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Enamide-Benzyne-[2 + 2] Cycloaddition: Stereoselective Tandem [2 + 2]−Pericyclic Ring-Opening−Intramolecular *N*-Tethered [4 + 2] Cycloadditions

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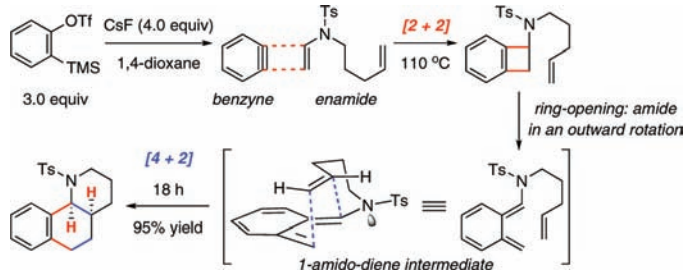
ABSTRACT



Benzyne-[2 + 2] cycloadditions with enamides are described. This effort led to the development of a highly stereoselective tandem [2 + 2] cycloaddition−pericyclic ring-opening−intramolecular-*N*-tethered-[4 + 2] cycloaddition for rapid assembly of nitrogen heterocycles.

Chemistry of benzynes[1] has reemerged, as evident by an elegant array of work that has appeared in the recent literature covering a number of different synthetic transformations.[2−4] As Larock[4] pointed out, this new surge is in part related to the usage of Kobayashi's[5] mild fluoride-based conditions for generating benzynes *in situ* from *o*-(trimethylsilyl)aryl triflates. In particular, Stoltz's[6] beautiful studies on annulations of enamides with benzynes en route to indolines and isoquinolines provoked us to envision another transformation also involving enamides but through a [2 + 2] cycloaddition as shown in Scheme 1. While benzyne-[2 + 2] cycloaddition is well-known,[1,7] there are very few examples

(1) For recent reviews on aryne chemistry, see: (a) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579. (b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (c) Kessar, S. V. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, pp 483−515. (d) Heaney, H. *Chem. Rev.* **1962**, *62*, 81.

(2) For leading examples of nucleophilic additions, see: (a) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 99. (b) Jeganmohn, M.; Chen, C.-H. *Org. Lett.* **2004**, *6*, 2821. (c) Jeganmohan, M.; Cheng, C.-H. *Synthesis* **2005**, 1693. (d) Bhuvaneswari, S.; Jeganmohan, M.; Yang, M.-C.; Cheng, C.-H. *Chem. Commun.* **2008**, 2158. (e) Xie, C.; Liu, L.; Zhang, Y.; Xu, P. *Org. Lett.* **2008**, *10*, 2393. (f) Sha, F.; Huang, X. *Angew. Chem., Int. Ed.* **2009**, *38*, 3458.

(3) For examples of interesting insertion-type processes, see: (a) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112. (b) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340. (c) Tambar, U. K.; Ebner, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *127*, 11752. (d) Pi, S.-F.; Tang, B.-X.; Li, J.-H.; Liu, Y.-L.; Liang, Y. *Org. Lett.* **2009**, *11*, 2309. (e) Also see ref 1a.

(4) For recent examples on annulations and cycloadditions, see: (a) Liu, Z.; Larock, R. C. *Tetrahedron* **2007**, *63*, 347. (b) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219. (c) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409. (d) Worlikar, S. A.; Larock, R. C. *Org. Lett.* **2009**, *11*, 2413. (e) Also see ref 6.

(5) For a mild and general preparation of arynes using *o*-(trimethylsilyl)aryl triflates, see: Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

(6) (a) Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 17270. (b) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558.

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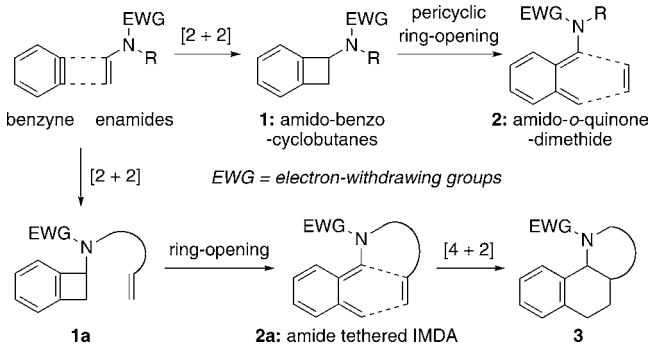
Scheme 1. Tandem Benzyne-Enamide-[2 + 2]−Diels-Alder

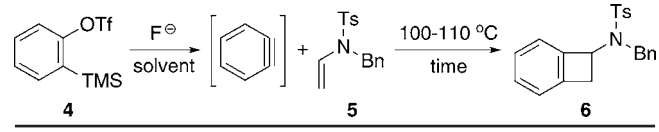


involving enamines,[8] with no systematic examinations of enamides in this capacity.[1,9,10] While conceptually simple, this endeavor is timely and significant because enamides represent an increasingly more accessible substrate[11−14] and a useful functional group in modern organic synthesis.[15,16]

More importantly, we recognized that the union of benzynes and enamides would lead to not only amido-benzocyclobutanes **1**, which are excellent precursors to amido-*o*-quinonedimethides **2** (or a 1-amidodiene)[17,18] through pericyclic ring-opening,[1,19] but also the possibility of a tandem sequence consisting of benzyne-[2 + 2] cycloaddition−ring-opening−*N*-tethered intramolecular [4 + 2] cycloaddition.[1,19,20] This tandem process should be useful for rapid assembly of complex nitrogen heterocycles [(benzyne+ enamide) → **1a** → **2a** → **3**]. We communicate here our success in this endeavor.

Feasibility of the enamide-benzyne [2 + 2] cycloaddition was established using benzyne precursor **4** and enamide **5** in the presence of a fluoride source (Table 1). The first fluoride anion source employed was TBAT (tetra-*n*-Bu-ammonium triphenyldifluorosilicate). After screening through a variety of solvents, 1,4-dioxane proves to be the optimal solvent (entries 6 and 7), leading to amido-benzocyclobutane **6**[21] in 83% yield. Intriguingly, THF, the commonly used

Table 1. Fluoride Sources and Solvents for Benzyne Formation



					yield [%]	
entry	**4** [equiv]	$F^{\ominus}$ [equiv][a]	solvent[b]	time [h]	NMR	isolated
1	2.0	TBAT [2.0]	THF	6		14
2	2.0	TBAT [2.0]	CH_3CN	22		
3	2.0	TBAT [2.0]	toluene	22	29	
4	2.0	TBAT [2.0]	$ClCH_2CH_2Cl$	22		
5	4.0	TBAT [4.0]	DME	12	51	
6	2.0	TBAT [2.0]	dioxane	22	41	
7	4.0	TBAT [4.0]	dioxane	12	71	83
8	3.0	HF-pyridine	dioxane	22		
9	3.0	TBAF [4.0]	dioxane	22		
10	3.0	CsF [4.0]	dioxane	22		87

[a] TBAT: tetra-*n*-butyl-ammonium triphenyldifluorosilicate. [b] DME: dimethoxyethane; dioxane: 1,4-dioxane.

(7) For some examples of aryne-[2 + 2] cycloaddition, see: (a) Barluenga, J.; Calleja, J.; Antón, M. J.; Álvarez-Rodrigo, L.; Rodríguez, F.; Fañanás, F. J. *Org. Lett.* **2008**, *10*, 4469. (b) Hamura, T.; Arisawa, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 6842.

(8) For [2 + 2] cycloadditions of arynes with enamines, see: (a) Gingrich, H. L.; Huang, Q.; Morales, A. L.; Jones, M. *J. Org. Chem.* **1992**, *57*, 3803. (b) Heaney, H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2693. (c) Crews, P.; Beard, J. *J. Org. Chem.* **1973**, *38*, 522. (d) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Hayasaka, T.; Kusama, O. *J. Chem. Soc. C* **1971**, 1051.

(9) For reports on amido-benzocyclobutane formation as side products through enamide-benzyne-[2 + 2] cycloaddition, see: (a) Castedo, L.; Guitian, E.; Saá, C.; Suau, R.; Saá, J. M. *Tetrahedron Lett.* **1983**, *24*, 2107. (b) Blackburn, T.; Ramtohul, Y. K. *Synlett* **2008**, 1159. For an example of using vinylogous amides which led to only addition reaction and not benzocyclobutane formation, see: (c) Ramtohul, Y. K.; Chartrand, A. *Org. Lett.* **2007**, *9*, 1029.

(10) For a leading example of [2 + 2] cycloadditions of chiral enamides that does not involve arynes, see: (a) Hegedus, L. S.; Bates, R. W.; Soderberg, B. C. *J. Am. Chem. Soc.* **1991**, *113*, 923. (b) For a review, see :Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105.

(11) For reviews on Cu-mediated C-N and C-O bond formations, see: (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (b) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (d) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. For reviews on Pd-catalyzed N-arylations of amines and amides, see: (e) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (f) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. *Acc. Chem. Res.* **1998**, *31*, 805.

(12) For a general review on the synthesis of enamides, see: Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Weinreb, S. M., Ed.; Georg Thieme Verlag KG: Stuttgart, 2005; Chapter 21.4.

(13) For leading examples of enamide syntheses, see: (a) Chechik-Lankin, H.; Livshin, S.; Marek, I. *Synlett* **2005**, 2098. (b) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr., *Org. Lett.* **2004**, *6*, 27. (c) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (d) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845. (e) Langner, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5984. (f) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (g) Shen, R.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650.

(14) For a synthesis of *Z*-enamides, see: Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170.

(15) For a leading review on recent chemistry of enamides, see: (a) Carbery, D. R. *Org. Biomol. Chem.* **2008**, *9*, 3455. Also see: (b) Rappoport, Z. *The Chemistry of Enamines in The Chemistry of Functional Groups*; John Wiley and Sons: New York, 1994.

(16) For recent examples, see: (a) Ylioja, P. M.; Mosley, A. D.; Charlot, C. E.; Carbery, D. R. *Tetrahedron Lett.* **2008**, *49*, 1111. (b) Lu, T.; Song, Z.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 541. (c) Nguyen, T. B.; Martel, A.; Dhal, R.; Dujardin, G. *J. Org. Chem.* **2008**, *73*, 2621. (d) Gohier, F.; Bouhadjera, K.; Faye, D.; Gaulon, C.; Maisonneuve, V.; Dujardin, G.; Dhal, R. *Org. Lett.* **2007**, *9*, 211. (e) Song, Z.; Lu, T.; Hsung, R. P.; Al-Rashid, Z. F.; Ko, C.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4069. (f) Martin, R.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 5221. (g) Ko, C.; Hsung, R. P.; Al-Rashid, Z. F.; Feltenberger, J. B.; Lu, T.; Wei, Y.; Yang, J.; Zificsak, C. A. *Org. Lett.* **2007**, *9*, 4459. (h) Barbazanges, M.; Meyer, C.; Cossy, J. *Org. Lett.* **2007**, *9*, 3245.

(17) For reviews on chemistry of dienamides, see: (a) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. (b) Petrzilka, M. *Synthesis* **1981**, 753. (c) Campbell, A. L.; Lenz, G. R. *Synthesis* **1987**, 421.

(18) For recent examples 1-amido-diene-[4 + 2] cycloadditions, see: (a) Smith, A. B., III; Wexler, B. A.; Tu, C.-Y.; Konopelski, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1308. (b) Schlessinger, R. H.; Pettus, T. R. R.; Springer, J. P.; Hoogsteen, K. *J. Org. Chem.* **1994**, *59*, 3246. (c) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165. (d) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 5950. (e) Robiette, R.; Cheboub-Benchaba, K.; Peeters, D.; Marchand-Brynaert, J. *J. Org. Chem.* **2003**, *68*, 9809.

(19) For a leading review, see: Sadana, A. K.; Saini, R. K.; Billups, W. E. *Chem. Rev.* **2003**, *103*, 1539.

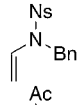
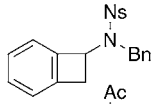
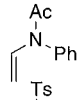
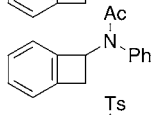
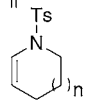
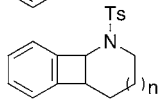
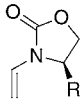
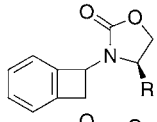
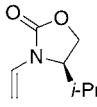
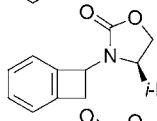
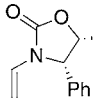
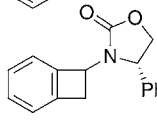
(20) For a pioneering example of benzocyclobutene ring-opening−dienamide Diels-Alder sequences, see: Oppolzer, W. *J. Am. Chem. Soc.* **1971**, *93*, 3834.

(21) See Supporting Information.

solvent for benzyne reactions, afforded the desired product in only 14% isolated yield (entry 1) with the formation of a significant side product.[22] Increasing the loading of silylaryl triflate **4** and fluoride ion afforded higher yields (entry 6 versus 7). When examining other fluoride sources (entries 8−10), none was effective except CsF, which was ultimately determined to be the best fluoride source for ease of operation (entry 10).

Having established these conditions, a variety of enamides were found to undergo the benzyne-[2 + 2] cycloaddition (Table 2). Electronically, cycloadditions of both *N*-acyl and *N*-sulfonyl

Table 2. General Benzyne-Enamide-[2 + 2] Cycloaddition

entry	enamides[a]	amido-benzocyclobutanes	yield [%][b]
1	 **7**	 **8**	63
2	 **9**	 **10**	63
3	 **11a:** n = 1	 **12a:** n = 1	95
4	**11b:** n = 0	**12b:** n = 0	95
5	 **13a:** R = H	 **14a**	62
6	**13b:** R = Ph	**14b**	55[c]
7	**13c:** R = Bn	**14c**	91[d]
8	 **13d**	 **14d**	64[d]
9	 **13e**	 **14e**	77[d]

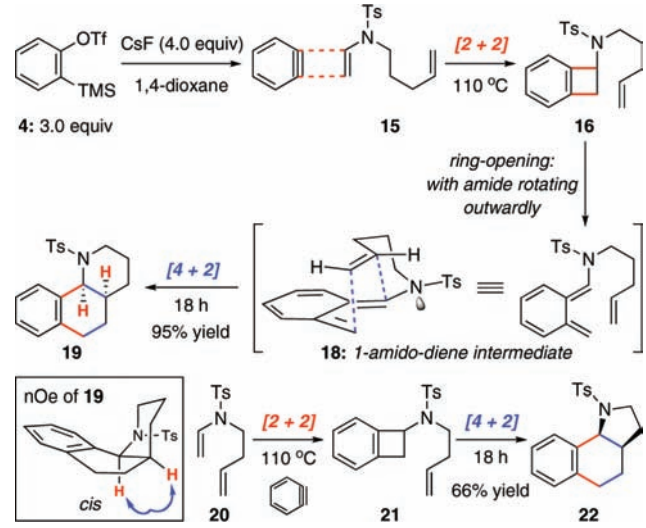
[a] Unless otherwise noted, all reactions were carried out in 1,4-dioxane at 110 °C with CsF (4.0 equiv) and **4** (3.0 equiv) being employed. [b] Isolated yields. [c] dr ratio is 2:1 as determined by ^{1}H NMR; major isomer unassigned. [d] dr ratio is 1:1 as determined by ^{1}H NMR.

enamides **7** and **9** proceeded well (entries 1 and 2). Cyclic enamides **11a** and **11b** were also excellent substrates, affording unique *aza*-tricycles **12a** and **12b**, respectively, in nearly quantitative yields (entries 3 and 4). In addition, achiral oxazolidinone substituted enamide **13a** was viable for the cycloaddition, leading to amido-benzocyclobutane **14a** in 62% yield (entry 5), while chiral enamides **13b−e** were equally efficient (entries 7−11). It is noteworthy that amido-benzocyclobutane product **14e** provides an access to free amino-benzocyclobutane via reductive ring-opening of the chiral oxazolidinone motif through hydrogenolysis.[23]

Although amido-benzocyclobutane products **14b−e** were isolated as an inseparable mixture of diastereomers with ratios of 1:1 to 2:1, to control this diastereoselectivity is not essential because the major application of these amido-benzocyclobutanes pertains to a pericyclic ring-opening, which would lose the stereochemical information en route to amido-*o*-quinonedimethides. In accord with this understanding, we recognized that while these new amido-benzocyclobutanes are synthetically useful, the most attractive feature here is to employ enamide-benzyne-[2 + 2] cycloaddition in tandem with the ring-opening to *o*-quinonedimethide for the ensuing [4 + 2] cycloaddition.

As shown in Scheme 2, this concept was readily achieved using enamide **15** tethered with an olefin to give *aza*-tricycle **19** in 95% yield as a single diastereomer (assigned via NOE

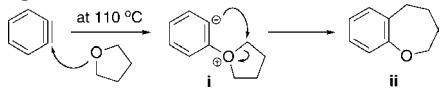
Scheme 2. Tandem Benzyne-Enamide-[2 + 2]−[4 + 2]



experiments). *Aza*-tricycle **22** could also be obtained from the respective enamide **20**. The formation of **19** (or **22**) would constitute a four-bond formation through benzocyclobutane synthesis (2 red bonds), a torquoselective pericyclic ring-opening in favor of the amido group rotating outwardly,[24,25] and an *N*-tethered intramolecular [4 + 2] cycloaddition. The latter two reactions in tandem already represents a highly useful synthetic strategy, as evident from elegant work by Oppolzer,[20] thereby further accentuating the potential significance of developing an enamide-benzyne-[2 + 2] cycloaddition manifold.

The synthetic scope of this tandem process can be illustrated in two facets. First, as shown in Scheme 3,

(22) We found THF had reacted with benzyne at 110 °C, leading to the formation of cyclic ether **ii**, thereby constituting a stepwise C-O insertion process through oxonium intermediate **i**.



(23) Song, Z.; Lu, T.; Hsung, R. P.; Al-Rashid, Z. F.; Ko, C.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4069.

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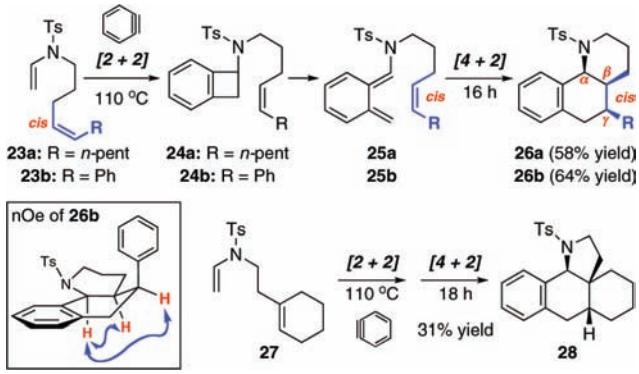
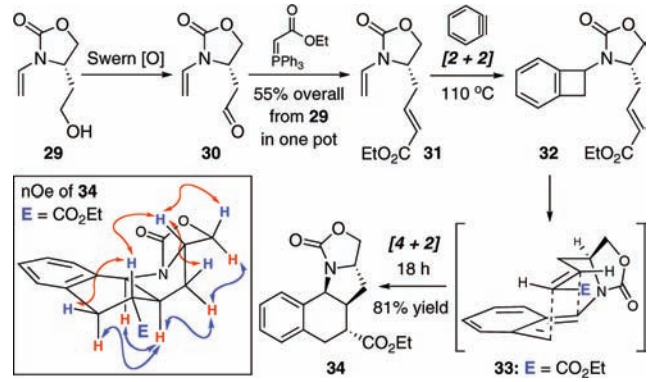
(25) Also see: (a) Murakami, M.; Miyamoto, Y.; Ito, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 189. (b) Murakami, M.; Miyamoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6441. (c) Murakami, M.; Hasegawa, M.; Igawa, H. *J. Org. Chem.* **2004**, *69*, 587. (d) Hasegawa, M.; Murakami, M. *J. Org. Chem.* **2007**, *72*, 3674.

Scheme 3. Substituted Olefins for [4 + 2] Cycloaddition



Scheme 4. Asymmetric Tandem [2 + 2]−[4 + 2]



cycloadditions of enamides **23a** and **23b** tethered to a *cis*-olefin gave respective cycloadducts **26a** and **26b** in good yields as a single isomer with all-*cis* relative stereochemistry at Cα, Cβ, and Cγ as assigned through NOE experiments. The *cis* relative stereochemistry at Cβ and Cγ suggests the concerted nature in the [4 + 2] cycloaddition, as the integrity of the olefin geometry is preserved.[1,19] In addition, enamide **27** with a trisubstituted olefin was also feasible for the tandem sequence, although the yield for the desired *aza*-tetracycle **28** is lower. We note here that even with the more electron-rich di- and trisubstituted olefins, the benzyne-[2 + 2] cycloaddition still favored the enamide motif.

The second facet features an asymmetric variant of this tandem sequence (Scheme 4). Chiral enamide **29**, derived from (*S*)-aspartic acid, could be transformed into enamide **31** tethered to a *trans*-acrylate motif through Swern oxidation and Wittig olefination. Subjecting **31** to the tandem benzyne-[2 + 2]−ring-opening−intramolecular [4 + 2] process afforded *aza*-tetracycle **34** in a highly stereoselective manner. This exercise underscores the timeliness and significance of this strategy because chiral enamides are readily accessible through the current state of art in their preparations. In addition, the robustness of enamides allows one to carry them through multiple organic transformations as a functional group while assembling greater complexity.

We have described here an enamide-benzyne-[2 + 2] cycloaddition. This work led to the development of a highly stereoselective tandem [2 + 2] cycloaddition−pericyclic ring-opening−intramolecular [4 + 2] cycloaddition that should be useful for the rapid construction of nitrogen heterocycles. Efforts in applying this tandem process to alkaloid synthesis are currently underway.

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Supporting Information Available: Experimental procedures as well as NMR spectra and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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