Dirhodium Caprolactamate Catalyzed Alkoxyalkylation of Terminal Alkynes

Xiarepati Tusun,[a,b] Chong-Dao Lu*[a]

[a] Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Urumqi 830011, P. R. of China
Fax +86(991)3838708; E-mail: clu@ms.xjb.ac.cn

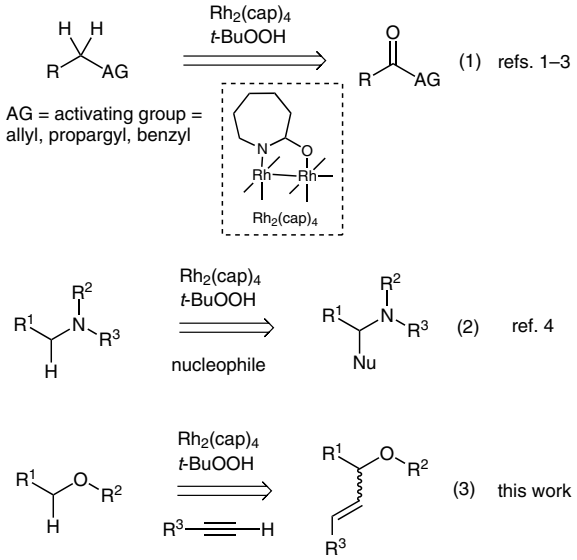
[b] University of Chinese Academy of Sciences, Beijing 100049, P. R. of China

Received: 23.04.2013; Accepted after revision: 27.05.2013

Abstract: Dirhodium caprolactamate [$Rh_2(cap)_4$] effectively catalyzes alkoxyalkylation of terminal alkynes in the presence of *tert*-butyl hydroperoxide (TBHP) under mild conditions.

Key words: alkoxyalkylation, alkynes, catalysis, dirhodium(II)

Pioneering work by Doyle and coworkers has demonstrated that dirhodium caprolactamate [$Rh_2(cap)_4$] is an effective catalyst when used in conjunction with *tert*-butyl hydroperoxide (TBHP) for allylic, benzylic, and propargylic oxidations (Scheme 1, eq 1).[1–3] This catalytic oxidative approach has been extended to the functionalization of the carbon adjacent to the nitrogen in tertiary amines (Scheme 1, eq 2).[4]

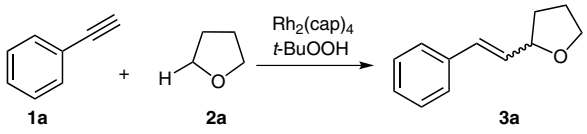


Scheme 1 $Rh_2(cap)_4$-catalyzed functionalization of the carbon adjacent to the ether oxygen

These catalytic oxidations involving TBHP are initiated by $Rh_2(cap)_4$-catalyzed cleavage of the peroxide bond of TBHP, generating *tert*-butoxy radical. This radical then abstracts a hydrogen atom from another TBHP to form *tert*-butylperoxy radical, which acts as an oxidant in subsequent transformations.[5] We envisaged that this radical-based protocol might be useful for functionalizing the carbon adjacent to the oxygen of ethers, given that ethers are potential precursors of α-alkoxyalkyl radicals.[6] Here we continue our research into dirhodium complexes and their catalytic applications[7] by reporting the direct addition of ethers to terminal alkynes in the presence of $Rh_2(cap)_4$ catalyst and TBHP. Using this approach, we have synthesized a variety of allyl ether derivatives (Scheme 1, eq 3).

We began our studies by testing the reaction of phenylacetylene (**1a**) and tetrahydrofuran (THF, **2a**) in the presence of $Rh_2(cap)_4$ catalyst and *t*-BuOOH. With 0.1 mol% catalyst loading, the reaction conducted at room temperature for 12 hours gave the allyl ether **3a** in 59% yield with an *E*/*Z* ratio of 1:1.7 (Table 1, entry 1). Higher yield (76%) was obtained when 0.5 mol% $Rh_2(cap)_4$ were used (Table 1, entry 2). The reaction was further improved by elevating the reaction temperature to 50 °C, affording the desired product **3a** in 84% yield in three hours (Table 1, entry 3). Comparable yield (82%) was obtained when the reaction was carried out on a 1 g scale (Table 1, entry 4). The yields obtained using our protocol is higher than yields reported in the literature.[8–10] For example, a microwave-assisted protocol for this reaction gave 60% yield;[8] a TBHP-promoted protocol, 51% yield at 50 °C[9a] and 61% yield[9b] at 120 °C; a CuBr/TBHP-promoted protocol, 62% yield;[9a] and an Me_2Zn/O_2-initiated protocol, 28% yield with high *E*-selectivity.[10]

Table 1 Optimization of Reaction Conditions[a]



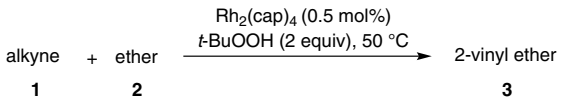
Entry	Catalyst loading (mol%)	Temp (°C)	Time (h)	Yield (%)[b] (*E*/*Z*)[c]
1	0.1	r.t.	12	59 (1:1.7)
2	0.5	r.t.	12	76 (1:1.7)
3	0.5	50	3	84 (1:1.7)
4[d]	0.5	50	4	82 (1:1.7)

[a] Reaction conditions: **1a** (0.5 mmol), *t*-BuOOH (2.0 mmol), and a catalytic amount of $Rh_2(cap)_4$ in THF (10 mL).
[b] Isolated yield.
[c] *E*/*Z* ratios were determined by ^{1}H NMR analysis of crude reaction mixtures.
[d] Reaction scale = 1 g.

SYNLETT 2013, 24, 1693–1696
Advanced online publication: 28.06.2013
DOI: 10.1055/s-0033-1339290; Art ID: ST-2013-W0378-L

With these promising preliminary results in hand, we examined the scope of the $Rh_2(cap)_4$-catalyzed alkoxyalkylation of terminal alkynes by varying the alkynes and ethers used (Table 2). As shown in Table 2, electron-rich (entries 2 and 3) and mild electron-poor aryl acetylenes (entry 4) performed well in the reaction and provided ready access to functionalized 2-vinyl tetrahydrofurans **3b–d**. Terminal alkynes bearing aliphatic substitutions appeared to be less reactive; longer reaction times were required to ensure alkyne consumption and give moderate yields of the desired products **3e–i** (Table 2, entries 5–9). Functional groups such as silyl ether (Table 2, entry 6), hydroxyl (Table 2, entry 8), and amide (Table 2, entry 9) were well tolerated under the reaction conditions.

Table 2 Substrate Scope for the Addition of Ethers to Alkynes



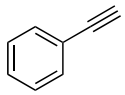
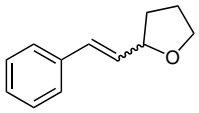
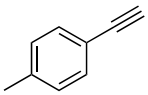
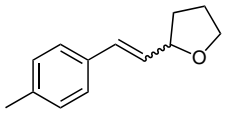
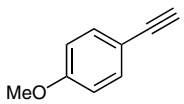
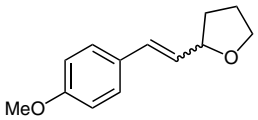
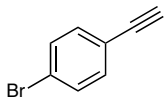
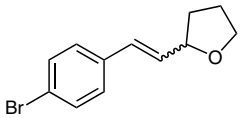
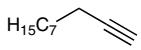
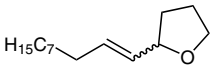
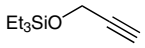
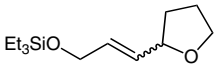
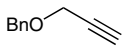
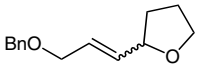
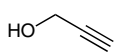
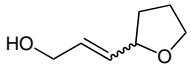
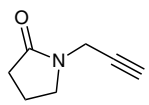
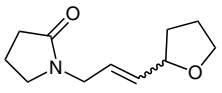
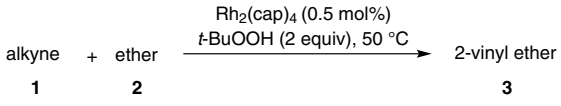
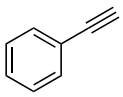
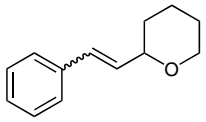
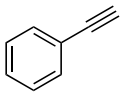
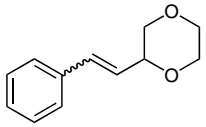
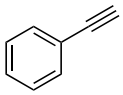
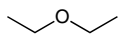
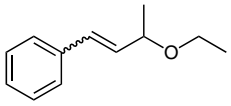
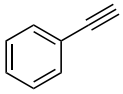
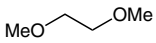
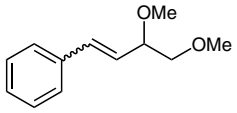
Entry	Alkyne	Ether	Time (h)	Product	Yield (%)[a] (*E*/*Z*)[b]
1	 **1a**	 **2a**	3	 **3a**	84 (1:1.7)
2	 **1b**	 **2a**	24	 **3b**	71 (1:1.7)
3	 **1c**	 **2a**	48	 **3c**	69 (1:1.7)
4	 **1d**	 **2a**	20	 **3d**	86 (1:1.7)
5	 **1e**	 **2a**	96	 **3e**	55 (2.0:1)[d]
6	 **1f**	 **2a**	96	 **3f**	69 (1.5:1)
7	 **1g**	 **2a**	96	 **3g**	57 (2.6:1)[d]
8	 **1h**	 **2a**	60	 **3h**	72 (2.5:1)[d]
9[c]	 **1i**	 **2a**	72	 **3i**	74 (2.8:1)[d]

Table 2 Substrate Scope for the Addition of Ethers to Alkynes (continued)



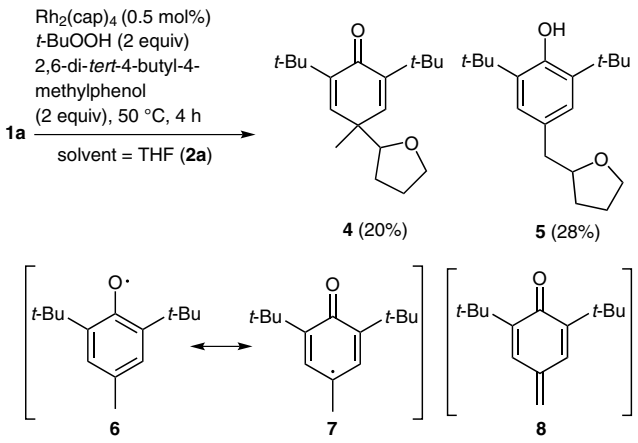
Entry	Alkyne	Ether	Time (h)	Product	Yield (%)[a] (*E*/*Z*)[b]
10	 **1a**	 **2b**	14	 **3j**	44 (1:1.7)[d]
11	 **1a**	 **2c**	16	 **3k**	53 (1:1.6)[d]
12	 **1a**	 **2d**	22	 **3l**	49 (1:1.3)[d]
13	 **1a**	 **2e**	14	 **3m**	42 (1:1.3)

[a] Isolated yield.
[b] *E*/*Z* ratios were determined by ^{1}H NMR analysis of crude reaction mixtures.
[c] Reaction conditions: **1e** (0.5 mmol), *t*-BuOOH (4 equiv), and $Rh_2(cap)_4$ (1 mol%) in THF (10 mL) at 70 °C.
[d] Inseparable geometric isomers.

The combination of $Rh_2(cap)_4$ and TBHP has already been reported to efficiently promote the oxidation of benzylic, allylic and propargylic C–H bonds (Scheme 1, eq 1).[2–4] In the present study, however, addition of ethers to alkynes occurred preferentially, giving the desired adducts without any significant formation of propargylic oxidation products derived from **1e**–**i** (Table 2, entries 5–9), allylic oxidation products derived from **3e**–**i** (Table 2, entries 5–9), or benzylic oxidation products derived from **1g** and **3g** (Table 2, entry 7). This reaction preference has been attributed to the presence of a large excess of ethers that serve as both solvents and reactants and that preferentially act as radical traps over other reactants and products containing the activated C–H bonds.[8–10]

In addition to THF, we tested several cyclic and acyclic substrates containing alkoxy groups in the alkoxyalkylation of phenylacetylene (Table 2, entries 9–13). Tetrahydropyran and 1,4-dioxane proved suitable addition partners under our reaction conditions (Table 2, entries 10 and 11). Moreover, we were able to use linear ethers **2d** and **2e** in the addition reaction to phenylacetylene, a result not reported for previous protocols;[8–10] these ethers produced adducts **3l** and **3m**, respectively, in low yields (Table 2, entries 12 and 13).[11] Low *E*/*Z* ratios were obtained for adducts **3a**–**m** in all reactions of Table 2. We also examined reactions of phenylacetylene (**1a**) with alcohols instead of ethers in the presence of $Rh_2(cap)_4$/TBHP. The reaction of **1a** and methanol at 50 °C led to a complex mixture of products, while the reaction of **1a** and ethanol led to only trace amounts of product even at elevated temperature (90 °C), with the alkyne **1a** remaining largely intact.[9b] These results indicate that the $Rh_2(cap)_4$/TBHP system is not suitable for promoting the addition of alcohols to phenylacetylene (**1a**).

To probe the impact of a radical scavenger on this radical-based addition, we conducted a control reaction (Scheme 2). We added the radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (BHT) to the reaction of **1a** and **2a**, and managed to completely suppress formation of **3a**; in this reaction, **1a** remained intact, and products **4** and **5** formed from reactions involving BHT and THF. We speculate that product **4** formed by radical combination between the α-ethereal radical[6] of THF (**2a**) and the phenoxy radical[5] **6** generated from radical-mediated abstraction of the phenolic hydrogen of BHT. Product **5**, for its part, may have formed through radical 1,6-Michael addition[12] of the ethereal radical to BHT quinone methide (BHT-QM)[13] intermediate **8**.



Scheme 2 Interception of the α-ethereal radical of THF by BHT

In summary, we have applied $Rh_2(cap)_4$/TBHP-based catalytic oxidation to the functionalization of carbons adjacent to ether oxygens. Using this protocol, we have synthesized a variety of 2-vinyl ethers via direct addition of ethers to terminal alkynes under mild reaction conditions.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (21172251), the Hightech R&D Program of Xinjiang Uygur Autonomous Region (201110111), and the Chinese Academy of Sciences.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) For $Rh_2(cap)_4$-catalyzed allylic oxidation, see: (a) Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622. (b) Choi, H.; Doyle, M. P. *Org. Lett.* **2007**, *9*, 5349. (c) McLaughlin, E. C.; Choi, H.; Wang, K.; Chiou, G.; Doyle, M. P. *J. Org. Chem.* **2009**, *74*, 730.

(2) For $Rh_2(cap)_4$-catalyzed benzylic oxidation, see: Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 5167.

(3) For $Rh_2(cap)_4$-catalyzed propargylic oxidation, see: McLaughlin, E. C.; Doyle, M. P. *J. Org. Chem.* **2008**, *73*, 4317.

(4) For $Rh_2(cap)_4$-catalyzed oxidation of tertiary amines to initiate the Mannich reaction, see: Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648.

(5) Ratnikov, M. O.; Farkas, L. E.; McLaughlin, E. C.; Chiou, G.; Choi, H.; El-Khalafy, S. H.; Doyle, M. P. *J. Org. Chem.* **2011**, *76*, 2585.

(6) (a) Wallace, T. J.; Gritter, R. J. *J. Org. Chem.* **1962**, *27*, 3067. (b) Wallace, T. J.; Gritter, R. J. *J. Org. Chem.* **1961**, *26*, 5256.

(7) (a) Tusun, X.; Lu, C.-D. *Synlett* **2012**, *23*, 1801. (b) Wusiman, A.; Tusun, X.; Lu, C.-D. *Eur. J. Org. Chem.* **2012**, 3088. (c) Wang, H.-T.; Lu, C.-D. *Tetrahedron Lett.* **2013**, *54*, 3015.

(8) Zhang, Y.; Li, C.-J. *Tetrahedron Lett.* **2004**, *45*, 7581.

(9) (a) Huang, L.; Cheng, K.; Yao, B.; Zhao, J.; Zhang, Y. *Synthesis* **2009**, 3504. (b) Liu, Z.-Q.; Sun, L.; Wang, J.-G.; Han, J.; Zhao, Y.-K.; Zhou, B. *Org. Lett.* **2009**, *11*, 1437.

(10) Chen, Z.; Zhang, Y.-X.; An, Y.; Song, X.-L.; Wang, Y.-H.; Zhu, L.-L.; Guo, L. *Eur. J. Org. Chem.* **2009**, 5146.

(11) **General Experimental Procedure for the Preparation of 2-Vinyl Ethers**
Alkyne (0.50 mmol) and $Rh_2(cap)_4$·2MeCN (0.0025 mmol, 1.8 mg, 0.5 mol%) were mixed in Et_2O (10 mL), and TBHP (5–6 M in decane, 1.0 mmol) was added. After stirring at 50 °C for the indicated time (Table 2), the reaction mixture was evaporated to give the crude product, which was purified by silica gel column chromatography using EtOAc–PE as eluent to obtain 2-vinyl ethers. This General Experimental Procedure was carried out using **1a** (51 mg, 0.50 mmol) and **2f** (10 mL). The reaction mixture was stirred for 14 h at 50 °C and purified by silica gel chromatography using PE–EtOAc (10:1) as eluent to give products (*E*)-**3m** and (*Z*)-**3m**.
Compound (*E*)-**3m**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.6 Hz, 2 H), 7.34 (t, *J* = 7.6 Hz, 2 H), 7.28 (s, 1 H), 6.65 (d, *J* = 16.0 Hz, 1 H), 6.11 (dd, *J* = 16.0, 7.6 Hz, 1 H), 4.02–3.90 (m, 1 H), 3.56–3.48 (m, 2 H), 3.42 (s, 3 H), 3.40 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.6, 133.8, 128.8, 128.1, 126.82, 126.80, 81.6, 75.9, 59.5, 56.9. ESI-HRMS: *m/z* calcd for $C_{12}H_{16}NaO_2$ [M + Na]$^+$: 215.1043; found: 215.1042.
Compound (*Z*)-**3m**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H), 6.78 (d, *J* = 11.6 Hz, 1 H), 5.58 (dd, *J* = 11.6, 9.6 Hz, 1 H), 4.46–4.37 (m, 1 H), 3.57–3.51 (m, 2 H), 3.43 (s, 3 H), 3.27 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.8, 134.2, 130.0, 128.9, 128.6, 127.6, 76.2, 75.5, 59.6, 56.6. ESI-HRMS: *m/z* calcd for $C_{12}H_{16}NaO_2$ [M + Na]$^+$: 215.1043; found: 215.1044. See the Supporting Information for experimental details and characterization data for all new compounds.

(12) Clive, D. L. J.; Fletcher, S. P.; Zhu, M. *Chem. Commun.* **2003**, 526.

(13) (a) Dyall, L. K.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2196. (b) Omura, K. *J. Org. Chem.* **1984**, *49*, 3046.

