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First Efficient and General Copper-Catalyzed [2,3]-Rearrangement of Tetrahydropyridinium Ylids

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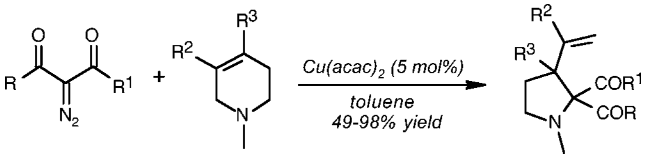
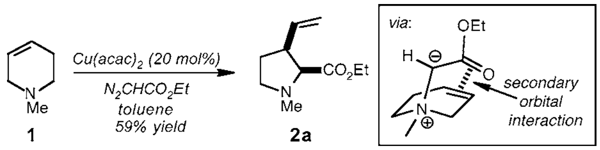
ABSTRACT



The factors affecting the copper-catalyzed rearrangement of ammonium ylids derived from tetrahydropyridines and diazoesters have been examined,and the first examples of high-yielding metal-catalyzed [2,3]-sigmatropic rearrangements of a wide range of such ylids are reported. The nature of the α-substituent in the diazo component of the reaction has a dramatic effect upon the yields of the reaction, with electron-withdrawing substituents enhancing the yield of the reaction.

The use of metal-catalyzed [2,3]-rearrangements of functionalized allylic ammonium ylids has received considerable attention of late. Such reactions generally proceed by means of an in situ generation of ylid by reaction of amines with diazo compounds.[1] Although the significance of the metal additive in these processes is unquestionable, the precise detail of its mode of action is still a source of debate.[2] Notwithstanding recent research, the application of metal catalysis to the [2,3]-rearrangement of ylids derived from tetrahydropyridines (a reaction originally described using ammonium salts by Ollis et al.)[3] has received little attention, despite the potential for application to the synthesis of a range of potent biological structures (such as kainoids and related structures).[4] We recently described the first such copper-catalyzed method for in situ formation and [2,3]-rearrangement using *N*-methyltetrahydropyridine (NMTP, **1**), ethyldiazoacetate (EDA), and Cu(acac)$_2$ (Scheme 1).[5]

Scheme 1. Copper-Catalyzed [2,3]-Rearrangement of NMTP



Though the reaction is highly *cis*-stereoselective and the process allows for the preparation of significant amounts of 3-vinylproline ester **2a**, the reaction conditions are very

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[1] (a) *Nitrogen, Oxygen and Sulfur Ylide Chemistry*; Clark, J. S., Ed.; Oxford University Press: Oxford, 2002. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley & Sons: New York, 1998.

[2] For a review, see: Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A.; *Chem. Soc. Rev.* **2001**, *30*, 50.

[3] (a) Mageswaran, S.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1953. (b) Mageswaran, S.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1973**, 656.

[4] For a review of synthetic studies see: Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149. *Synthesis of Optically Active* α*-Amino Acids*; Williams, R. M., Ed.; Pergamon Press: New York, 1989.

[5] (a) Heath, P.; Roberts, E.; Sweeney, J. B.; Wessel, H.-P.; Workman, J. A. *J. Org. Chem*, **2003**, *68*, 4083. (b) For previous studies in salt rearrangements, see: Sweeney, J. B.; Tavassoli, A.; Carter, N. B.; Hayes, J. F.; *Tetrahedron* **2002**, *58*, 10113.

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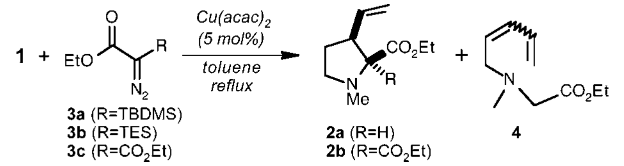
precisely defined. Although only 1 equiv of EDA is required for optimal results,[6] slow addition (via syringe pump) of reagents is required along with a relatively high catalyst loading (20 mol %), and the product is occasionally contaminated with an elimination byproduct. Thus, we sought to study the factors underlying this reaction, with a view to probing the mechanism of the process and assessing the scope of the method. We report here that, by suitable choice of substituents, high-yielding copper-catalyzed [2,3]-tetrahydropyridinium rearrangements are feasible in a diverse range of structural motifs. To our knowledge, these are the first examples of such metal-mediated reactions in which the alkene component of the sigmatropic rearrangement is constrained in a six-membered ring.[1a]

Although considered to be stable, EDA slowly polymerizes at elevated temperatures. The corresponding α-silyl derivatives are known to possess enhanced stability,[7] and we sought to utilize this property to avoid the need for slow addition. Thus, α-silyldiazoacetates **3a** and **3b** were reacted with NMTP in the presence of Cu(acac)$_2$. To our surprise, the reactions proceeded in *lower* yield than the reaction using EDA itself. Only after extensive variation in catalyst structure could even mediocre yields of vinyl proline be obtained (Table 1, entries 4 and 8−11). Where the reaction did proceed, a number of features emerged. First, though yields were uniformly lower than those of the reactions using EDA itself, a lower catalyst loading was needed (5 versus 20 mol %). Second, in all cases where rearrangement did occur, the products did not contain a silyl substituent, in contrast to other systems.[8] Reactions carried out at lower temperature (entry 3), in an attempt to suppress desilylation and improve yields, yielded only starting materials. Third, it was not necessary to use a slow addition process to obtain highest yields: the diazoester solution was simply added dropwise over a 5-min period. Thus, though proving too inefficient to act as a method of general utility, these preliminary studies demonstrated the principle that the introduction of a stabilizing substituent in the diazo component of the reaction would lead to an enhanced process, at least in terms of logistics.

We next sought to introduce a more powerful anion-stabilizing group as a means of optimizing the reactions and were delighted to observe a smooth reaction when diethyl diazomalonate was used in the reaction (entry 14). The yield of rearranged product was excellent and there was no trace of byproduct in the crude reaction mixture; this parallels our previous observations of ylids derived from *N*-(2-malonyl) NMTP ammonium salts.[5b] The use of Rh(I) as a catalyst[6] (entry 15) was less efficient, in line with our original observations using EDA. The best yield of rearrangement was obtained when adding neat diazomalonate in a single portion to a heated solution of catalyst and NMTP (entry 16), representing a vastly simplified process compared to the original reaction.

Table 1. Metal-catalyzed Reaction of 2-Substituted Diazoesters with NMTP

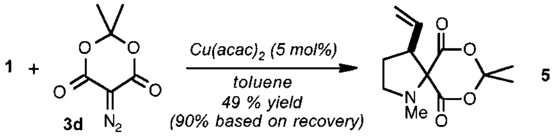


entry[a]	R	catalyst	addition rate (mL/h)	yield **2**, %	yield **4**, %
1	H	Cu(acac)$_2$[b]	1.45[c]	**2a**, 59	0
2	TBDMS	Cu(acac)$_2$	1.45	**2a**, 19	0
3	TBDMS	Cu(acac)$_2$	150[d]	**2a**, <5[e]	0
4	TBDMS	Cu(tfacac)$_2$	150	**2a**, 33	tr[f]
5	TBDMS	Cu(hfacac)$_2$	150	**2a**, 11	5
6	TBDMS	Cu(OTf)$_2$	150	0	0
7	TBDMS	Rh$_2$(OAc)$_4$	150	0	0
8	TES	Cu(acac)$_2$	1.45	**2a**, 31	tr[f]
9	TES	Cu(acac)$_2$	150	**2a**, 28	tr[f]
10	TES	Cu(tfacac)$_2$	150	**2a**, 15	3
11	TES	Cu(hfacac)$_2$	150	**2a**, 33	5
12	TES	Cu(OTf)$_2$	150	0	0
13	TES	Rh$_2$(OAc)$_4$	150	0	0
14	CO$_2$Et	Cu(acac)$_2$	150	**2b**, 80	
15	CO$_2$Et	Rh$_2$(OAc)$_4$	150	**2b**, 25	
16	CO$_2$Et	Cu(acac)$_2$	*g*	**2b**, 90	

[a] Typical procedure: a toluene solution of the diazoester was added, via syringe, to a stirred solution of the catalyst and NMTP (1 equiv) in refluxing toluene. [b] 20 mol % catalyst used. [c] Addition via syringe pump. [d] Dropwise addition over 5 min, 80 °C. [e] Products not isolated, yield estimated from ^{1}H NMR spectra. [f] As judged from ^{1}H NMR. [g] Reagent added neat, in a single portion.

When diazo Meldrum's acid (**3d**) was employed using the same conditions, spiro proline **5** was obtained; although the reaction was less efficient in terms of isolated yield, nearly half of the starting material was recovered from the reaction (Scheme 2). In the absence of detailed kinetic data, it is not possible to comment directly upon the mechanistic reasons for this observation, though perhaps the enhanced stability (and concomitant diminished reactivity) of the ylid intermediate in this reaction led to a diminution in the rate of rearrangement.

Scheme 2. Copper-Catalyzed [2,3]-Rearrangement Using Diazo Meldrum's Acid



Although the proline derivatives **2a**, **2b**, and **5** are flexible synthetic intermediates in their own right, we next sought

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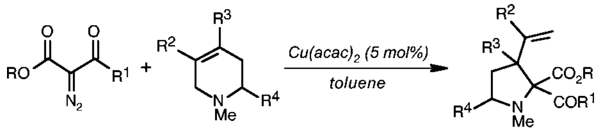
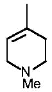
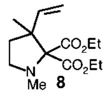
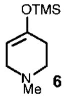
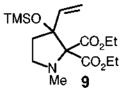
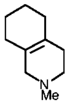
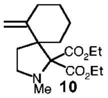
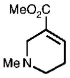
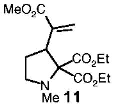
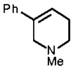
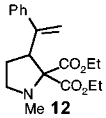
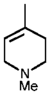
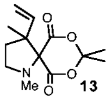
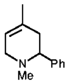
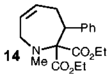
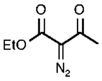
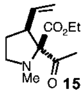
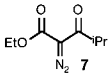
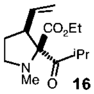
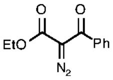
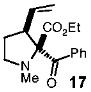
(6) Doyle et al. found that Rh(I)-catalyzed rearrangement of acyclic allyamines required 5 equiv of amine for satisfactory yield: Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094.

(7) Schöllkopf, U.; Hoppe, D.; Rieber, N.; Jacobi, V. *Liebigs Ann. Chem.* **1969**, *730*, 1. For the synthesis of silyl diazo reagents, see: Allspach. T.; Gümbel, H.; Regitz, M. *J. Organomet. Chem.* **1985**, *290*, 33.

(8) See, for instance: Bolm, C.; Saladin, S.; Kasyan, A. *Org. Lett.* **2002**, *4*, 4631. Marsden, S. P.; Pang, W.-K. *J. Chem. Soc., Chem. Commun.* **1999**, 1199.

Table 2. Scope of Metal-Catalyzed [2,3]-Rearrangement



Entry	Amine	3	Product	Yield/% (*cis*:*trans*)
1		**3c**	 **8**	98
2	 **6**	**3c**	 **9**	89
3		**3c**	 **10**	90
4		**3c**	 **11**	83
5		**3c**	 **12**	85
6		**3d**	 **13**	60 (86^b)
7		**3c**	 **14**	51
8	**1**		 **15**	58 (66:33)
9	**1**	 **7**	 **16**	56 (75:25)
10	**1**		 **17**	68 (52:48)

[a] Typical procedure: the diazo reagent was added rapidly to a refluxing mixture of amine (1 equiv) and Cu(acac)$_2$ (5% mol) in refluxing toluene. [b] Yield based on recovery of unreacted starting material.

to assess the effect of alkene substitution upon the process, by using a range of substituted NMTP derivatives. Thus, when a range of tetrahydropyridines were reacted with diazoesters using the optimized protocol, we observed generally smooth [2,3]-rearrangement (Table 2), giving a diverse range of highly functionalized vinyl proline products. It should be noted that the reaction is only slightly affected by electronic or steric perturbation, proceeding in excellent yield even when the reactive center bears electron-rich (entries 1−3) or electron-deficient (entries 4 and 5) substituents. The reaction also proceeds well when diazo ketoesters are used (entries 8−10); the yields of the processes are similar to those seen using **3e**, as would be predicted if increased stability of the ylid intermediate reduces its reactivity. In particular, the rearrangements using silyl enol ether **6** (entry 2) and diazo ketoester **7** (entry 9) are noteworthy as a demonstration of the synthetic power of this process. These reactions rapidly generate products directly related to the densely functionalized pyrrolidinone subunits of the oxazolomycin[9] (product **9**) and lactacystin[10] (product **16**) classes of natural products, respectively.

Only when a 6-phenyl substituent was present in the NMTP was [2,3]-rearrangement not efficient. In this case (entry 7), the [1,2]-Stevens rearrangement was favored, yielding only ring-expanded product in moderate yield.

In summary, we have reported the first metal-catalyzed [2,3]-sigmatropic rearrangements of tetrahydropyridinium ylids, via reaction of diazo esters with *N*-methyltetrahydropyridines. A range of diazo and amine components have been used to generate a collection of structurally diverse, densely functionalized pyrrolidines in good yields. We believe that this protocol will find widespread use in the synthesis of biologically significant compounds.

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Supporting Information Available: Representative experimental and spectra data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Mori, T.; Takahashi, K.; Kashiwabara, M.; Uemura, D.; Katayama, C.; Iwadare, S.; Shizuri, Y.; Mitomo, R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett*. **1985**, *26*, 1073.

(10) For recent synthetic efforts directed towards the synthesis of lactacystin, see: Page, P. C. B.; Leach, D. C.; Hayman, C. M.; Hamzah, A. S.; Allin. S. M.; McKee, V. *Synlett* **2003**, 1025. Green, M. P.; Prodger, J. C.; Hayes, C. J.; *Tetrahedron Lett.* **2002**, *43*, 6609 and references therein.