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Profound Catalyst Effects in the Generation and Reactivity of Carbenoid-Derived Cyclic Ylides[1]

F. G. West,* B. N. Naidu, and Richland W. Tester

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

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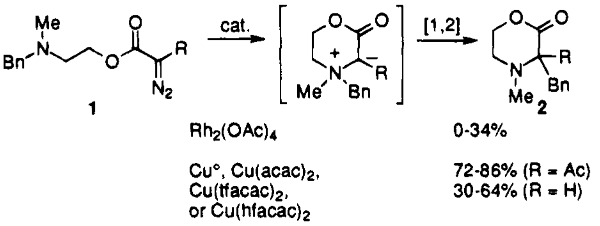
Summary: In contrast to results with $Rh_2(OAc)_4$, good yields of ylide-derived [1,2]-shift (or in some cases [1,4]-shift) products were obtained upon treatment of amino diazo ketone substrates **3b,c** and alkoxy diazo ketone substrates **5b,c** with soluble Cu(II) catalysts.

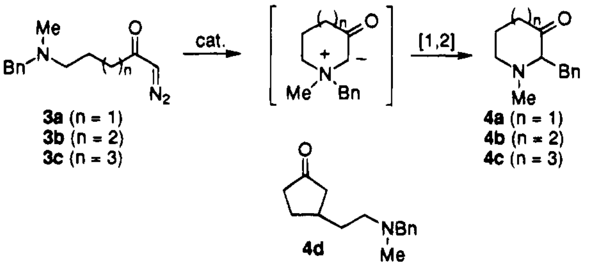
The generation and rearrangement of cyclic ylides from diazocarbonyl precursors has evolved as an important strategy in heterocycle and carbocycle synthesis.[2] We have sought to develop this methodology in conjunction with the Stevens [1,2]-shift[3] of ammonium[4] and oxonium[5] ylides, furnishing amino acid derivatives, functionalized tetrahydrofuranones, piperidones, and medium-sized carbocycles. While attractive in its simplicity and directness, this approach is sometimes complicated by alternative pathways available to the metal carbenoid precursors, such as C–H insertion.[5] We report here examples where drastic reactivity differences between rhodium and copper carbenoids are observed, leading in several cases to entirely different products with different catalysts. In particular, soluble copper catalysts furnish much greater amounts of ylide-derived products, including heretofore unreported oxonium ylide [1,4]-shift products.

It was expected that $Rh_2(OAc)_4$ would be unsuitable as a catalyst for the intermolecular addition of diazocarbonyl compounds to tertiary amines,[4b] due to saturation of empty sites on the Rh–Rh dimer by excess amine. However, we were surprised to find that *intramolecular* examples employing diazo esters **1** also proceeded poorly (eq 1).[6] On the basis of the intermolecular precedent, we examined several copper-based catalysts.[7] In the event, substrates **1** were cleanly converted to morpholones **2** in high yield with any of the copper catalysts. In some cases (e.g., R = H), only copper(II) acetylacetonate ($Cu(acac)_2$) furnished the [1,2]-shift product in acceptable yield.[9] Given the large catalyst differences observed in the morpholone series, we decided to reexamine several other substrates for which ylide formation has proven ineffective with $Rh_2(OAc)_4$ catalysis. While all catalysts were surveyed with each substrate, for the sake of brevity only those cases showing the most profound catalyst effects are discussed below.



(1)

In the earlier study of cyclic ammonium ylides, the method seemed applicable only to cases proceeding via six-membered ylide intermediates, such as **3a** (eq 2).[4a]



(2)

Attempts to apply identical conditions to substrates **3b,c** with one or two additional methylene units in the linker met with little success (Table 1, entries 3 and 5). Not surprisingly, intramolecular C–H insertion to give cyclopentanones (e.g., **4d**) appeared to be the major pathway in these cases. Examination of the same examples with Cu°, $Cu(acac)_2$, copper(II) trifluoroacetylacetonate, and copper(II) hexafluoroacetylacetonate ($Cu(hfacac)_2$) led to modest reductions in the yield of piperidone **4a** but significant improvement in the conversion of homologous substrates **3b** and **3c** to the corresponding azapinone **4b** and azocinone **4c**. *Most notably,* $Cu(acac)_2$ *furnished* **4b,c** *in 58–61% (entries 4 and 6), suggesting a remarkably efficient and selective capture of the copper carbenoid by amine to give a medium-sized cyclic ylide in preference to other carbenoid pathways.*

[⊗] Abstract published in *Advance ACS Abstracts,* October 15, 1994.

[1] Presented in preliminary form: West, F. G.; Tester, R. W.; Naidu, B. N. *Abstracts of Papers*; 207th National Meeting of the American Chemical Society, San Diego, CA, March, 1994; American Chemical Society: Washington, DC, 1994; ORGN 255.

[2] (a) Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561. (b) Clark, J. S.; Krowiak, S. A.; Street, L. J. *Tetrahedron Lett.* **1993**, *34*, 4385. Reviews: (c) Ye, T.; McKervey, A. *Chem. Rev.* **1994**, *94*, 1091. (d) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (e) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. (f) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.

[3] For a recent review, see: Markó, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 3.10.

[4] (a) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1993**, *115*, 1177. (b) West, F. G.; Glaeske, K. W.; Naidu, B. N. *Synthesis* **1993**, 977.

[5] (a) Eberlein, T. H.; West, F. G.; Tester, R. W. *J. Org. Chem.* **1992**, *57*, 3479. (b) West, F. G.; Eberlein, T. H.; Tester, R. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2857.

[6] West, F. G.; Naidu, B. N. *J. Org. Chem.*, in press.

[7] The use of copper-based catalysts was recommended by (1) their relatively low cost (permitting the use of larger quantities, if necessary, to prevent coordinative saturation) and (2) evidence reported by Doyle that copper carbenoids are more electrophilic than their rhodium counterparts, with a corresponding increase in ratio of ylide-derived to other products in competition experiments.[8a] Importantly, Clark has also employed soluble Cu(II) catalysts for the generation and [2,3]-shift of oxonium ylides[2b] to overcome similar shortcomings of $Rh_2(OAc)_4$ and, recently, to generate five- to eight-membered cyclic ammonium ylides: Clark, J. S.; Hodgson, P. B. *J. Chem. Soc., Chem. Commun.*, in press. We thank Dr. Clark for kindly providing a preprint of his manuscript.

[8] (a) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094. (b) For a review of pioneering work in the generation of ylides from copper carbenoids, see: Ando, W. *Acc. Chem. Res.* **1977**, *10*, 179.

[9] In a synthesis of the quinolizidine alkaloid epilupinine, we have also found that $Cu(acac)_2$ catalysis leads to the highest levels of diastereoselectivity in the [1,2]-shift of an ammonium ylide bearing a chiral migrating group: West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420.

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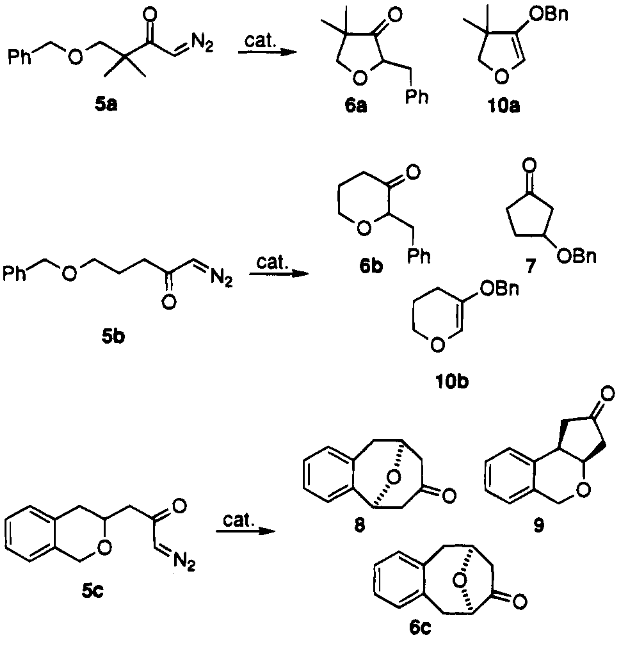
Table 1. Formation and [1,2]-Shift of Cyclic Ylides[a]

entry	substrate	condns[b]	products	yield[c] (%)
1[d]	**3a**	$Rh_2(OAc)_4/CH_2Cl_2$/rt	**4a**	99
2	**3a**	$Cu(acac)_2/PhCH_3$/reflux	**4a**	69
3	**3b**	$Rh_2)OAc)_4/CH_2Cl_2$/rt	**4b**	35
4	**3b**	$Cu(acac)_2/PhCH_3$/reflux	**4b**	61
5	**3c**	$Rh_2(OAc)_4/CH_2Cl_2$/rt	**4c**	0
			4d	61
6	**3c**	$Cu(acac)_2/PhCH_3$/reflux	**4c**	58
7[e]	**5a**	$Rh_2(OAc)_4/CH_2Cl_2$/rt	**6a**	65
8	**5a**	$Cu(hfacac)_2/CH_2Cl_2$/reflux	**6a**	24
			10a	6
9[e]	**5b**	$Rh_2(OAc)_4/CH_2Cl_2$/rt	**6b**	16
			7	47
10	**5b**	$Cu(hfacac)_2/CH_2Cl_2$/reflux	**6b**	35
			7	6
			10b	24
11[f]	**5c**	$Rh_2(OAc)_4/CH_2Cl_2$/rt	**8**	10
			9	40
12	**5c**	$Cu(hfacac)_2/CH_2Cl_2$/reflux	**6c**	95

[a] See eq 2 and Scheme 1. All substrates were tested with all catalysts; cases showing intermediate effects have been omitted. [b] Catalyst amounts: 3 mol % of $Rh_2(OAc)_4$ and 5 mol % of $Cu(acac)_2$ (ammonium ylides) or 15 mol % of $Cu(hfacac)_2$ (oxonium ylides). [c] Isolated yields after chromatography. Satisfactory IR, ^1H and ^{13}C NMR, and combustion analysis or HRMS were obtained for all substrates and products. [d] Previously reported in ref 4a. [e] Previously reported in ref 5a. [f] Previously reported in ref 5b.

Scheme 1



We had also encountered examples in the oxonium ylide series which underwent C−H insertion in preference to ylide formation under Rh(II) catalysis.[5,10] For example, cases proceeding through five-membered cyclic oxonium ylides (e.g., **5a**) typically led to good conversion to tetrahydrofuranone [1,2]-shift products such as **6a** (Scheme 1, Table 1). On the other hand, homologous substrate **5b** underwent predominant C−H insertion to give 3-(benzyloxy)cyclopentanone (**7**) and only minor amounts of ylide-derived product **6b**.[5a] In the case of **5c**, although a five-membered oxonium ylide intermediate was available to the carbenoid, it yielded only C−H insertion products **8** and **9**.[5b] The latter result was rationalized in terms of equilibration between ylide and carbenoid, with slow homolysis and [1,2]-shift by the ylide.

Strikingly different results were obtained with copper catalysis. Diazo ketone **5a** furnished modest yields of **6a**, along with varying amounts of a new product, **10a**,[11] arising from [1,4]-shift of the ylide benzyl group. Importantly, with $Cu(hfacac)_2$, **5b** gave a combined 59% yield of ylide-derived products **6b** and **10b** and only minor amounts of C−H insertion product **7** (entry 10). The most extreme example of catalyst dependent reactivity was seen with **5c** (entries 11 and 12). *Thus, while $Rh_2(OAc)_4$ catalysis led to only C−H insertion products* **8** *and* **9**, *$Cu(hfacac)_2$ furnished only benzocyclooctenone [1,2]-shift product* **6c** *in 95% yield.*

The drastic catalyst differences seen here may result from a variety of factors. The reputedly greater electrophilicity of copper carbenoids[7,8] may work in concert with a diminished propensity for C−H insertion[12] to favor ylide formation. Optimal results with $Cu(acac)_2$ for the formation of ammonium ylides, and with the somewhat more electron-deficient $Cu(hfacac)_2$ for oxonium ylide formation, suggest that fine-tuning of metallocarbene electrophilicity is necessary with variation of heteroatom nucleophilicity.[13] Equilibration between ylides and Rh−carbenoids has been previously suggested,[2a,5b] and it is possible that ylide to carbenoid reversal may be less favorable in the case of Cu−carbenoids. Isolation of oxonium ylide [1,4]-shift products is unprecedented, and the significant quantities of **10a,b** formed are less easily explained. We assume that **10** derives from the same ylide and radical pair intermediates that lead to **6**,[5a,14] but with recombination at oxygen instead of carbon[15,16] (Scheme 2, path a). Importantly, however, radical homodimers were not isolated in any of the copper-catalyzed cases, in contrast to earlier $Rh_2(OAc)_4$ examples. Thus, an alternative, metal-assisted mechanism (path b) must also be considered in these cases.[17] Regardless of mechanism, it is not surprising that the [1,4]-shift product derived from **5c** was not observed, as it would experience significant strain due to the presence of a bridgehead alkene.

In summary, we have described a number of ω-amino or ω-alkoxy diazo ketone substrates whose reactivity upon diazo decomposition is highly sensitive to catalyst choice. Use of homogeneous Cu(II) catalysts greatly enhances the production of products derived from cyclic

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[10] Preliminary experiments with other Rh(II) catalysts, such as $Rh_2(caprolactam)_4$ and $Rh_2(pfb)_4$, furnished less ylide-derived product that with $Rh_2(OAc)_4$.

[11] Greater amounts of [1,4]-shift product **10a** were obtained with Cu^0 or $Cu(tfacac)_2$ catalysis (10−32%) or with $Cu(hfacac)_2$ in refluxing toluene (19%).

[12] Taber, D. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 4.2.

[13] For recent reports of Rh(II) ligand effects on carbenoid chemoselectivity, see: (a) Brown, D. S.; Elliott, M. C.; Moody, C. J.; Mowlem, T. J.; Marino, J. P., Jr.; Padwa, A. *J. Org. Chem.* **1994**, *59*, 2447. (b) Cox, G. C.; Moody, C. J.; Austin, D. J.; Padwa, A. *Tetrahedron* **1993**, *49*, 5109.

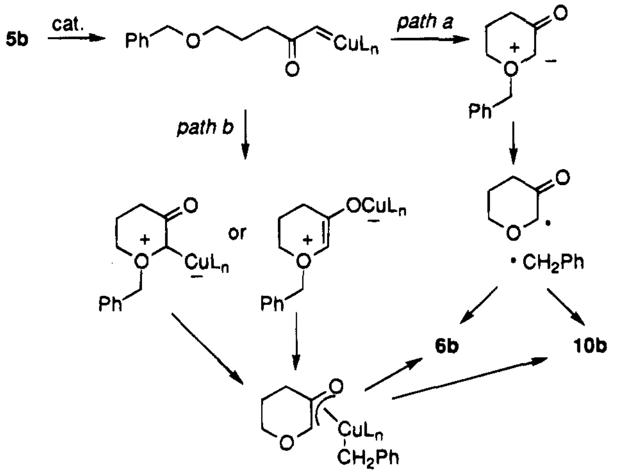
[14] Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009.

[15] Prior reports of minor amounts of [1,4]-shift products in rearrangements of sulfonium and ammonium ylides: (a) Baldwin, J. E.; Erickson, W. F.; Hackler, R. E.; Scott, R. M. *J. Chem. Soc., Chem. Commun.* **1970**, 576. (b) Chantrapromma, K.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1049.

[16] It has been suggested that [1,4]-shifts by unconstrained ylides could occur via a concerted mechanism.[15b] However, the necessary transition state should not be available to the cyclic ylide precursors of **10a,b**.

[17] Involvement of the metal in [1,2]-shifts of ylides formed by either copper or rhodium catalysis has been previously proposed: (a) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062. (b) See ref 8a. (c) Copper-mediated oxonium ylide [2,3]-shifts have also been suggested: Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193.

Scheme 2



ammonium and oxonium ylides. As a consequence, solutions are now in hand to several unsuccessful cases which had previously suggested significant limitations to this methodology. Medium-sized azapinone and azocinone rings can be obtained in good yield from acyclic precursors. The undersirable C−H insertion pathway can be substantially or totally suppressed in favor of oxonium ylide formation, most notably in the case of **5c**, and unprecedented amounts of [1,4]-shift products were observed. Studies are underway to understand the origins of these dramatic catalyst effects, and to apply them in the synthesis of natural products.

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Supplementary Material Available: Experimental procedures and physical data for **3b**,**c**, **4b**-**d**, **5c**, **6c**, and **10a**,**b** and ^{1}H and ^{13}C NMR spectra for **3c**, **4c**,**d**, **5c**, and **10a**,**b** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.