Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 1237–1239

Tetrahedron Letters

Iridium(III)-catalyzed tandem Claisen rearrangement–intramolecular hydroaryloxylation of aryl allyl ethers to form dihydrobenzofurans

Virginia H. Grant[†] and Bing Liu[*]

Chemical Development, GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709, USA

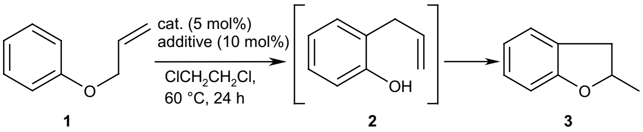
Received 3 December 2004; revised 23 December 2004; accepted 5 January 2005
Available online 18 January 2005

Abstract—Iridium(III)-catalyzed tandem Claisen rearrangement and intramolecular hydroaryloxylation of ally aryl ethers is described, which provides a mild method to prepare dihydrobenzofurans.

The Claisen rearrangement is a classic reaction for carbon–carbon formation in organic synthesis.[1] Although the reaction is traditionally performed under thermal conditions, there is considerable current interest in catalysis of the Claisen rearrangement by metal catalysts under mild conditions.[2] The Claisen rearrangement of allyl aryl ethers has been achieved efficiently with stoichiometric amount of Lewis acids[3,4] and substoichiometric amount of metal catalysts such as $Yb(OTf)_3$,[5] $Sc(OTf)_3$ in ionic liquid,[6] and $Mo(CO)_6$.[7] We are interested in the metal catalyzed tandem Claisen rearrangement and hydroaryloxylation of allyl aryl ethers as a general method to make dihydrobenzofurans.[6,7] Herein we report our results from a thorough screen, which identified $IrCl_3$/AgOTf as an efficient catalyst for the tandem Claisen rearrangement cyclization of allyl aryl ethers to form dihydrobenzofurans.

Transition metal complexes, known to either promote Claisen rearrangement[2] or facilitate the intramolecular hydroalkoxylation of hydroxy-olefins,[8] were included in the screen. Table 1 summarized the results from the screening study. With the exception of $Cu(OTf)_2$, none of these metal catalysts examined proved effective for the conversion of phenyl allyl ether to dihydrofurans at 60 °C. $PdCl_2(CH_3CN)_2$ afforded undesired products, mainly phenol from cleavage of allyl phenyl ether. $Sc(OTf)_3$ as well as $Yb(OTf)_3$ promoted only the Claisen rearrangement of allyl phenyl ether to 2-allylphenol (**2**) but not the subsequent cyclization to dihydrofuran.

Table 1. Results of catalyst screening for Claisen hydroaryloxylation of **1**



Entry	Catalyst	Additive	Yield[a] (%)
1	$RuCl_3$	None	0
2	$RuCl_3$	AgOTf	43
3	$PtCl_2$	None	0
4	$PtCl_2$	AgOTf	11
5	$PtCl_4$	AgOTf	12
6	$PtCl_2(CH_2{=}CH_2)$	Ph_3P	0
7	$Cu(OTf)_2$	None	44
8	$Cu(OTf)_2$	AgOTf	20
9	$Sc(OTf)_3$	None	0
10	$Sc(OTf)_3$	AgOTf	22
11	$Yb(OTf)_3$	None	0
12	$Yb(OTf)_3$	AgOTf	25
13	$IrCl_3$	None	0
14	**$IrCl_3$**	**AgOTf**	**65**
15	$PdCl_2(CH_3CN)_2$	None	0
16	None	AgOTf	0

[a] The reaction was performed at 0.5 M of **1** in 1,2-dichloroethane at 60 °C for 24 h.

Keywords: Iridium(III) chloride; Claisen rearrangement; Hydroaryloxylation; Dihydrobenzofuran.

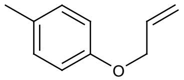
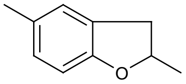
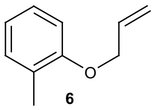
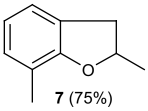
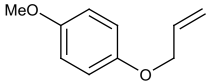
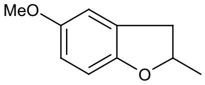
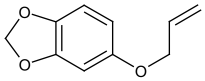
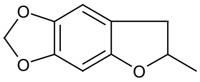
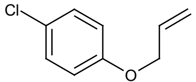
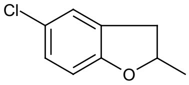
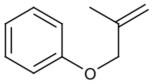
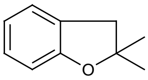
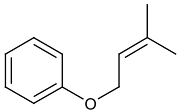
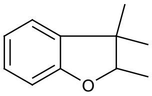
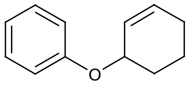
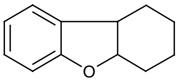
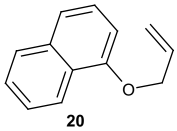
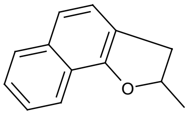
[*] Corresponding author. Tel.: +1 919 483 8165; fax: +1 919 315 8735; e-mail: bing.b.liu@gsk.com

[†] Current address: Department of Chemistry, Vanderbilt University, Nashville, TN 37235, USA.

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.01.006

The platinum based system, $[PtCl_2(CH_2{=}CH_2)]_2/PPh_3$, successful for the intramolecular hydroalkoxylation of hydroxy-olefins failed to facilitate the formation of dihydrofuran from either **1** or 2-allylphenol.[8] In order to increase the electrophilicity at the metal centers, we attempted to add silver salts to the reaction mixture.[9] It was found that the addition of AgOTf promoted the formation of dihydrofuran **3** except in the case of $Cu(OTf)_2$, where the yield of the desired product **3** decreased upon the addition of AgOTf due to the formation of multiple undesired products. To our delight, the combination of $IrCl_3$/AgOTf afforded **3** in 65% yield.[10] Interestingly, neither $IrCl_3$ nor AgOTf individually was able to promote the formation of dihydrofuran **3** from allyl phenyl ether. It was found that AgOTf was somewhat effective to catalyze the formation of dihydrofuran from 2-allylphenol, albeit only in 11% yield.[11] These results suggest that a more reactive iridium catalyst is generated in situ upon the addition of AgOTf.

Table 2. Iridium catalyzed Claisen hydroaryloxylation of aryl ethers

Entry	Substrate	Product[a] (%)
1	 **4**	 **5** (70%)
2	 **6**	 **7** (75%)
3	 **8**	 **9** (76%)
4	 **10**	 **11** (72%)
5[b]	 **12**	 **13** (59%)
6[c]	 **14**	 **15** (80%)
7	 **16**	 **17** (0)
8	 **18**	 **19** (50%)
9	 **20**	 **21** (63%)

[a] All reactions were performed with 5 mol % of $IrCl_3$ and 10 mol % of AgOTf in $ClCH_2CH_2Cl$ (0.5 M) at 60 °C for 24 h, unless otherwise noted.

[b] Performed at 60 °C for 36 h.

[c] Performed at 60 °C for 4 h.

The tandem Claisen hydroaryloxylation was next explored on a range of allyl aryl ethers to probe the scope of this cascade process (Table 2). This method was applicable to substrates with functional groups such as methoxy, methylenedioxy, and chloro. All substituents gave moderate to good yields, although it should be noted that the conversion of **12** to hydrobenzofuran **13** was slightly sluggish. The reaction was also observed tolerant of substitution at the internal olefinic position. In the case of 1,1-disubstituted olefin **14**, the reaction was facile and nearly complete in three hours. The tandem Claisen cyclization reaction appeared to be sensitive to terminal olefinic disubstitution. For example, phenyl prenyl ether **16** failed to produce dihydrofuran **17**, giving phenol as the major product. Iridium-catalyzed tandem Claisen hydroaryloxylation was also amenable to the formation of fused cyclic ether such as **19**, albeit in a lower yield due to the competing ether cleavage. Allyl 1-naphthyl ether also underwent the iridium-catalyzed tandem process to afford dihydrofuran **21** in 63% yield.

In summary, we have developed a tandem Claisen hydroaryloxylation of ally aryl ethers using $IrCl_3$/AgOTf catalyst. A variety of dihydrobenzofurans are accessible through this protocol under mild conditions. Our future efforts are directed to expand this protocol into tandem amino-Claisen cyclization for the indoline synthesis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.006. The ^1H NMR and ^{13}C NMR data for dihydrofurans is available online with the paper in ScienceDirect.

References and notes

1. Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939.
2. Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 1461.
3. Maruoka, K.; Sato, J.; Banno, H.; Yamamoto, H. *Tetrahedron Lett.* **1990**, *31*, 377, and references cited therein.
4. Wipf, P.; Ribe, S. *Org. Lett.* **2001**, *3*, 1503.
5. Sharma, G. V. M.; Ilangovan, A.; Sreenivas, P.; Mahalingam, A. K. *Synlett* **2000**, 615.
6. Zulfiqar, F.; Kitazume, T. *Green Chem.* **2000**, *2*, 296.
7. Bernard, A. M.; Cocco, M. T.; Onnis, V.; Piras, P. P. *Synthesis* **1997**, 41, and references cited therein.
8. Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536.
9. Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581.
10. A typical experiment was as follows: A mixture containing allyl phenyl ether (1.34 g, 10 mmol), $IrCl_3$ (0.15 g,

0.5 mmol), AgOTf (0.26 g, 1 mmol), and 1,2-dichloroethane (20 mL) was heated under nitrogen at 60 °C for 24 h. After removal of solvents, the residue was purified by silica gel column chromatography (hexane/dichloromethane = 9/1) to afford dihydrobenzofuran **3** (0.87 g, 65%) as a colorless oil. IR (neat, cm^{-1}) 1479, 1463, 1228, 746. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.15 (d, $J = 7.3$ Hz, 1H), 7.10 (t, $J = 7.8$ Hz, 1H), 6.82 (t, $J = 7.3$ Hz, 1H), 6.76 (d, $J = 7.8$ Hz, 1H), 4.87–4.96 (m, 1H), 3.30 (dd, $J = 15.4$ and 8.8 Hz, 1H), 2.82 (dd, $J = 15.4$ and 7.7 Hz, 1H), 1.47 (d, $J = 6.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.0, 37.4, 79.7, 109.5, 120.4, 125.2, 127.2, 128.2, 159.7. Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.32; H, 7.29. All products were successfully characterized using ^1H NMR, ^{13}C NMR, and elemental analysis.

11. For a $RuCl_3{\cdot}xH_2O$ catalyzed cyclization of 2-allylphenol, see: Hori, K.; Kitagawa, H.; Miyoshi, A.; Ohta, T.; Furukawa, I. *Chem. Lett.* **1998**, 1083.