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Stereoselective formation and rearrangement of morpholinium ylides derived from copper carbenoids

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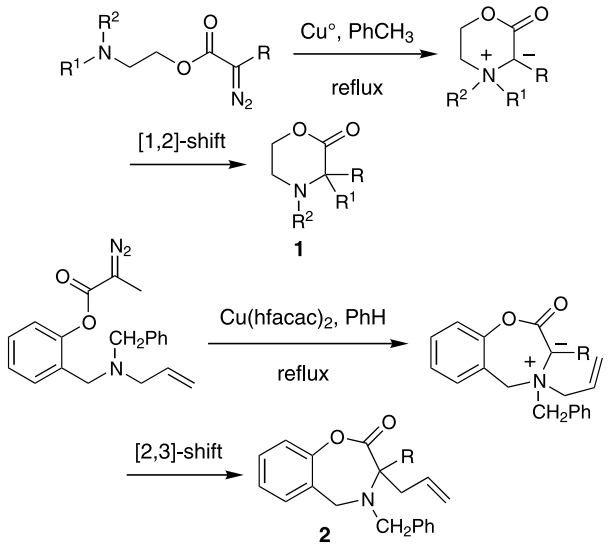
Abstract—Amino diazoacetoacetates **4a–e** and **7a,b** were prepared from readily available amino alcohols and subjected to copper-catalyzed carbene-transfer reaction. Substrates **4c–e** furnished the morpholin-2-ones **5c–e** in good yield via the corresponding cyclic ammonium ylides, albeit with poor diastereoselectivity. Substrates **4a,b** failed to provide the corresponding morpholinones, perhaps as a result of steric congestion. Cyclic substrates **7a,b** underwent conversion to bicyclic morpholinones **8** and **9** in good yield and with moderate to good diastereoselectivity. This result is rationalized via control of the transiently stereogenic ammonium center of the intermediate bicyclic ylides.

Ammonium ylides are readily accessible from diazocarbonyl precursors and tertiary amines, and their subsequent rearrangement by a [1,2]- or [2,3]-shift of one of the ammonium substitutents introduces functionality adjacent to the nitrogen.[1] We[2] and others[3] have shown that this approach can be used for the construction of amino acid derivatives. Formation of cyclic amino esters such as morpholin-2-ones 1[2b] or related azlactones 2[3d] is especially appealing (Scheme 1). Tethering the diazoester metallocarbene precursor to the amine trap maximizes the efficiency of ylide formation relative to other normally competitive carbene processes, and the resulting products are subject to selective processing to reveal fully substituted amino acid derivatives. Moreover, the starting amino alcohols are readily available and are easily converted into diazo ester substrates using standard, high-yielding chemistry.

Formation of racemic products is an obvious limitation of this strategy and the power of this methodology would be greatly leveraged if the new stereogenic center could be formed with control of configuration.[4] Establishing a particular configuration at the α position would presumably require prior stereoselective quaternization at the ammonium nitrogen atom of the intermediate ylide.

We have shown that cyclic ammonium salts of known configuration at nitrogen undergo rearrangement with good to excellent chirality transfer, involving migration of benzyl or allylic groups in a facially selective manner.[5] Related studies involving catalytic generation and rearrangement of spirocyclic ammonium ylides via metallocarbene intermediates also demonstrated a high



Scheme 1. Cyclic amino acid derivative via ammonium ylides.

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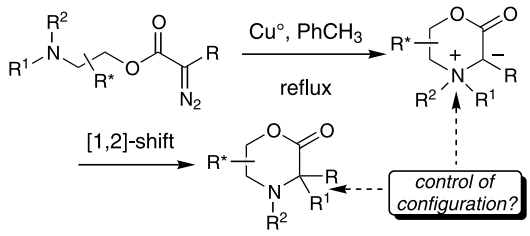
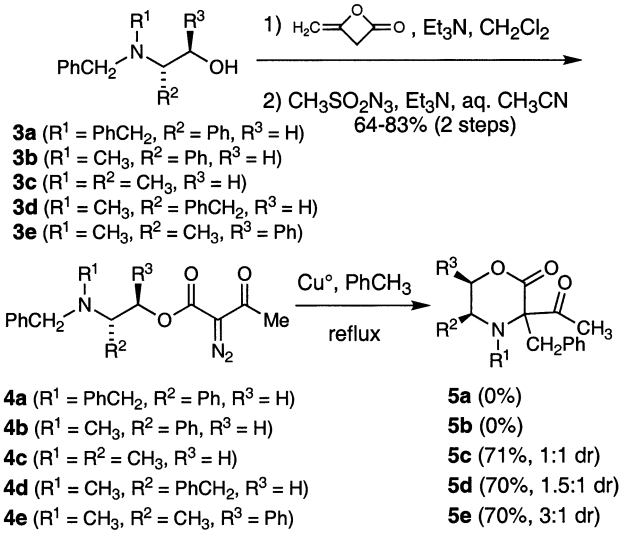


Scheme 2. Diastereoselective ylide formation via chiral diazo esters.



Scheme 3. Preparation and rearrangement of diazoacetoacetates **4a–e**.

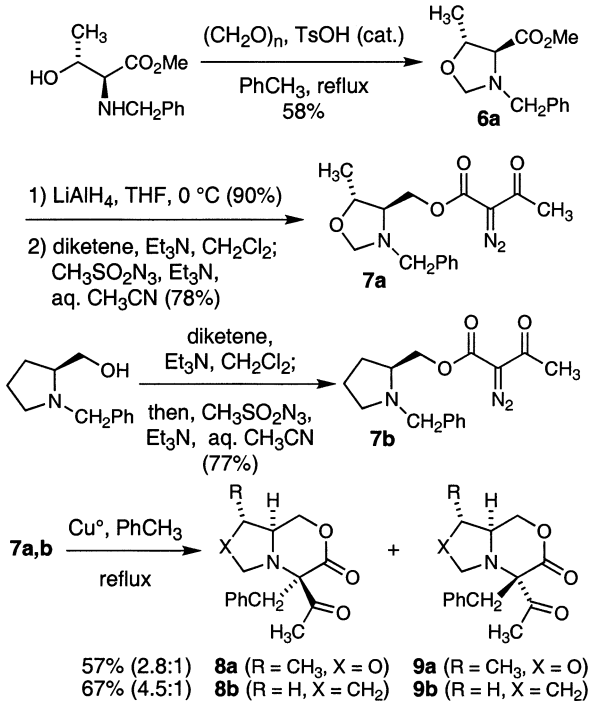
degree of N→C chirality transfer.[6] Given this precedent, we were interested in exploring the morpholinone strategy using amino alcohols possessing a chiral backbone (Scheme 2). Such an approach would generate morpholinium ylides subject to rearrangement as before, but would rely on preexisting stereogenic centers to establish the ammonium stereocenter. Herein, we describe our preliminary results in this study.

Our initial efforts focused on the use of acyclic ethanolamine derivatives from the chiral pool possessing one or two stereocenters. Thus, treatment of *N*,*N*-dialkylphenylglycinols **3a**,**b**, *N*-methyl-*N*-benzylalaninol **3c**, *N*-methyl-*N*-benzylphenylalaninol **3d** and *N*-benzylephedrine[7] **3e** with diketene followed by diazotransfer with MsN_3 furnished substrates **4a–e** in good yield (Scheme 3). Diazoacetoacetates **4c–e** underwent efficient conversion to the corresponding morpholones **5c–e** upon treatment with copper powder in refluxing toluene, but with limited diastereoselectivity. Only the ephedrine-derived substrate **4e** showed any significant stereoselectivity, suggesting that the presence of a single stereocenter adjacent to nitrogen was insufficient to effect selective quaternization of the amine.

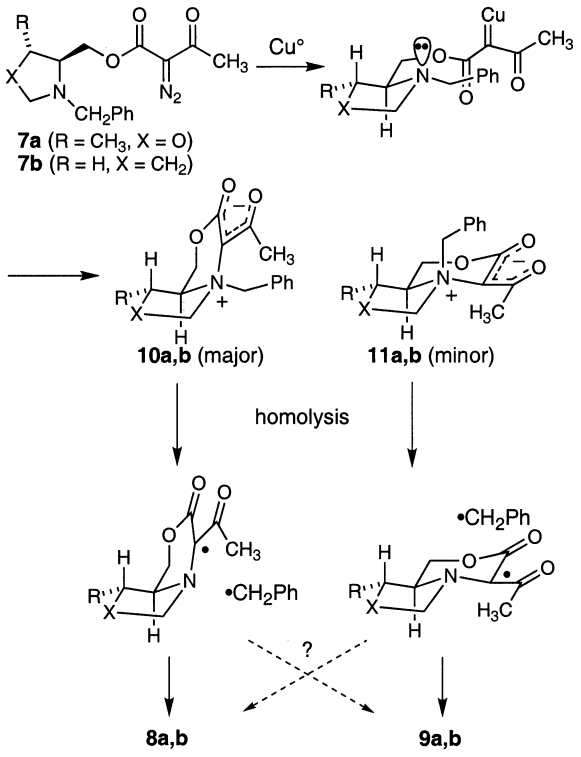
Phenylglycinol derivatives **4a** and **4b** failed to yield any of the desired morpholones **5a** and **5b**, perhaps as a result of high steric demand near the amine nitrogen.[8] Given the modest selectivity and capricious reactivity seen in these cases, the configuration of the major diastereomers of **5d** and **5e** was not determined.

The low stereoselectivity seen with **4c–e** was disappointing, and indicated that asymmetric centers in a flexible intervening chain provided very little bias in favor of one configuration at the ammonium nitrogen. On the presumption that greater conformational rigidity should be beneficial in this regard, we next examined two cyclic cases (Scheme 4). *N*-Benzylthreonine methyl ester was converted to oxazolidine **6a** by treatment with formaldehyde in the presence of *p*-toluenesulfonic acid. Reduction to the primary alcohol and treatment as before with diketene and MsN_3 furnished diazoacetoacetate **7a**. In a similar sequence, *N*-benzylprolinol[9] was converted to diazoacetoacetate **7b**. When these substrates were subjected to copper powder in refluxing toluene, the corresponding fused bicyclic morpholones **8a**,**b** and **9a**,**b** were obtained in 57–67% yield.[10] Both cases showed significant stereoselectivity, especially **7b**, which provided a 4.5:1 ratio of diastereomers **8b** and **9b**. It was possible to obtain a crystalline sample of minor diastereomer **9a** suitable for X-ray diffraction analysis,[11] and it clearly showed an *endo* disposition for the migrating benzyl group. The opposite configuration at the quaternary carbon was therefore assigned to the major isomer, and the structures of **8b** and **9b** were assigned by analogy.

Our rationale for the observed stereoselectivity in these cases is based upon preferred attack by the metallocarbene intermediate from the β-face of the 5-membered heterocycle (Scheme 5) to form ylides **10a** and **10b**. Two factors should reinforce this bias. First, the amine



Scheme 4. Preparation and rearrangement of diazoacetoacetates **7a,b**.



Scheme 5. Rationale for stereoselective rearrangement of **7a,b**.

nitrogen should exist primarily in the invertomer that places the benzyl group and the carbenoid side chain in a *trans* arrangement, with the lone pair *cis* to the carbenoid.[12] Second, ring-closure to form the *cis*-fused bicyclo[4.3.0]nonane ring system **10** should be kinetically favored over closure to the less stable *trans*-fused ylides **11**. Formation of **8** and **9** then proceeds via N-C benzyl homolysis and recombination at the adjacent carbon.[13] The major products **8** would result from migration of the benzyl group along the bottom, *exo* face of the bicyclic radical, in analogy to the earlier monocyclic examples employing stepwise quaternization/deprotonation.[5a] Minor products **9** could arise from the *trans*-fused ylides **11**, or more likely, via diffusion of the radical pairs derived from ylides **10**. Since recombination after diffusion is likely to favor approach of the benzyl group from the more accessible *exo* face, the possibility that the observed selectivities result entirely from this preference cannot be ruled out.

These preliminary studies have shown that morpholin-2-ones with a quaternary center at C-3 can be formed with useful stereoselectivity using readily available amino acid-derived diazoacetoacetates. This process is presumed to involve diastereoselective ammonium ylide formation, followed by facially selective [1,2]-migration of a benzyl group. Future efforts will include examination of the corresponding [2,3]-shift chemistry, and elaboration of the bicyclic morpholones to acyclic α-quaternary amino acid derivatives.

Acknowledgements

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10. **Representative experimental procedures: Diazoacetoacetate 7b.** Diketene (0.58 mL, 7.5 mmol) was added neat over a period of 5 min to a 0°C solution of (*S*)-*N*-benzylprolinol (2.65 g, 5.0 mmol) and Et_3N (0.69 mL, 5.0 mmol) in 20 mL dry CH_2Cl_2. The reaction mixture was stirred at 0°C for 3 h, then solvent and excess diketene were removed under reduced pressure and the resulting orange liquid was immediately dissolved in 20 mL CH_3CN. To this solution were added Et_3N (0.69 mL, 5.0 mmol), H_2O (0.10 mL, 5.0 mmol) and MsN_3 (0.56 mL, 6.5 mmol). The reaction mixture was stirred at rt for 12 h, then most of the solvent was removed and the residual oil was dissolved in Et_2O (100 mL) and washed successively with 1 N NaOH (4×20 mL) and brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated, and the resulting yellow oil was purified by flash chromatography (silica gel, 2 cm×15 cm column, 3:1 hexanes/EtOAc) to give 1.16 g (77%) of **7b** as a yellow oil: $[\alpha]_D^{22} = -43.4$ ($c = 0.47$, CH_2Cl_2); R_f 0.24 (7:3 hexanes/EtOAc); IR (thin film) 2962, 2139, 1718, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29–7.20 (m, 5H), 4.22 (d, 1H, $J = 2.1$ Hz), 4.19 (d, 1H, $J = 2.1$ Hz), 4.01 (d, 1H, $J = 13.2$ Hz), 3.41 (d, 1H, $J = 13.2$ Hz), 2.97–2.82 (m, 2H), 2.48 (s, 3H), 2.27 (dd, 1H, $J = 17.1$, 8.4 Hz), 2.00–1.91 (m, 1H), 1.77–1.63 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.6, 161.0, 139.1, 128.3, 127.9, 126.6, 76.0, 66.9, 61.7, 59.1, 54.2, 28.1, 28.0, 22.9. Anal. calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.89; H, 6.41; N, 13.79%. **Morpholinones 8b and 9b.** A solution of **7b** (0.301 g, 1.0 mmol) in dry $PhCH_3$ (20 mL) was added dropwise via cannula to a refluxing suspension of copper powder (32 mg, 0.5 mmol) in dry $PhCH_3$ (50 mL) over a period of 45 min. The addition flask was rinsed with $PhCH_3$ (5 mL) and this solution was added to the reaction mixture. After an additional 2 h at reflux, the reaction mixture was cooled, concentrated and the residue was purified by flash chromatography (silica gel, 4 cm×15 cm column, 7:3 hexanes/EtOAc) to afford 0.182 g (67%) of a 4.5:1 mixture of **8b** and **9b**. Pure samples of each diastereomer **6b** could be obtained by iterative chromatography. **8b**: white solid (mp 103–105°C; $[\alpha]_D^{22} = +62.8$ ($c = 0.05$, CH_2Cl_2); R_f 0.33 (7:3 hexanes/EtOAc); IR (KBr) 2977, 1731, cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29–7.20 (m, 5H), 4.28 (dd, 1H, $J = 10.0$, 3.2 Hz), 4.04 (dd, 1H, $J = 10.5$, 10.1 Hz), 3.43 (s, 2H), 3.13 (dt, 1H, $J = 8.6$, 5.9 Hz), 2.78 (dt, 1H, $J = 7.8$, 5.3 Hz), 2.60–2.50 (m, 1H), 2.23 (s, 3H), 1.95–1.63 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.4, 168.3, 136.8, 130.3, 128.5, 126.8, 76.8, 75.3, 51.7, 45.0, 35.4, 27.1, 25.5, 23.4. Anal. calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.41; H, 7.07; N, 5.02%. **9b**: yellow oil; $[\alpha]_D^{22} = -100.8$ (c = 0.03, CH_2Cl_2); R_f 0.31 (7:3 hexanes/EtOAc); IR (thin film) 2948, 1729, cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29–7.14 (m, 5H), 4.06 (dd, 1H, $J = 10.2$, 3.0 Hz), 3.36–3.26 (m, 1H), 3.22 (s, 2H), 3.18 (dt, 1H, $J = 8.1$, 2.7 Hz), 3.07 (dd, 1H, $J = 10.2$, 9.6 Hz), 2.65 (dt, 1H, $J = 8.4$, 5.4 Hz), 2.20 (s, 3H), 2.05–1.81 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.5, 169.1, 135.6, 130.4, 128.0, 126.9, 76.8, 72.5, 53.2, 45.6, 38.6, 28.6, 27.1, 23.5. Anal. calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.07; H, 6.95; N, 4.99%.

11. Crystallographic data (excluding structure factors) for compound **9a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 200163. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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