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A Highly Diastereoselective MgI_2-Mediated Ring Expansion of Methylenecyclopropanes

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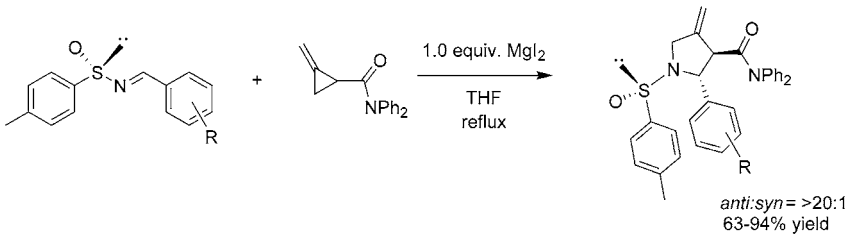
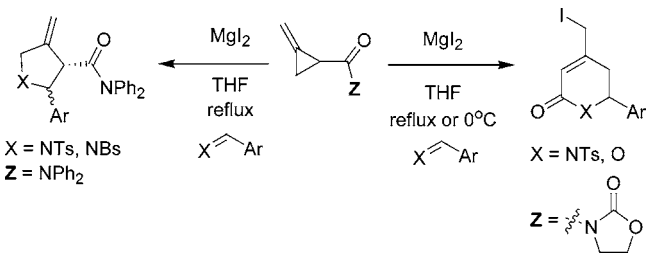
ABSTRACT



A highly diastereoselective MgI_2-mediated ring expansion of methylenecyclopropane amides to functionalized pyrrolidines has been developed using chiral aromatic sulfinimines. The 2,3,4-trisubstituted pyrrolidines were isolated in generally good to excellent yields and in excellent diastereoselectivities for aromatic and heterocyclic sulfinimines.

Ring expansion of highly strained methylenecyclopropane (MCP) derivatives represents an attractive and efficient approach to heterocyclic compounds.[1,2] Typically, ring expansion of an activated MCP occurs *via* nucleophilic addition to generate an enolate, or enol intermediate, which then acts as a nucleophile in the subsequent formal [3 + 2] cyclization. Recently, we reported a divergent MgI_2-mediated ring expansion of monoactivated MCPs (Scheme 1),[3] an idea that arose from preliminary reports by Carreira and co-workers on the MgI_2-mediated ring expansion of monoactivated cyclopropanes.[4] Following this early report, the broad utility of this methodology has been subsequently demonstrated by Carreira in the total synthesis of several biologically active compounds.[5] In all cases, an enantiomeric/diastereomeric mixture of products was obtained. This issue also plagued our earlier work on the MgI_2-mediated ring expansion of *N*,*N*-diphenyl MCP amides, since the diastereoselectivity of the products was found to vary with the location of the substituent on the aromatic ring of the aldimines. Although these 2,3,4-trisubstituted pyrrolidine products are biologically interesting scaffolds, most notably in the Kainoid amino acid family,[6] major advances toward making the ring expansion/closure more stereoselective were required in order

Scheme 1. Divergent MgI_2-Mediated Ring Expansion of Tertiary MCP Amide/Imides



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(1) For a recent review of MCPs used for the preparation of heterocyclic compounds, see: Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213−1269.

(2) For a recent review on the preparation of MCPs, see: Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589−635.

(3) (a) Lautens, M.; Han, W. *J. Am. Chem. Soc.* **2002**, *124*, 6312−6316. (b) Lautens, M.; Han, W.; Liu, J. H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 4028−4029.

(4) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186−3189.

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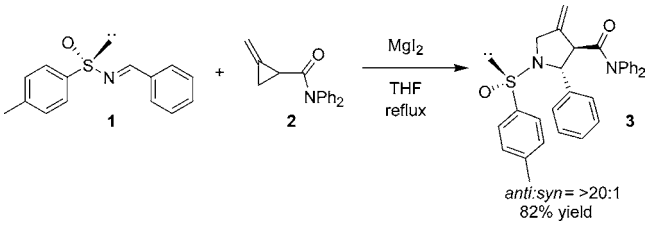
Scheme 2. Preliminary Results for the Diastereoselective MgI_2-Mediated Ring Expansion of an MCP Amide



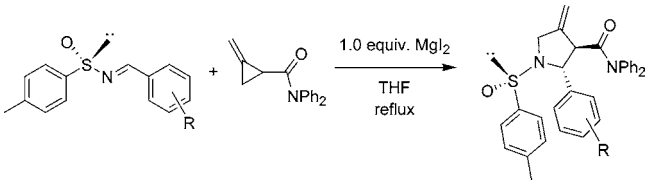
for our methodology to be synthetically useful. While a variety of chiral auxiliary approaches were considered,[7] we selected chiral *N*-sulfinimines since they have been reported to induce chirality for a variety of nucleophilic additions.[8] Initial

MgI_2-mediated ring expansions of *N*,*N*-diphenyl MCP amide **2** in the presence of (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide **1**[9] gave the expected 2,3,4-trisubstituted pyrrolidine product in good yield and in excellent diastereoselectivity (Scheme 2). Herein, we report a novel diastereoselective cyclization of a bifunctional vinylogous enolate generated by an MgI_2-mediated ring opening of a monoactivated MCP.

Optimization of this diastereoselective cyclization focused on solvent, quantity of metal iodide, and chiral auxiliary used. Screening of common solvent systems (acetonitrile, dimethoxyethane, dichloroethane, and 1,4-dioxane) gave either starting materials, decomposition products, or low yields of the pyrrolidine product (<20%) compared to initial experiments performed in THF.

In addition, although catalytic in MgI_2, use of <1 equiv of MgI_2 was found to slow the rate of reaction, giving the product in slightly lower yields but nevertheless with excellent diastereoselectivity.[10] Finally, the effect of employing a related chiral auxiliary was also investigated. Use of the *tert*-butyl sulfinyl group, developed by Ellman,[11] gave the expected pyrrolidine product in excellent diastereoselectivity, albeit with slightly lower yield and prolonged reaction time.[12]

Table 1. Aromatic Sulfinimine Scope for Diastereoselective MCP Amide Ring Expansion



entry	R	time (h)	yield (%)	dr[a] (2*R*,3*R*)/(2*S*,3*S*)	*anti*/*syn*[a]
1	H	3.25	90	>20:1	>20:1
2	2-Br	6.5	63	>20:1	>20:1
3	3-Br	7.5	72	>20:1	>20:1
4	4-Br	7.5	80	>20:1	>20:1
5	4-MeO	7.0	76	>20:1	>20:1
6	4-NO_2	4.5	72	>20:1	>20:1
7	2-Me	6.0	65	>20:1	>20:1
8	4-Me	7.0	85	>20:1	>20:1
9	4-CF_3	4.0	94	>20:1	>20:1

[a] Determined by crude ^{1}H NMR. >20:1 indicates only one isomer was observed.

The substrate scope for this reaction was found to be broad for a variety of substituted aromatic sulfinimines (Table 1). Diastereoselectivities were excellent regardless of the electronic nature and substitution pattern about the aryl moiety. For all examples (Table 1), crude ^{1}H NMR was used to determine the relative amounts of the other diastereomers present. We note that for the simple substituted aromatic sulfinimines, no evidence for the *syn* isomer was observed by ^{1}H NMR and only one *anti* isomer was observed, for which the absolute configuration was determined by X-ray crystallography. Efforts to accurately quantify the relative amounts of each enantiomer for the *anti* isomer were undertaken for the case of the phenyl-substituted sulfinimine (entry 1). In this case, oxidation of the crude reaction mixture to the sulfonamide using *m*-CPBA at 0 °C in CH_2Cl_2, followed by HPLC analysis,[13] gave an ee of >99% for the *anti* isomer.

In contrast to the diastereoselectivity, reaction yields were found to be dependent on the placement of the aromatic substituent on the sulfinimine. The more remote the substituent from the 1-position, the higher the yield. This trend was observed for R = Br (entries 2−4) and Me (entries 7−8), suggesting a steric, rather than electronic, effect.

This methodology was also extended to heteroaromatic systems (Table 2). In general, the yields were good for all

(5) (a) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175−1181. (b) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826−14827. (c) Meyers, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 694−696.

(6) For a review on recent developments in Kainoid amino acid chemistry, see: Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149−4174.

(7) Just prior to submission, a two-step, diastereoselective cycloether formation was reported using an Et_2AlI-mediated cyclopropane ring opening: Timmons, C.; Chen, D.; Cannon, J. F.; Headley, A. D.; Li, G. *Org. Lett.* **2004**, *6*, 2075−2078.

(8) For use of chiral sulfoxides in a 1,3-dipolar cycloaddition, see: Koizumi, T.; Hirai, H.; Yoshii, E. *J. Org. Chem.* **1982**, *47*, 4005−4008. For recent examples of chiral sulfoxides being used in nucleophilic additions, see: (a) Balasubramanian, T.; Hassner, A. *Tetrahedron Lett.* **1996**, *37*, 5755−5758. (b) García Ruano, J. L.; Alemán, *J. Org. Lett.* **2003**, *5*, 4513−4516. (c) Davis, F. A.; Wu, Y.; Yan, H.; McCoull, W.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 2410−2419. (d) Gremmen, C.; Willemse, B.; Wanner, M. J.; Koomen, G.-J. *Org. Lett.* **2000**, *13*, 1955−1958. (e) McMahon, J. P.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1645−1647.

(9) (a) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Portonovo, P. S. *Tetrahedron Lett.* **1993**, *34*, 6229−6232. (b) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403−1406. (c) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555−2563.

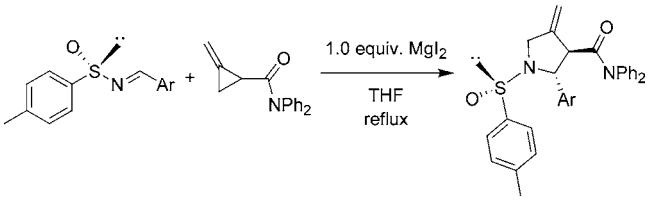
(10) Use of 0.5 equiv of MgI_2 in THF gave the product in 72% yield with a dr of *anti*/*syn* = >20:1 and (2*R*/3*R*)/(2*S*/3*S*) = >20:1 in 6.5 h compared to the usual 90% yield obtained in 3.25 h using 1.0 equiv of MgI_2 in THF.

(11) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011−8019.

(12) Use of (*S*)-*N*-(benzylidene)-*tert*-butylsulfinamide for the ring expansion of the *N*,*N*-diphenyl MCP amide gave the pyrrolidine product in 79% yield with a dr of *anti*/*syn* = >20:1 and (2*R*/3*R*)/(2*S*/3*S*) = >20:1 after 4.0 h.

(13) HPLC analysis was performed using a Daicel Chiralcel OD column (4:96 *i*-PrOH/hexanes, 50 °C). Racemic *anti* and *syn* sulfonamide products used for comparison were prepared as previously reported.[3a]

Table 2. Hetereoaromatic Sulfinimine Scope for Diastereoselective MCP Amide Ring Expansion



entry	Ar	time (h)	yield (%)	dr[a] (2*R*,3*R*)/(2*S*,3*S*)	*anti*/*syn*[a]
1	3-pyridyl	16	82	>20:1	>20:1
2	4-pyridyl	3.25	76	>20:1	>20:1
3	2-furyl	11	82	>20:1	1.1:1 [b]
4	3-furyl	3.25	85	>20:1	84:16

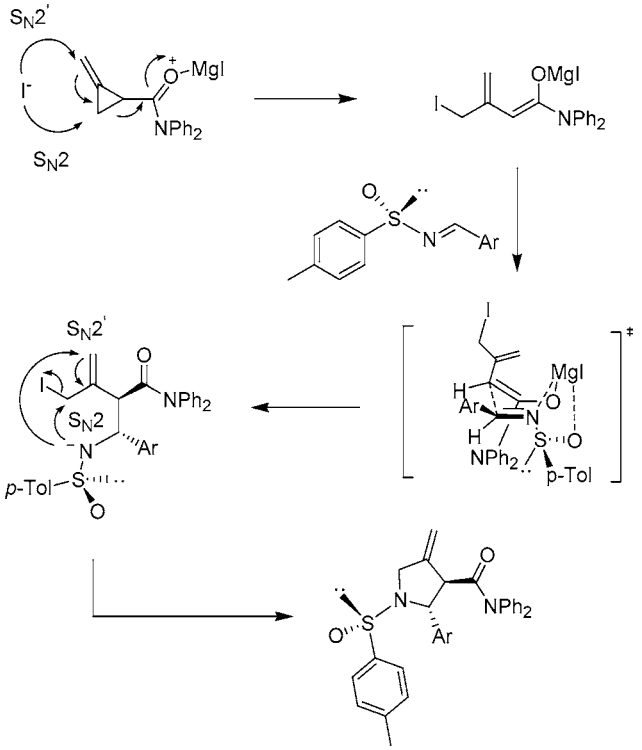
[a] Determined by crude ^{1}H NMR. >20:1 indicates only one isomer was observed. [b] Diastereoselectivities are based on the ratio of isolated yields.

heteroatom-containing aromatic systems with the exception of the 2-pyridyl-substituted pyrrolidine; in this case, the product was obtained in low yield (<20%) as the deprotected amine. In this example, no *syn* product was observed by crude ^{1}H NMR. Although sulfoxides are typically removed under acidic conditions,[14] deprotection of the amine functionality presumably occurs due to neighboring group participation by the adjacent nitrogen atom of the pyridine ring in the presence of the Lewis acid MgI_2.[15]

Diastereoselectivities for heteroatom containing aromatic groups were dependent on the position of the heteroatom in the aromatic ring. The absolute stereochemical assignment for the *anti* isomer was determined by analogy and comparison with the ^{1}H NMR spectra for non-heteroaromatic-substituted pyrrolidine compounds. The *syn* stereochemical assignment for the minor isomer, obtained from the reactions of the 2-furyl-substituted sulfinimine, was made on the basis of NOE analysis.[16] By analogy, the minor 3-furyl-substituted pyrrolidine product was also determined to be *syn*.[17]

For the pyridyl series (entries 1−2), the diastereoselectivity was found to be excellent in all cases. However, in the furyl series, the diastereoselectivity was observed to decrease when the oxygen was *ortho* to the imine substituent (entries 3 and 4). Incorporating these results (Scheme 3), we propose that the mechanism initially involves activation of the amide functionality followed by iodide attack in either an S_N2 or S_N2' manner to give a vinylogous enolate intermediate. To account for the observed stereochemistry, the enolate must attack the sulfinimine *via* a boat transition state, giving the observed *anti* relationship between the amide and aromatic substituents. The sulfoxide adopts a conformation in this boat

Scheme 3. Proposed Mechanism and Transition State for the Diastereoselective MgI_2-Mediated Ring Expansion of MCP Amide

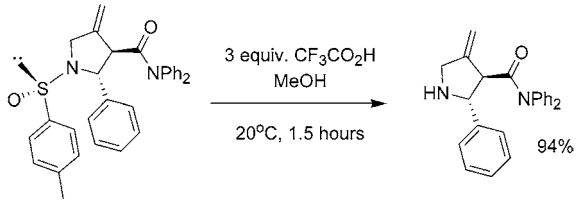


transition state such as to minimize 1,3-allylic strain while maximizing the stabilization of this intermediate *via* coordination of the magnesium to the oxygen of the sulfoxide. We believe that this interaction is vital to the high diastereoselectivity since the presence of an *ortho* heteroatom in the sulfinimine results in dramatic lowering of the product diastereoselectivity, presumably due to competing coordination of magnesium to the *ortho* heteroatom. Examples of such stabilized transition states containing a chiral sulfoxide have been previously proposed in the literature.[8c,18] In the final part of the mechanism, ring closure occurs by either an S_N2 or S_N2' mechanism to give the *anti* pyrrolidine product.[19]

One benefit of this approach toward the synthesis of diastereoselectively pure substituted pyrrolidines is that upon deprotection, the resulting isolated pyrrolidine is obtained as one diastereomer in high ee. Another advantage of this methodology is that the chiral sulfoxyl group can be more easily removed in higher yields compared to the correspond-

(14) Fanelli, D. L.; Szewczyk, J. M.; Zhang, Y.; Reddy, G. V.; Burns, D. V.; Davis, F. A. *Org. Synth.* **2000**, *77*, 50−63.
(15) Adamczyk, M.; Reddy, R. E. *Tetrahedron: Asymmetry* **2001**, *12*, 1047−1054.
(16) 1D NOE spectra for the *syn*-2-furyl case are included in the Supporting Information.
(17) Numerous attempts to purify this minor isomer by preparative HPLC failed. Assignment of the *syn* stereochemistry was made by comparison to the ^{1}H NMR of the *syn*-2-furyl-substituted pyrrolidine product.
(18) (a) Sklute, G.; Amsallem, D.; Shabli, A.; Varghese, J. P.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 11776−11777. (b) Aggarwal, V. K.; Castro, A. M. M.; Mereu, A.; Adams, H. *Tetrahedron Lett.* **2002**, *43*, 1577−1581. (c) Tang, T. P.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772−8778.
(19) Although an S_N2' ring closing pathway (5-*endo*-*trig*) is unfavored by Balwin's rules, similar 5-*endo*-*trig* ring-closing reactions have been reported: (a) Padwa, A.; Norman, B. H. *J. Org. Chem.* **1990**, *55*, 4801−4807. (b) Craig, D.; Smith, A. M. *Tetrahedron Lett.* **1992**, *33*, 695−698. (c) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 4455−4458. (d) Berry, M. B.; Craig, D.; Jones, P. S.; Rowlands, G. J. *Chem. Commun.* **1997**, *22*, 2141−2142. (e) Craig, D.; Ikin, N. J.; Mathews, N.; Smith, A. M. *Tetrahedron Lett.* **1995**, *36*, 7531−7534.

Scheme 4. Deprotection of the Sulfinyl-Protected Pyrrolidine



ing tosyl group deprotection. Use of classical conditions developed by Davis and co-workers[14] were found to be suitable for the deprotection of our pyrrolidine products (Scheme 4).

In summary, a novel one-step, highly diastereoselective tandem MgI_2-mediated ring-opening/-closing reaction has been reported in which 2,3,4-trisubstituted pyrrolidine products are obtained in good to excellent yields and with excellent diastereoselectivities. Work is currently underway to extend this methodology to more substituted MCPs and to further elucidate the mechanism of this reaction.

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Supporting Information Available: Experimental procedures and full characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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