ORGANIC LETTERS

2007
Vol. 9, No. 4
591−593

Enantioselective Catalytic Ring Expansion of Methylenecyclopropane Carboxamides Promoted by a Chiral Magnesium Lewis Acid

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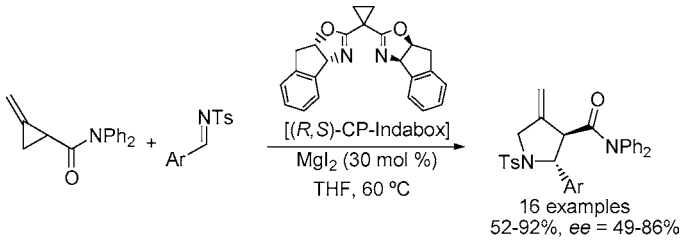
Received November 24, 2006

ABSTRACT



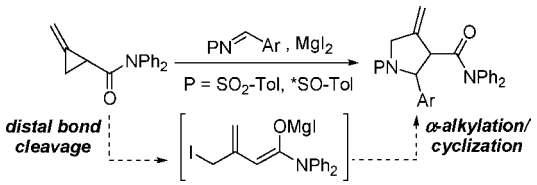
A catalytic enantioselective ring expansion of monoactivated methylenecyclopropanes (MCP) in the presence of *N*-tosyl aldimines was developed using a chiral bis(oxazoline) ligand–MgI_2 complex. After evaluation of ligands and optimization of the reaction conditions, the reaction has been applied to a variety of aromatic and heteroaromatic aldimines providing the corresponding *trans*-C_2,C_3-disubstituted methylenepyrrolidines in generally good yields (greater than 52%) and up to 86% ee.

We previously reported the preparation of methylene pyrrolidines via a cascade ring opening/cyclization of monoactivated methylenecyclopropanes (MCPs) with aldimines and chiral sulfinimines in the presence of MgI_2.[1] A key step of this transformation is the ring opening of MCPs with MgI_2, generating a vinylogous enolate intermediate, which incorporates both nucleophilic and electrophilic sites within the same molecule. Subsequent reaction of the enolate with electrophiles at the α-site, followed by cyclization, then led to the formation of the corresponding five-membered heterocyclic compounds (Scheme 1).

We now report the first enantioselective catalytic variant of the ring expansion of MCP amides allowing direct access to enantioenriched methylenepyrrolidines. The strategy used to induce stereoselection was based on the use of chiral magnesium complexes, the advantage being the availability of either enantiomer of the ligand, which should enable the synthesis of either enantiomer of the target molecule.

In our initial studies, the enantioselectivity was assessed in the ring expansion of *N*,*N*-diphenyl MCP amide **1** with aldimine **2** (Table 1). In recent years, C_2-symmetric chiral bis(oxazoline) ligand−metal complexes have received a great deal of attention through their use in various catalytic processes.[2] Our optimization thus began with an evaluation

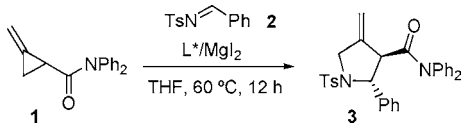
Scheme 1. MgI_2-Mediated Ring Expansion of MCP Tertiary Amides



(1) (a) Lautens, M.; Han, W. *J. Am. Chem. Soc.* **2002**, *124*, 6312−6316. (b) Scott, M. E.; Han, W.; Lautens, M. *Org. Lett.* **2004**, *6*, 3309−3312. (c) For an early report on the use of MgI_2 for ring opening of cyclopropyl derivatives, see: Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, M. E. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186−3189.

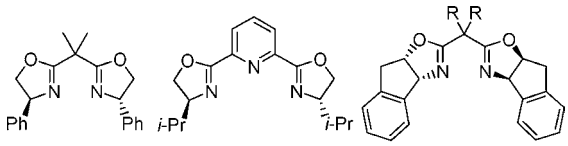
10.1021/ol0628614 CCC: $37.00 © 2007 American Chemical Society
Published on Web 01/25/2007

Table 1. Evaluation of Ligands and Reaction Conditions



entry	MgI_2 equiv	ratio L*/MgI_2	L*	product	yield[a] (%)	ee[b] (%)
1	1.0	1:1	(*S*)-**4**	*ent*-**3**	56	16
2	1.0	1:1	(*S*)-**5**	*ent*-**3**	74	39
3	1.0	1:1	(*R,S*)-**6a**	**3**	60	52
4	0.3	1:1	*R,S*)-**6a**	**3**	43	40
5	0.3	1:1	*R,S*)-**6b**	**3**	62	18
6	0.3	1:1	(*R,S*)-**6c**	**3**	65	56

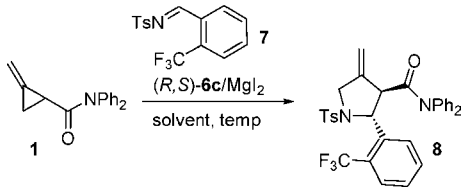
[a] Isolated yields. [b] Determined by HPLC on the chiral stationary phase.



(*S*)- 4 **(*S*)- 5**

(*R,S*)-6a (R = H)
(*R,S*)-6b (R = Me)
(*R,S*)-6c (R = -CH_2-)

Table 2. Optimization of the Reaction Conditions



entry	MgI_2 equiv	ratio L*/MgI_2	solvent	temp (°C)	reaction time[a]	yield[b] (%)	ee[c] (%)
1	0.3	1.1:1	THF	60	16 h	62	80
2	0.3	1.25:1	THF	60	12 h	60	81
3	0.3	1.5:1	THF	60	12 h	64	86
4	0.3	2.0:1	THF	60	12 h	56	84
5	0.6	1.5:1	THF	60	12 h	56	84
6	0.15	1.5:1	THF	60	24 h	51	79
7	0.3	1.5:1	DCM	40	24 h	0[d]	83
8	0.3	1.5:1	DCE	60	24 h	0[d]	–
9	0.3	1.5:1	benzene	60	12 h	0[e]	–
10	0.3	1.5:1	toluene	80	6 h	46	86

[a] Time needed to get complete conversion of the starting MCP. [b] Isolated yields. [c] Determined by HPLC on the chiral stationary phase. [d] No reaction. [e] Decomposition.

of magnesium complexes prepared in situ by mixing MgI_2 and bis(oxazoline) ligands **4**−**6** containing two and three coordination sites.[3]

Reactions were first performed using stoichiometric amounts of bis(oxazoline) ligands (**4**−**6**)/MgI_2 complexes. In all cases, ring expansion proceeded smoothly and the *trans*-pyrrolidine **3** was obtained in good yields (entries 1−3). It is noteworthy that the analogous reaction in the absence of the ligand gave a mixture of *cis* and *trans* adducts.[4] Whereas the use of ligands **4** and **5** provided low enantioselectivities, ring expansion with the MgI_2−Indabox **6a** complex proceeded with a higher level of asymmetric induction. Interestingly, when a substoichiometric amount (30 mol %) of the chiral Lewis acid was used, the ring-expanded product **3** was formed in 53% yield but with lower ee (40%) (entry 4). Subsequent optimization experiments demonstrated that use of DiMe−Indabox **6b** resulted in low enantioselectivity (entry 5), whereas CP−Indabox **6c** was effective in affording **3** in 65% yield and with the best ee (entry 6).[5]

To avoid background reactions arising from noncomplexed MgI_2 that could diminish the ee, the use of an excess of ligand compared to MgI_2 was tested. As anticipated, by increasing the ratio L*/Mg, both reactivity and enantioselectivity could be significantly increased (Table 2, entries 1−4). Use of CP−Indabox **6c** (45 mol %) and MgI_2 (30 mol %) was found to be the optimal conditions providing the ring-expanded product **8** in 64% yield and 86% ee.[6] When the reaction was carried out in the presence of ligand **6c** with twice as much MgI_2 (60 mol %), no significant improvement was observed in terms of reactivity or selectivity (entry 5). On the other hand, use of only 15 mol % of MgI_2 was found to slow the rate of the reaction, giving the product in only 21% yield after a prolonged reaction time but with comparable selectivity (entry 6).

Our next set of experiments focused on solvent screening. When the ring expansion was run in dichloromethane at reflux, good selectivity but low reactivity were observed (entry 7). Surprisingly, no reaction occurred in dichloroethane and only decomposition of the starting materials was observed in benzene (entries 8 and 9). Finally, a fast and selective reaction was observed in toluene at 80 °C, but pyrrolidine **8** was isolated in only 46% yield (entry 10).

To further demonstrate the efficiency of the MgI_2−bis(oxazoline) **6c** complex in ring expansion reactions of MCP **1**, a series of aromatic *N*-tosyl aldimines were subjected to the optimal reaction conditions described above [MgI_2 (30 mol %), CP−Indabox **6c** (45 mol %), THF, 60 °C]. In all cases, the reactions proceeded smoothly giving the *trans*-methylene pyrrolidine derivatives as the major product in yields greater than 50% with ee's up to 86% (Table 3).

Use of (*R,S*)-CP−Indabox **6c** produced methylene pyrrolidine **8a** with 86% ee (entry 1), whereas (*S,R*)-**6c** delivered the opposite enantiomer of **8a** with 84% ee (entry 2).[7,8] When

(2) For reviews on the use of oxazoline-containing ligands in asymmetric catalysis, see: (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45. (b) McManus, H.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151−4202.

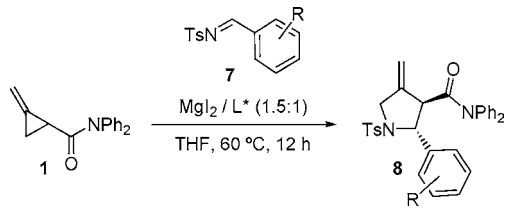
(3) For an early report of the use of a bis(oxazoline)−Mg complex, see: Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807−6810.

(4) Indeed, MgI_2-mediated ring expansion usually affords mixtures of diastereomers depending on the substitution pattern of the aldimines. However, when the reaction was performed in the presence of bis(oxazoline) ligand **6c**, only traces of the *cis* diastereomer were observed.

(5) (a) Davies, I. E.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Synth. Commun.* **1996**, 1753−1754. (b) Davies, I. E.; Deeth, R. J.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **1999**, *40*, 1233−1236.

(6) Other conditions, such as solvent, temperature, concentration, and quantity of the chiral complex, were also tested, but these reaction conditions were found to give the optimal balance of reaction yields and enantioselectivity.

Table 3. Enantioselective Ring Expansion of MCP **1** with Various Aromatic Aldimines



entry	imine	R	L*	product	yield[a] (%)	ee[b] (%)
1	**7a**	2-CF_3	(*R,S*)-**6c**	**8a**	64	86
2	**7a**	2-CF_3	(*R,S*)-**6c**	*ent*-**8a**	61	84
3	**7a**	2-CF_3	(*R,S*)-**6c**[c]	**8a**	55	70
4	**7a**	2-CF_3	(*R,S*)-**6c**[d]	**8a**	59	47
5	**7b**	4-CF_3	(*R,S*)-**6c**	**8b**	52	83
6	**7c**	2-Br	(*R,S*)-**6c**	**8c**	52	76
7	**7d**	3-Br	(*R,S*)-**6c**	**8d**	54	76
8	**7e**	4-Br	(*R,S*)-**6c**	**8e**	55	78
9	**7f**	2,4-dichloro	(*R,S*)-**6c**	**8f**	60	78
10	**7g**	2,4-dimethyl	(*R,S*)-**6c**	**8g**	71	71
11	**7h**	2-OMe	(*R,S*)-**6c**	**8h**	55	76
12	**7i**	4-OMe	(*R,S*)-**6c**	**8i**	70	57
13	**7j**	3,4-O-CH_2-O	(*R,S*)-**6c**	**8j**	61	69
14	**7k**	4-OAc	(*R,S*)-**6c**	**8k**	59	71

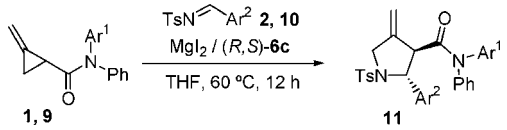
[a] Isolated yields. [b] Determined by HPLC on the chiral stationary phase. [c] Ligand **6c** of 80% ee was used. [d] Ligand **6c** of 50% ee was used.

the reaction was performed with ligand (*R,S*)-**6c** of 80% ee and 50% ee, the *trans*-methylenepyrrolidine **8a** could be obtained in 70% ee and 47% ee, respectively, suggesting that monomeric species are involved in the catalytic process (entries 3 and 4).[9]

Surprisingly, the electronic nature and the position of the substituents seemed to have little or no influence on the success of the ring expansion process or on the diastereoselectivity.[10] It was also found that higher ee's were obtained in the case of substrates bearing electron-withdrawing groups on the aromatic ring (entries 1−10). In contrast, the position of electron-donating substituents on the aromatic ring of the imine seemed to have a greater influence on the enantioselectivity. Indeed, *ortho*-substituted substrates **7g** and **7h** exhibited higher enantioselectivities compared to *meta*- and *para*-substituted imines **7i**, **j** (entries 11−14).

This methodology was further extended to heteroaromatic systems (Table 4). When 2-furyl and 3-furyl *N*-tosyl aldimines **10a** and **10b** were employed, reactions appeared to be equally selective and the corresponding *trans*-pyrrolidines were isolated in 55% (72% ee) and 66% yield (72% ee), respectively (entries 1 and 2). On the other hand, ring expansion with *N*-Me-pyrrole imine **10c** also gave the *trans* product in good yield but with lower enantioselectivity (entry 3). Finally, it was tested whether the introduction of a second site for Lewis acid coordination on the MCP moiety would influence the enantioselectivity. *N*-Phenyl-*N*-(2-pyridyl) MCP amide **9** was then subjected to the optimized reaction conditions in the presence of aldimine **2**. The reaction was found to be particularly efficient, but no improvement was observed on the enantioselectivity (entry 4).

Table 4. Reaction with Heteroaromatic Substrates



entry	MCP	Ar^1	imine	Ar^2	product	yield[a] (%)	ee[b] (%)
1	**1**	Ph	**10a**	2-furyl	**11a**	55	72
2	**1**	Ph	**10b**	2-furyl	**11b**	66	72
3	**1**	Ph	**10c**	2-(*N*-Me-pyrrole)	**11c**	67	49
4	**9**	2-pyridine	**2**	Ph	**11d**	92	78

[a] Isolated yields. [b] Determined by HPLC on the chiral stationary phase.

In conclusion, we have developed the first catalytic enantioselective ring expansion of monoactivated MCPs using a chiral magnesium Lewis acid. The reaction has been shown to proceed in good yields and with good enantioselectivities in a number of cases, yielding *trans*-methylenepyrrolidines. Elucidation of the factors responsible for the enantioselectivity, improvements in the ee, the search for more efficient catalysts, and expansion of the scope to less reactive substrates are currently being investigated in our laboratory.

Acknowledgment. This work is supported by NSERC (Canada), Merck Frosst (IRC), and the University of Toronto. We also thank Dr. Yann Béthuel and Mark Scott (University of Toronto) for helpful discussions.

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

OL0628614

(7) The absolute configuration assignment was based upon the published[1b] X-ray structure of the methylenepyrrolidine resulting from MgI_2-mediated ring expansion of MCP **1** with the chiral *p*-methoxy-substituted aromatic sulfinime. After oxidation with *m*-CPBA, it was possible to assign the absolute configuration of the ring-expanded product **8i** to be (2*R*,3*R*) by comparison of both optical rotations and chiral HPLC retention times (see Supporting Information).

(8) The absolute configuration of the other products was assigned in analogy to **8i**.

(9) The plot $ee_{prod} = f(ee_{L^*})$ was found to be linear showing that diastereomeric dimeric species are not involved in the catalytic process. Kagan, H. B. *Synlett* **2001**, 888−899.

(10) Only traces of *cis*-pyrrolidines were occasionally detected in reaction mixtures.