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Development of a 2-Aza-Cope-[3 + 2] Dipolar Cycloaddition Strategy for the Synthesis of Quaternary Proline Scaffolds

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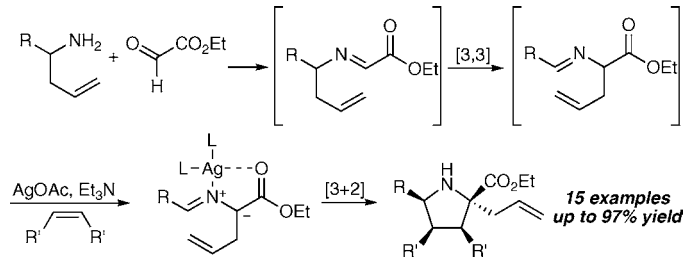
ABSTRACT



A one-pot multicomponent procedure for the synthesis of highly functionalized pyrrolidine rings through a domino 2-aza-Cope-[3 + 2] dipolar cycloaddition sequence has been demonstrated. This protocol was found to be both high-yielding and stereoselective for the *endo* cycloadduct.

The pyrrolidine ring represents a prevalent scaffold for many compounds of pharmaceutical interest, as well as a structural element common to the *Amaryllidaceae* and *Erythrina* alkaloids.[1] The development of mild, efficient, and operationally simple methods for their construction continues to warrant interest. As chemical synthesis places an ever-increasing emphasis on concise molecular assembly, processes that rapidly assemble complex structures in a stereocontrolled fashion are highly desirable. Toward these ends, multicomponent reactions have played an important role.[2] The orchestration of two or more distinct chemical events involving multiple components permits a magnification of structural complexity in a minimal number of synthetic steps.[3] In the context of heterocyclic chemistry, strategic extensions of the 2-aza-Cope rearrangement could potentially meet these criteria. Specifically, the merging of the 2-aza-Cope rearrangement with a [3 + 2] dipolar cycloaddition reaction could provide new and more concise routes to a variety of pyrrolidine-containing targets.

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(1) For reviews of these alkaloid classses, see: (a) Lewis, J. R. *Nat. Prod. Rep.* **1993**, *10*, 291–299. (b) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, p 252. (c) Tsuda, Y.; Sano, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1996; Vol. 48, p 239. For selected syntheses, see: (d) Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 2050–2051. (e) Overman, L. E.; Shim, J. *J. Org. Chem.* **1993**, *58*, 4662–4672. (f) Ishizaki, M.; Hoshino, O.; Iitaka, Y. *Tetrahedron Lett.* **1991**, *32*, 7079–7082. (g) Pansare, S. V.; Lingampally, R.; Kirby, R. L. *Org. Lett.* **2010**, *12*, 556–559. (h) Jones, M. T.; Schwartz, B. D.; Willis, A. C.; Banwell, M., G. *Org. Lett.* **2009**, *11*, 3506–3509. (i) Yamada, K.; Yamashita, M.; Sumiyoshi, T.; Nishimura, K.; Tomioka, K. *Org. Lett.* **2009**, *11*, 1631–1633.

(2) (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.

(3) (a) Parsons, J. P.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195–206. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.

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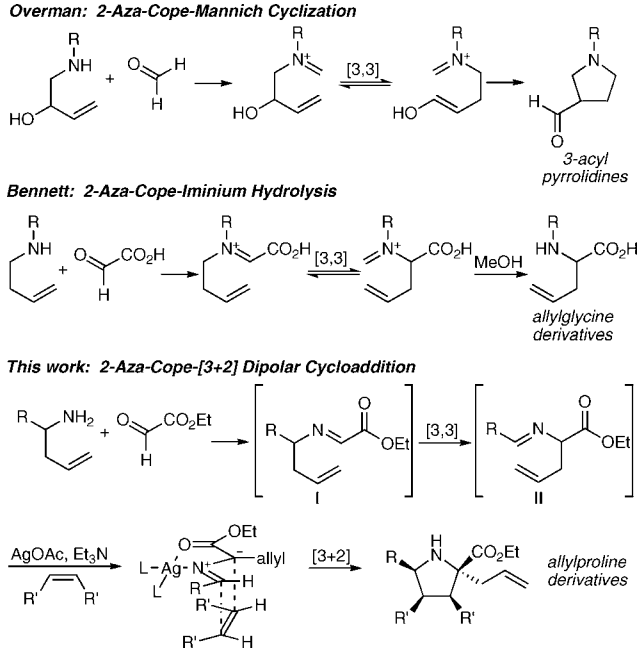
The 2-aza-Cope rearrangement affords imine or iminium products, which could in principle be used directly for additional carbon−carbon bond-forming events. A classic example of this strategy is well illustrated by Overman's aza-Cope−Mannich reaction (Scheme 1).[4] In this powerful variant, a charge-accelerated cationic 2-aza-Cope rearrangement affords an iminium ion having an enol moiety correctly positioned for Mannich cyclization. The utility of this process has been amply demonstrated by Overman[5] and others[6] in many elegant total syntheses. Bennett and others have used a 2-aza-Cope-iminium ion solvolysis protocol to prepare allylglycine derivatives.[7]

Scheme 1. Applications of the 2-Aza-Cope Rearrangement



Inspired by these advancements, we took interest in developing conceptually new unions of the 2-aza-Cope rearrangement with other carbon−carbon bond-forming reactions. We first envisioned that the 2-aza-Cope rearrangement could be used to prepare azomethine ylide precursors for direct use in [3 + 2] dipolar cycloadditions. Such a strategy would capitalize on the considerable bond-reorganization properties of the Cope rearrangement, as well as the diversity and facility of azomethine ylide cycloaddition. Condensation of a homoallylic amine with a glyoxylate ester would provide imine **I** (Scheme 1), which after thermodynamically driven 2-aza-Cope rearrangement would afford imine **II**. The addition of a metal/amine base pair would result in the formation of a metalated azomethine ylide for subsequent [3 + 2] dipolar cycloaddition with a wide range of dipolarophiles.[8]

Central to our plans was the need for stereocontrol. Cycloaddition could potentially generate up to four stereogenic centers, with at least one quaternary, within the proline cycloadduct. Predictions as to which stereoisomers will dominate would require analyses of both azomethine ylide geometry as well as *endo* versus *exo* approach of the dipolarophile. Cognizant that imines bearing electron-withdrawing groups (e.g., **II**) lead to metalated azomethine ylides with rigid geometries,[9] more accurate predictions regarding the stereochemical outcome should be possible. As a result, the 2-aza-Cope-[3 + 2] dipolar cycloaddition sequence should stereoselectively generate functionalized proline scaffolds bearing a quaternary center.

Our survey of substrates centered on homoallylamines **1a**−**e** (Figure 1),[10] ethyl glyoxylate (**2**) as the aldehyde component, and dipolarophiles **3a**−**c**. For our initial optimization studies, homoallylic primary amine **1a**, ethyl glyoxylate (**2**), and *N*-phenyl maleimide (**3a**) were selected, and each step of the process was monitored via ^{1}H NMR analysis of sequential aliquots. Condensation of **1a** and **2** was rapid (15 min) at rt in toluene (concentration 0.33 M) to afford an imine product of type **I** (Scheme 1).[11] Bringing the mixture to reflux for 2 h effected clean 2-aza-Cope rearrangement, determined to be complete and quantitative

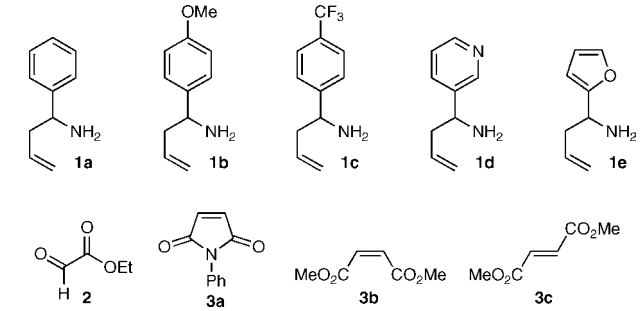


Figure 1. Survey of amine, aldehyde, and alkene components.

(4) For a recent perspective, see: Overman, L. E. *Tetrahedron* **2009**, *65*, 6432–6446. For earlier accounts, see: (a) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352–359. (b) Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329–4336.

(5) For selected examples, see: (a) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568–7569. (b) Dunn, T. B.; Ellis, J. M.; Kofink, C. C.; Manning, J. R.; Overman, L. E. *Org. Lett.* **2009**, *11*, 5658–5661. (c) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776–5788.

(6) (a) Brummond, K. M.; Hong, S. *J. Org. Chem.* **2005**, *70*, 907–916. (b) Agami, C.; Cases, M.; Couty, F. *J. Org. Chem.* **1994**, *59*, 7937–7940.

(7) (a) Bennett, D. J.; Hamilton, N. M. *Tetrahedron Lett.* **2000**, *41*, 7961–7964. (b) Agami, C.; Couty, F.; Lin, J.; Mikeaeloff, A.; Poursoulis, M. *Tetrahedron* **1993**, *49*, 7239–7250.

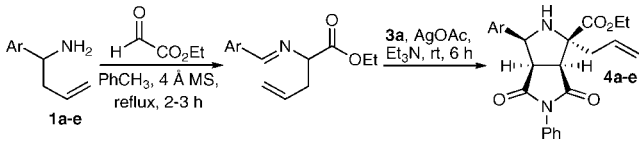
(8) (a) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484–4517. (b) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765–2809. (c) Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105–1150.

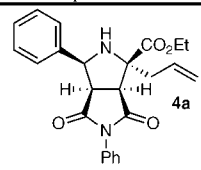
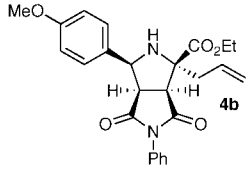
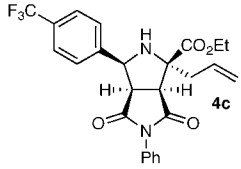
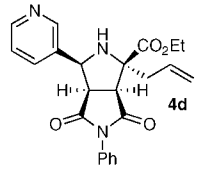
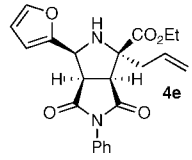
(9) (a) Grigg, R.; Sridharan, V. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: London, 1993; Vol. 3, p 161. (b) Grigg, R.; Montgomery, J.; Somasunderam, A. *Tetrahedron* **1992**, *48*, 10431–10442. (c) Grigg, R.; Gunaratne, H. Q. N. *Chem. Commun.* **1982**, 384–386. (d) Grigg, R.; Kemp, J.; Malone, J.; Tangthongkum, A. *Chem. Commun.* **1980**, 648–650.

(10) Preparation of **1a**, **1b**, and **1e**: (a) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T. K. *J. Org. Chem.* **1983**, *48*, 289–294. Preparation of **1d**: (b) McCoy, C. P.; Morrow, R. J.; Edwards, C. R.; Jones, D. S.; Gorman, S. P. *Bioconjugate Chem.* **2007**, *18*, 209–215. (c) Felpin, F. X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305–6312. For the preparation of **1c**, see Supporting Information.

by ^{1}H NMR, to furnish a new imine of type **II**. When the dipolarophile (1.5 equiv), AgOAc (1.5 equiv), and Et_3N (2.0 equiv) were added to the reaction mixture and stirred at rt, azomethine ylide formation and [3 + 2] dipolar cycloaddition occurred within 6 h to provide 2-allyl proline **4a** (entry 1, Table 1) in 84% yield. Stereochemical analysis of **4a** by 1-D

Table 1. Exploring the Substrate Scope of the 2-Aza-Cope-[3 + 2] Dipolar Cycloaddition: Homoallylamines **1a**−**e** and Maleimide **3a**[a]



entry	amine	product	yield[b]
1	**1a**		84%
2	**1b**		70%
3	**1c**		97%
4	**1d**		87%
5	**1e**		36%

[a] Reaction conditions: homoallylic amine **1a**−**e** (1.0 mmol), ethyl glyoxylate (**2**, 1.0 mmol), 4 Å MS, toluene (3 mL), reflux, 2−3 h; then add *N*-phenyl maleimide (**3a**, 1.5 mmol), AgOAc (1.5 mmol), Et_3N (2.0 mmol), rt, 6 h. [b] Isolated yields after flash column chromatography on silica gel or recrystallization.

NOE enhancement experiments revealed that the cycloaddition exhibited *endo*-selectivity as evidenced from through-space coupling of the protons indicated below (Figure 2), which was unambiguously confirmed via X-ray crystallographic analysis.

The scope of the 2-aza-Cope-[3 + 2] dipolar cycloaddition was next extended to other homoallyl amine substrates (Table 1). For all cases, only the *endo* cycloadducts were detected

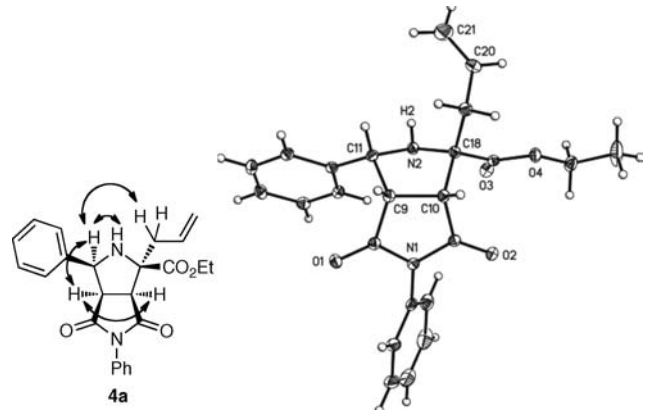


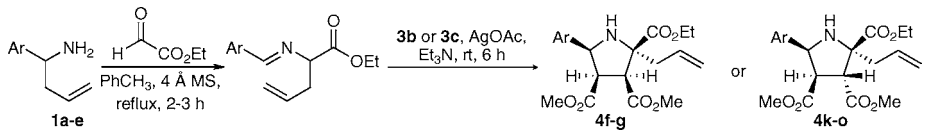
Figure 2. NOE enhancements and X-ray crystal structure of **4a**.

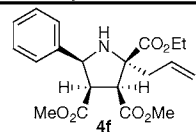
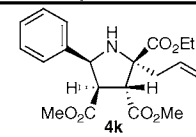
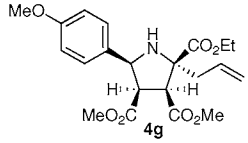
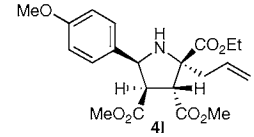
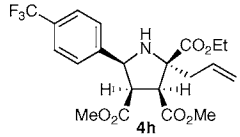
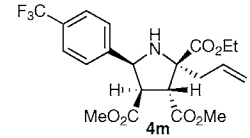
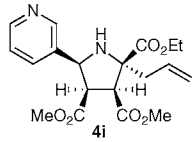
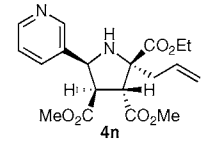
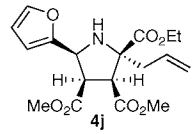
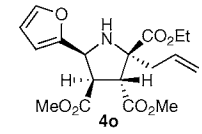
by ^{1}H NMR analysis of the reaction mixtures. Each product (**4a**−**e**) displayed NOE enhancements consistent with the stereoisomer expected to result from cycloaddition of a W-shaped azomethine ylide through *endo* approach of the dipolarophile, as drawn in Scheme 1. The only other compounds observed in the reaction mixtures were variable amounts of unreacted imine after 2-aza-Cope rearrangement. The overall yields were generally good and, as anticipated, appeared to be dependent on the electronic characteristics of the aromatic moiety. Electron-deficient *p*-trifluoromethylbenzyl amine **1c** gave a higher yield (97%) than electron-rich *p*-methoxybenzyl amine **1b** (70% yield), likely attributable to increased acidity and therefore more facile azomethine ylide formation in the case of substrates bearing electron-withdrawing groups. Gratifyingly, 3-pyridinyl amine **1d** also underwent the transformation in good yield (87%). Overall, furanylamine **1e** was the only difficult substrate as the 2-aza-Cope rearrangement required an additional 1 h and the resultant imine did not readily undergo either azomethine ylide formation or [3 + 2] dipolar cycloaddition even after 14 h of stirring at rt (entry 5, Table 1).

We also investigated the reactivities of two other dipolarophiles, dimethyl maleate (**3b**) and dimethyl fumarate (**3c**, Table 2). For each homoallylamine substrate (**1a**−**e**) explored, the overall yields were good and were generally found to parallel those observed with *N*-phenyl maleimide (**3a**), with yields somewhat better for reactions with fumarate **3c** (entries 6−10, Table 2) than maleate **3b** (entries 1−5). The relative stereochemistries of the isolated 2-allyl prolines **4f**−**o** once again proved to be those consistent with [3 + 2] dipolar cycloaddition via an *endo* transition state maleate with a W-shaped azomethine ylide.

In summary, we demonstrate here the first examples of a one-pot domino 2-aza-Cope-[3 + 2] dipolar cycloaddition for the synthesis of functionalized 2-allyl proline derivatives. The resultant allyl and ester moieties provide convenient points for additional structural elaboration. Importantly, the multicomponent nature of the protocol is evident as a wide variety of amine, glyoxylic ester, and dipolarophile components could potentially be used. The reaction stereoselectively generates four new chiral centers and one quarternary carbon

Table 2. Extending the Substrate Scope of the 2-Aza-Cope-[3 + 2] Dipolar Cycloaddition with Dimethyl Maleate and Dimethyl Fumarate[a]



entry	amine	dipolarophile	product	yield[b]	entry	amine	dipolarophile	product	yield[b]
1	**1a**	**3b**	 **4f**	69%	6	**1a**	**3c**	 **4k**	97%
2	**1b**	**3b**	 **4g**	50%	7	**1b**	**3c**	 **4l**	75%
3	**1c**	**3b**	 **4h**	71%	8	**1c**	**3c**	 **4m**	87%
4	**1d**	**3b**	 **4i**	86%	9	**1d**	**3c**	 **4n**	70%
5	**1e**	**3b**	 **4j**	29%	10	**1e**	**3c**	 **4o**	52%

[a] Reaction conditions: homoallylic amine **1a**−**e** (1.0 mmol), ethyl glyoxylate (**2**, 1.0 mmol), 4 Å MS, toluene (3 mL), reflux, 2−3 h; then add **3b** or **3c** (1.5 mmol), AgOAc (1.5 mmol), Et_3N (2.0 mmol), rt, 6 h. [b] Isolated yields after flash column chromatography on silica gel or recrystallization.

with a high degree of functionalization around a pyrrolidine ring, and we anticipate applying this strategy toward the synthesis of alkaloid natural products. Our route to azomethine ylide precursors via the 2-aza-Cope rearrangement is complementary to the condensation of aldehydes with allylglycine derivatives and may afford azomethine ylides not accessible by other means. The transition to nonbenzylic homoallylic amine components, monoactivated dipolarophiles, and catalytic asymmetric variants[12] are all important avenues currently under investigation.

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra for all new compounds. X-ray crystallographic information for 2-allyl proline **4a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) We found it convenient to conduct the reactions in the presence of 4 Å molecular sieves, thereby reducing the possibility of byproduct formation from competing processes with water.

(12) (a) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400–13401. (b) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174–10175. (c) Zeng, W.; Zhou, Y. G. *Org. Lett.* **2005**, *7*, 5055–5058.