ORGANIC LETTERS

2013
Vol. 15, No. 22
5862–5865

Ruthenium-Catalyzed C−H Functionalization of Arylpyrazoles: Regioselective Acylation with Acid Chlorides

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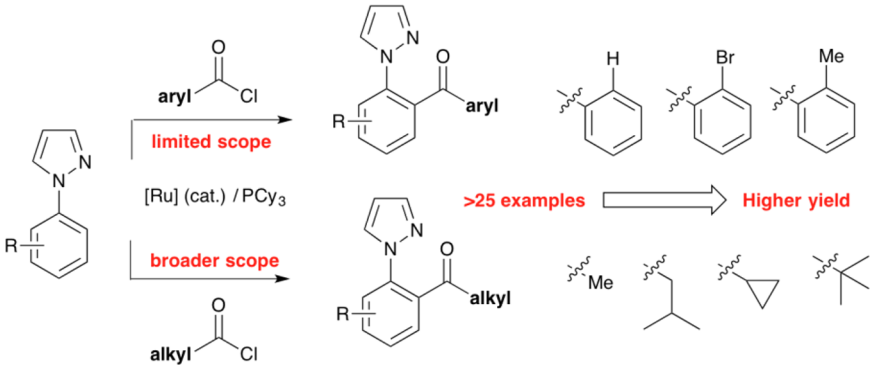
Received October 11, 2013

ABSTRACT



A ruthenium-catalyzed C−H acylation of arylpyrazoles with a variety of acyl chlorides is described. The acylation reaction exhibits good regioselectivity and both aromatic and aliphatic acyl chlorides can be effectively coupled to the arylpyrazoles at the ortho-position.

Pyrazoles are important structural motifs that are frequently featured at the core of biologically active molecules.[1] Thus, the development of new synthetic methods for the preparation of functionalized pyrazole derivatives is of broad interest to the pharmaceutical and agrochemical industry. Transition-metal catalyzed C−H functionalization has emerged as fundamental methodology for the straightforward elaboration of organic molecules.[2] In this context, pyrazole serves as an effective directing group for C−H functionalization methods involving cyclometalation.[3]

Herein we describe an effective catalytic C−H acylation of arylpyrazoles that proceeds *via* cyclometalation to afford the *ortho* product with excellent selectivity. To our knowledge, this transformation represents the first intermolecular transition-metal catalyzed C−H acylation of 1-arylpyrazoles with both aromatic and aliphatic acyl chlorides as the coupling partner. At present, methods for acylating 1-arylpyrazole are relatively scarce. This study complements the classic Friedel−Crafts reactions where the acyl chloride is substituted on the 4-position of the pyrazole ring[4] (Scheme 1 a) and the known direct catalytic C−H carbonylation process that also affords the *ortho* product but is limited to alkyl substituents (Scheme 1 b).[5]

The recent significant achievements of selective catalytic C−H bond functionalizations with Ru(II) species prompted us to explore the catalytic directed cyclometalation and subsequent acylation of 1-phenylpyrazole **1** with acyl chlorides.[6] The successful introduction of carbonyl functionality to the *ortho* site of 2-arylpyridine derivatives employing catalytic Ru(II) complexes has been

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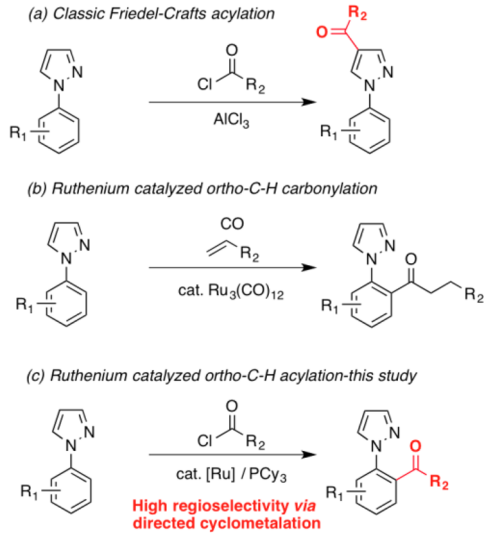
10.1021/ol402936c
Published on Web 11/06/2013

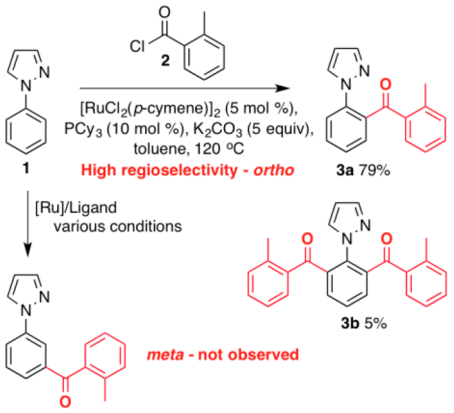
Scheme 1. Catalytic Acylation of 1-Arylpyrazoles



established.[7] More recently, the Ru(II)-catalyzed functionalization of *meta* sites by remote *para* activation has also been demonstrated for sulfonations and alkylations (including 1-phenylpyrazole).[8]

Interestingly, with acyl chlorides (e.g., *o*-toluoyl chloride **2**) only the product from *ortho* C−H functionalization is observed under a broad range of conditions with no trace of the *meta* product (Scheme 2). This is consistent with a

Scheme 2. Ruthenium-Catalyzed *Ortho* Acylation of 1-Phenylpyrazole



mechanism involving chelation-assisted cyclometalation and oxidative addition of the acyl chloride rather than σ-activation by ruthenium and electrophilic attack.

The optimized conditions for the catalytic *ortho* C−H acylation of 1-phenylpyrazole **1** employed 5 mol % of $[RuCl_2(p\text{-cymene})]_2$ in the presence of 10 mol % of PCy_3 and 5 equiv of K_2CO_3.[9] The reaction of 1-phenylpyrazole with a range of acyl chlorides afforded *ortho* acylated products in moderate-to-good yields (Scheme 2). In general, acylation of 1-phenylpyrazole with aryl acid chlorides gives both mono- and diacylated products that are difficult to purify and isolated yields that are low (**4a**–**8a**). However, reproducible experiments indicated that the more sterically hindered *o*-toluoyl chloride was more effective in the *ortho* acylation of 1-phenylpyrazole than benzoyl chloride.

We were pleased to discover that alkyl acid chlorides were converted to the corresponding products **9a**–**19a** in predominantly respectable yields with recovery of unreacted 1-phenylpyrazole. Notably, the reaction proceeded with acetyl chloride to afford **9a**; although a modest yield (28%) was obtained, this is the first example of **9a** being prepared via catalytic C−H functionalization and it provides evidence that the reaction proceeds through

(3) Cu-catalyzed C−H functionalization: (a) Zhang, L.; Liu, Z.; Li, H.; Fang, G.; Barry, B.-D.; Belay, T. A.; Bi, X.; Liu, Q. *Org. Lett.* **2011**, *13*, 6536–6539. (b) Jin, J.; Wen, Q.; Lu, P.; Wang, Y. *Chem. Commun.* **2012**, *48*, 9933–9935. Pd-catalyzed C−H functionalization: (c) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301. (d) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483–11498. (e) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634–12635. (f) Liu, Y.-K.; Lou, S.-J.; Xu, D.-Q.; Xu, Z.-Y. *Chem.—Eur. J.* **2010**, *16*, 13590–13593. (g) Lou, S.-J.; Xu, D.-Q.; Xia, A.-B.; Wang, Y.-F.; Liu, Y.-K.; Du, X.-H.; Xu, Z.-Y. *Chem. Commun.* **2013**, *49*, 6218–6220. Rh-catalyzed C−H functionalization: (h) Miyamura, S.; Tsurugi, H.; Satoh, T.; Miura, M. *J. Organomet. Chem.* **2008**, *693*, 2438–2442. (i) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7094–7099. (j) Umeda, N.; Hirano, K.; Satoh, T.; Shibata, N.; Sato, H.; Miura, M. *J. Org. Chem.* **2011**, *76*, 13–24. (k) Li, X.; Yu, S.; Wang, F.; Wan, B.; Yu, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 2577–2580. (l) Huang, L.; Wang, Q.; Qi, J.; Wu, X.; Huang, K.; Jiang, H. *Chem. Sci.* **2013**, *4*, 2665–2669. (m) Pan, F.; Lei, Z.-Q.; Wang, H.; Li, H.; Sun, J.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2063–2067. Ru-catalyzed C−H functionalization: (n) Kakiuchi, F.; Igi, K.; Matsumoto, M.; Hayamizu, T.; Chatani, N.; Murai, S. *Chem. Lett.* **2002**, 396–397. (o) Ackermann, L.; Althammer, A.; Born, R. *Synlett* **2007**, *18*, 2833–2836. (p) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299–2302. (q) Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043–5045. (r) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045–6048. (s) Ackermann, L.; Novák, P.; Vicente, R.; Pirovano, V.; Potukuchi, H. K. *Synthesis* **2010**, *13*, 2245–2253. (t) Luo, N.; Yu, Z. *Chem.—Eur. J.* **2010**, *16*, 787–791. (u) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2011**, *13*, 3075–3078. (v) Li, W.; Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2011**, *13*, 2315–2319. (w) Hashimoto, Y.; Ueyama, T.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2011**, *40*, 1165–1166. (x) Ackermann, L.; Kozhushkov, S. I.; Yufit, D. S. *Chem.—Eur. J.* **2012**, *18*, 12068–12077. (y) Hashimoto, Y.; Hirano, K.; Satoh, T.; Kakiuchi, F.; Miura, M. *Org. Lett.* **2012**, *14*, 2058–2061. (z) Hashimoto, Y.; Hirano, K.; Satoh, T.; Kakiuchi, F.; Miura, M. *J. Org. Chem.* **2013**, *78*, 638–646.

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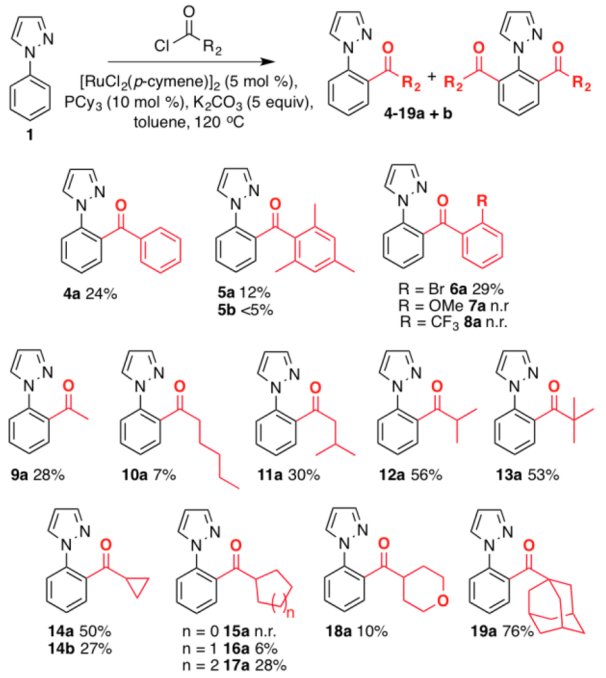
(9) See Supporting Information for details.

Scheme 3. Scope of Catalytic Acylation of 1-Phenylpyrazole



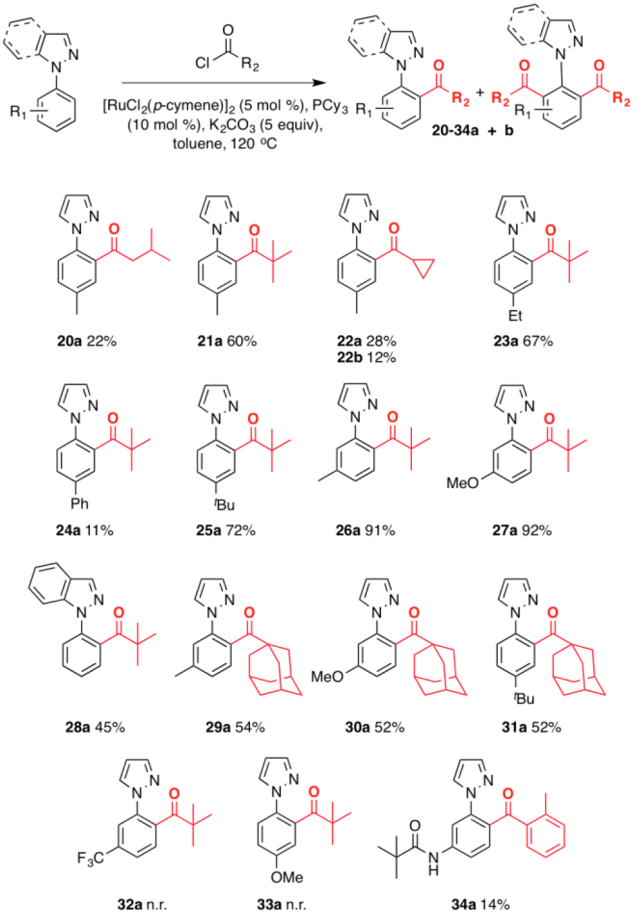
cyclometalation and oxidative addition and not *via* a classic Friedel–Crafts pathway. For both acyclic and cyclic alkyl acid chlorides, there is a notable correlation in which higher yields of acylation products are obtained for the more sterically hindered acid chloride substrates. One example is when trimethylacetyl chloride and adamantanecarbonyl chloride were used as the electrophile (**13a** and **19a**, Scheme 3). This could arise from steric acceleration in the reductive elimination step.[10]

To further evaluate the scope of this reaction, a range of 1-arylpyrazole derivatives were synthesized and coupled with various acyl chlorides under identical conditions.[11] The electronic properties of the 1-arylpyrazole substrate significantly affected the feasibility of the reaction (Scheme 4). The reaction was promoted by electron-donating groups on the aryl ring and retarded by electron-deficient substituents. The selectivity of catalytic mono- and diacylation appears to be influenced by steric hindrance on the aryl ring. For the majority of examples shown in Scheme 4, only the monoacylated product was obtained. In particular the electron-rich *meta* substituted substrates in combination with sterically hindered acyl chlorides afforded products in high yields (for example, **26a** and **27a**). Interestingly, changing the *meta* CH_3 to a CF_3 group switched off the reactivity (no formation of **32a** was observed) despite the increased propensity of the substrate to undergo cyclometalation. It appears that the reaction is sensitive to substituent effects, and the introduction of any electron-withdrawing groups to the substrate is detrimental to the reactivity. 1-Phenylindazole was found to be a suitable substrate for catalytic C–H acylation and afforded **28a** in 45% yield, which is comparable to **13a**.

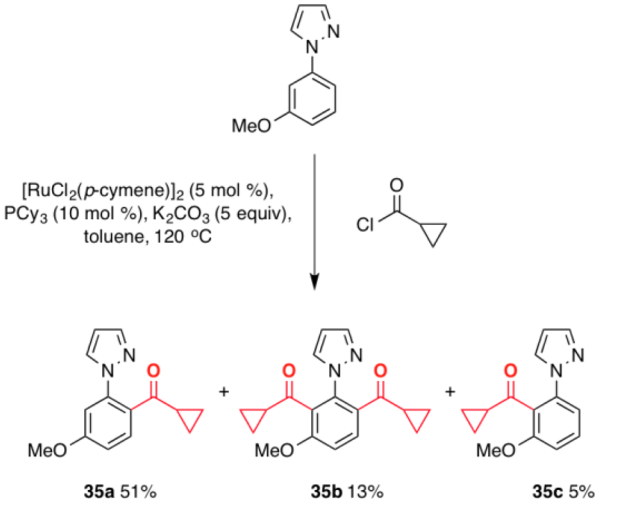
(10) Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936–1947and references therein.

(11) General protocol for the synthesis of 1-arylpyrazole derivatives: Correa, A.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 2673–2676.

Scheme 4. Catalytic *Ortho* Acylation of 1-Arylpyrazoles and 1-Phenylindazole



Scheme 5. Regioselectivity with *Meta* Substituted Substrates



Interestingly, an intramolecular competition experiment with 1-(3-methoxyphenyl)pyrazole as the substrate resulted in the formation of three products in the reaction with cyclopropanecarbonyl chloride (Scheme 5). The major product was the *ortho* monoacylated product **35a** and this is based on steric arguments for the cyclometalation. The electron-rich OMe-substitutent would be expected to promote acylations based on *ortho*-/*para*-directing effects. In this case, formation of the alternative regioisomer of the monoacylated product **35c** was observed in low yield along with the diacylated product **35b**. The lower yield was due to increased steric interactions between the C-3 substituent and the ruthenium fragment hindering cyclometalation in the *ortho* position.

In summary, we have developed a new protocol for ruthenium(II) catalyzed C−H acylation of phenylpyrazole with acyl chlorides. This useful transformation represents the first intermolecular transition-metal catalyzed C−H acylation of 1-arylpyrazoles with alkyl acid chlorides and complements emerging catalytic methods for the site-selective functionalization of heteroaromatics. Further studies are in progress to provide insight into the mechanism and expand further the scope of catalytic C−H acylation processes, and these results will be reported in due course.

Acknowledgment. This work was supported by the EPSRC. Dr. Anneke Lubben (Mass Spectrometry Service at the University of Bath) and Dr. John Lowe (NMR) are also thanked for valuable assistance.

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

The authors declare no competing financial interest.