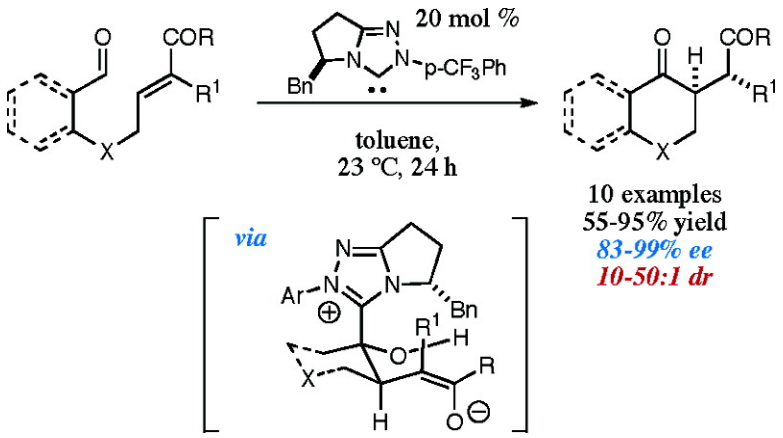
Article

A Highly Enantio- and Diastereoselective Catalytic Intramolecular Stetter Reaction

Javier Read de Alaniz, and Tomislav Rovis

J. Am. Chem. Soc., **2005**, 127 (17), 6284-6289• DOI: 10.1021/ja0425132 • Publication Date (Web): 02 April 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 34 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 04/02/2005

A Highly Enantio- and Diastereoselective Catalytic Intramolecular Stetter Reaction

Javier Read de Alaniz and Tomislav Rovis*

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received December 13, 2004; E-mail: rovis@lamar.colostate.edu

Abstract: A highly enantio- and diastereoselective intramolecular Stetter reaction has been developed. Subjection of α,α-disubstituted Michael acceptors to an asymmetric intramolecular Stetter reaction results in a highly enantioselective conjugate addition and a diastereoselective proton transfer. Available evidence suggests the diastereoselective protonation occurs via intramolecular delivery to the sterically more hindered face of the enolate. The scope of the trisubstituted Michael acceptors has been examined and found to be broad with respect to the size of the α-substituent and nature of the Michael acceptor. Aliphatic and aromatic aldehydes were examined and found to afford the desired product in good overall yield with high enantio- and diastereoselectivity.

Introduction

Umpolung reactivity of functional groups is a powerful method for reversing the normal mode of reactivity and has been widely employed by organic chemists.[1] Traditional methods for the conversion of aldehydes into Umpolung reagents involve the use of dithianes or protected cyanohydrin derivatives. However, these methods are stoichiometric and often require strong bases to generate the acyl anion equivalent. Recent advances in the catalyzed Umpolung reactivity of carbonyls by cyanide anion, heteroazolium carbenes, or metallophosphites illustrate the synthetic capability of polarity reversal as a nontraditional approach to carbon−carbon bond construction.[2] Two examples of catalytic Umpolung reactivity that have seen substantial advances with respect to the generality of reaction partners and catalyst employed are the benzoin[3] and Stetter[4] reactions. The Stetter reaction, where a Michael acceptor traps the acyl-anion equivalent generated by nucleophilic attack of the catalyst, offers an alternative approach to the well-established conjugate addition reaction manifold.

Over the last 30 years the asymmetric conjugate addition of nucleophiles to α,β-unsaturated carbonyl compounds has played an important role in the development of asymmetric reactions.[5] More recently, the tandem reaction resulting from the conjugate addition of a nucleophile into a Michael acceptor followed by trapping of the anionic intermediate with an electrophile forming two contiguous stereocenters has been realized. A variety of compatible electrophiles have been demonstrated, including aldehydes,[6a,b,d] ketones, esters and nitriles,[6g] Pd−π-allyls,[6a,c] halides and tosylates,[6e,f] oxocarbenium ions,[6h] and less frequently, a proton source.[6i,j] Useful catalytic examples, forming two contiguous stereocenters in good levels of enantio- and diastereoselectivity, include the asymmetric 1,4-addition of organozinc reagents catalyzed by chiral copper complexes[6] and of organoboronic acids and derivatives catalyzed by chiral rhodium complexes.[7] Stoichiometric methods include the use

(1) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239−258. (b) Eisch, J. *J. Organomet. Chem.* **1995**, *500*, 101−115.
(2) For reviews, see: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534−541. (b) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326−1328. (c) Pohl, M.; Lingen, B.; Müller, M. *Chem. Eur. J.* **2002**, *8*, 5288−5295.
(3) (a) Sheehan, J. C.; Hara, T. *J. Org. Chem.* **1974**, *39*, 1196−1199. (b) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743−1745 and references therin. (c) Dünkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Lingen, B.; Baumann, M.; Pohl, M.; Müller, M. *J. Am. Chem. Soc.* **2002**, *124*, 12084−12085. (d) Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432−8433. For examples of the benzoin reaction with acyl silanes see: (e) Linghu, X.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2534−2536. (f) Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070−3071.
(4) (a) Stetter, H.; Kuhlmann, H. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1991; Vol. 40, pp 407−496. (b) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899−1902. (c) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298−10299. (d) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934−1936. (e) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876−8877. (f) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, 2025−2035. (g) Mennen, S.; Blank, J.; Tran-Dube, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195−197. For examples of the Stetter reaction with acyl silanes, see: (h) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314−2315.
(5) (a) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.1. (b) Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.2. (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061 and references therein. (d) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236.
(6) For examples of copper-catalyzed 1,4-addition-aldol reactions, see: (a) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 5141−5144. (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, H. M. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620−2623. (c) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104−1105. (d) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841−5842. For an example of a halide and tosylate trap, see: (e) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779−781. (f) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *124*, 755−756. For examples of a ketone, ester, and nitrile trap, see: (g) Agapiou, K.; Cauble, D. F.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4528−4529. For an example of oxocarbenium trap, see: (h) Alexakis, A.; Trevitt, G. P.; Bernardinelli, G. *J. Am. Chem. Soc.* **2001**, *123*, 4358−4359. For an example of a proton trap, see: (i) Degrado, S.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362−13363. (j) Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376−1378.

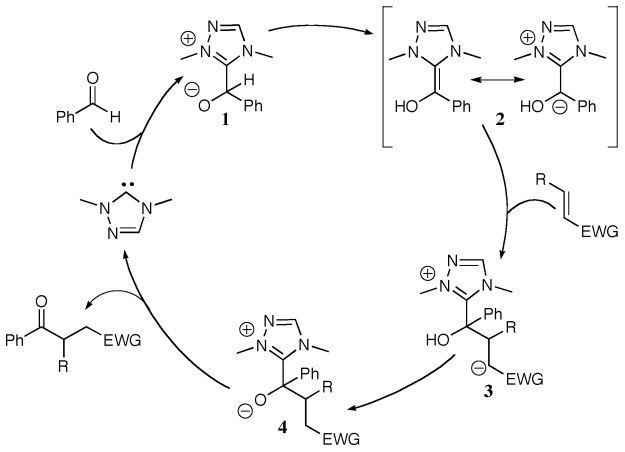
10.1021/ja0425132 CCC: $30.25

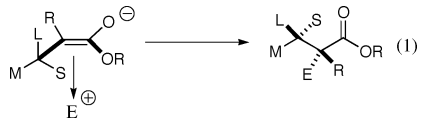
of chiral auxiliaries,[8] chiral nucleophiles,[9] and chiral radical sources.[10] However, the majority of these examples are confined to cyclic Michael acceptors, in which the double bond is part of the ring. In these cases, the constraints imposed by the ring system govern the diastereoselective trapping reaction, where the electrophile approaches from the less hindered face. Extension of such protocols to include acyclic enones is limited, in part due to the lack of diastereocontrol resulting from the freely rotating acyclic system. The concerted addition of hydroxylamine to electron-deficient alkenes is one elegant approach that addresses this problem.[11] Despite the previous example, there are few protocols that are able to control the absolute and relative stereochemistry of both new stereocenters in acyclic systems, with only two catalytic examples. Hoveyda and co-workers reported the Cu-catalyzed asymmetric conjugate addition of alkylzinc reagents to acyclic aliphatic enones.[6e] They observed excellent diastereoselectivity when an intramolecular trap was used to generate cyclic products; however, the use of benzyl bromide as the electrophilic trap for the zinc-enolate resulted in poor diastereoselectivity (3.2:1). The most general catalytic protocol was recently reported by Sibi and co-workers, who found that a variety of alkyl radicals add to α,*β*-disubstituted imide substrates in the presence of a chiral Lewis acid, followed by a diastereoselective hydrogen atom transfer.[12]

When a Michael acceptor bearing a single substituent alpha to the electron-withdrawing group is employed, an enantioselective protonation event may result in the control of α-stereocenters. Recently, tandem 1,4-addition/enantioselective protonation catalyzed by rhodium complexes has been reported.[13] In a related process, the radical conjugate addition to α-methylacrylates and α-methylacrylamides followed by an enantioselective hydrogen atom transfer has been developed.[14]

In the above examples it is believed that the diastereoselective transfer event is governed by the newly formed *β*-stereocenter, where the electrophile approaches from the less hindered face of the enolate. Zimmerman[15] and Fleming[16a] have conducted extensive studies involving the addition of a variety of electrophiles to carbon−carbon double bonds adjacent to a stereogenic center, where the electrophile approaches from the less hindered face, according to the general model (eq 1).

Scheme 1. Proposed Mechanistic Cycle





Recent work from our laboratory has shown that chiral triazolinylidene carbenes are competent catalysts for the asymmetric intramolecular Stetter reaction with α,*β*-unsaturated esters, ketones, and nitriles.[4c,d] In addition, we have demonstrated the use of chiral triazolinylidene carbenes for the formation of quaternary stereocenters starting with *β*,*β*-disubstituted Michael acceptors.[4e] We report herein that subjection of α,α-disubstituted Michael acceptors to an asymmetric intramolecular Stetter reaction results in a highly enantioselective conjugate addition and a diastereoselective intramolecular proton transfer.

A thorough study of the mechanism of the Stetter reaction has not, to our knowledge, been conducted. In its absence, the most reasonable mechanism, Scheme 1, is an adaptation of the related, and much better studied, benzoin reaction.[17]

According to the proposed mechanism, intermediate **1** would result from nucleophilic attack of the carbene into the aldehyde. Subsequent proton transfer would afford acyl-anion equivalent **2**. Carbon−carbon bond formation results from nucleophilic attack of acyl-anion equivalent **2** into a Michael acceptor,

(7) For examples of Rh-catalyzed 1,4-addition-aldol reaction, see: (a) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528−4529. (b) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 10984−10985. (c) Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110−1111 and references therein.

(8) For selective examples of 1,4-addition/tandem reactions with chiral auxiliaries, see: (a) Chernaga, A. N.; Davies, S. G.; Lewis, C. N.; Todd, R. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3603−3608. (b) Miller, D. B.; Raychaudhuri, S. R.; Avasthi, K.; Lal, K.; Levison, B.; Salomon, R. G. *J. Org. Chem.* **1990**, *55*, 3164−3175.

(9) For selective examples of conjugate addition/tandem reactions of chiral nucleophiles, see: (a) Hanessian, S.; Gomtsyan, A.; Malek, N. *J. Org. Chem.* **2000**, *65*, 5623−5631. (b) Enders, D.; Vázquez, J.; Raabe, G. *Eur. J. Org. Chem.* **2000**, 893−901.

(10) For example of tandem radical reactions, see: Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472−9473.

(11) For examples of concerted conjugate addition to Michael acceptors, see: (a) Niu, D.; Zhao, K. *J. Am. Chem. Soc.* **1999**, *121*, 2456−2459. (b) Sibi, M. P.; Liu, M. *Org. Lett.* **2000**, *21*, 3393−3396. (c) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796−11797.

(12) Sibi, M. P.; Petrovic, G.; Zimmerman, J. *J. Am. Chem. Soc.* **2005**, *127*, 2390−2391.

(13) (a) Reetz, M. T.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *25*, 4083−4085. (b) Navarre, L.; Darses, S.; Genet, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 719−723. (c) Moss, R. J.; Wadsworth, K. J.; Chapman, C. J.; Frost, C. G. *Chem. Commun.* **2004**, 1984−1985. (d) For a related enantioselective hydrophosphination of methacrylonitrile, see: Sadow, A. D.; Haller, I.; Fadini, L.; Togni, A. *J. Am. Chem. Soc.* **2004**, *126*, 14704−14705.

(14) (a) Giese, B.; Hoffmann, U.; Roth, M.; Velt, A.; Wyss, C.; Zehnder, M.; Zipse, H. *Tetrahedron Lett.* **1993**, *34*, 2445−2448. (b) Taber, D. F.; Gorski, G. J.; Liable-Sands, L. M.; Rheingold, A. L. *Tetrahedron Lett.* **1997**, *38*, 6317−6318. (c) Sibi, M. P.; Asano, Y.; Sausker, J. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1293−1296 and references therein. (d) Sibi, M. P.; Sausker, J. P. *J. Am. Chem. Soc.* **2002**, *124*, 984−991.

(15) (a) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263−268. (b) Zimmerman, H. E.; Wang, P. *Org. Lett.* **2002**, *15*, 2593−2595. For an intramolecular proton transfer, see: (c) Berrada, S.; Metzner, P. *Tetrahedron Lett.* **1987**, *28*, 409−412.

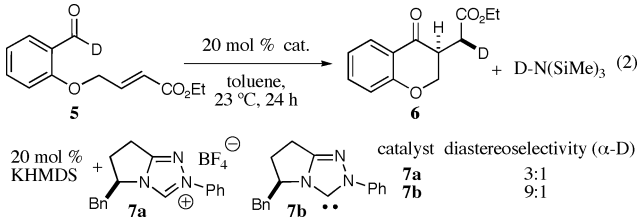
(16) (a) Fleming, I.; Lewis, J. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3257−3266 and references therein. For related examples that study the approach of electrophiles on carbon−carbon double bond adjacent to a stereogenic center, see: (b) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162−7166. (c) Yamamoto, Y.; Maruyama, K. *J. Chem. Soc., Perkin Trans. 1* **1984**, 904−905. (d) Kawasaki, H.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1985**, *26*, 3031−3034. (e) Mohrig, J. R.; Rosenberg, R. E.; Apostol, J. W.; Bastienaansen, M.; Evans, J. W.; Franklin, S. J.; Frisbie, D. C.; Fu, S. S.; Hamm, M. L.; Hirose, C. B.; Hunstad, D. A.; James, T. L.; King, R. W.; Larson, C. J.; Latham, H. A.; Owen, D. A.; Stein, K. A.; Warnet, R. *J. Am. Chem. Soc.* **1997**, *119*, 479−486.

(17) For the mechanism of the thiamine-catalyzed benzoin condensation reaction, see: (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719−3726. (b) Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 699−702. (c) White, M.; Leeper, F. *J. Org. Chem.* **2001**, *66*, 5124−5131. Mechanism of the cyanide-catalyzed reaction, see: (d) Lapworth, A. *J. Am. Chem. Soc.* **1903**, *83*, 995. (e) Linghu, X.; Bausch, C. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 1833−1840.

generating enolate **3**. Enolate protonation followed by catalyst turnover generates the desired product.

Results and Discussion

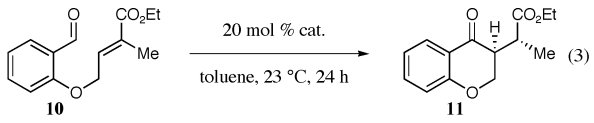
Our research on the enantio- and diastereoselective intramolecular Stetter reaction began during investigations involving the intramolecular Stetter reaction of deuterioaldehyde **5**. We observed a diastereoselective deuteron transfer proceeding with 3:1 selectivity (eq 2). Following the Stetter reaction of **5** by ^{2}H NMR, we noted the formation of three new deuterium resonances, two of which corresponded to deuteration of the enolate after carbon−carbon bond formation as suggested by the proposed mechanism (Scheme 1). The third resonance corresponded to the proton−deuteron exchange with the conjugate acid of the base, hexamethyldisilazane (HMDS). The experiment was repeated in the absence of HMDS (removed under high vacuum),[18] and only the two resonances corresponding to deuteration at the diastereomeric α-positions of the Michael acceptor were observed. More importantly, this protocol led to an increase in diastereoselectivity of deuteron transfer from 3:1 to 9:1 (eq 2).

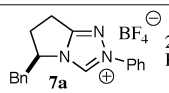
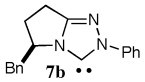
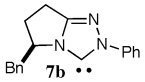
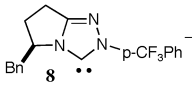
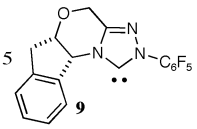


Having realized the viability of a diastereoselective deuteron transfer, we turned our attention to prochiral trisubstituted Michael acceptors. The cyclization of α-methyl α,β-unsaturated ethyl ester **10** was chosen as a model substrate for our investigation. Cyclization of **10** under standard reaction conditions of 20 mol % salt and 20 mol % KHMDS in toluene afforded the desired product in good enantioselectivity although the diastereoselectivity varied from 3:1 to 13:1 (Table 1, entry 1). The reaction conducted in the presence of 100 mol % HMDS resulted in 12:1 diastereoselectivity albeit in lower yield (entry 2). To our gratification, the reaction run in the absence of HMDS resulted in an increase in diastereoselectivity without loss of enantioselectivity (entry 3). Further catalyst optimization revealed an increase in enantio- and diastereoselectivity when using the slightly more electron-deficient carbene **8**.[19] It is important to note at this time that the aminoindanol catalyst **9**, also developed in our lab, can be used to afford the opposite enantiomeric series of the desired product in high enantio- and diastereoselectivity with slightly lower yields (entry 5), resulting from its somewhat diminished reactivity relative to that of **8**. For this reason, we chose to develop this methodology, utilizing the pyrrolidinone-based catalyst **8**.

As highlighted in Table 1, the source of variable diastereoselectivity in entry 1 is unclear but suggests that there is a factor involved which is not understood. In an effort to elucidate if the basic reaction conditions affect the diastereoselectivity, the enantio- and diastereoenriched product **11** was subjected to the reaction conditions (Table 2). The standard reaction conditions

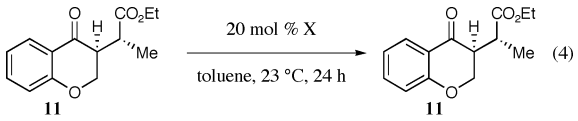
Table 1. Optimization of the Reaction Conditions



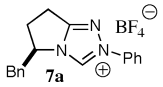
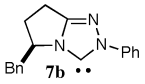
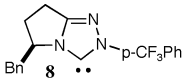
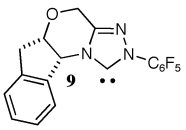
Entry	Catalyst	Base	HMDS	Yield (%)	ee (%)[a]	dr (%)[a]
1	 **7a**	20 mol % KHMDS	—	85-88	90	3:1 to13:1
2	 **7b** ••	—	100 mol % HMDS	60	88	12:1
3	 **7b** ••	—	—	88	90	15:1
4	 **8** ••	—	—	94	95	30:1
5	 **9** ••	—	—	80	- 99	150:1

[a] Enantiomeric excess of the major diasteromer and diastereomeric ratio determined by HPLC or GC analysis using a chiral stationary phase.

Table 2. Epimerization of Product by the Reaction Conditions



95 % ee
30:1 dr

Entry	X	Base	ee (%)[a]	dr (%)[a]
1	 **7a**	20 mol % KHMDS	94	3:1
2	 **7b** ••	—	94	10:1
3	 **8** ••	—	95	28:1
4[b]	 **9** ••	—	- 99	150:1
5	—	20 mol % HMDS	95	20:1
6	—	10 equiv. of DBU	0	1.5:1

[a] Enantiomeric excess of the major diasteromer and diastereomeric ratio determined by HPLC or GC analysis using a chiral stationary phase. [b] The carbene was subjected to **11** (−99% ee, 150:1 dr).

of 20 mol % salt and 20 mol % KHMDS epimerized the product from 30:1 to 3:1 diastereoselectivity without loss of enantioselectivity (entry 1). Subjection of product **11** to 20 mol % carbene **7b** in the absence of HMDS or 20 mol % HMDS resulted in minor epimerization with no loss of enantioselectivity (entries

(18) See Experimental Section for generation of the free carbene.
(19) We have shown that varying the electronic nature of the catalyst can have an affect on reactivity and selectivity; see ref 4c.

2 and 5). On the other hand, subjection of product **11** to 20 mol % carbene **8** or **9**, possessing an electron-withdrawing group on the triazolinylidene carbene, resulted in negligible erosion of diastereoselectivity and no erosion of enantioselectivity (entries 3 and 4). The thermodynamic diastereomeric ratio was determined to be 1.5:1 (entry 6). These results illustrate that varying degrees of epimerization can occur under the basic reaction conditions, although the free carbene protocol leads to minimal epimerization of the resultant product.[20] In addition, the electronic nature of the chiral triazolinylidene carbenes can be tuned to reduce the amount of epimerization of the desired product. Utilization of the free carbene affords reproducible high enantio- and diastereoselectivity, and therefore all subsequent reactions were performed utilizing these conditions.

With these optimized conditions in hand, a series of prochiral trisubstituted Michael acceptors were prepared to test the scope of the enantio- and diastereoselective Stetter reaction (Table 3).

The reaction displays impressive generality with respect to nature and size of the α-substituted Michael acceptors. Moderate steric bulk can be tolerated at the α-position of various α-disubstituted α,β-unsaturated esters (entries 1−5). Alkylidene lactone and cyclopentanone each afford the desired product in high enantio- and diastereoselectivity (entries 6−7). Furthermore, aliphatic aldehydes are also viable substrates, affording the desired product in >80% yield with good enantio- and diastereoselectivity (entries 9−10).

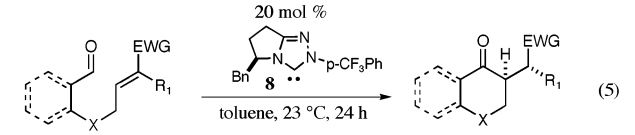
Stereochemical Model for Selectivity

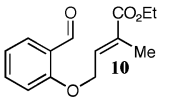
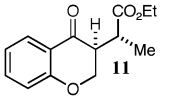
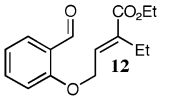
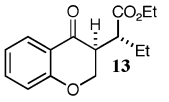
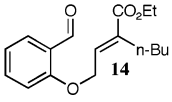
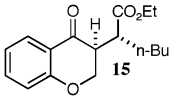
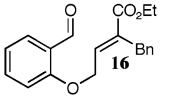
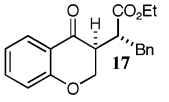
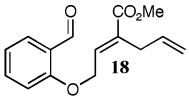
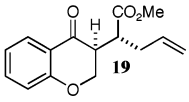
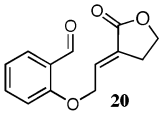
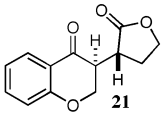
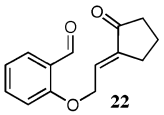
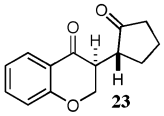
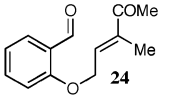
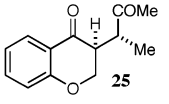
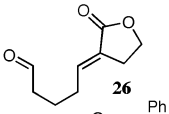
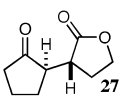
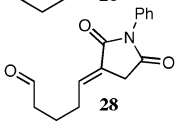
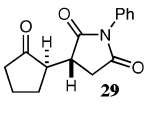
The relative stereochemistry of the newly formed contiguous stereocenters was assigned as syn on the basis of single-crystal analysis for **11** and **21**.[21] This stereochemistry could arise from a diastereoselective proton transfer event from two possible enolate rotamers that result from the highly enantioselective carbon−carbon bond formation, **30** or **31** (Scheme 2). It is also conceivable that the α-hydroxy-α-azolium anion adds to the Michael acceptor in concerted fashion, analogous to the reverse Cope elimination mechanism seen with hydroxylamine additions.[22]

The latter rotamer is governed by electrostatic interaction between the enolate and the azolium, where protonation from the less hindered face would result in the observed stereochemistry. The former rotamer is in accord with the Zimmerman model where the electrophile may be expected to approach from the less hindered face (eq 1).[15,16a] However, an intermolecular protonation of **30** would afford the minor diastereomer. Zimmerman has shown that in designed systems a pendant pyridine delivers a proton to the sterically more hindered face of enolates by intramolecular proton transfer.[15] We hypothesize that the reaction proceeds by the Zimmerman model **30** to afford **32**, via an intramolecular proton transfer. Intramolecular proton transfer (intermediate **3** in Scheme 1) should be faster than a bimolecular protonation event. In addition, rotamer **31** has severe $A^{1,3}$ strain and requires protonation from another molecule, presumably from intermediate **1**, **2**, or **3** (Scheme 1).

Support for the intramolecular proton transfer was gained by examining isomeric Michael acceptors.[23] According to the Zimmerman model **30** or the electrostatic model **31** (where the electrophile approaches from the less hindered face in an intermolecular fashion), the relative diastereoselectivity should be independent of the olefin geometry of the Michael acceptor.[16a] On the other hand, an intramolecular proton transfer should result in opposite relative diastereoselectivity for the (*E*) vs (*Z*) trisubstituted Michael acceptor, assuming proton transfer is faster

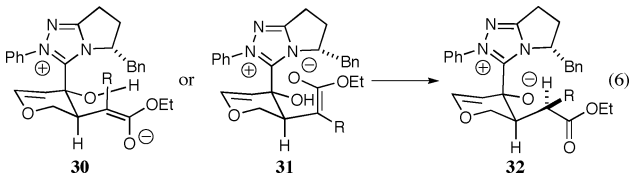
Table 3. Scope of the Enantio- and Diastereoselective Intramolecular Stetter Reaction



Entry	Substrate	Product	Yield (%)	ee (%)[a]	dr (%)[a]
1	 **10**	 **11**	94	95	30:1
2	 **12**	 **13**	95	92	35:1
3[b]	 **14**	 **15**	53	94	12:1
4	 **16**	 **17**	80	84	20:1[c]
5	 **18**	 **19**	95	83	13:1
6	 **20**	 **21**	95	94	10:1
7	 **22**	 **23**	80	95	18:1
8	 **24**	 **25**	85	55	10:1
9	 **26**	 **27**	94	99	50:1
10	 **28**	 **29**	80	88	15:1

[a] Enantiomeric excess of the major diasteromer and diastereomeric ratio determined by HPLC or GC analysis using a chiral stationary phase. [b] Catalyst added in two portions, see Supporting Information. [c] Diastereomeric ratio determined by ^{1}H NMR.

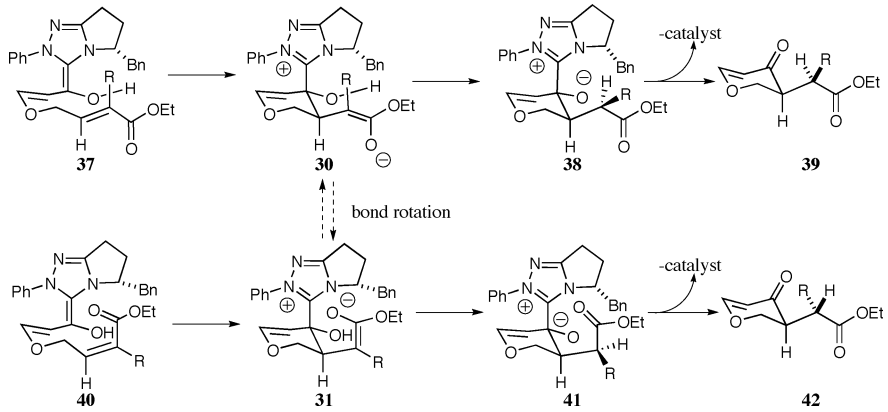
Scheme 2. Possible Enolate Rotamers



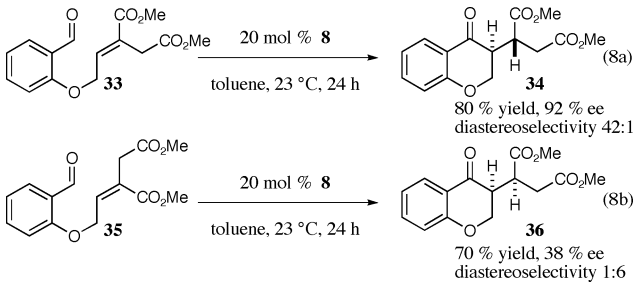
30 **31** **32**

(20) The exact mode of the epimerization is still under investigation.
(21) See Supporting Information for crystal structure data.
(22) For examples of the reverse Cope elimination mechanism of hydroxylamine additions, see ref 11.

Scheme 3. Intramolecular Protonation vs Bond Rotation



than bond rotation. Substrates **33** and **35** were subjected to the reaction conditions and found to provide complementary diastereoselectivity. The (*E*)-isomer proved highly enantio- and diastereoselective, affording **34** in 42:1 diastereoselectivity (eq 8a), while the (*Z*)-isomer preferentially afforded **36** in 1:6 diastereoselectivity, albeit low enantioselectivity (eq 8b).



The control of the relative diastereoselectivity suggests enolate protonation must occur prior to bond rotation (Scheme 3).[24] Intramolecular protonation of enolate **30** or **31** would result in the observed diastereoselectivity. Bond rotation of either **30** or **31** would access a common enolate intermediate that would result in the same relative diastereoselectivity.

Conclusion

In conclusion, we have demonstrated a highly enantio- and diastereoselective intramolecular Stetter reaction on a variety of trisubstituted Michael acceptors. We are able to control both newly formed stereocenters in a relative and absolute sense using catalytic amounts of chiral triazolinylidene carbenes. The initial carbon−carbon bond formation proceeds in excellent enantioselectivity, and available evidence suggests that proton transfer occurs at the sterically more hindered face in an intramolecular fashion. The relative diastereoselectivity can be controlled by the olefin geometry of the Michael acceptor, and varying the electronic nature of the chiral triazolinylidene carbene can lead to increased enantio- and diastereoselectivity.

(23) Further support for the intramolecular proton-transfer event was gained by conducting the reactions at various concentrations. Lowering the reaction concentration from 0.3 to 0.02 M increased the diastereoselectivity from 10:1 to 30:1. The reactions were monitored by GC analysis over the course of 24 h and the diastereoselectivity remained constant for each reaction, suggesting that a bimolecular event leads to a slight degradation of selectivity. However, it cannot be ruled out that higher concentration leads to a greater amount of epimerization.

(24) As mentioned above, it is also possible that the α-hydroxy-α-azolium anion adds to the Michael acceptor in concerted fashion, analogous to the reverse Cope elimination mechanism seen with hydroxylamine additions.

Experimental Section

General Procedure for the Asymmetric Intramolecular Stetter Reaction. A flame-dried round-bottom flask was charged with triazolium salt (0.2 equiv) and 2 mL of toluene. To this solution was added KHMDS (0.5 M in toluene, 0.2 equiv) via syringe, and the solution was stirred at ambient temperature for 5 min. Toluene and HMDS were removed in vacuo by placement under high vacuum for 1 h.[25] Toluene (3 mL) was added, followed by a solution of the substrate (1 equiv, 0.12 mmol) in 2 mL of toluene; the resulting solution was allowed to stir at ambient temperature for 24 h. The reaction was quenched with 15% AcOH/toluene (2 mL), and the resulting solution was purified by flash column chromatography and eluted with a suitable solution of hexane and ethyl acetate (typically 6:1). Evaporation of solvent afforded analytically pure product.

(2*S*,3′*R*)-(4-Oxo-chroman-3-yl-2-deuterio)acetic Acid Ethyl Ester (6). According to the general procedure, 13.0 mg (0.031 mmol) of **7** and 61.0 μL (0.031 mmol) of KHMDS and 35.0 mg (0.148 mmol) of **5** were reacted for 24 h. Workup afforded 31.5 mg (90%) of the desired product as colorless oil in 90% ee and 9:1 dr. R_f (1:1 hexane to ethyl acetate) = 0.7; $[\alpha]^{23}_D = +5.27°$ ($CHCl_3$); HPLC analysis: Chiracel AD column 97:3 hexanes to 2-propanol 0.5 mL/min. Minor enantiomer: 22.95 min. Major enantiomer: 32.22 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, d, J = 7.9 Hz), 7.45 (1H, dd, J = 8.6, 8.6 Hz), 6.99 (1H, dd, J = 7.5, 7.5 Hz), 6.94 (1H, d, J = 8.3 Hz), 4.57 (1H, dd, J = 5.3, 11.1 Hz), 4.27 (1H, dd, J = 11.6, 11.6 Hz), 4.16 (2H, q, J = 7.0 Hz), 3.3 (1H, m), 2.90 (0.2H, dd, J = 4.8, 16.9 Hz), 2.38 (1H, m), 1.25 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 171.6, 161.9, 136.2, 127.6, 121.7, 120.7, 118.0, 70.4, 61.2, 42.6, 30.2 (t, J = 20.1 Hz), 14.4; IR (NaCl, CH_2Cl_2) 1738, 1694, 1600 cm^{-1}; HRMS (FAB^+) calcd for $C_{13}H_{13}DO_4$ 235.0954, Found 236.1034.

(2*R*,3′*S*)-(4-Oxo-chroman-3-yl)-propionic Acid Ethyl Ester (11). According to the general procedure, 13.0 mg (0.031 mmol) of **8** and 61.0 μL (0.031 mmol) of KHMDS and 38.0 mg (0.153 mmol) of **10** were reacted for 24 h. Workup afforded 35.7 mg (94%) of the desired product as a white solid in 95% ee and 30:1 dr. R_f (1:1 hexane to ethyl acetate) = 0.7; $[\alpha]^{23}_D = +7.85°$ ($CHCl_3$); HPLC analysis: Chiracel OB-H column 97:3 hexanes to 2-propanol 0.3 mL/min. Minor enantiomer: 98.1 min. Major enantiomer: 54.9 min. GC analysis: CP Wax 52CB column 130 °C at 3 mL/min. Minor diastereomer: 16.7 min, Major diastereomer: 19.0 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, d, J = 7.9 Hz), 7.45 (1H, m), 6.99 (1H, m), 6.94 (1H, d, J = 8.3 Hz), 4.59 (1H, dd, J = 5.3, 11.3 Hz), 4.34 (1H, dd, J = 11.7, 11.7 Hz), 4.16 (2H, q, J = 7.0 Hz), 3.26 (1H, ddd, J = 5.3, 5.3, 12.2 Hz), 3.10 (1H, dq, J = 6.0, 7.1 Hz), 1.25 (3H, t, J = 7.1 Hz), 1.2 (3H, d,

(25) A control experiment was run in the absence of KBF_4 salt, and the enantio- and diastereoselectivity of the reaction was not affected. The KBF_4 salt was removed by passing a solution of toluene containing the carbene and KBF_4 salt, which was prepared according to general procedure, through a Gelman 0.45 μm filter.

$J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 174.9, 161.8, 136.1, 127.6, 121.7, 122.2, 117.9, 68.7, 61.1, 47.8, 36.6, 14.4, 13.7; IR (NaCl, CH_2Cl_2) 1723, 1701, 1600 cm^{-1}; HRMS (FAB^+) calcd for $C_{14}H_{16}O_4$ 248.1049, Found 249.1119.

Acknowledgment. We thank the National Science Foundation (CAREER), National Institutes of Health (minority supplement for J.R.A.), and Colorado State University for support. J.R.A. thanks the National Institutes of Health (Ruth L. Kirschstein Minority Pre-doctoral fellowship) and Colorado PEAKS AGEP (graduate fellowship). T.R. gratefully acknowledges Merck Research Laboratories, GlaxoSmithKline, Amgen, Johnson & Johnson, and Eli Lilly. T.R. is a Fellow of the Alfred P. Sloan Foundation. We also thank Mark S. Kerr and Susan Miller for solving the X-ray structure of **11** and **21**.

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

JA0425132