heating protonated and deuterated benzamide ($C_6D_5C(O)NHPh$) in equimolar ratios in the absence of acrylate resulted in scrambling of deuterium into the *ortho* sites of both benzamides, which indicates that the *ortho* C−H activation here is a reversible process. See ref 12.

(21) Nitrogen coordination in benzamide substrates has been recently proposed in related coupling reactions. See ref 10d.

(22) The methyl group in PhC(O)NHMe makes the amide oxygen more coordinating and should make amide oxygen a stronger chelator, favoring oxygen-directed C−H cleavage if oxygen metalation is followed. However, this does not seem to be consistent with the experimental results.