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Ruthenium-Catalyzed Para-Selective Oxidative Cross-Coupling of Arenes and Cycloalkanes‡

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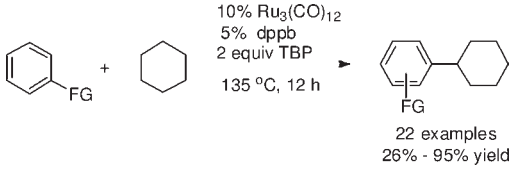
ABSTRACT



A novel, direct para-selective oxidative cross-coupling of benzene derivatives with cycloalkanes catalyzed by ruthenium was developed. A wide range of arenes bearing electron-withdrawing substituents was functionalized directly with simple cycloalkanes with high para-selectivity; arenes with electron-donating groups were mainly para-functionalized. Benzoic acid can be used directly.

Regiocontrolled functionalization of aromatic rings has been an important subject throughout the history of organic chemistry because of the vital role of aromatic compounds in materials, fine chemicals, and biological compounds. The Friedel–Crafts-type[1] electrophilic substitution of arenes constituted a key pillar of classical synthetic chemistry, leading to *o*- and *p*-aryl C–C bonds with electron-donating substituents and meta-functionalization with electron- withdrawing substituents. The ortho-lithiation[2] and chelation-controlled transition-metal catalyzed cross-couplings are milestones of modern achievements in creating alternatives,[3] furnishing ortho-functionalized products regioselectively. Recently, a significant advance has been made by Gaunt[4] and others[5] in achieving meta-functionalization of substituted arenes through transition-metal catalysis. However, the regioselective transition-metal-catalyzed functionalization of arenes at the para-position remains virtually unexplored.[6]

On the other hand, the formation of a carbon–carbon (C–C) bond directly from carbon–hydrogen (C–H) bonds via an oxidative cross-coupling has emerged as a powerful synthetic methodology.[7] Such a process will allow the use of less functionalized starting materials and greatly reduce the number of synthetic operations.[7] For oxidative cross-coupling involving arenes, Fujiwara[8] pioneered a palladium-catalyzed arene–alkene oxidative Heck-type coupling, which has recently been achieved in water by Lipshutz.[9] The use of ruthenium catalyst for such a coupling was achieved by Milstein.[10] Recently, Fagnou[11] and others[12] reported a direct arene–arene coupling reaction using simple benzene as reagent. Very recently, the oxidative arene–alkyne coupling[13] was also achieved. For the more challenging

‡ Dedicated to Prof. Barry M. Trost on the occasion of his 70th birthday.

(1) Friedel, C.; Crafts, J. M. *Compt. Rend.* **1877**, *84*, 1392.

(2) (a) Kauch, M.; Hoppe, D. *Synthesis* **2006**, 1575. (b) Nguyen, T.-H.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2006**, *8*, 765. (c) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *J. Org. Chem.* **2007**, *72*, 1271.

(3) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215.

(4) (a) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (b) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2010**, *50*, 463.

(5) For examples on meta-selective C–H bond functionalization, see: (a) Zhou, Y.; Zhao, J.; Liu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 7126. (b) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (c) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864–13867.

(6) Amboya, A.; Nguyen, T.; Huynh, H. T.; Brown, A.; Ratliff, G.; Yonutas, H.; Cizmeciyan, D.; Natarajanb, A.; Garibay, M. A. G. *Org. Biomol. Chem.* **2009**, *7*, 2322.

(7) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998. (b) Lewis, J. C.; Bergman, R. G.; Ellman, J. *Acc. Chem. Res.* **2008**, *41*, 1013. (c) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 2010.

(8) (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119. (b) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166.

(9) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 1972.

(10) Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337.

(11) (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (b) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072.

(12) (a) Li, R.; Liang, L.; Lu, W. *Organometallics* **2006**, *25*, 5973. (b) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137. (c) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (d) Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. *J. Am. Chem. Soc.* **2010**, *132*, 14676.

(13) (a) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212. (b) Shimizu, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 3478.

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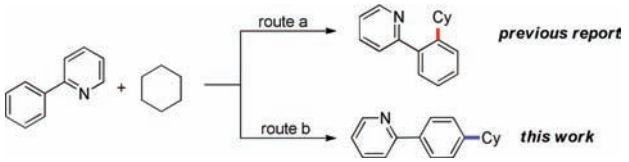
transition-metal-catalyzed arene−alkane coupling, we previously reported an ortho-cycloalkylation of phenylpyridine via chelation control[14] (Scheme 1, route a). Herein, we report an unprecedented direct para-selective oxidative cross-coupling of benzene derivatives with cycloalkanes catalyzed by ruthenium. A wide range of arenes with both electron-donating and electron-withdrawing substituents were functionalized directly using simple cycloalkanes with high para-selectivity, even with the overwhelming strongly ortho-directing effect of chelating substituents (Scheme 1, route b).

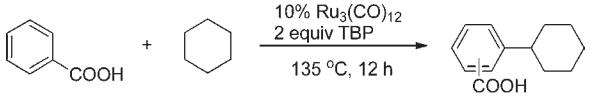
Scheme 1. Regioselectivity of Aromatic Substitutions



The mechanistic insights on the radical nature of our previous arene functionalizations[14] inspired us to take advantage of stabilizing the resonance of a radical-charactered intermediate by both electron-donating and electron-withdrawing groups through FMO interactions,[15,16] thereby leading to selective para-functionalization. To test this hypothesis, we chose benzoic acid and cyclohexane as the standard substrates for the optimization of the reaction conditions (Table 1). Di-*tert*-butyl peroxide (TBP) was used as external oxidant in this reaction. We found that the desired product **3a** could be generated without any catalyst in a trace amount. When 10% $Ru_3(CO)_{12}$ was added to the system, 35% yield of the desired product **3a** could be obtained (Table 1, entry 1).

We then focused our efforts on changing the ligands. Sulfinyl groups were found to be good ligands for this reaction (entries 2 and 3). Phosphine ligands gave similar results, except for dppb (bis(diphenylphosphino)butane) and binap (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) achieving 75% and 60% yields, respectively (entries 4−13). Dppb oxide gave a similar yield to dppb, and it was found that dppb (^{31}PNMR $\delta = -15.0$) was oxidized to dppb oxide (^{31}PNMR $\delta = 33.1$) after 3 h during the course of the reaction based on a phosphorus NMR, while the product yield was less than 10%. Therefore, it appears that the real ligand in this reaction is dppb oxide. Neither a higher or lower temperature improved the yield (entries 14 and 15). While lowering the amount of TBP used in this reaction reduced the yield, increasing the loading of TBP to 4 equiv only increased the yield slightly (entries 16 and 17). Thus, further studies used 2 equiv of oxidant. Other oxidants such as TBHP, dicumyl peroxide, benzoic peroxyanhydride, and *tert*-butyl benzoperoxoate gave much lower yields (not shown). The product yield dropped to 53% with a reduced loading of the catalyst and ligand (entry 18). Using either more or less ligand decreased the product yield (entries 19 and 20). Thus, we chose 10% $Ru_3(CO)_{12}$ together with 5% dppb and 2 equiv of TBP at 135 °C for 12 h under air as our standard conditions.

Table 1. Optimization of Reaction Conditions[a]



1a (0.2 mmol) **2a** ~9 equiv **3a**

entry	additives	% NMR yield
1	none	35
2	10% $Na(OAc)_2$ + 10% DMSO	45
3	5% 1,2-bis(phenylsulfinyl)ethane	55
4	10% Ph_3P	50
5	10%/*n*-Bu_3P	35
6	5% dppm	52
7	5% dppe	53
8	5% dppp	53
9	5% dppb	75
10	5% dppb oxide	75
11	5% binap	60
12	5% 1,2-bis(diphenylphosphino)benzene	41
13	3% $(Ph_2PCH_2CH_2)_2PPh$	38
14	5% dppb	38[b]
15	5% dppb	70[c]
16	5% dppb	77[d]
17	5% dppb	61[e]
18	2.5% dppb	53[f]
19	10% dppb	48
20	2.5% dppb	55

[a] Conditions: **1a** (0.2 mmol), **2a** (0.2 mL, ~9 equiv), 10% $Ru_3(CO)_{12}$, 2 equiv of TBP (di-*tert*-butyl peroxide), 135 °C, 12 h under air. [b] 120 °C. [c] 150 °C. [d] 4 equiv of TBP. [e] 1 equiv of TBP. [f] 5% $Ru_3(CO)_{12}$.

With the optimized conditions in hand, other benzene derivatives and cycloalkanes were investigated (Table 2). The reaction proceeded efficiently for a wide range of benzene derivatives. Electron-withdrawing group was found to be efficient for this reaction. Other than benzoic acid, methyl benzoate worked similarly well and gave a 70% separated yield (**3b**). Acetophenone, 2,2,2-trifloroacetophenone, and cyanobenzene achieved much higher yields (**3c**, 83%, **3d**, 95%, and **3e**, 90%). Halobenzenes also reacted smoothly with cyclohexane in good yields (**3g**, 75%, and **3h**, 72%) with the halogen group untouched. Fluorobenzene gave a moderate yield, possibly due to the low boiling point of fluorobenzene (84 °C), and only a trace amount maybe present in the catalytic mixture (**3f**). Iodobenzene gave a complicated mixture. Amides were also effective, although they gave moderate yields (**3i**, 45%, and **3j**, 50%). A free N−H bond can be tolerated without any protection during the reaction (**3j**). It is interesting to note that even unfunctionalized

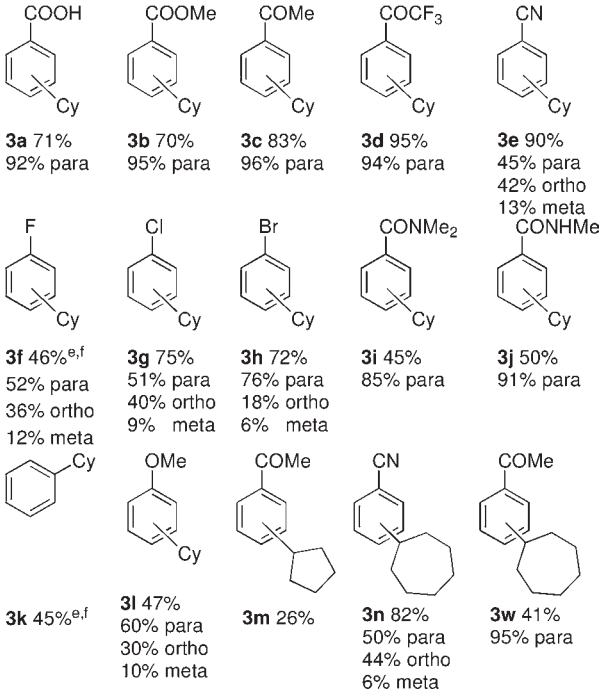
(14) (a) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278. (b) Deng, G.; Chen, W.; Li, C.-J. *Adv. Synth. Catal.* **2009**, *351*, 353. (c) Deng, G.; Ueda, K.; Yanagisawa, S.; Itami, K.; Li, C.-J. *Chem.—Eur. J.* **2009**, *15*, 333. (d) Deng, G.; Li, C.-J. *Org. Lett.* **2009**, *11*, 1171.

(15) Recently, a number of radical-based arene functionalizations have been reported; see: (a) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673. (b) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K.-H.; He, C.; Wang, H.; Kwong, F.-Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737. (c) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044.

(16) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, New York, 1976.

benzene can be used for this reaction (**3k**, 45%). Electron-donating groups such as a methoxyl group on the benzene ring gave moderate yield (**3l**). Other cycloalkanes are also effective in this reaction. The ring size of alkanes had a dramatic influence on the reaction: while cyclopentane gave a much lower yield (**3m**), cycloheptane gave a good yield (**3n**, 82%, **3w**, 41%). In all these reactions, only trace amounts (about 5%) of the disubstituted products were observed.

Table 2. Cross-Coupling of Benzene Derivatives with Cycloalkanes[a–d]



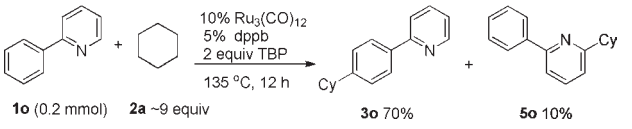
[a] Conditions: **1** (0.2 mmol), **2** (0.2 mL), 10% $Ru_3(CO)_{12}$, 5% dppb, 2 equiv of TBP (di-*tert*-butyl peroxide), 135 °C, 12 h under air; yield was given as a total yield of mixtures of ortho/meta/para products. [b] Regioselectivity ratio determined by GC–MS. [c] Cy = cyclohexyl. [d] Isolated yield, otherwise noted. [e] NMR yield. [f] 72 h.

The reaction proceeded predominately at the para position in all cases for monosubstituted benzene derivatives (**3a** to **3d**, **3i**, **3j** ,and **3w**). However, for benzene derivatives with a halogen or alkoxy substitutent (**3e**–**h**, **3l**), the amount of ortho product was increased.

The commonly used 2-phenylpyridine was also tested in this reaction. We found that the coupling took place exclusively at the para position (>99%) (Scheme 2). A small amount of product due to the reaction of the pyridine ring was also observed.

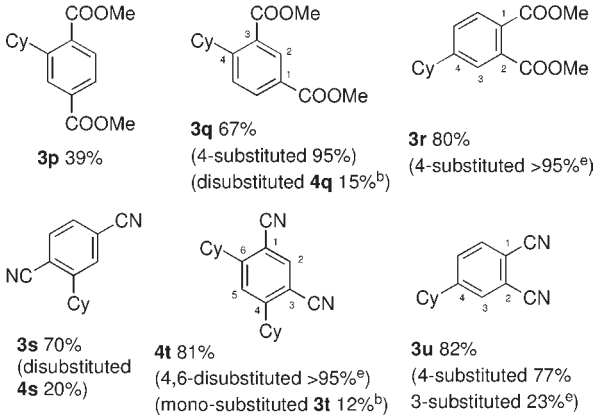
Disubstituted benzene derivatives were also examined (Table 3). As methyl benzoate has a very high para-selectivity, dimethyl terephthalate only gave a low yield (39%) at the ortho position because of the inaccessibility of the para-position (**3p**). By making the para-position available, excellent yields of the corresponding products were obtained. (80–93%). Para selectivity showed a stronger control than ortho or meta selectivities (**3q**, **3r**, and **3u**).

Scheme 2. Reaction of 2-Phenylpyridine (Separated Yields Given)



With the less selective but stronger activating cyano group, 1,3-dicyanobenzene generated dicyclohexyl-substituted product **4t** as the major product with an 81% yield.

Table 3. Cross-Coupling of Disubstituted Benzene Derivatives with Cyclohexanes[a,c,d]



[a] Conditions: **1** (0.2 mmol), **2** (0.2 mL, ~9 equiv), 10% $Ru_3(CO)_{12}$, 5% dppb, 2 equiv of TBP (di-*tert*-butyl peroxide), 135 °C, 12 h under air. [b] determined by GC-MS. [c] Cy = cyclohexyl; [d] yields are separated yields, if not otherwise noted; [e] determined by ^1H NMR.

A kinetic isotope study revealed that the reaction showed a nonisotope effect, with $k_H/k_D = 1.00$, when chlorobenzene and chlorobenzene-d_5 were used as the substrates. These results suggested that the reaction most likely proceeds via a radical mechanism.

In summary, we have developed a novel direct para-selective oxidative cross-coupling of benzene derivatives with cycloalkanes catalyzed by ruthenium. A wide range of arenes with electron-withdrawing substituents was functionalized directly with simple cycloalkanes with high para-selectivity; arenes with electron-donating groups were mainly para-functionalized. The reaction overwhelmed the effect of strongly ortho-directing of chelating substituents. Notably, benzoic acid can be used directly. Further research on the reaction mechanism is underway in our laboratory.

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Supporting Information Available. Experimental procedures, characterization data of new compound, and ^1H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.