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Synthesis of Highly Functionalized Pyrrolidines via a Selective Iodide-Mediated Ring Expansion of Methylenecyclopropyl Amides

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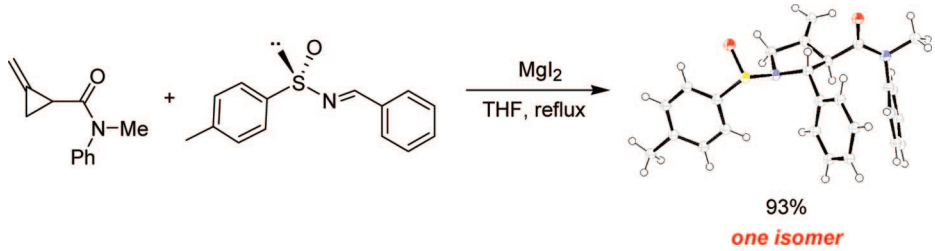
Received September 16, 2008



This manuscript describes a highly selective iodide-mediated, tandem Mannich/cyclization to afford trans-2,3-disubstituted pyrrolidines from methylenecyclopropyl amides in good to excellent yields and selectivities. The reaction scope has been drastically expanded to include a wide array of aromatic, heteroaromatic and α,β-unsaturated imines, as well as a variety of methylenecyclopropyl amides. Additionally, mechanistic studies were carried out to ascertain the nature of the ring-opening/ring-closing mechanism using deuterated substrates. Results from these studies indicate that the primary mechanism is an S_N2/S_N2 ring opening/ring closing and that iodine- or iodide-mediated isomerization of the iodo enolate is likely occurring.

Introduction

The development of all-carbon 1,3-dipole synthons represents an important facet of organic chemistry, primarily due to their ability to quickly construct a broad range of complex carbo- and heterocyclic scaffolds. While transition-metal-catalyzed cycloaddition strategies[1] involving trimethylmethylene (TMM) complexes are a valuable method for generating these types of 1,3-dipoles, new and complementary approaches to their synthesis and preparation are of value. Recently, cyclopropanes[2] and their more highly strained methylenecyclopropane (MCP) derivatives[3,4] have garnered significant interest in the synthetic community due to their ease of preparation and diverse range of reactivity. In particular, the ability to selectively tune the reactivity pattern of these systems based on their substitution pattern and reaction conditions has ultimately led to the use of these three-membered ring systems as highly versatile 1,3-carbon dipole equivalents in a variety of [3 + 3] and [3 + 2] cycloaddition processes.[5,6]

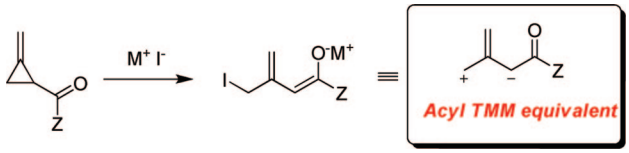
Our own interest in this area has focused on the halide-mediated ring expansion of monoactivated MCP systems for the construction of a variety of heterocyclic motifs.[7] In this system, a Lewis acid and halide act in concert to facilitate halide addition to the activated cyclopropane, affording a bifunctional

(1) For reviews of transition-metal-catalyzed cycloadditions, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Varela, J. A.; Saa, C. *Chem. Rev.* **2003**, *103*, 3787. (c) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (d) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (e) Gevorgyan, V.; Yamamoto, Y. *J. Organomet. Chem.* **1999**, *576*, 232.

(2) For a review of the synthetic use of cyclopropanes, see: (a) de Meijere, A. In *Houben-Weyl Methods of Organic Chemistry*; Thieme: Stuttgart, 1997*E17c*. (b) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C. *Chem. Rev.* **1989**, *89*, 165. (c) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1. (d) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (e) *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1987; Vols. 1−2, Chapters 9−13. For some recent select articles on the synthetic use of cyclopropanes, see: (f) Yang, Y.-H.; Shi, M. *Org. Lett.* **2006**, *8*, 1709. (g) Shi, M.; Tang, X.-Y.; Yang, Y.-H. *Org. Lett.* **2007**, *9*, 4017. (h) Tanaka, M.; Ubukata, M.; Matsuo, T.; Yasue, K.; Matsumoto, K.; Kajimoto, Y.; Ogo, T.; Inaba, T. *Org. Lett.* **2007**, *9*, 3331. (i) Zhang, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6704. (j) Ganton, M. D.; Kerr, M. A. *J. Org. Chem.* **2004**, *69*, 8554. (k) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *26*, 3023. (l) Young, I. S.; Kerr, M. A. *Org. Lett.* **2004**, *6*, 139. (m) Carson, C. A.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 8242. (n) Lebold, T. P.; Carson, C. A.; Kerr, M. A. *Synlett* **2006**, *3*, 364. (o) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704. (p) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764. (q) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953. (r) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014. (s) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642.

10.1021/jo802049u CCC: $40.75
Published on Web 10/08/2008

SCHEME 1. Halide-Mediated Ring Expansion of Monoactivated Methylenecyclopropanes



halo enolate that is equivalent to a functionalized 1,3-carbon dipole (Scheme 1). The resulting intermediate can subsequently undergo a formal [3 + 2] cycloaddition process in the presence of a suitable electrophile to afford a variety of pharmaceutically relevant heterocyclic scaffolds. Inspired by the work of Carreira and others,[5,6] we sought to develop highly stereoselective variants of this halide-mediated cycloaddition transformation.

Recently, we reported a tandem Lewis acid iodide-mediated ring expansion of methylenecyclopropanes (Scheme 2, eq 1).[7a] Although yields for this process were good, selectivities were found to be highly dependent on the substitution on the aryl imine. Notably, the application of this methodology toward aryl imines lacking an *ortho* substituent led to low diastereoselectivities between the cis and trans 2,3-disubstituted pyrrolidine products. Subsequent efforts by our group[7c] led to the discovery that readily available chiral sulfinimines[8] could be used with magnesium iodide to achieve the first highly stereoselective iodide-mediated, tandem Mannich/cyclization of a monoactivated methylenecyclopropane system to afford trans 2,3-disubstituted pyrrolidines (Scheme 2, eq 2).

In addition to providing access to a variety of stereochemically defined pyrrolidine building blocks, this versatile and highly selective methodology has subsequently been used by our group to synthesize (−)-kainic acid,[7d] showcasing the potential utility of this methodology. Herein we report a full account of our studies toward the development of the first highly stereoselective halide-mediated tandem Mannich/cyclization of monoactivated methylenecyclopropanes, including extensive studies of reaction scope as well as new mechanistic studies.

Reaction Optimization. Initial studies found that addition of MgI_2 followed by immediate heating of the reaction mixture led to generally irreproducible yields of the desired trans pyrrolidine product **1** (Table 1, entry 1). Instead, extensive decomposition was observed along with significant formation of the allylic iodide **2**. Additional attempts to improve the yield of the pyrrolidine product using longer reaction times also failed, owing to the instability of the allylic iodide intermediate. Surprisingly, significant improvement in reaction yields could be achieved by ensuring the dissolution of MgI_2 by prestirring the reaction mixture for a period of 20 min prior to heating (entry 2). In doing so, the desired pyrrolidine **1** was obtained in a highly reproducible 82% yield. More importantly, the crude ^{1}H NMR showed no evidence of the unreacted allylic iodide **2**. Using this protocol, the amount of MgI_2 employed in the reaction could also be reduced to 1 equivalent without any detrimental effect on the yield (entry 4). These conditions were effective using catalytic amounts of MgI_2, although in this case the desired pyrrolidine product was obtained in somewhat lower yields (entry 5). Further improvement in reaction efficiency could be realized by increasing the concentration of the reaction mixture (entry 6), affording a single pyrrolidine product in 90% isolated yield. Finally, we examined the use Ellman's chiral *tert*-butyl sulfinimine derivative, since it has been shown to have improved reactivity over the Davis sulfoxide derivative in some instances.[9] Unfortunately, use of the corresponding chiral *tert*-butyl sulfinimine under our reaction conditions resulted in lower yields along with some detectable amounts of the unreacted allylic iodide (entry 7).

Results and Discussion

The substrate scope for this reaction was found to be broad for a variety of aromatic and heteroaromatic sulfinimines (Table 2). For nonheteroaromatic imines, only the trans isomer was observed by ^{1}H NMR, the absolute configuration for which was

(3) For some recent select articles on the Lewis and Brønsted acid ring opening of methylenecyclopropane derivatives, see: (a) Shao, L.-X.; Shi, M *Curr. Org. Chem* **2007**, *11*, 1135. (b) Yao, L.-F.; Shi, M. *Org. Lett.* **2007**, *9*, 5187. (c) Tian, G.-Q.; Shi, M. *Org. Lett.* **2007**, *9*, 4917. (d) Li, W.; Shi, M. *Tetrahedron* **2007**, *63*, 11016. (e) Lu, J.-M.; Shi, M. *Tetrahedron* **2007**, 7545. (f) Zhang, Y.-P.; Lu, J.-M.; Xu, G.-C.; Shi, M. *J. Org. Chem.* **2007**, *72*, 509. (g) Tian, G.-Q.; Shi, M. *Org. Lett.* **2007**, *9*, 2405. (h) Liu, L.-P.; Shi, M. *Tetrahedron* **2007**, *63*, 4535. (i) Lu, J.-M.; Shi, M. *Org. Lett.* **2007**, *9*, 1805. (j) Zhu, Z.-B.; Liu, L.-P.; Shao, L.-X.; Shi, M. *Synlett* **2007**, *1*, 115. (k) Shi, M.; Liu, L.-P.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 7430. (l) Wang, B.-Y.; Jiang, R.-S.; Li, J.; Shi, M. *Eur. J. Org. Chem.* **2005**, *18*, 4002. (m) Xu, G.-C.; Ma, M.; Liu, L.-P.; Shi, M. *Synlett* **2005**, *12*, 1869. (n) Xu, G.-C.; Liu, L.-P.; Lu, J.-M.; Shi, M. *J. Am. Chem. Soc.* **2005**, *127*, 14552. (o) Huang, J.-W.; Shi, M. *Synlett* **2004**, *13*, 2343. (p) Huang, J.-W.; Shi, M. *Tetrahedron Lett.* **2003**, *44*, 9343. (q) Shi, M.; Xu, B. *Org. Lett.* **2002**, *4*, 2145. (r) Shao, L.-X.; Xu, B.; Huang, J.-W.; Shi, M. *Chem.−Eur. J.* **2006**, *12*, 510. (s) Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835.

(4) For some reviews on transition metal-mediated reactions of methylenecyclopropanes, see: (a) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (b) Binger, P.; Schmidt, T. Metal-Catalyzed Cycloadditions of Methylenecyclopropanes. In *Carbocyclic three- and four-membered ring compounds*; de Meijere, A., Ed.; Houben-Weyl Thieme: Stuttgart, Germany, 1997; Vol. E *17b*, p 2217. (c) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. For some recent select articles on transition metal-mediated reactions of methylenecyclopropanes, see: (d) Saito, S.; Komagawa, S.; Azumaya, I.; Masuda, M. *J. Org. Chem.* **2007**, *72*, 9114. (e) Saito, S.; Takeuchi, K. *Tetrahedron Lett.* **2007**, *48*, 595. (f) Maeda, K.; Saito, S. *Tetrahedron Lett.* **2007**, *48*, 3173. (g) Gulías, M.; Durán, J.; López, F.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2007**, *129*, 11026.

(5) (a) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186. (b) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175. (c) Meyers, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 694. (d) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505. (e) Lerchner, A.; Carreira, E. M. *Chem.−Eur. J.* **2006**, *12*, 8208. (f) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 3147. (g) Huang, W.; Chin, J.; Karpinski, L; Gustafson, G.; Baldino, C. M.; Yu, L. *Tetrahedron Lett.* **2006**, *47*, 4911. (h) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 4333.

(6) Several two-step procedures involving halide-mediated ring opening of activated cyclopropane systems followed by treatment with base have been reported as a route to cyclic frameworks: (a) Wiedemann, S. H.; Noda, H.; Harada, S.; Matsunaga, S.; Shibasaki, M *Org. Lett.* **2008**, *10*, 1661. (b) Xiong, T.; Zhang, Q.; Zhang, Z.; Liu, Q. *J. Org. Chem.* **2007**, *72*, 8005. (c) Timmons, C.; Guo, L.; Liu, J.; Cannon, J. F.; Li, G. *J. Org. Chem.* **2005**, *70*, 7634. (d) Brown, S. P.; Bal, B. S.; Pinnick, H. W. *Tetrahedron Lett.* **1981**, *22*, 4891. (e) Fleming, A.; Sinai-Zingde, G.; Natchus, M.; Hudlicky, T. *Tetrahedron Lett.* **1987**, *28*, 167. (f) Han, Z.; Uehira, S.; Tsuritani, T.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 987. (g) Timmons, C.; Chen, D.; Cannon, J. F.; Headley, A. D.; Li, G. *Org. Lett.* **2004**, *6*, 2075.

(7) (a) Lautens, M.; Han, W. *J. Am. Chem. Soc.* **2002**, *124*, 6312. (b) Lautens, M.; Han, W.; Liu, J. H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 4028. (c) Scott, M. E.; Han, W.; Lautens, M. *Org. Lett.* **2004**, *6*, 3309. (d) Scott, M. E.; Lautens, M. *Org. Lett.* **2005**, *7*, 3045. (e) Scott, M. E.; Schwarz, C. A.; Lautens, M. *Org. Lett.* **2006**, *8*, 5521. (f) Taillier, C.; Lautens, M. *Org. Lett.* **2007**, *9*, 591. (g) Taillier, C.; Bethuel, Y.; Lautens, M. *Tetrahedron* **2007**, *63*, 8469. (h) Scott, M. E.; Bethuel, Y.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 1482.

(8) Chiral *p*-tolyl sulfinimines can easily be prepared from the starting aldehyde and chiral sulfinamide on large scale according to the procedure by Davis and co-workers: Fanelli, D.; Szewczyk, J M.; Zhang, Y.; Reddy, G. V.; Burns, D. M.; Davis, F. A *Org. Synth.* **2000**, *77*, 50. For the synthesis of the requisite menthol ester, see: Hulce, M.; Mallomo, J. P.; Frye, L. L.; Kogan, T. P.; Posner, G. H. *Org. Syn.* **1986**, *64*, 196. Alternatively, the starting chiral sulfinamide is commercially available from Aldrich in either antipode.

(9) For example, see: (a) Han, Z.; Krishnamurthy, D.; Pflum, D. A.; Grover, P.; Wald, S. A.; Senanayake, C. H. *Org. Lett.* **2002**, *4*, 4025. (b) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Pflum, D. A.; Senanayake, C. H *Tetrahedron Lett.* **2003**, *44*, 4195. (c) For the synthesis of enantiomerically enriched *tert*-butanesulfinamide, see: Weix, D. J.; Ellman, J. A *Org. Lett.* **2003**, *5*, 1317.

SCHEME 2. Development of a Stereoselective Iodide-Mediated Ring Expansion of Monoactivated Methylenecyclopropanes

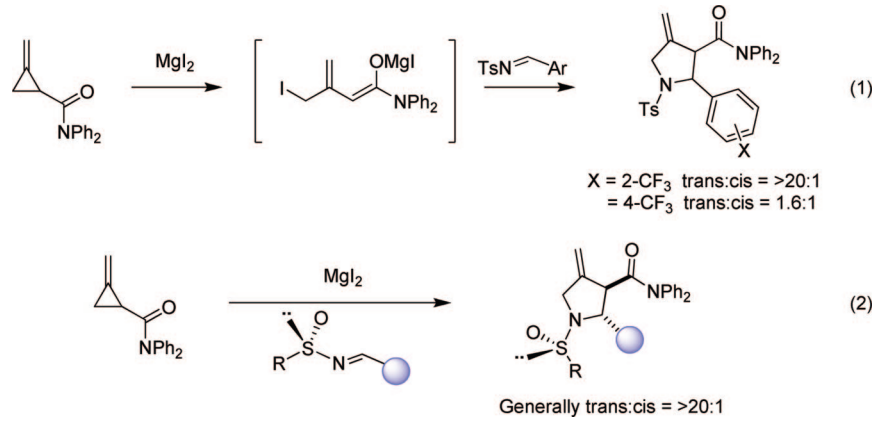
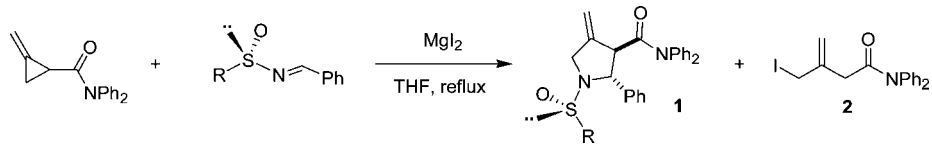


TABLE 1. Select Optimization Studies



entry	R	MgI_2 (equiv)	protocol[a]	% yield[b]	trans/cis[c]
1	*p*-Tol	3.0	THF added to mixture and immediately heated to reflux	30−60	20:1
2	*p*-Tol	3.0	prestirred with THF prior to reflux	82	20:1
3	*p*-Tol	1.5	prestirred with THF prior to reflux	82	20:1
4	*p*-Tol	1.0	prestirred with THF prior to reflux	84	20:1
5	*p*-Tol	0.5	prestirred with THF prior to reflux	72	20:1
6	*p*-Tol	1.0	prestirred with THF prior to reflux[d]	90	20:1
7	*t*-Bu	1.0	prestirred with THF prior to reflux[e]	79	20:1

[a] Reactions carried out using 0.05 M MCP (0.1 mmol) and 1.2 equiv of sulfinimine in THF for 3.25 h. See the Supporting Information for full details. [b] Isolated yields. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Reaction carried out at 0.1 M. [e] Reaction carried out at 0.1 M for 4 h.

determined by X-ray crystallography (for Table 2, entry 8).[10] In general, reaction yields and diastereoselectivities were excellent for aromatic imines, regardless of the electronic nature and substitution pattern on the aryl moiety. In particular, the reaction was found to afford good to excellent yields for the desired trans pyrrolidine for a variety of electron-rich (entries 5 and 7 and 8) and electron-poor (entries 6 and 9) imines. The reaction was also tolerant of sterically-demanding substrates (entries 2, 5 and 10), furnishing the pyrrolidine product in good yield and in >20:1 selectivity over the other three possible isomers. In particular, we were pleased to see that our conditions allowed for a highly selective route to trans pyrrolidines bearing meta- and para-substituted aromatic groups (entries 3, 4, 6−9, and 11), since our previous studies using the corresponding tosyl imines[7a] resulted in lower trans selectivities for these imine classes.

This methodology could also be extended to a variety of heteroaromatic systems (Table 2). In general, yields were good for all heteroatom-containing aromatic sulfinimines, while the diastereoselectivity was dependent on the location of the heteroatom in the aromatic ring. For pyridine and quinoline-derived sulfinimines (entries 12−14), the desired pyrrolidines were obtained in good yields and in excellent levels of diastereocontrol. In the furyl series however, the diastereoselectivity decreased in favor of the cis isomer when the oxygen was adjacent to the imine substituent (entry 15 versus 16).[11] In contrast, use of the corresponding 3-thienyl analogue (entry 17) was found to give the desired trans-pyrrolidine in excellent yield and selectivity, with no evidence of the cis isomer.[12] Finally, this methodology was found to be compatible with pyrrole-based systems (entry 18), affording the desired pyrrolidine in good yield, albeit in a modest, yet synthetically useful diastereoselectivity.

Given the success of aromatic-based sulfinimines in this transformation, we wished to extend the scope of the reaction to include nonaromatic imines. While simple aliphatic systems were found to give complex mixtures (Table 3, entry 1), nonenolizable α,β-unsaturated sulfinimines gave the desired trans pyrrolidines in modest yields and in good to excellent diastereoselectivities. In particular, use of *E*-substituted sulfinimines (Table 3, entries 2 and 3, Table 3) could also be employed in the reaction, although in these examples the trans pyrrolidine product was obtained in somewhat reduced selectivity.[13] Gratifyingly, use of α-substituted α,β-unsaturated sulfinimine derivatives (entries 4−8) were found to drastically improve selectivity in favor of the expected trans-pyrrolidine product for a variety of trisubstituted olefinic imines.

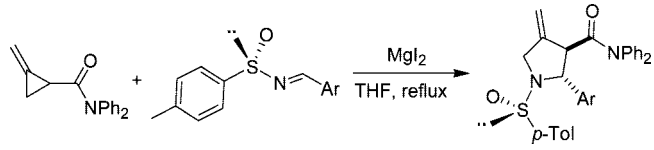
(10) See the Supporting Information for X-ray structures. Full crystallographic details have been deposited in the Cambridge Crystallographic database.

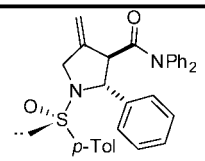
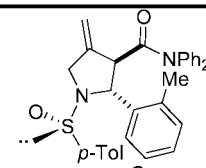
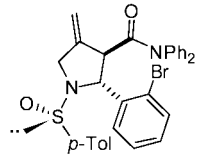
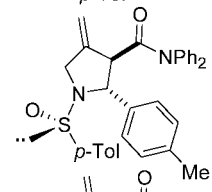
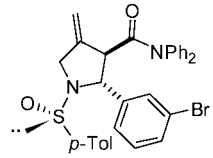
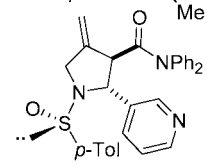
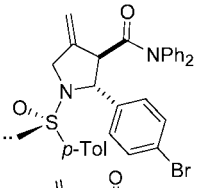
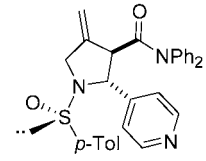
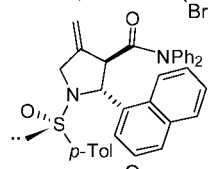
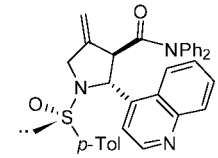
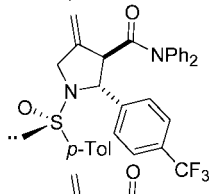
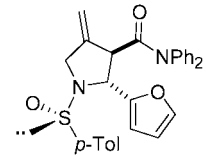
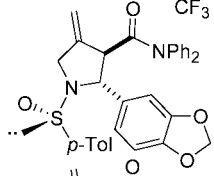
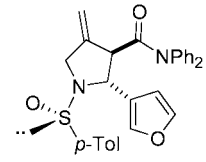
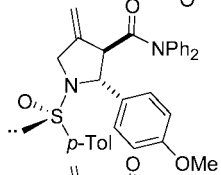
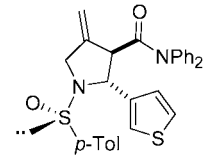
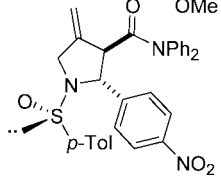
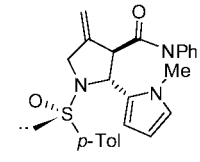
(11) In these cases, unequivocal proof of the minor cis isomer was determined by TFA/MeOH cleavage of the auxiliary for both the major and minor isomers followed by comparison of their corresponding 1H NMR. In addition, the trans geometry for the major isomer was proven by NOE experiments.

(12) Confirmation of the trans geometry for the 3-thiophenyl example was also proven by NOE experiments.

(13) Confirmation of the stereochemistry of the major trans isomer was made on the basis of comparison with coupling and chemical shifts of other compounds previously reported. In the case of entries 2 and 3 (Table 3), the stereochemistry for the cis and other trans isomer was determined by removal of the chiral auxiliary and comparing the resulting ^{1}H NMR spectra of the corresponding free amines to that obtained by auxiliary removal for the major trans isomer.

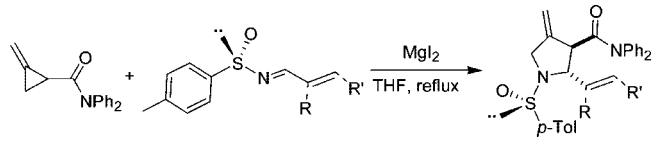
TABLE 2. Reaction Scope Using Aromatic and Heteroaromatic Imines[a]

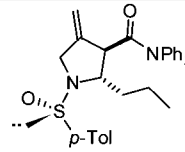
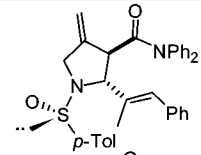
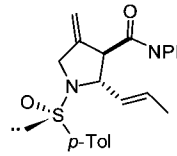
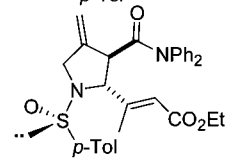
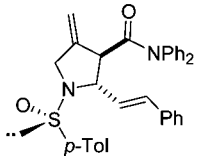
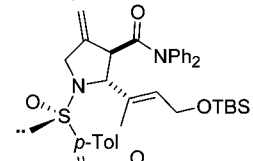
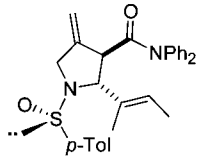
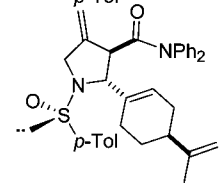


entry	product	% yield[b]	dr[c,d]	trans:cis[d]	entry	product	% yield[b]	dr[c,d]	trans:cis[d]
1		90	>20:1	>20:1	10		65	>20:1	>20:1
2		63	>20:1	>20:1	11		85	>20:1	>20:1
3		72	>20:1	>20:1	12		82	>20:1	>20:1
4		80	>20:1	>20:1	13		82	>20:1	>20:1
5		73	>20:1	>20:1	14		83	>20:1	13:1
6		94	>20:1	>20:1	15		82	>20:1	1:1[e]
7		77	>20:1	>20:1	16		85	>20:1	5:1
8		76	>20:1	>20:1	17		93	>20:1	>20:1
9		72	>20:1	>20:1	18		77	>20:1	2:1[e]

[a] Reactions carried out using 0.1 M MCP (0.2 mmol), 1.2 equiv of sulfinimine, and 1.0 equiv of MgI_2 in THF at reflux. [b] Combined isolated yield of diastereomers. [c] In this instance, the diastereomeric ratio refers to the ratio of (2*R*,3*R*):(2*S*,3*S*) products. [d] Determined by crude ^1H NMR. >20:1 indicates only one isomer was observed. [e] Diastereoselectivities are based on the ratio of isolated yields.

TABLE 3. Reaction Scope Using α,β-Unsaturated Imines[a]



entry	product	% yield[b]	dr[c,d]	trans:cis[d]	entry	product	% yield[b]	dr[c,d]	trans:cis[d]
1		-[e]	-	-	5		84	>20:1	>20:1
2		75	2:1[f]	6:1[g]	6		66	>20:1	>20:1
3		79	3:1[f]	7:1[g]	7		66	>20:1	>20:1
4		55	>20:1	>20:1	8		63	>20:1	>20:1

[a] Reactions carried out using 0.1 M MCP (0.2 mmol), 1.2 equiv of sulfinimine, and 1.0 equiv of MgI_2 in THF at reflux unless otherwise noted in the Supporting Information. [b] Combined isolated yield of diastereomers. [c] In this instance the diastereomeric ratio refers to the ratio of (2*R*,3*R*):(2*S*,3*S*) products. [d] Determined by crude ^{1}H NMR. >20:1 indicates only one isomer was observed. [e] Complex mixtures were obtained. [f] The major trans isomer for the structure indicated in the general scheme is actually (2*S*,3*S*) for this example. [g] Diastereoselectivities are based on the ratio of isolated yields.

Our methodology could also be extended to a variety of other activated methylenecyclopropyl derivatives (Table 4). While less activating esters did not undergo ring opening under our standard conditions (entry 1), the use of a more electron-withdrawing *tert*-butyl thioester group (entry 2) was found to afford the desired pyrrolidine product in a modest yield. In this example, the low yields obtained for the desired pyrrolidine product are attributed to the low reactivity of the intermediate iodo enolate, since the intermediate allylic iodide was observed by TLC and also by crude ^{1}H NMR even after prolonged heating. Interestingly, we note that a small amount of the isomerized α,β-unsaturated pyrrolidine product was observed in this case (<10%), presumably due to the decreased 1,3-allylic strain compared with the corresponding amide-substituted derivatives. Our conditions could also be used with a variety of aromatic and aliphatic tertiary amide MCPs. For all of these examples (entries 3−7), the desired pyrrolidines were obtained in generally good yields and in excellent selectivities over all other diastereomers for this reaction. For the *N*-methyl-*N*-phenyl amide example (entry 4), the absolute stereochemistry was confirmed to be identical to that of the 4-methoxyphenyl-*N*,*N*-diphenyl amide adduct (Table 2, entry 8).[10]

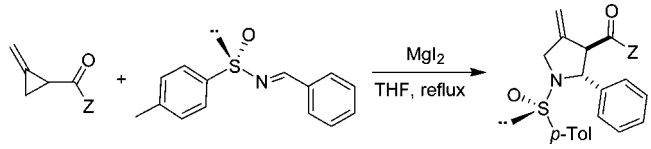
Stereochemical Analysis and Mechanistic Studies. We next investigated the ring-opening and ring-closing mechanism for this process, since it has been proposed by both Liu[14] and Ma[15] that ring opening of activated methylenecyclopropanes may occur either via an S_N2 or S_N2' ring-opening pathway. In addition, our system is further complicated by the possibility that ring closing may occur by either an S_N2 or a Baldwin-disfavored S_N2' process.[16] Accordingly, there are three possible pathways by which the overall iodide-mediated ring expansion may occur. The first, but highly unlikely, pathway (Scheme 3, pathway A) is one that involves initial ring opening by imine addition to the MCP amide (through either an S_N2 or S_N2' mechanism) to afford an iminium enolate which could then undergo cyclization to generate the requisite pyrrolidine product. The poor nucleophilicity of the imine nitrogen disfavors this pathway, as does the observation of the allylic iodide **2** during our optimization and scope investigations. The second, and more likely pathway (Scheme 3, pathway B) is Lewis acid activation of the MCP followed by iodide-mediated ring opening by either an S_N2 or S_N2' mechanism. Subsequent enolate attack of the sulfinimine would then generate the intermediate sulfinamide

(14) (a) Li, D.; Guo, Z.; Liu, H.-W. *J. Am. Chem. Soc.* **1996**, *118*, 275. (b) Li, D.; Agnihotri, G.; Dakoji, S.; Oh, E.; Lantz, M.; Liu, H.-W. *J. Am. Chem. Soc.* **1999**, *121*, 9034.

(15) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645.

(16) Although an S_N2' ring closing pathway is disfavored by Baldwin's rules, similar 5-*endo-trig* ring-closing reactions have been reported for the synthesis of pyrrolidines. See, for example: (a) Padwa, A.; Norman, B. H. *J. Org. Chem.* **1990**, *55*, 4801. (b) Craig, D.; Jones, P. S.; Rowlands, G. J. *Synlett* **1997**, 1423. (c) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 4455. (d) Berry, M. B.; Craig, D.; Jones, P. S.; Rowlands, G. J. *Chem. Commun.* **1997**, *22*, 2141. (e) Jones, A. D.; Knight, D. W. *Chem. Commun.* **1996**, 915. (f) Dell'Erba, C.; Mugnoli, A.; Novi, M.; Pani, M.; Petrillo, G.; Tavani, C. *Eur. J. Org. Chem.* **2000**, 903. (g) Chang, K. T.; Jang, H. Y.; Kim, Y. K.; Park, K. H.; Lee, W. S. *Heterocycles* **2001**, *55*, 1173.

TABLE 4. Reaction Scope Using Other Activated Methylenecyclopropanes[a]



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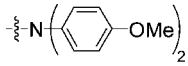
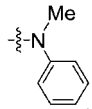
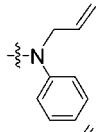
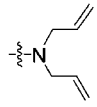
2		43	8:1	>20:1
3		86	>20:1	>20:1
4		93	>20:1	>20:1
5		83	>20:1	>20:1
6		85	>20:1	>20:1
7		57	>20:1	>20:1

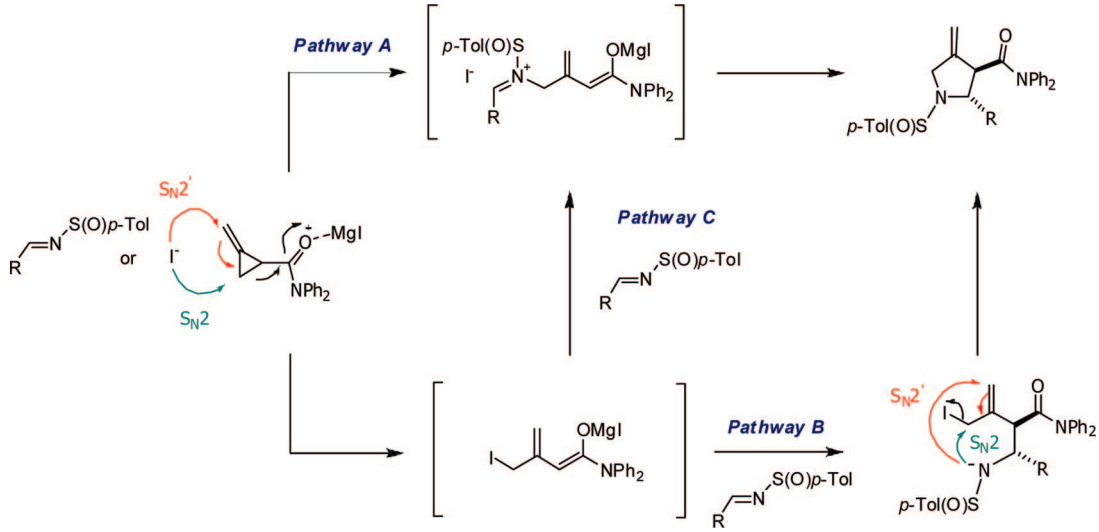
[a] Reactions carried out using 0.1 M MCP (0.2 mmol), 1.2 equiv of sulfinimine, and 1.0 equiv of MgI_2 in THF at reflux. [b] Combined yield of diastereomers. [c] In this instance, the diastereomeric ratio refers to the ratio of (2*R*,3*R*):(2*S*,3*S*) products. [d] Determined by crude ^{1}H NMR. >20:1 indicates only one isomer was observed. [e] No ring opening observed.

which would undergo cyclization by an S_N2 or S_N2' mechanism to afford the desired pyrrolidine product. The final possible pathway (Scheme 3, pathway C) involves initial ring opening by MgI_2 by either an S_N2 or S_N2' mechanism followed by nucleophilic displacement of the allylic iodide moiety by imine to generate an iminium intermediate. Intramolecular cyclization of the enolate would then produce the pyrrolidine product. Again, this pathway is unlikely given the poor nucleophilicity of this nitrogen and the fact that ^{1}H NMR experiments showed no evidence of such an intermediate.

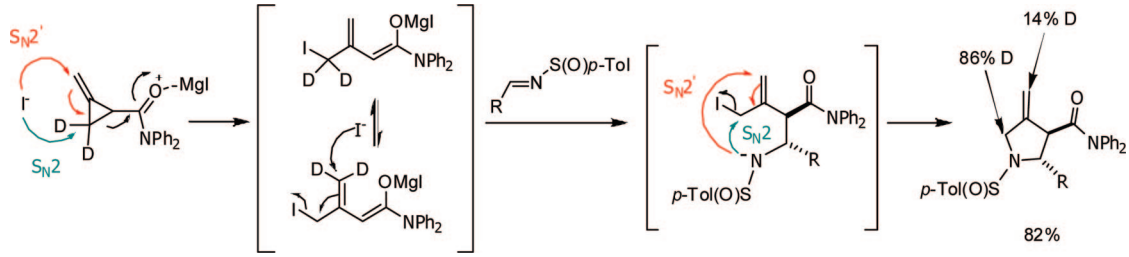
In order to examine the exact nature of the ring-opening/ring-closing mechanism, we carried out the reaction using a deuterium-labeled tertiary MCP amide (Scheme 4). Initial ring-opening studies in the presence of a chiral sulfinimine found 86% of the deuterium were incorporated at the 5-position of the pyrrolidine ring, indicating that the major mechanism by which ring opening/ring closing was occurring was via either an S_N2/S_N2 or S_N2'/S_N2' process. Interestingly, a small amount of deuterium scrambling at the *exo*-methylene position (14%) was also observed, presumably by a nonselective ring-opening/ring-closing process or alternatively, by iodide-[17] or iodine-mediated[18] scrambling of the allylic iodide. Additional ring-opening studies using DMSO in place of the sulfinimine afforded the intermediate allylic iodide with 74% of the deuterium incorporated at the allylic position (Scheme 5). These experiments indicate that the major pathway for ring opening and ring closing occurs by an S_N2/S_N2 process, while suggesting that an iodine or iodide-mediated interconversion between the enolates is likely operative under the reaction conditions. Although we note that these results do not completely rule out the possibility of a minor S_N2' ring opening process, orbital arguments would prevent such a possibility since a coplanar alignment of the alkene π^* and the σ^* of the C-leaving group is required for S_N2' processes to occur.[19] However, in our system the π^* of the alkene and the σ^* of the C−C cyclopropane system are almost orthogonal, thereby disfavoring such a ring-opening process (Scheme 6).

Initial ring opening of the activated MCP should afford the expected *Z*(O) enolate intermediate. Support for this enolate geometry is provided from our early optimization studies in which we observed the formation of the highly air-sensitive 2-aminofuran byproduct (Scheme 7). The formation of this 2-aminofuran presumably arises via cyclization of the *Z*(O) iodo enolate followed by isomerization. In fact, concurrent with our studies, Ma and co-workers reported the synthesis of substituted

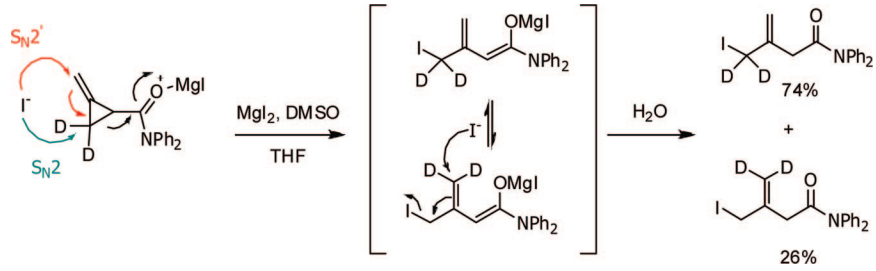
SCHEME 3. Proposed Mechanisms for the Iodide-Mediated Ring-Opening/Ring-Closing of Monoactivated Methylenecyclopropyl Amides



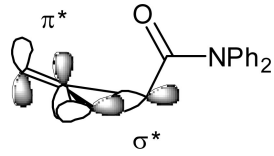
SCHEME 4. Pyrrolidine Formation Using a Deuterium-Labeled Tertiary Methylenecyclopropyl Amide



SCHEME 5. Ring-Opening Studies Using a Deuterium-Labeled Tertiary Methylenecyclopropyl Amide



SCHEME 6. Orbital Argument for S_N2 Addition of Iodide



furan derivatives by a similar NaI-mediated ring expansion of substituted MCP ketones.[15,20] Furthermore, Oshima and coworkers have also reported a similar iodo enolate intermediate in their $TiCl_4$/TBAI-mediated ring opening of cyclopropyl ketones.[6f]

Given this enolate geometry and based on the absolute stereochemistry of the pyrrolidine products, the sulfinimine must approach the intermediate *Z*(O) enolate from the Si face via either a boat or twist-boat transition state (Scheme 8). This conformation prevents any unfavorable 1,3-diaxial interactions between the diphenylamide and imine aromatic moieties, while still allowing for possible stabilization of the transition state via coordination of the sulfoxide oxygen to the nearby magnesium.[21] Alternatively, the cis pyrrolidine product arises via a less favored chair transition state. Based on X-ray crystallographic analysis of the minor cis isomer for the 2-phenyl substituted pyrrolidine (Table 2, entry 1),[22] we propose that

SCHEME 7. Synthesis of 2-Aminofuran Byproduct

SCHEME 8. Proposed Transition States for Both the *trans*- and *cis*-Pyrrolidine Diastereomers

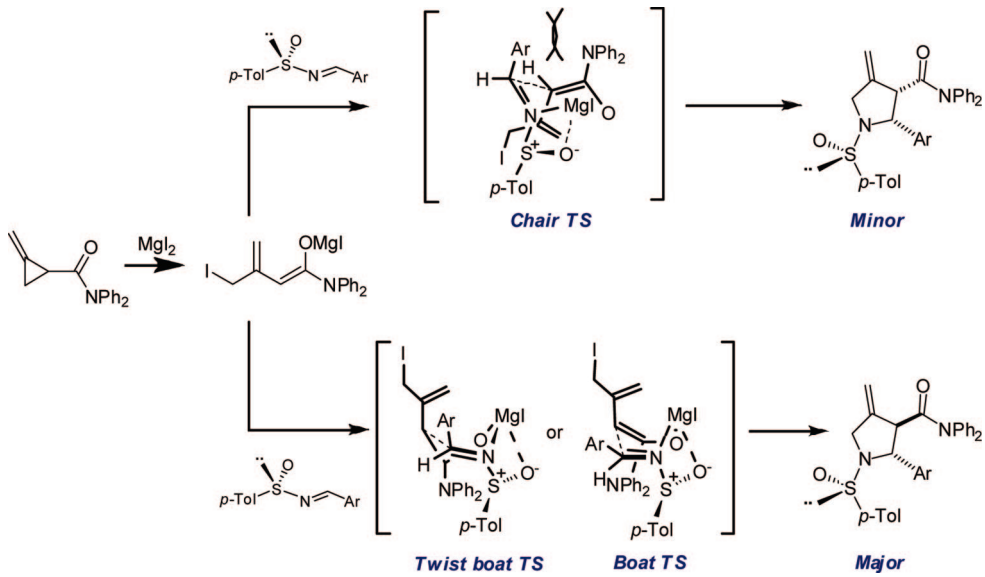
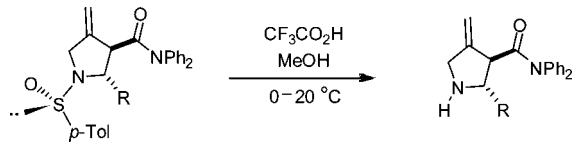


TABLE 5. Pyrrolidine Deprotection



entry	R	Time (h)	% yield[a]
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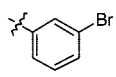
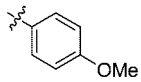
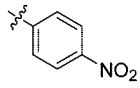
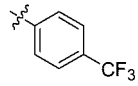
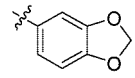
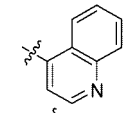
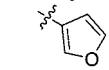
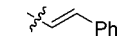
2		2	95
3		2	99
4		2	80
5		2	94
6		2	92
7		2	95
8		1.5	87
9		3	94

[a] Isolated yield.

attack of the imine in this case occurs from the Re face of the enolate as shown in Scheme 8.

Pyrrolidine Deprotection. The utility of this highly stereoselective methodology for the synthesis of enantioenriched pyrrolidines is highlighted in Table 5. Facile deprotection of the chiral sulfoxide protecting group could be achieved under mild conditions, affording enantioenriched free pyrrolidines in high yields for a wide range of aromatic, heteroaromatic, as well as aliphatic-based pyrrolidines (Table 5).[23]

Conclusions

The broad synthetic utility of MCPs has made these three carbon synthons attractive building blocks for a variety of carbo- and heterocyclic motifs. Recent studies by our group have focused on an iodide-mediated ring expansion of monoactivated MCPs as an *in situ* route to an all-carbon 1,3-dipole. These studies report for the first time a one-step, highly stereoselective halide-mediated Mannich/cyclization to afford a wide range of trans-2,3-pyrrolidines using chiral sulfinimines. In general, yields and diastereoselectivities for this transformation were good to excellent, allowing for the use of a range of aromatic, heteroaromatic, and α,β-unsaturated sulfinimines. Mechanistic studies indicate that ring opening/ring closing occurs primarily by an S_N2/S_N2 route, and that iodine- or iodide-mediated isomerization of the iodo enolate is likely occurring under the reactions conditions. Subsequent auxiliary removal could also be carried out under mild reaction conditions to efficiently afford a variety of valuable enantioenriched pyrrolidine building blocks.

Experimental Section

General Procedure for the MgI_2-Mediated Ring Expansion of Tertiary Methylenecyclopropyl Amides. To a flame dried flask was added MCP (1 equiv), MgI_2 (1 equiv), and sulfinimine (1.2 equiv). THF was added (0.1 M), and the solution was stirred for 20 min at room temperature before heating to reflux. Reaction completion was monitored by TLC. The reaction was then cooled to room temperature, diluted with ethyl acetate (2.0 mL), and quenched with saturated aqueous sodium sulfite (2.0 mL). The aqueous layer was separated and a 0.5 M tetrasodium ethylenediaminetetraacetic acid salt (EDTA) solution was added (50 mL). The aqueous phase was then extracted with ethyl acetate (4 × 50 mL), and the combined organic layers were dried with Na_2SO_4, filtered and concentrated in vacuo.

(2*R*,3*R*,S*S*)-4-Methylene-2-naphthalen-1-yl-1-(toluene-4-sulfinyl)pyrrolidine-3-carboxylic Acid Diphenylamide (Table 2, Entry 5). Following the general procedure outlined above (heat at reflux for 3.25 h) for the MgI_2-mediated ring expansion of 2-methylenecyclopropane carboxylic acid diphenylamide in the presence of (*S*)-(+)-*N*-(naphthalen-1-ylmethylene)-*p*-toluenesulfinamide. Following workup, chromatography on silica gel using 1:2 ethyl acetate/hexanes ($R_f = 0.26$) gave the title compound (0.0796 g, 73%) as an amorphous white foam: $[\alpha]^{20}_D = +20.8$ ($c = 0.9$, $CHCl_3$); IR (neat, cm^{-1}) 3008, 1674, 1595, 1490, 1373, 1091, 1068, 804, 777, 755, 702; δ_H (400 MHz, $CDCl_3$) 8.29 (bs, 2H), 7.94 (t, 2H, $J = 8.8$ Hz), 7.70 (bs, 1H), 7.55−7.47 (m, 5H), 7.26−7.17 (m, 5H), 7.10−6.96 (m, 5H), 6.27 (bs, 1H), 5.15 (bs, 1H), 5.06 (bs, 1H), 4.30 (d, 1H, $J = 14.0$ Hz), 3.20 (d, 1H, $J = 14.0$ Hz), 2.36 (s, 3H); δ_C (125 MHz, $CDCl_3$) 170.5, 144.7, 142.3, 141.9, 141.3, 140.7, 134.4, 131.7, 129.6, 129.5, 129.2, 128.9, 128.2, 127.7, 126.3, 126.2, 125.6, 125.4, 108.4, 45.7, 21.5 (remaining carbons not observed); $C_{35}H_{31}N_2O_2S$ (MH^+) (EI) requires 543.2106, found 543.2114.

Acknowledgment. We thank Dr. Wooseok Han for initial experimental contributions and helpful suggestions at the outset of this work. We also thank Merck-Frosst Canada, the Natural Sciences and Engineering Research Council (NSERC) of Canada and the University of Toronto for supporting this research. M.E.S. thanks NSERC and the Walter C. Sumner Foundation for providing postgraduate funding.

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Supporting Information Available: X-ray data for Table 2, entry 8, and Table 4 entry 4, as well as the minor cis isomer of Table 2, entry 1, experimental procedures, and characterization data (^{1}H and ^{13}C NMR, HRMS, IR) of all new pyrrolidine compounds listed in Tables 2−5 as well as starting materials. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802049U