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Communication

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Rh(III)-catalyzed Redox-Neutral Unsymmetrical C-H Alkylation and Amidation Reactions of *N*-Phenoxyacetamides

Yunxiang Wu,[a,b,‡] Zhaoqiang Chen,[c,‡] Yaxi Yang,[a,b] Weiliang Zhu,*[,c] Bing Zhou*[,a,b]

[a]Department of Medicinal Chemistry, Shanghai Institute of Materia Medica, Chinese Academy of Sciences

[b]University of Chinese Academy of Sciences, Beijing 100049, China

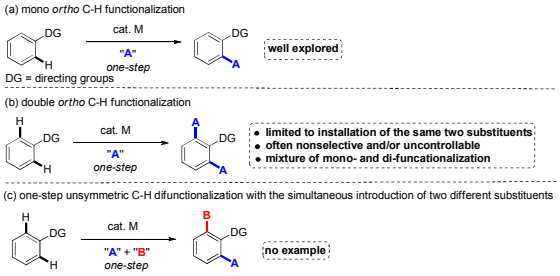
[c]Drug Discovery and Design Center, Shanghai Institute of Materia Medica, Chinese Academy of Sciences

Supporting Information Placeholder

ABSTRACT: A Rh(III)-catalyzed unsymmetrical C-H alkylation and amidation of *N*-phenoxyacetamides with diazo compounds has been developed under mild and redox-neutral conditions, producing dinitrogen as the only by-product. The reaction represents the first example of one-step, unsymmetrical difunctionalization of two *ortho* C-H bonds. Experimental and computational studies support that *N*-phenoxyacetamides most likely undergo an initial *ortho* C-H alkylation with diazo compounds via a Rh(III)-catalyzed C-H activation, and the resulting Rh(III) intermediate subsequently undergo an intramolecular oxidative addition into the O–N bond to form a Rh(V) nitrenoid species that is protonated and further directed toward electrophilic addition to the second *ortho* position of the phenyl ring. This work might provide a new direction for unsymmetrical C-H difunctionalization reaction in an efficient manner.

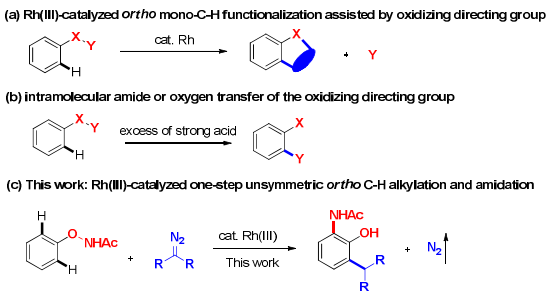
The transition-metal-catalyzed directed functionalization of C(sp^2)-H bonds has emerged as a powerful and straightforward tool for the synthesis of various structurally diverse organic molecules from less less-functionalized substrates in the past decades.[1] While *ortho* mono-C-H functionalization of arene with various coupling partners is efficiently accomplished by chelation-assisted metalation (Scheme 1a),[1] double C-H functionalization is often nonselective and/or uncontrollable and largely limited to introduction of the same two coupling partners (Scheme 1b).[2,3] Usually, additional steps, and/or different catalytic systems, and/or different reaction conditions are required for the second *ortho* C-H functionalization to install another different functional group.[4] Therefore, catalytic, one-step, unsymmetrical C-H difunctionalization with the simultaneous introduction of two different substituents under the single reaction condition is highly desirable (Scheme 1c).[5]

Scheme 1. Transition-metal-catalyzed C-H mono- or di-functionalization



In recent years, transition-metal-catalyzed C-H functionalization assisted by an oxidizing directing group (N-O or N-N DGs) has been emerged as a redox-economic and waste-reducing strategy in the formation of C-C bonds (Scheme 2a).[6,7] In this strategy, the oxidizing directing group also acts as an internal oxidant by the cleavage of an oxidizing bond (X–Y), with the liberation of the cleaved unit "Y".[8] On the other hand, the oxidizing directing group can undergo an intramolecular migration of the unit "Y" to the *ortho* postion of the phenyl ring in the presence of large excess of strong acids[9] or via a Ir- or Rh-catalyzed C-H activation strategy developed by Zhao and Glorius very recently (Scheme 2b).[10] However, these two areas were developed separately and there has been no report which combines *ortho* C-H functionalization and an intramolecular migration of the cleaved unit from the oxidizing directing group to the arene simultaneously, thus leading to the realization of a one-step, unsymmetrical C-H difunctionalization of arenes.

Scheme 2.Redox-neutral C-H activationassisted by an oxidizing directing group

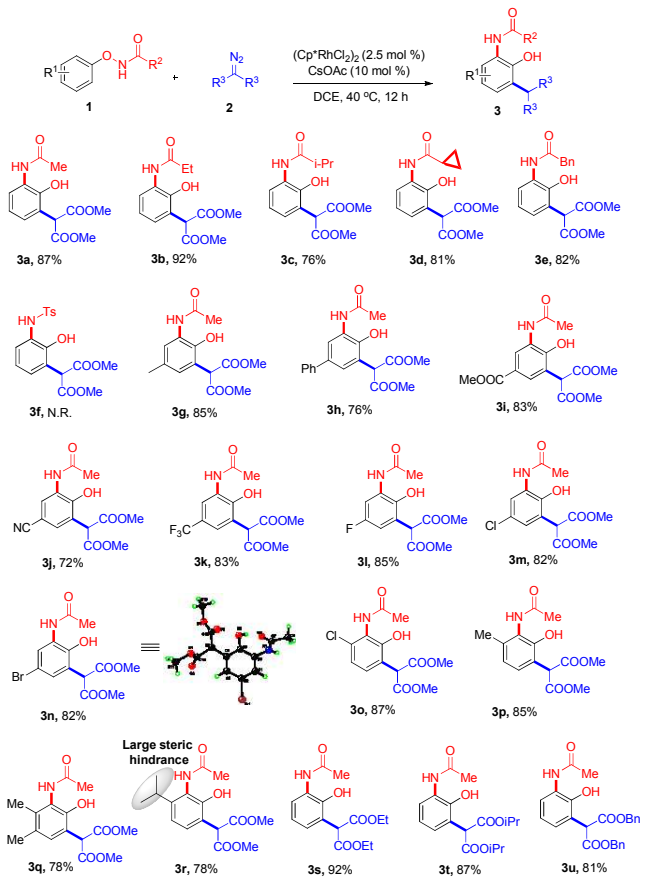


In this context, we wondered whether a Rh(III)-catalyzed *ortho* unsymmetrical C-H difunctionalization of *N*-phenoxyacetamides is possible by choosing appropriate coupling partner and reaction condition provided that the acetamide group could function as a cleavable directing group to facilitate the *ortho* C–H fuctionaliztion, and also an essential coupling partner for the second *ortho* C–H amidation via an intramolecular migration strategy. With our continuing interest in the Rh(III)-catalyzed C-H functionalization with diazo compounds,[11] we herein report the first Cp*Rh(III)-catalyzed, one-step, mild, redox-neutral *ortho* unsymmetrical C-H alkylation and amidation of *N*-phenoxyacetamides via a *ortho* C-H alkylation with diazo compounds and subsequent intramolecular amide transfer strategy (Scheme 2c).

We initiated our studies with the investigation of the Rh-, Ir-, Ru-, Co-catalyzed unsymmetrical *ortho* C-H difunctionalization of *N*-phenoxyacetamide (**1a**) with various coupling partners such as alkynes, alkenes and diazo compounds. To our delight, when treating **1a** with diazomalonate (**2a**)in the presence of $(Cp^*RhCl_2)_2$ (2.5 mol %) and $AgSbF_6$ (10 mol %) in DCE at room temperature for 12 h, the desired unsymmetrical *ortho* C-H alkylation and amidation product **3a** was obtained in 8% yield (Table S1 in the Supporting Information, entry 1). Encouraged by this result, other additives were next screened. An addition of acid completely inhibited the reaction (entry 2) and gratifyingly, replacement the additive $AgSbF_6$ with CsOAc (10 mol %) significantly improved the yield to 74% (entry 3). When Ir(III), Co(III) and Ru(II) catalysts were employed, the desired reaction did not occur (entries 4-6). A screening of solvents indicated that toluene and 1,4-dioxane provided inferior results (entries 7-8). MeOH gave the *mono* C-H alkylation product in agreement with previous report[8j] and no any desired C-H difunctionalization product **3a** was observed, indicating that protic solvent is adverse to intramolecular amide transfer (entry 9). Control experiments revealed that Cp*Rh(III) catalyst is necessary for this transformation (entry 10). Finally, we were pleased to find that the product **3a** could be obtained in 87% yield by slightly increasing the reaction temperature to 40 °C (entry 11).

With the optimized reaction conditions in hand, we embarked on an investigation of the scope of the unsymmetrical C-H alkylation and amidation reaction (Scheme 3). *N*-Phenoxyamides with acetyl, propionyl, isobutyryl, cyclopropylcarbonyl, and phenylacetyl substituents on nitrogen gave the corresponding products **3a-e** in 76-92% yields. However, no product was obtained with a N-Ts group. Significantly, electron-rich (**3g**) and electron-withdrawing (**3i-n**) substituents at the *para* positions all afforded good yields. To our delight, the functional groups such as ester (**3i**), nitrile (**3j**) and halogen (**3m** and **3n**) were all nicely tolerated, enabling further functionalization. The structure of **3n** was unambiguously confirmed by an X-ray crystallographic analysis (CCDC 1573557).

Scheme 3. Substrate Scope[a]



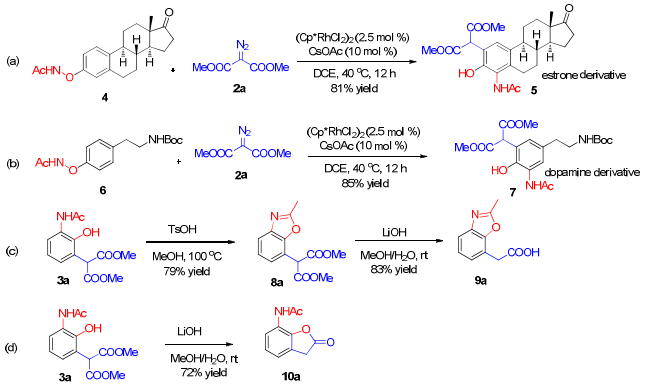
[a]Reaction conditions: Reactions were carried out by using $(RhCp^*Cl_2)_2$ (2.5 mol%), CsOAc (10 mol%), **1** (0.2 mmol) and **2** (0.24 mmol) in a DCE (2 mL) at 40 °C for 12 h; Isolated yield.

More significantly, for *meta*-substituted and *meta*, *para*-disubstituted substrates, the C-H alkylation with diazo compounds showed excellent regioselectivity in favor of the sterically more accessible C-H bond, and the subsequent C-H amidation could also take place smoothly, despite the large steric hindrance of the second C-H bond,delivering 1,2,3,4-tetrasubstituted and 1,2,3,4,5-pentasubstituted benzene derivatives **3o-3r** in 78-87% yield. In particular, the *meta*-isopropyl-substituted derivative is also a productive substrate (**3r**), thus indicating a high steric tolerance of this system. Various α-diazomalonates (**3s-u**) were investigated under the optimized condition and coupled smoothly in 81-92% yields. When diazoacetoacetate was used, no desired product was obtained, suggesting that the electron nature of diazo substrates is important for this C-H alkylation and subsequent amidation process.

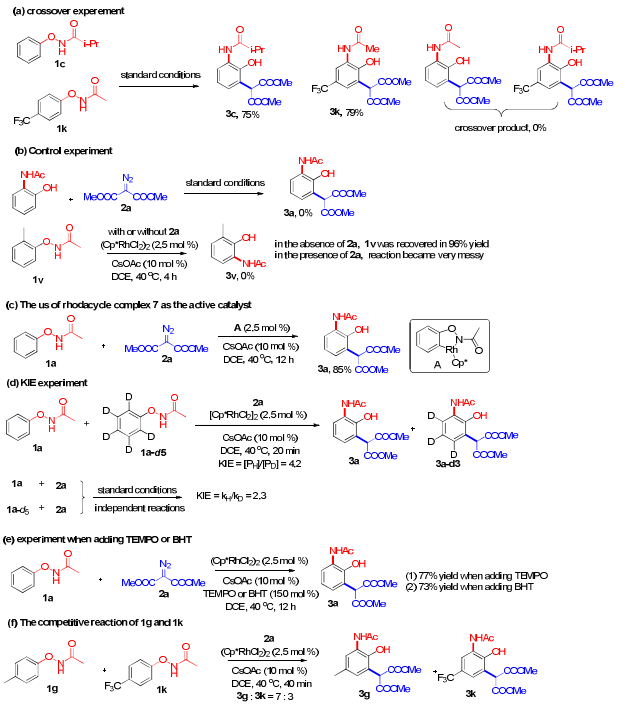
Phenols are ubiquitous in many natural products, pharmaceuticals, biologically active compounds, and they are also used as important intermediates in synthetic organic chemistry.[12] One-step, unsymmetrical twofold *ortho* C–H functionalization in these bioactive skeletons could provide a powerful tool in the chemical synthesis of functionalized analogues. The utility of this unsymmetrical C–H alkylation and amidation reaction as a tool for late-stage modification of bioactive complex estrone derivative **4** was demonstrated,

providing the alkylation and amidation product **5** in 81% yield and exhibiting excellent site-selectivity (Scheme 4a). Moreover, dopamine derivative **7** was successfully obtained in excellent yields, highlighting the method's mild conditions and excellent functional group tolerance (Scheme 4b). To further highlight the synthetic utility of the reaction developed herein, treatment of **3a** under acidic reaction condition provides benzoxazole **8a** in 79% yield which can further undergo a decarbonylation to deliver 7-benzoxazoleacetic acid **9a** in 83% yield (Scheme 4c). In addition, treatment of **3a** with LiOH resulted in decarbonylation and esterification to afford bioactive 7-amino-2(3H)-benzofuranone **10a** in good yield (Scheme 4d).

Scheme 4.The synthetic application of the C-H alkylation and amidation reaction.



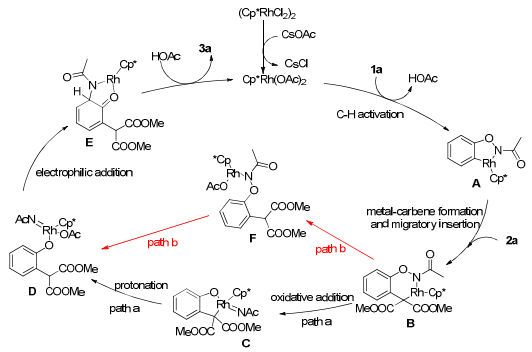
Scheme 5. Experimental Mechanistic Studies



To understand the mechanism of the C-H alkylation and amidation reaction, the crossover experiment using equally reactive substrates **1c** and **1k** was first carried out under the standard conditions. The reaction of the mixture gave only products **3c** and **3k** and no any crossover products were observed, indicating that the *ortho* amidation takes place intramolecularly (Scheme 5a). The reaction of 2-acetamidophenol with dizaomalonate **2a** did not deliver the product **3a** and the reaction of *N*-(o-tolyloxy)acetamide **1v** in the presence or absence of **2a** did not give **3v** (Scheme 5b), ruling out the pathway involving an initial intramolecular amidation transfer and subsequent phenol-directed C-H alkylation with diazo compounds. Furthermore, we prepared a rhodacycle **A**,[8a,8l] which successfully catalyzed the current C-H alkylation and amidation reaction, suggesting that complex **A** is most likely involved in the catalytic cycle (Scheme 5c). A KIE of 4.2 was observed in a competitive experiment (Scheme 5d). Moreover, a kinetic isotopic effect (KIE) of 2.3 was observed from two side-by-side reactions using **1a** and **1a-d_5** (Scheme 5d). Both results indicated that the C(sp^2)-H bond cleavage might be related to the rate-limiting step.[13] Addition of TEMPO or BHT had a negligible effect on the reaction, suggesting that the C-H alkylation and amidation reaction is not likely involved in a radical pathway (Scheme 5e). The competitive reaction of an equimolar amount of **1g**, **1k**, and **2a** under the standard conditions provided a mixture of **3g** and **3k** in a 7:3 ratio, indicating that the electron-rich arenes inherently react preferentially (Scheme 5f).

On the basis of these preliminary studies, we propose the catalytic cycle involving an initial C-H activation to form rhodacycle **A** (Scheme 6). Coordination of the diazo substrate **2a** to **A** and a subsequent intramolecular 1,2-migratory insertion of the aryl group provides the intermediate **B** with extrusion of N_2. In path a, an oxidative addition of Rh(III) into the N-O bond gives the five-membered Rh(V) nitrenoid **C**[14]and subsequent protonation of **C** affords the intermediate **D**. In addition, **D** can also be formed by a protonation of **B** and subsequent intramolecular oxidative addition of Rh into the N-O bond (path b). An intramolecular electrophilic nitrenoid addition gives the intermediate **E** which undergoes a protonation with HOAc and subsequent isomerization to release product **3a** and regenerate the active catalyst.

Scheme 6.Proposed Mechanism.



To gain further insights into this unprecedented unsymmetrical C-H alkylation and amidation reactions, including the distinction between pathway a and pathway b, DFT calculations were performed with Gaussian 09 (Figure 1).[15] First, the coordination of the diazo substrate to rhodacycle **A** and subsequent denitrogenation forms intermediate **A-1** which undergoes a Rh–aryl migratory insertion to give **B** with an overall 28.3 kcal/mol exothermicity. In path a, an intramolecular oxidative addition of Rh into the O–N bond occurs

via **TS1** with anactivation energy barrier of 17.9 kcal/mol, forming Rh(V) nitrenoid species **C**.[14]Protonation of **C** by HOAc provides acyclic intermediate **D** with 9.3 kcal/mol endothermicity and subsequent nitrenoid addition to the second *ortho* carbon has a low barrier of 5.7 kcal/mol (**TS2**), producing a dearomatized intermediate **E**. Finally, Protonolysis of **E** with HOAc and subsequent aromatization generates **3a** and regenerates the active catalyst $Cp^*Rh(OAc)_2$ with 35.8 kcal/mol exothermicity. In pathway b, intermediate **B** undergoes a protonation first to give **F** with 11.6 kcal/mol endothermicity and subsequent oxidative addition of Rh(III) into the O–N bond has a high barrier of 32.5 kcal/mol (**TS3**), which is clearly disfavored in comparison to pathway a.

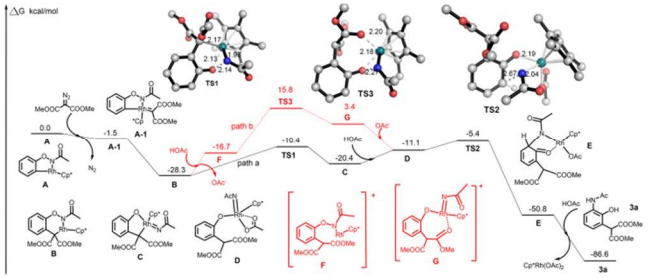


Figure 1. Energy profiles and geometry information for the C-H alkylation and amidation reactions.

In summary, we have developed an unprecedented Cp*Rh(III)-catalyzed unsymmetrical C-H alkylation and amidation reaction of *N*-phenoxyacetamides with diazo compounds under mild and redox-neutral conditions, giving N_2 as the sole by-product. Through experimental and computational studies, we elucidated that an initial Rh(III)-catalyzed *ortho* C-H alkylation of *N*-phenoxyacetamides with diazo compounds occurs first and the resulting Rh(III) intermediate subsequently undergo an intramolecular oxidative addition into the O–N bond, forming a Rh(V) nitrenoid species that is protonated by HOAc and subsequently further directed toward electrophilic addition to the second *ortho* position of the phenyl ring. The unprecedented one-step, unsymmetrical C-H difunctionalization of phenol derivatives shows potential applications in the late-stage diversification of natural products. This work might provide a new direction for unsymmetrical C-H difunctionalization reaction in an efficient manner.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, andDFT data. This material is available free of charge via theInternet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

E-mail (B.Z.): zhoubing2012@hotmail.com; zhoubing@simm.ac.cn;E-mail (W.Z.): wlzhu@mail.shcnc.ac.cn;

Author Contributions

‡These authors contributed equally.

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REFERENCES

(1) For selected reviews: (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.***2009**, *42*, 1074. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (c) Ackermann, L. *Chem. Rev.***2011**, *111*, 1315. (d) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.***2011**, *40*, 5068. (e) Yeung, C. S.; Dong, V. M. *Chem. Rev.***2011**, *111*, 1215. (f) Hartwig, J. F. *Acc. Chem. Res.* **2012**, *45*, 864; (g) Zhu, C.; Wang, R.; Falck, J. R. *Chem. - Asian J.***2012**, *7*, 1502. (h) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.***2012**, *51*, 8960. (i) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.***2013**, *52*, 11726. (j) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (k) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.***2015**, *48*, 1053. (l) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal.* **2016**, 6, 498. (m) Gandeepan, P.; Cheng, C.-H. *Chem. Asian J.***2016**, *11*, 448. (n) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (o) Hummel, J. R.; Boerth, J. A.; Ellman, J. A. *Chem. Rev.* **2017**, *117*, 9163. (p) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.*, **2017**, *117*, 9247.

(2) a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.***2010**, *110*, 1147; b) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.***2011**, *40*, 1926; c) McMurray, L.; OQHara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885; d) Newhouse, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, 50, 3362; e) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.***2012**, *112*, 5879; f) Engle, K. M.; T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.***2012**, *45*, 788; g) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236;

(3) For selected example: a) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.***2010**, *132*, 12249; b) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.***2011**, *133*, 428; c) Ano, Y.; Tobisu, M.; Chatani, N. *Synlett***2012**, 2763. d) Landge, V. G.; Jaiswal, G.; Balaraman, E. *Org. Lett.*, **2016**, *18*, 812;

(4) selected examples: a) Sarkar, D.; Melkonyan,F. S.; Gulevich,A. V.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2013**, 52, 10800; b) Rosen,B. R.; Simke, L. R.; Thuy-Boun, P. S.; Dixon, D. D.; Yu, J.-Q.; Baran, P. S. *Angew. Chem. Int. Ed.* **2013**, 52, 7317; c) Kim, H. J.; Ajitha, M. J.; Lee, Y.; Ryu, J.; Kim, J.; Lee, Y.; Jung, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 1132; d) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2015**, *137*, 531. e) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2010**, *49*, 6169; f) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M.; *J. Org. Chem.*, **2009**, *74*, 7094.

(5) Selected examples of Catellani reactions: (a) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed.* **1997,** *36*, 119. (b) Catellani, M. *Top. Organomet. Chem.* **2005**, *14*, 21. (c) Malacria, M.; Maestri, G. *J. Org. Chem.* **2013**, *78*, 1323. (d) Ye, J.; Lautens, M. *Nat. Chem.* **2015**, 7, 863. (e) Della Ca, N.; Fontana, M.; Motti, E.; Catellani, M. *Acc. Chem. Res.* **2016**, *49*, 1389.

(6) For reviews on Rh(III)-catalyzed C–H activations, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Satoh, T.; Miura, M. *Chem. Eur. J.***2010**, *16*, 11212. (c) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (d) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.***2012**, *45*, 814. (e) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *AldrichimicaActa* **2012**, 45, 31. (f) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.***2014**, *356*, 1443. (g) Song, G.; Li, X. *Acc. Chem. Res.***2015**, *48*, 1007. (h) Ye, B.; Cramer, N. *Acc. Chem. Res.* **2015**, *48*, 1308.

(7) For reviews of oxidizing directing groups, see: (a) Sun, H.; Huang, Y. *Synlett***2015**, *26*, 2751. (b) Mo, J.; Wang, L.; Liu, Y.; Cui, X. *Synthesis* **2015**, *47*, 439. (c) Huang, H.; Ji, X.; Wu, W.; Jiang, H. *Chem. Soc. Rev.* **2015**, *44*, 1155.

(8) Selected examples: (a) Liu, G.; Shen, Y.; Zhou, Z.; Lu, X. *Angew. Chem., Int. Ed.* **2013**, 52, 6033. (b) Shen, Y.; Liu, G.; Zhou, Z.; Lu, X. *Org. Lett.***2013**, *15*, 3366. (c) Zhang, H.; Wang, K.; Wang, B.; Yi, H.; Hu, F.; Li, C.; Wang, J. *Angew. Chem., Int. Ed.,***2014**, 53, 13234. (d) Yan, H.; Wang, H.; Li, X.; Xin, X.; Wang, C.; Wan, B. *Angew. Chem., Int.*

Ed. **2015**, *54*, 10613. (e) Dateer, R. B.; Chang, S. *J. Am. Chem. Soc.***2015**, *137*, 4908. (f) Zhou, J.; Shi, J.; Qi, Z.; Li, X.; Xu, H. E.; Yi, W. *ACS Catal.,* **2015**, *5*, 6999. (g) Zhou, Z.; Liu, G.; Chen, Y.; Lu, X. *Org. Lett.*, **2015**, *17*, 5874. (h) Piou, T.; Rovis, T., *Nature* **2015**, *527*, 86. (i) Li, B.; Lan, J.; Wu, D.; You, J. *Angew. Chem., Int. Ed.,***2015**, *54*, 14008; (j) Zhou, J.; Shi, J.; Liu, X.; Jia, J.; Song, H.; Xu, H. E.; Yi, W. *Chem. Commun.,***2015**, *51*, 5868. (k) Lerchen, A.; Knecht, T.; Daniliuc, C. G.; Glorius, F. *Angew. Chem. Int. Ed.,* **2016**, 55, 15166. (l) Wu, Q.; Chen, Y.; Yan, D.; Zhang, M.; Lu, Y.; Sun, W. Y.; Zhao, J. *Chem. Sci.,* **2017**, *8*, 169; (m) Wang, X.; Lerchen, A.; Gensch, T.; Knecht, T.; Daniliuc, C. G.; Glorius, F. *Angew. Chem. Int. Ed.***2017**, *56*, 1381.

(9) (a) Endo, Y.; Shudo, K.; Okamoto, T. *J. Am. Chem. Soc.,* **1982**, *104*, 6393. (b) Endo, Y.; Shudo, K.; Okamoto, T. *Synthesis* **1983**, 471. (c) Endo, Y.; Kataoka, K.; Haga, N.; Shudo, K. *Tetrahedron Lett.* **1992**, *33*, 3339. (d) Haga, N.; Endo, Y.; Kataoka, K.; Yamaguchi, K.; Shudo, K. *J. Am. Chem. Soc.,***1992**, *114*, 9795. (e) Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *J. Chem. Soc., Perkin Trans. 2,* **1998**, 7.

(10) (a) Wu, Q.; Yan, D.; Chen, Y.; Wang, T.; Xiong, F.; Wei, W.; Lu, Y.; Sun, W.-Y.; Li, J. J.; Zhao, J. *Nat. Commun.,* **2017**, *8*, 14227. (b) Wang, X.; Gensch, T.; Lerchen, A.; Daniliuc, C. G.; Glorius, F. *J. Am. Chem. Soc.,***2017**, *139*, 6506.

(11) a) Zhou, B.; Chen, Z.; Yang, Y.; Ai, W.; Tang, H.; Wu, Y.; Zhu, W.; Li, Y. *Angew. Chem. Int. Ed.* **2015**, 54, 12121-12126; b) Yang, Y.; Wang, X.; Li, Y.; Zhou, B. *Angew. Chem. Int. Ed.* **2015**, 54, 15400-15404.

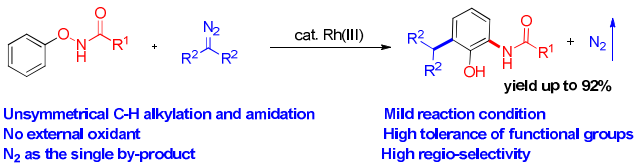
(12) (a) Tyman, J. H. P. Synthetic and Natural Phenols; Elsevier: New York, 1996. (b) Rappoport, Z. The Chemistry of Phenols; Wiley-VCH: Weinheim, 2003.

(13) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.*, **2012**, *51*, 3066.

(14) For selected example involving a Rh(V) nitrenoid intermediate, see: (a) Xu, L.; Zhu, Q.; Huang, G.; Cheng, B.; Xia, Y. *J. Org. Chem.***2012**, 77, 3017. (b) Shin, K.; Baek, Y.; Chang, S. *Angew. Chem., Int. Ed.***2013**, 52, 8031. (c) Park, S. H.; Kwak, J.; Shin, K.; Ryu, J.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, 136, 2492. (d) Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am. Chem. Soc.* **2014**, 136, 4780. (e) Figg, T. M.; Park, S.; Park, J.; Chang, S.; Musaev, D. G. *Organometallics* **2014**, 33, 4076. (f) Guo, W.; Zhou, T.; Xia, Y. *Organometallics* **2015**, 34, 3012. (g) Zhou, T.; Guo, W.; Xia, Y. *Chem. - Eur. J.***2015**, 21, 9209. (h) Yu, S.; Liu, S.; Lan, Y.; Wan, B.; Li, X. *J. Am. Chem. Soc.***2015**, 137, 1623. (j) Yang, Y.-F.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **2016**, 138, 6861.

(15) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision D.01; Gaussian, Inc.: Wallingford, CT, **2013**.

One-Step Unsymmetrical C-H Alkylation and Amidation



Unsymmetrical C-H alkylation and amidation
No external oxidant
N_2 as the single by-product

Mild reaction condition
High tolerance of functional groups
High regio-selectivity