ORGANIC LETTERS

2004
Vol. 6, No. 4
581−584

Ru(III)-Catalyzed Cyclization of Arene-Alkene Substrates via Intramolecular Electrophilic Hydroarylation

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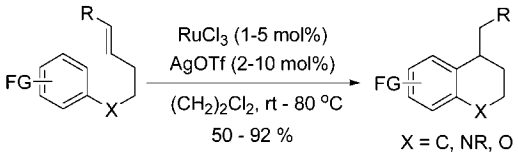
Received December 6, 2003

ABSTRACT



We herein report that $RuCl_3$/AgOTf has proven to be a hydroarylation catalyst with an efficiency and scope superior to previously known methods. This catalyst demonstrated consistent performance with arene-ene substrates of diverse structural features, providing good to excellent yields of cyclization products (chromanes, tetralins, terpenoids, dihydrocoumarins).

Intramolecular hydroarylation, a formal addition of arene C−H bonds across multiple bonds in an intramolecular manner, provides a direct route to valuable organic compounds such as annulated arene heterocycles and carbocycles. In contrast to the Heck reaction, a hydroarylation approach not only eliminates the requirement for a halogen (or triflate) substituent but also allows for multiple mechanistic possibilities, which in turn may lead to different regioisomeric products (Figure 1). These alternative mechanistic routes include arene metalation−Heck-type addition[1] and multiple-bond activation−electrophilic substitution.[2,3]

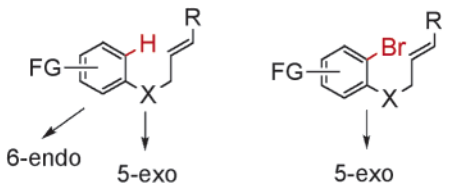


Figure 1. Hydroarylation vs Heck reaction.

We have recently developed a new platinum-catalyzed hydroarylation method that provides direct access to chromene, coumarin, and dihydroquinoline scaffolds from arene-yne substrates.[3a,b] We became interested in the possibility of

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(1) For examples of non-oxidative cyclization, see: (a) Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1301−1303. (b) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202−3203. (c) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 9692−9693. For examples of oxidative cyclizations, see: (d) Beccalli, E. M.; Broggini, G. *Tetrahedron Lett.* **2003**, *44*, 1919−1920. (e) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578−9579.

(2) (a) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505−1506. (b) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992−1995.

(3) For examples of alkyne activation/cyclization, see: (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055−1058. (b) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859−8868. (c) Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609−1611. (d) Martin-Matute, B.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757−5766. (e) Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* **2002**, *67*, 1414−1417. (f) Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264−6267. (g) Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4913−4918. (h) Jia, C.; Piao, D.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* **2000**, *65*, 7516−7522.

10.1021/ol036385i CCC: $27.50
Published on Web 01/16/2004

extending intramolecular hydroarylation to arene-alkene substrates. In contrast to the intermolecular versions,[4] only a handful of examples have surfaced regarding transition metal-catalyzed intramolecular hydroarylation of alkenes.[1a−c,2] These methods have been limited to specific substrate classes; a general hydroarylation method has not emerged for arene-ene substrates. Herein we report our results from a thorough screen, which identified $RuCl_3$/AgOTf as a mild and efficient catalyst for the intramolecular hydroarylation of a broad range of arene-ene substrates.

We focused our initial efforts in this area on the cyclization of homoallylic aryl ether **1**, which was selected as the first substrate for screening of a broad spectrum of metal salts and complexes. Transition metal complexes were chosen from nearly all regions of the periodic table, and we assured that reagents and catalysts, reported previously to either promote reactivity of alkenes and alkynes toward nucleophiles or facilitate electrophillic metalation of arenes, were included in the screen. A total of 67 metal salts and complexes were evaluated under 233 reaction conditions (Table 1, for complete data, see Supporting Information). Metal complexes were examined in a variety of solvents, and the effects of silver salt additives were determined.

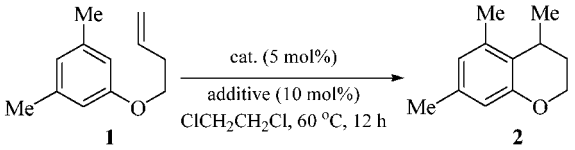
Careful analysis of the crude reaction mixtures by ^{1}H NMR during the early screening period reaffirmed our initial worries that olefin isomerization would be problematic. In fact, nearly all of the complexes tested induced some degree of olefin isomerization in **1**, with the cases of Pd, Rh, and Ru being particularly extensive. To further complicate matters, multiple products were formed; in addition to **2**, seven compounds were identifed. With the exception of $PtCl_4$, $[PtCl_2(CH_2CH_2)]_2$, $Cu(OTf)_2$, $Sc(OTf)_3$, and $HfCl_4$, none of the metal complexes examined showed the ability to produce the desired product **2**.

In an attempt to increase the electrophilicity at the metal centers, reactions were run in the presence of silver salt additives (AgX, where X = SbF_6, OTf, BF_4). As a general trend, it was found that the conversion of **1** increased upon the addition of silver salts, implying that more reactive catalysts were generated in situ. However, the increased reactivity of the metal did not always translate into better yields of the desired product **2** but rather to increased amounts of undesired products (see Supporting Information). In the case of $PtCl_4$ and $HfCl_4$, the addition of AgOTf had only a marginal effect, resulting in 2 and 5% increases in the yield of **2**, respectively (Table 1).

We were delighted to identify an exciting lead, which unambiguously stood out in the array of experiments. Remarkably, the combination of $RuCl_3 \cdot xH_2O$/AgOTf produced **2** in 83% yield.[5] In addition to $RuCl_3$, the hydrates of $IrCl_4$ and $RhCl_3$ were also able to promote the formation of **2** in combination with AgOTf, albeit in a lower yield. Interestingly, neither of the three metal chlorides were able to promote the formation of **2** without the silver additive. Additionaly, it was found that AgOTf was not responsible for product formation. We suspected that trace amounts of TfOH, formed in situ, might catalyze the coupling reaction. However, substituting anhydrous $RuCl_3$ for the hydrate resulted in similar yields of **2** (Table 1). A catalytic amount of TfOH (5 mol %) did result in the production of **2**, albeit only in 16% yield. These results suggest that ruthenium plays an important role in the hydroarylation process, and prompted us to explore both the efficiency and scope of this Ru(III) catalyst in the hydroarylation of arene-ene substrates.

The utility of $RuCl_3$/AgOTf for the cyclization of a variety of arene-ene substrates is shown in Table 2. This method demonstrated good compatibility with various functional groups, including halide, methoxy, free phenol, and protected amines (Table 2). In addition to the desired chromane products, homoallylic aryl ether substrates produced small quantities of dihydrobenzofuran products, which likely form through a sequential isomerization, Clasien rearrangement,

Table 1. Selected Data from a Systematic Screening



1 **2**

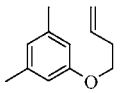
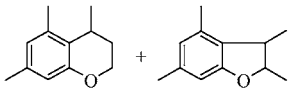
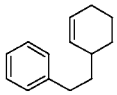
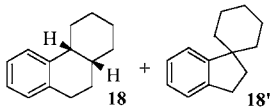
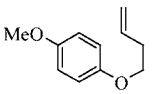
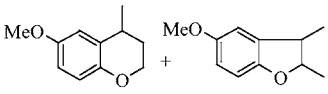
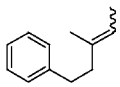
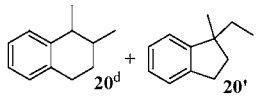
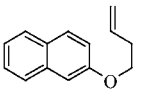
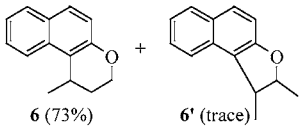
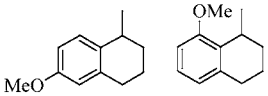
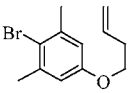
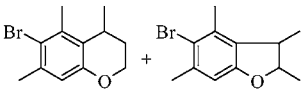
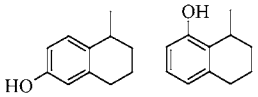
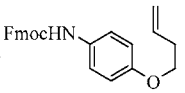
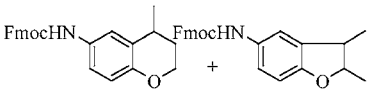
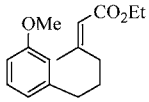
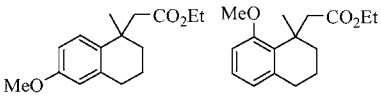
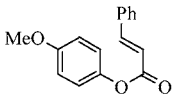
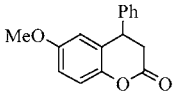
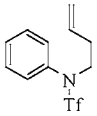
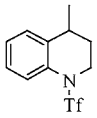
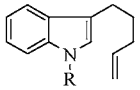
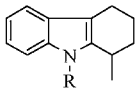
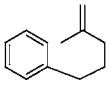
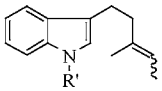
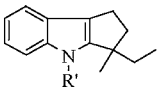
entry	catalyst	additive	yields (%)[a]
1	$PtCl_4$		15
2		$AgSbF_6$	5
3		AgOTf	20
4	$PtCl_2$	AgOTf	4
5	Pt(2,2′-Bipy)Cl_2	AgOTf	23
6	$[PtCl_2(CH_2CH_2)]_2$[b]		4
7	$Cu(OTf)_2$		40
8	$Sc(OTf)_3$		56
9	$HfCl_4$		18
10		AgOTf	25
11	$RuCl_3 \cdot xH_2O$		0
12		$AgSbF_6$	20
13		AgOTf	83
14		$AgBF_4$	0
15		$AgPF_6$	0
16	$RuCl_3$	AgOTf	80
17	$RuCl_2$(COD)	AgOTf	6
18	$RuCl_2(PPh_3)_3$	AgOTf	0
19	$Ru_3(CO)_{12}$	AgOTf	0
20	$[RuCl_2(C_6H_6)]_2$[b]	AgOTf	2
21	$RhCl_3 \cdot xH_2O$	AgOTf	40
22	$IrCl_4 \cdot xH_2O$	AgOTf	45

[a] Determined by ^{1}H NMR using trichloroethylene as an internal standard. [b] Using 2.5 mol % of the dimeric complex.

(4) For representative examples, see: (a) Lail, M.; Arrowood, B. N.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2003**, *125*, 7506−7507. (b) Matsumoto, T.; Periana, R. A.; Taube, D. J.; Yoshida, H. *J. Mol. Catal. A* **2002**, *180*, 1−18. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1769 and references therein. (d) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894−7895 and references therein. (e) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160−163.

(5) For some examples of C−C bond formation reactions involving $RuCl_3$, see: (a) Fürstner, A.; Voigtländer, D.; Schrader, W.; Giebel, D.; Reetz, M. T. *Org. Lett.* **2001**, *3*, 417−420. (b) Weissman, H.; Sing, X.; Milstein, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 337−338. (c) Tsou, D. T.; Burrington, J. D.; Maher, E. A.; Grasselli, R. K. *J. Mol. Catal.* **1985**, *30*, 219−222. (d) Rhone-Poulenc. Netherlands Patent 6603115/1966.

Table 2. Catalytic Cyclization of Selected Substrates

entry	substrate	products (%)[a]	entry	substrate	products (%)[a]
1	 **1**	 **2** (56%) + **2'** (6%)	9[c]	 **17**	 **18** + **18'** 63% (**18**: **18'**=9:1)
2	 **3**	 **4** (84%) + **4'** (trace)	10	 **19**	 **20**[d] + **20'** 80% (**20**:**20'**=82:18)
3	 **5**	 **6** (73%) + **6'** (trace)	11[e]	 **21**	 **22** (50%) **22'** (27%)
4	 **7**	 **8** (49%) + **8'** (5%)	12[e]	 **23**	 **24** (45%) **24'** (34%)
5[b]	 **9**	 **10** (53%) + **10'** (4%)	13	 **25**	 **26** (54%) **26'** (31%)
6[b]	 **11**	 **12** (42%)	14[b]	 **27**	 **28** (53%)
7[c]	 **13**	 **14** (82%)	15	 R = Me (**29**)[f], H (**31**)[g]	 R = Me (**30**) : 65% H (**32**) : 21%
8[c]	 **15**	 **16** (92%)	16	 R = Me (**33**)[f], H (**35**)[g]	 R' = Me (**34**) : 40% H (**36**) : 27%

All reactions were performed with 5 mol % $RuCl_3 \cdot xH_2O$ and 10 mol % AgOTf in $ClCH_2CH_2Cl$ at 60 °C, unless otherwise noted. [a] Isolated yields. [b] Performed with 20 mol % $RuCl_3$ and 40 mol % AgOTf at 80 °C. [c] Performed with 1 mol % $RuCl_3 \cdot xH_2O$ and 2 mol % AgOTf at 60 °C. [d] Cis:trans = 82:18. [e] Performed with 2 mol % $RuCl_3 \cdot xH_2O$ and 4 mol % AgOTf at 60 °C. [f] Performed with 10 mol % $RuCl_3 \cdot xH_2O$ and 20 mol % AgOTf at 70 °C. [g] Performed with 20 mol % $RuCl_3 \cdot xH_2O$ and 40 mol % AgOTf at 70 °C.

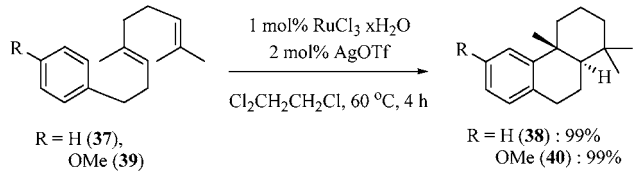
and cyclization pathway (Table 2, entries 1−5). 3,4-Dihydrocoumarin products could be successfully produced from their corresponding acyclic precursors; however, higher catalyst loading and temperatures were required (Table 2, entry 6). Carbon-based tethers of mono-, di-, and trisubstituted olefins produced tetralin products in good to excellent yields, with cyclization proceeding exclusively through the 6-*exo* mode. In contrast, substrate **19** with a shorter carbon tether cyclized preferentially through the 6-*endo* mode (Table 2, entry 10). Cyclization of carbon-tethered substrates was induced with significantly lower catalyst loadings (1 mol %) relative to oxygen-tethered substrates (5 mol %). This is notable because carbon-tethered substrates are inherently less electron rich than those derived from phenols. In the case of nitrogen-tethered substrates, the *N*-triflate protecting group proved to be essential, with free *N*-H, *N*-alkyl, *N*-Ac, or *N*-Boc substrates being unreactive (Table 2, entry 14). Finally, C(3)-substituted indole derivatives participated in this intramolecular hydroarylation reaction.[6] Both free *N*-H and *N*-methyl derivatives could be utilized; however, the

N-methyl derivatives provided the tricyclic products in higher yields (Table 2, entries 15 and 16). Noteworthy is the fact that the regiochemistry of cyclization for indole substrates **33** and **35** (5-*exo*) differs from the phenyl substrate **19** with the same carbon tether (6-*endo*).

In the next stage of the project, we set out to address the question of whether the hydroarylation protocol would be applicable to substrates of higher complexity. Acid-catalyzed polyene cyclization is one of the most widely used methods for the synthesis of polycyclic terpenoids.[7]

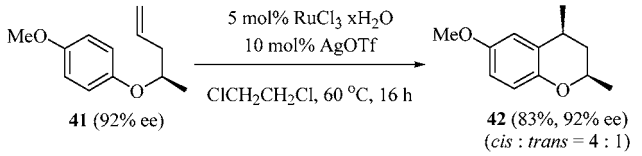
We were interested to see if our $RuCl_3$/AgOTf hydroarylation protocol could provide a mild alternative to traditional methods. Accordingly, polyenes **37** and **39** were prepared and subjected to the hydroarylation protocol. We found that very mild conditions, namely, 1 mol % $RuCl_3$ and 2 mol % AgOTf, smoothly cyclized the polyenes to the tricyclic terpenoids **38** and **40** in nearly quantitative yields with high stereoselectivities (trans:cis = 99:1∼98:2). Diterpenoid **40** is a valuable synthetic intermediate, having been converted to the natural product ferruginol by King[8] and Ghatak.[9]

Scheme 1



Last, we addressed an important question of whether a stereogenic center in chiral homoallylic ethers would be compromised during the cyclization. We were delighted to find that chiral ether **41** afforded chromane **42** in 83% yield (cis:trans = 4:1), while no racemization was observed (Scheme 2). This finding rules out reversible alkene migration and significantly expands the scope of this hydroarylation methodology.

Scheme 2



In summary, an extensive and systematic study identified $RuCl_3$/AgOTf as an intramolecular hydroarylation catalyst of arene-ene substrates. A variety of annulated arene heterocycles and carbocycles are accessible under mild conditions using this method, including chromane, tetralin, terpenoid, dihydrocoumarin, tetrahydroquinoline, and indolocyclohexane and cyclopentane systems. It is likely that this reaction proceeds via an electrophilic pathway involving alkene activation, C−C bond formation, and the protonation of a C−Ru intermediate. The contrast between the reactivity of arene-yne[3] and arene-ene substrates raises interesting questions regarding the role of the metal catalyst on these seemingly related pathways. Better understanding of these issues will facilitate the development of an asymmetric version of hydroarylation cyclizations.

Acknowledgment. Generous support for this work was provided by GlaxoSmithKline, Johnson & Johnson Focused Giving Grant. D.S. is a recipient of the Alfred P. Sloan Fellowship and the Camille Dreyfus Teacher−Scholar Award.

Supporting Information Available: Complete Experimental Section, complete data for the systematic screening, experimental details, and compound spectral characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036385I

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