ORGANIC LETTERS

2004
Vol. 6, No. 10
1657−1660

Catalyst and Ring Size Effects on Periselectivity of Oxonium Ylide Rearrangements

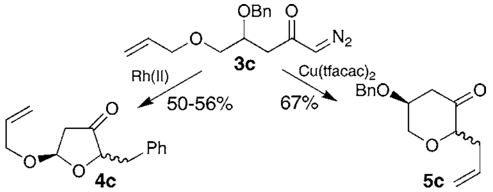
Fredrik P. Marmsäter,[†,‡] John A. Vanecko,[‡] and F. G. West*[,†]

Department of Chemistry, University of Alberta, W5-67 Gunning-Lemieux Chemistry
Centre, Edmonton, AB T6G 2G2, Canada, and Department of Chemistry,
University of Utah, 315 S. 1400 East, Rm 2020, Salt Lake City, Utah 84112

frederick.west@ualberta.ca

Received March 17, 2004

ABSTRACT



Diazoketones were subjected to carbene-transfer with Rh(II) or Cu(II) catalysts to probe the selectivity for rearrangement via five- or six-membered oxonium ylides. 4,5-Bis(benzyloxy) and 4-allyloxy-5-benzyloxy substrates 3a,b showed a large preference for rearrangement via the five-membered ylide under all conditions. However, a sharp divergence was seen with 5-allyloxy-4-benzyloxy substrate 3c, which underwent predominantly a [2,3]-shift to pyran 5c via the six-membered ylide with Cu(II) catalysis and a [1,2]-shift to furan 4c via the five-membered ylide with Rh(II) catalysis.

Cyclic oxonium ylides are readily generated from acyclic diazoketone precursors with pendant ether moieties and undergo rearrangement to functionalized tetrahydrofurans or tetrahydropyrans when the ether contains a group capable of migrating via [1,2]- or [2,3]-shift.[1] This convenient entry to cyclic ethers has been used in the construction of medium-sized carbocycles[2] and ethers,[3] the natural product griseofulvin,[4] the cores of neoliacinic acid[5] and the cladiellins,[6] and polypyran domains such as those found in the marine ladder toxins.[7] The catalyst used in the carbene-transfer step can play a dominant role in the product mixture. Alternative metallocarbene processes can compete effectively with ylide formation, and it has been noted on several occasions that copper(II) catalysts are typically superior for the selective formation of oxonium ylides at the expense of alternative C−H insertion pathways.[1f,3,7,8] Less well appreciated is the potential for the catalyst to affect the ratio of *ylide-derived products*. Although catalyst involvement in the ylide rearrangement step is not mechanistically necessary, there is evidence that oxonium ylide rearrangements can proceed via

---

[†] University of Alberta.

[‡] University of Utah.

(1) (a) Pirrung, M. P.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060−6062. (b) Johnson, C. R.; Roskamp, E. J. *J. Am. Chem. Soc.* **1986**, *108*, 6062−6063. (c) Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817−824. (d) Eberlein, T. H.; West, F. G.; Tester, R. W.; *J. Org. Chem.* **1992**, *57*, 3479−3472. (e) Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193−6196. (f) Clark, J. S.; Krowiak, S. A.; Street, L. J. *Tetrahedron Lett.* **1993**, *34*, 4385−4388. (g) Clark, J. S.; Fretwell, M.; Whitlock, G. A.; Burns, C. J.; Fox, D. N. A. *Tetrahedron Lett.* **1998**, *39*, 97−100.

(2) (a) West, F. G.; Eberlein, T. H.; Tester, R. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2857−2859. (b) Clark, J. S.; Bate, A. L.; Grinter, T. *Chem. Commun.* **2001**, 459−460. (c) Marmsäter, F. P.; Murphy, G. K.; West, F. G. *J. Am. Chem. Soc.* **2003**, *125*, 14724−14725.

(3) Tester, R. W.; West, F. G. *Tetrahedron Lett.* **1998**, *39*, 4631−4634.

(4) Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561−8562.

(5) Clark, J. S.; Dossetter, A. G.; Whittingham, W. G. *Tetrahedron Lett.* **1996**, *37*, 5605−5608.

(6) Clark, J. S.; Wong, Y. S. *Chem. Commun.* **2000**, 1079−1080.

(7) (a) Marmsäter, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144−5145. (b) Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58*, 2027−2040.

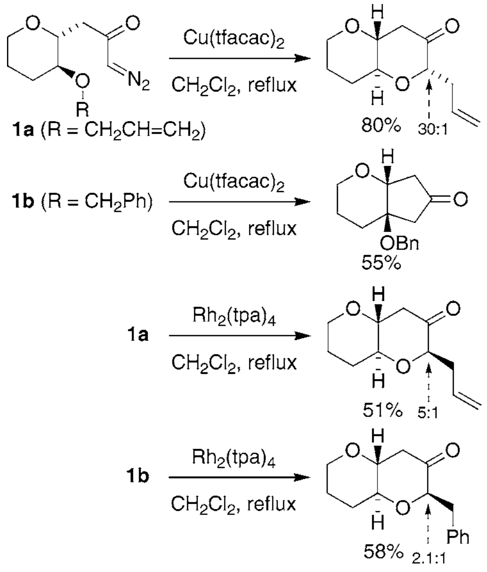
(8) West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892−6894.

10.1021/ol049493t CCC: $27.50

metal-associated ylides.[4,9] Here we describe a remarkable, catalyst-dependent selectivity for two isomeric ylide rearrangement products based on the nature of the migrating groups.

While developing an oxonium ylide-based iterative procedure for the synthesis of polyethers, we observed that reactions catalyzed by copper(II) trifluoroacetylacetonate (Cu(tfacac)$_2$) proceeded in excellent yield with an allyl migrating group (**1a**). In contrast, with a benzyl migrating group (**1b**), the main product resulted from C−H insertion adjacent to the benzyl ether oxygen (Scheme 1).[7] Since the cyclic oxonium ylide derived from **1b** should have formed under these conditions, this result was rationalized in terms of a lower activation barrier for the concerted [2,3]-shift pathway available in allyl migration as compared with the stepwise [1,2]-shift mechanism required for benzyl migration.[10] Slow rearrangement of the benzyl-substituted ylide would allow reversion to the metallocarbene precursor with consequent consumption via alternative pathways. However, acceptable yields of benzyl migration by **1b** *were* observed with catalysis by rhodium(II) triphenylacetate (Rh$_2$(tpa)$_4$). This result suggested a fundamental difference in the nature of the ylides derived from **1b** under copper and rhodium catalysis. The catalyst-dependent reversal in diastereoselectivity observed for the rearrangement of **1a** lent further support to this notion.

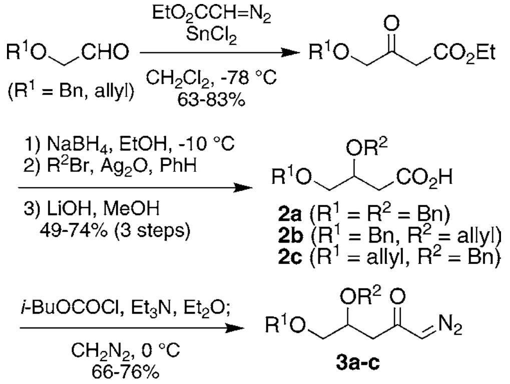
Scheme 1



The results seen with **1a**,**b** were intriguing but involved comparisons of product ratios from two structurally distinct (albeit very similar) substrates. Therefore, a group of diazoketone substrates was selected in which competitive formation and rearrangement of two different oxonium ylides via the same metallocarbene precursor was possible. We[1d,7b] and others[1e] had previously noted that rearrangements proceeding through five-membered cyclic oxonium ylides generally occur with much higher efficiency than their counterparts involving six-membered ylides. The substrates to be examined would contrast the effect of ylide ring size with the migrating group as a function of catalyst.

The necessary diazoketones **3a**−**c** could be prepared by coupling ethyl diazoacetate with benzyloxyacetaldehyde or allyloxyacetaldehyde in the presence of SnCl$_2$ (Scheme 2).[11] The resulting ketoesters were then reduced, O-alkylated, and converted to carboxylic acids **2a**−**c**. These intermediates underwent efficient carboxyl activation and diazomethane acylation to furnish **3a**−**c**.

Scheme 2



Treatment of **3a**−**c** with Rh$_2$(OAc)$_4$, Rh$_2$(tpa)$_4$, Cu(tfacac)$_2$, and copper(II) hexafluoroacetylacetonate (Cu(hfacac)$_2$) furnished rearrangement products **4** and **5** in generally good to excellent overall yields (mixtures of cis and trans diastereomers) and varying ratios (Table 1). Bis(benzyl) ether substrate **3a**, with comparable migrating groups on both oxygens, was examined first (entries 1−4). In all cases, regardless of catalyst, the major product was **4a**, resulting from benzyl [1,2]-shift via the five-membered cyclic oxonium ylide. Small amounts of the corresponding pyranone **5a** were seen in all cases, and enol ether **6a**, the product of benzyl [1,4]-shift, was also observed under copper catalysis. Enol ether **6a** is presumed to form from the same five-membered ylide that furnishes **4a**; thus, products derived from the five-membered ylide were favored in all four cases by ratios ranging from 3.2 to 9.1:1. Both **4a** and **5a** were

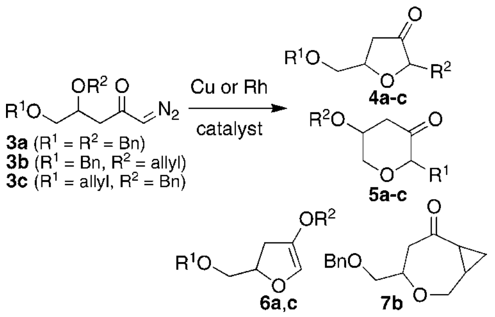
---

(9) Observation of significant levels of asymmetric induction in rhodium- or copper-catalyzed oxonium ylide rearrangements suggests that the metal remains associated during the rearrangement step: (a) Pierson, N.; Fernádez-Garciá, C.; McKervey, M. A. *Tetrahedron Lett.* **1997**, *38*, 4705−4708. (b) Doyle, M. P.; Forbes, D. C.; Vasbinder, M. M.; Peterson, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 7653−7654. (c) Clark, J. S.; Fretwell, M.; Whitlock, G. A.; Burns, C. J.; Fox, D. N. A. *Tetrahedron Lett.* **1998**, *39*, 97−100. (d) Hodgson, D. M.; Petroliagi, M. *Tetrahedron: Asymmetry* **2001**, *12*, 877−881. (e) Kitagaki, S.; Yanamoto, Y.; Tsutsui, H.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2001**, *42*, 6361−6364. See also ref 1g. (f) Review: Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50−61.

(10) Radical-pair mechanism for ammonium ylide rearrangements is well established: Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009−1027. We have also observed dimeric products consistent with radical intermediates (ref 1d).

(11) (a) Marotta, E.; Righi, P.; Rosini, G. *Org. Lett.* **2000**, *2*, 4145−4148. (b) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258−3260.

Table 1. Copper and Rhodium-Catalyzed Carbene-Transfer Reactions of **3a**−**c**



entry	substrate	catalyst/ conditions[a]	yield **4** (%)[b]	yield **5** (%)[b]	other products
1	**3a**	Cu(tfacac)$_2$/40 °C	33	8	**6a** (40%)
2	**3a**	Cu(hfacac)$_2$/40 °C	48	13	**6a** (16%)
3	**3a**	Rh$_2$(OAc)$_4$/rt	56	13	
4	**3a**	Rh$_2$(tpa)$_4$/rt	58	18	
5	**3b**	Cu(tfacac)$_2$/40°C	96		
6	**3b**	Cu(hfacac)$_2$/40°C	71		
7	**3b**	Rh$_2$(OAc)$_4$/rt	96		
8	**3b**	Rh$_2$(tpa)$_4$/rt	51		**7b** (12%)
9	**3b**	Rh$_2$(tpa)$_4$/40 °C	54		**7b** (20%)
10	**3c**	Cu(tfacac)$_2$/40 °C	16	67	**6c** (12%)
11	**3c**	Cu(hfacac)$_2$/40 °C	38	29	**6c** (19%)
12	**3c**	Rh$_2$(OAc)$_4$/rt	50	27	
13	**3c**	Rh$_2$(tpa)$_4$/rt	54	22	
14	**3c**	Rh$_2$(tpa)$_4$/rt/hexane	56	18	

[a] Dichloromethane (0.01 M) was used as the solvent in all cases except entry 14. Catalyst loading was 10 mol % for copper catalysts and 3 mol % for rhodium catalysts. [b] Isolated yields after chromatography. Both diastereomers of **4a**−**c** and **5a**,**c** were isolated in all cases (ratios generally ≤ 2:1).

formed as mixtures of diastereomers in all cases (1.5:1 to 4:1). Given the relatively low ratios and the primary mechanistic focus on migrating group selectivity,[12] individual stereoisomers were not rigorously assigned in this case.

Substrate **3b** has the option of allyl migration via a five-membered ylide or benzyl migration via a six-membered ylide (entries 5−9). The apparent preference for reaction via five-membered ylides seen with **3a** was expected to be reinforced by the more facile allyl [2,3]-shift vs a benzyl [1,2]-shift. This was the case, with good to excellent yields of **4b** and none of the pyranone **5b** isolated in all runs. However, Rh$_2$(tpa)$_4$ did furnish minor amounts of cyclopropane **7b**. Raising the temperature led to small increases in the yields of both **4b** and **7b**. As with **3a**, furanone **4b** was formed as a mixture of diastereomers (ca. 1:1).

The two ylide reactivity options available for substrate **3c** were expected to be more evenly balanced. Ring-closure kinetics should favor the five-membered ylide, while migrating group preferences should lead to products derived from the six-membered ylide. In the event, a strong catalyst dependence was observed for this substrate (entries 10−14). With Cu(tfacac)$_2$, pyranone **5c** was formed in good yield (1.4:1 dr), with minor amounts of furanone **4c** and enol ether **6c**. In contrast, both rhodium(II) catalysts furnished mainly the furanone **4c** (**4c**/**5c** = 1.8 to 3.1:1). Only Cu(hfacac)$_2$ was relatively unselective, giving similar amounts of **4c** and **5c** along with 19% of **6c**.

In previous examples containing *only* a γ-alkoxy group, large amounts of cyclopentanone products resulting from C−H insertion were formed at the expense of [1,2]-shift products resulting from six-membered ylides.[1,8] In these cases, the relative contributions of diminished six-membered ylide cyclization rate and the known activating effect of an adjacent alkoxy group on C−H insertion rate[13] were difficult to determine. The metallocarbenes derived from **3a**−**c** have a greater range of options. Aside from addition to the γ-alkoxy group and cyclopentanone formation by C−H insertion, the metallocarbenes can add to the closer β-alkoxy group to give a five-membered ylide. Five-membered ylide formation is possible for **1a**,**b**; however, these ylides lack a competent migrating group, and this process remains undetectable. In contrast, either ylide derived from **3a**−**c** is subject to rearrangement. Cyclopropanation of the remote alkene is also possible for the allyl ethers **3b** and **3c**. Bis(benzyl) ether **3a** furnished furanone **4a** as the major product with all catalysts (with Rh(II) catalysts providing higher yields), and no cyclopentanone C−H insertion products were isolated. These results suggest that cyclization to the five-membered ylide is strongly favored over C−H insertion. Also, the results with **3b** are in accord with prior observations seen with **1a**,**b**: allyl-substituted oxonium ylides appear to undergo fast rearrangement, leading to good yields of furanone **4b** regardless of the catalyst.

Substantial catalyst dependence for furanone vs pyranone products was seen for mixed bis(ether) substrate **3c**. Selective formation of **4c** with Rh(II) catalysts is consistent with preferential cyclization to the five-membered ylide. However, reversal to a >4:1 ratio of **5c**/**4c** in the case of Cu(tfacac)$_2$ indicates that the nature of the migrating group can override the inherent selectivity for five- vs six-membered ylides. This result strongly suggests that equilibration may occur between the two possible ylide intermediates **8** and **9** (Scheme 3). The presence of a better migrating group in the minor ylide isomer would allow predominant reactivity via that intermediate. The contrasting results with rhodium catalysts may be due to either diminished ylide equilibration or no special preference by Rh-derived ylides for allyl vs benzyl migration. Moreover, even a relatively minor change in the ligand of the copper catalyst (Cu(tfacac)$_2$ vs Cu(hfacac)$_2$) eliminated the selectivity for pyranone **5c**. As with **3a** and **3b**, no C−H insertion products were isolated in any of these examples.

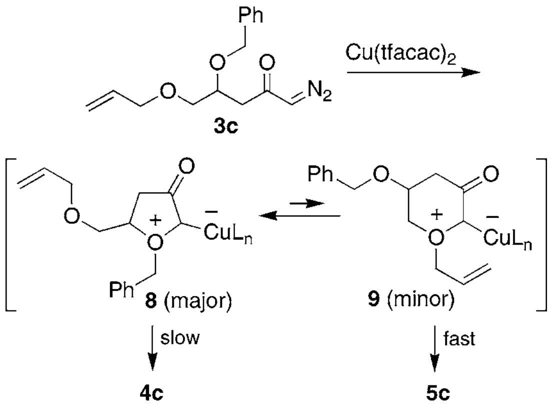
The origin of the large preference for allyl over benzyl migrating groups by oxonium ylides derived from Cu(tfacac)$_2$

---

[12] Rigorous distinction of furanones **4** from pyranones **5** was accomplished using HMBC correlations through the ring oxygen, IR C=O stretches (1755−1760 cm^{-1} for **4** and 1715−1730 cm^{-1} for **5**) and characteristic C=O ^{13}C chemical shifts (215−216 ppm for **4** and 207−209 ppm for **5**).

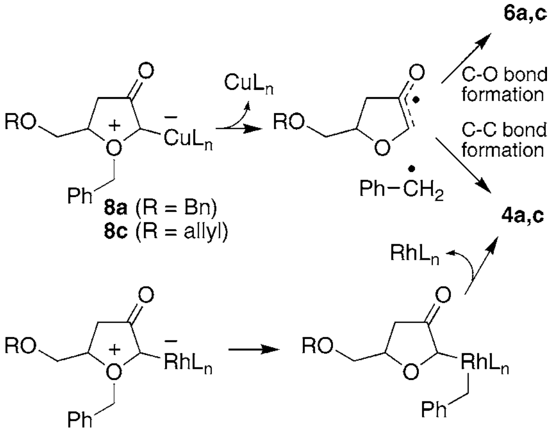
[13] (a) Adams, J.; Poupart, M. A.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749−1752. (b) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296−3305. (c) Davies, H. M. L.; Antoulinakis, E. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 383−385. (d) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063−3070.

Scheme 3



is uncertain. As noted above, this could be due simply to the availability of a lower energy concerted [2,3]-shift mechanism, whereas benzyl groups must migrate by a stepwise [1,2]-shift. The isolation of [1,4]-shift products **6a** and **6c** from the copper-catalyzed rearrangement of **3a** and **3c** is consistent with the notion that the intermediate O-benzyl ylides **8a**,**c** rearrange via radical-pair intermediates (Scheme 4). However, the corresponding rhodium-catalyzed reactions furnished none of the [1,4]-shift products and showed no preference for allyl over benzyl migrating groups. One possible explanation is direct involvement by the Rh catalyst in the [1,2]-shift mechanism, in accord with previous examples of catalyst-dependent asymmetric induction.[9] Metal participation could take the form of a concerted benzyl-transfer in analogy to that proposed by Roskamp and Johnson,[1b] or may proceed through stepwise benzyl-transfer to the metal followed by reductive elimination, a process suggested by Dhavale and co-workers.[14]

Scheme 4



The critical role played by the choice of transition metal catalyst used in carbene-transfer processes is well-known. Given the indirect evidence for continuing association of the metal catalyst following metallocarbene addition to ethers to form oxonium ylides, it should not be surprising that catalyst choice can also impact ylide reactivity. The simple 4,5-dialkoxy-1-diazo-2-pentanones examined in this study present options for competing ylides of different ring sizes and migrating groups. There is a strong preference for rearrangement via the five-membered oxonium ylide over the six-membered alternative. However, in the case of Cu(tfacac)$_2$, selective allyl migration can override the five-ring preference to give mainly pyranone products from the six-membered ylide. This can be rationalized by slow rearrangement of the initially formed five-membered *O*-benzyl oxonium ylide, permitting equilibration with the six-membered *O*-allyl isomer and relatively fast rearrangement of this intermediate. The absence of cyclopentanone products in *any* of the examples is especially notable, indicating the favorability of ylide formation over C−H insertion processes. These results highlight the importance of catalyst choice not only in control of metallocarbene generation and chemoselectivity but also in the optimization of any process proceeding via oxonium ylide intermediates.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. We also thank the Natural Sciences and Engineering Research Council of Canada and the University of Alberta.

Supporting Information Available: Full experimental procedures for the preparation and rearrangement of **3a**−**c** and characterization data and copies of NMR spectra for **3**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049493T

---

(14) Karche, N. P.; Jachak, S. M.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 6323−6332.