J|A|C|S ARTICLES

Published on Web 06/24/2010

Dynamic Kinetic Asymmetric Synthesis of Substituted Pyrrolidines from Racemic Cyclopropanes and Aldimines: Reaction Development and Mechanistic Insights

Andrew T. Parsons, Austin G. Smith, Andrew J. Neel, and Jeffrey S. Johnson*

Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

Received February 5, 2010; E-mail: jsj@unc.edu

Abstract: An enantioselective preparation of 2,5-*cis*-disubstituted pyrrolidines has been achieved via a dynamic kinetic asymmetric transformation (DyKAT) of racemic donor−acceptor cyclopropanes and (*E*)-aldimines. Mechanistic studies suggest that isomerization of the aldimine or resultant iminium to the *Z* geometry is not a pathway that furnishes the observed 2,5-*cis*-disubstituted products.

Introduction

Nitrogen-containing heterocycles are abundant in naturally occurring and pharmaceutically relevant molecules.[1] In particular, substituted pyrrolidine derivatives are ubiquitous, and their value is reflected by continued interest in the development of methods for their preparation.[2,3] Efforts in our lab[4] and others[5−7] have focused on the asymmetric synthesis of hetero- and carbocycles via ring-opening reactions of strained donor−acceptor (D−A) cycloalkanes. We recently reported a dynamic kinetic asymmetric transformation (DyKAT) of racemic 1,1-cyclopropanediesters (**1**) via (pybox)MgI_2-catalyzed (3 + 2) annulation with aldehydes to afford 2,5-*cis*-disubstituted tetrahydrofurans in a highly enantioselective manner.[4f] This article describes the asymmetric synthesis of pyrrolidines from racemic cyclopropanes and (*E*)-aldimines (eq 1) and experiments that reveal a surprising mechanistic dichotomy with the extant cyclopropane/aldehyde annulations.

(1)

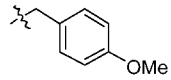
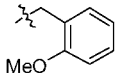
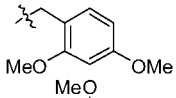
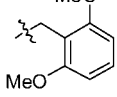
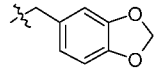
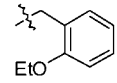
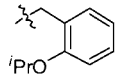
Results and Discussion

Independent reports by Kerr and Tang demonstrated that (*E*)-aldimines are competent dipolarophiles in Lewis acid-catalyzed (3 + 2) annulations with D−A cyclopropanes **1**, yielding pyrrolidines of type **3**.[6] A range of diastereoselectivities was observed, depending on the aldimine protecting group (PG), with an *N*-benzyl group providing the greatest levels of 2,5-*cis* diastereoselectivity. These observations led us to focus our early efforts on enantioselective annulation of **1a** with (*E*)-*N*-benzylidene-1-phenylmethanamine (**2a**) catalyzed by **L1**·MgI_2

(1) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.
(2) For a recent review of the stereoselective preparation of substituted pyrrolidines, see: Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484.
(3) For selected examples, see: (a) Pichon, M.; Figadère, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927. (b) Cabrera, S.; Arrayas, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (c) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213. (d) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571. (e) Wang, C.-J.; Liang, G.; Xue, Z.-Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250.
(4) (a) Pohlhaus, P. D.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 1057. (b) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014. (c) Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8*, 573. (d) Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541. (e) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642. (f) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122. (g) Sanders, S. D.; Ruiz-Olalla, A.; Johnson, J. S. *Chem. Commun.* **2009**, 5135. (h) Campbell, M. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 10370. (i) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 14202.
(5) (a) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186. (b) Sugita, Y.; Kawai, K.; Yokoe, I. *Heterocycles* **2000**, *53*, 657. (c) Sugita, Y.; Kawai, K.; Yokoe, I. *Heterocycles* **2001**, *55*, 135. (d) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704. (e) Lautens, M.; Han, W. *J. Am. Chem. Soc.* **2002**, *124*, 6312. (f) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023. (g) Cardona, F.; Goti, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7832. (h) Korotkov, V. S.; Larionov, O. V.; Hofmeister, A.; Magull, J.; de Meijere, A. *J. Org. Chem.* **2007**, *72*, 7504. (i) Bajtos, B.; Yu, M.; Zhao, H. D.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631. (j) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689. (k) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. G.; Vereletskii, P. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 1107. (l) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196. (m) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Eur. J. Org. Chem.* **2008**, 5329. (n) Sapeta, K.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 2081. (o) Lebold, T. P.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 4354. (p) Lebold, T. P.; Leduc, A. B.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 3770. (q) Qu, J.-P.; Deng, C.; Zhou, J.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2009**, *74*, 7684. (r) Chagarovskiy, A. O.; Budynina, E. M.; Ivanova, O. A.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Tetrahedron* **2009**, *65*, 5385. (s) Yadav, J. S.; Reddy, B. V. S.; Narasimhulu, G.; Chandrakanth, D.; Satheesh, G. *Synthesis* **2009**, 3443. (t) Leduc, A. B.; Lebold, T. P.; Kerr, M. A. *J. Org. Chem.* **2009**, *74*, 8414. (u) Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 1133. (v) Wu, L.; Shi, M. *Chem.−Eur. J.* **2010**, *16*, 1149. (w) Xing, S. Y.; Pan, W. Y.; Liu, C.; Ren, J.; Wang, Z. W. *Angew. Chem., Int. Ed.* **2010**, *49*, 3215.

10.1021/ja1032277

Table 1. Evaluation of Substituted *N*-Benzyl Aldimine Protecting Groups[a]

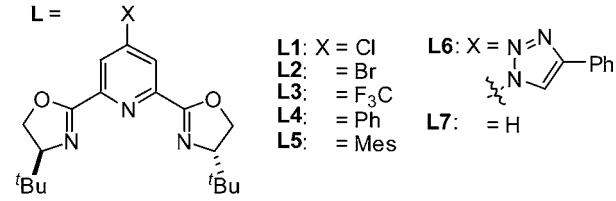
entry	protecting group (PG)		yield (%)[b]	dr[c]	er[d]
1[e]	CH_2Ph	(**2a**)	83 (**3aa**)	97:3	85.5:14.5
2	CH_2Ph	(**2a**)	74 (**3aa**)	95:5	91:9
3		(**2b**)	77 (**3ab**)	96:4	90.5:9.5
4		(**2c**)	71 (**3ac**)	96:4	95:5
5		(**2d**)	75 (**3ad**)	96:4	93:7
6		(**2e**)	69 (**3ae**)	99:1	89.5:10.5
7		(**2f**)	68 (**3af**)	80:20	92:8
8		(**2g**)	76 (**3ag**)	95:5	94:6
9		(**2h**)	74 (**3ah**)	94:6	96:4

[a] Conditions: **1a** (1.0 equiv), aldimine (1.1 equiv), MgI_2 (0.10 equiv), 4-Cl-^{t}Bu-pybox (**L1**, 0.12 equiv), $[\mathbf{1a}]_0 = 0.05$ M in CCl_4, rt, 24 h. [b] Determined by ^{1}H NMR spectroscopy using a mesitylene internal standard. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral supercritical fluid chromatography (SFC) analysis. [e] Using 2.0 equiv of the aldimine.

(**L1** = 4-Cl-^{t}Bu-pybox).[8,9] Under our previously reported reaction conditions, pyrrolidine **3aa** was obtained in 83% yield and 85.5:14:5 er (Table 1, entry 1). An increase in er to 91:9 was achieved by decreasing the amount of aldimine from 2.0 to 1.1 equiv, although a notable decrease in yield occurred.

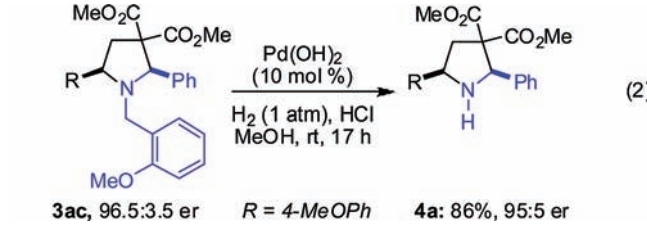
Table 2. Evaluation of 4-Substituted ^{t}Bu-pybox Ligands[a]

entry	L	yield (%)[b]	dr[c]	er[d]
1	**L1**	66	95:5	89.5:10.5
2	**L2**	79[e]	96:4	93:7
3	**L3**	69	96:4	92:8
4	**L4**	63 (93)[f]	95.5:4.5	83:17
5	**L5**	56 (64)[f]	91:9	89:11
6	**L6**	76	95:5	80:20
7	**L7**	39 (44)[f]	84:16	74:26



[a] Conditions: **1a** (1.0 equiv), **2i** (1.1 equiv), MgI_2 (0.10 equiv), **L** (0.12 equiv), $[\mathbf{1a}]_0 = 0.05$ M in CCl_4, rt, 24 h. [b] Determined by ^{1}H NMR spectroscopy using a mesitylene internal standard. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral SFC analysis. [e] Average isolated yield of two independent trials. [f] The value in parentheses refers to conversion of **1a**.

We proceeded to examine the effect of the benzyl PG on the enantioselectivity. Alkoxy-substituted benzyl groups were evaluated, with 2-methoxybenzyl- and 2-isopropoxybenzyl-protected aldimines (**2c** and **2h**, respectively) providing the highest yield and stereoselectivity (Table 1, entries 4 and 9). Since the parent 2-methoxybenzylamine is commercially available, we chose to proceed with 2-methoxybenzyl-protected aldimine dipolarophiles. It is noteworthy that the free pyrrolidine can be revealed by removal of the 2-methoxybenzyl group under hydrogenolytic conditions (eq 2).[10]

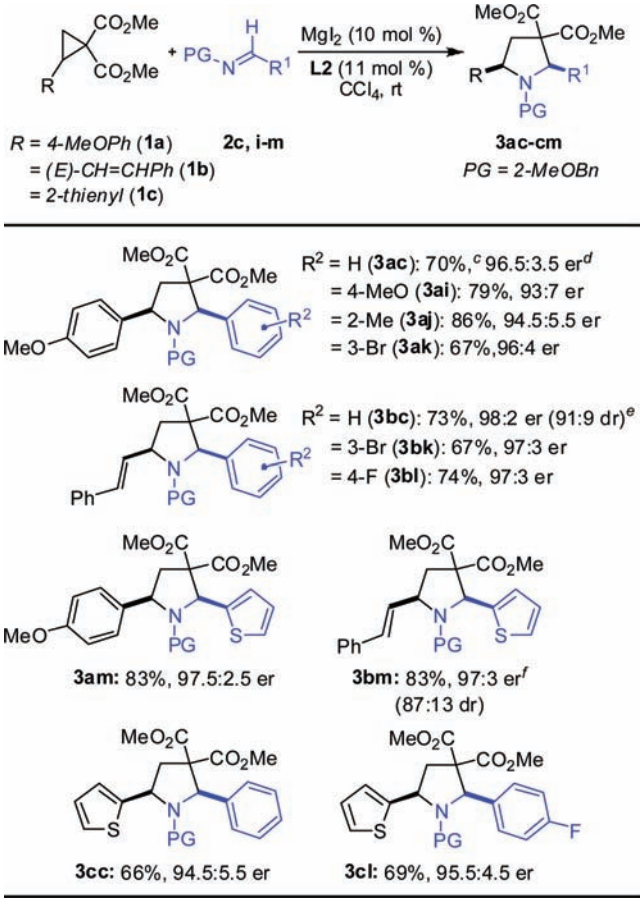


(2)

Having determined a suitable protecting group, we continued the reaction optimization by examining various 4-X-^{t}Bu-pybox ligands. In our previous studies with aldehydes, highly electron-rich dipolarophiles proved to be challenging substrates because of a decrease in enantioselectivity of the transformation. Thus, electron-rich aldimine **2i** was chosen as the dipolarophile in a screen of 4-X-^{t}Bu-pybox ligands. 4-Br-^{t}Bu-pybox (**L2**) provided the highest yield and er of pyrrolidine **3ai** (Table 2, entry 2), which is in contrast to the aldehyde system, where **L1** (X =

(6) (a) Carson, C. A.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 8242. (b) Kang, Y.-B.; Tang, Y.; Sun, X.-L. *Org. Biomol. Chem.* **2006**, *4*, 299.
(7) For enantioselective transformations of racemic D−A cyclopropanes, see: (a) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764. (b) Kang, Y.-B.; Sun, X.-L.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3918.
(8) For examples of 4-substituted pybox ligands used in asymmetric transformations, see: (a) Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 4306. (b) Park, S.-B.; Murata, K.; Matsumoto, H.; Nishiyama, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2487. (c) Clark, J. S.; Clarke, M.-R.; Clough, J.; Blake, A. J.; Wilson, C. *Tetrahedron Lett.* **2004**, *45*, 9447. (d) Wang, H.; Wang, H.; Liu, P.; Yang, H.; Xiao, J.; Li, C. *J. Mol. Catal. A: Chem.* **2008**, *285*, 128. (e) Reference 4f. (f) Karimi, B.; Maleki, A. *Chem. Commun.* **2009**, 5180. We have found that the *tert*-butyl substituent is optimal for chiral recognition of malonyl cyclopropanes. See: (g) Parsons, A. T. Ph.D. Thesis, University of North Carolina, 2010.
(9) For MgI_2-catalyzed annulations of aldimines and cyclopropanes, see: (a) Reference 5a. (b) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175. (c) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826. (d) Meyers, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 694.
(10) Onomura, O.; Kirira, P. G.; Tanaka, T.; Tsukaka, S.; Matsumara, Y.; Demizu, Y. *Tetrahedron* **2008**, *64*, 7498.

Table 3. Aldimine and Cyclopropane Substrate Scope[a,b]



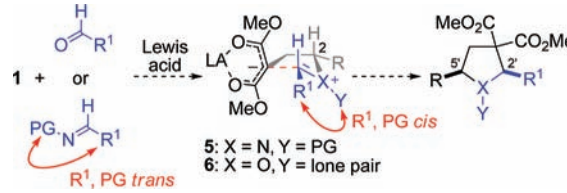
[a] Conditions: **1** (1.0 equiv), **2** (1.1 equiv), MgI_2 (0.10 equiv), 4-Br-^{t}Bu-pybox (**L2**, 0.11 equiv), $[\mathbf{1}]_0$ = 0.05 M in CCl_4, rt. [b] The dr was determined by ^{1}H NMR spectroscopy to be >92:8, unless otherwise noted. [c] Yield refers to the average isolated yield (of the diastereomeric mixture) of two independent trials. [d] Determined by chiral SFC analysis. [e] The er of the minor (*trans*) diastereomer was 98:2. [f] The er was determined for the major *cis* diastereomer.

Cl) was the preferred ligand. Furthermore, the range of yields and stereoselectivities within this class of ligands was quite broad, with electron-neutral species producing the poorest results of those examined.

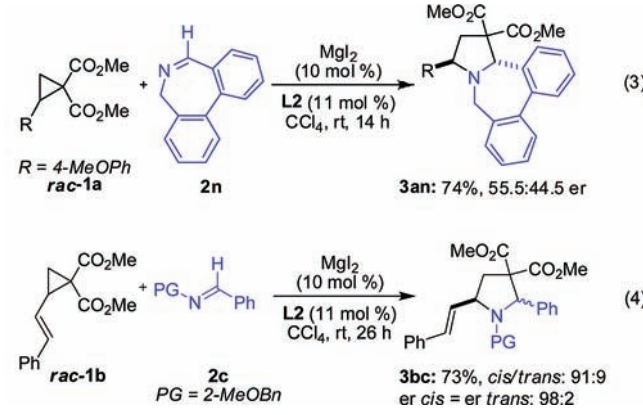
After the optimized reaction conditions had been identified, a range of *N*-2-methoxybenzyl-protected aryl aldimines and D−A cyclopropanes were subjected to the **L2**·MgI_2 conditions (Table 3, footnote *a*). Previous studies had indicated that electron-rich cyclopropane donor groups are required to achieve dynamic behavior; thus, cyclopropanes bearing 4-MeOPh (**1a**), (*E*)-CH═CHPh (**1b**), and 2-thienyl (**1c**) donor groups were competent substrates.[11] Electron-rich and -neutral aryl aldimines of type **2** provided high yields and enantioselectivities (up to 86% yield and 98:2 er; Table 3). Electron-poor aryl, alkenyl, and aliphatic aldimines were not successful coupling partners, consistent with Kerr's observations.[6a]

Models that account for the high 2,5-*cis*-diastereoselectivity in cyclopropane/aldimine annulations have posited a "meridional" orientation of the R, Y, and R^1 substituents (all pseudoequatorial) in an envelope-type transition state (**5** in Scheme 1).[6] Such an arrangement would be analogous to the all-equatorial transition structure **6** that has been invoked for THF-forming cyclopropane/aldehyde annulations.[4] For the all-equatorial transition structure **5** to be viable in the present case, the aldimine must exhibit fluxional geometric behavior (*E*/*Z* isomerization) at some point during the reaction.

Scheme 1. Previously Proposed Stereochemical Models for Aldehyde/Cyclopropane and Aldimine/Cyclopropane Annulation



Experiments that directly probe the aldimine geometric stability are illustrated in eqs 3 and 4. We selected (*Z*)-aldimine **2n** as a reaction partner that, through cyclic constraint, would preclude *E*/*Z* isomerization. Strikingly, Lewis acid-catalyzed annulation of **2n**[12] and cyclopropane **1a** delivered pyrrolidine (**3an**) exclusively as the 2,5-*trans* isomer with negligible enantioenrichment (diastereoselection >20:1, er 55.5:44.5) (eq 3). Conversely, the minor 2,5-*trans* adduct obtained from annulation of (*E*)-aldimine **2c** and **1b** was produced with high enantioselectivity (eq 4).



Previous studies have led us[4b,e] and others[5j,13] to propose that Lewis acid-catalyzed (3 + *n*) annulations of cyclopropanes **1** proceed via stereospecific nucleophilic attack by the dipolarophile on the donor-substituted site of the cyclopropane, leading to inversion at that position. Our experiments with the **L1**·MgI_2 complex revealed preferential reaction with cyclopropane (*S*)-**1**.[14] The absolute configurations of the pyrrolidine products in this study are consistent with both of these findings.[15] With respect to diastereoselectivity, the configuration of the C2′ pyrrolidine stereocenter arising via Mannich cyclization may

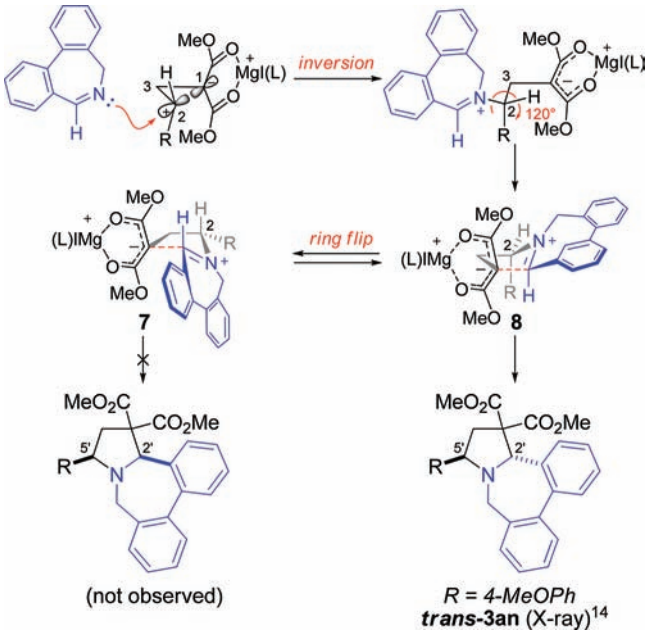
(11) For annulation results with diisopropyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1d**) and dibenzyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1e**), see the Supporting Information.

(12) Weitzberg, M.; Abu-Shakra, E.; Azeb, A.; Aizenshtat, Z.; Blum, J. *J. Org. Chem.* **1987**, *52*, 529.

(13) (a) Sapeta, K.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 8597. (b) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 10251.

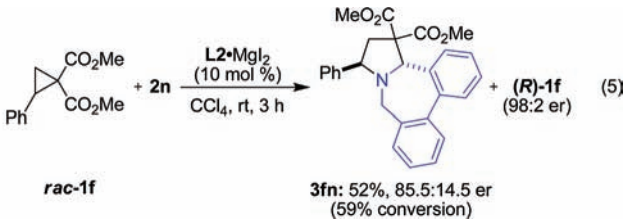
(14) Previous work in our group has shown that dipolarophiles are selective for nucleophilic attack on the (*S*)-cyclopropane when (*S*,*S*)-4-X-^{t}Bu-pybox·MgI_2 is used (see ref 4f.) For cyclopropane **1c**, the Cahn−Ingold−Prelog priorities change because of the thienyl group, so it is the *R* enantiomer that is the reactive one. Our allusions to the general preference of **L2**·MgI_2 for (*S*)-**1** should be understood to mean selective reaction of (*S*)-**1a**, (*S*)-**1b**, (*R*)-**1c**, and (*S*)-**1d**, all of which possess the same disposition of the C-2 alkyl substituent.

Scheme 2. Mechanistic Proposal To Account for the Observed 2,5-*trans* Relationship Obtained from Annulation of **1** with (*Z*)-Aldimine **2n**



vary as a result of at least two different factors: (a) ring flip prior to ring closure and (b) iminium isomerization prior to ring closure. The application of the nonfluxional (*Z*)-aldimine **2n** allowed us to separately examine (a) and (b), since iminium isomerization was precluded. In conjunction with the results from eq 3, the analysis in Scheme 2 reveals that the "meridional" transition structure **7** resulting from a ring flip is not competitive, since *cis*-**3an** was not observed. Nonbonded steric compression apparently favors placing R (the C5′ substituent) in the axial position (transition state **8**).

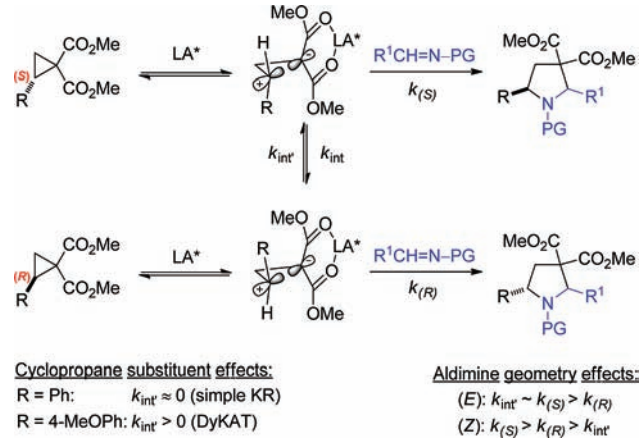
The low enantioselectivity exhibited in eq 3 could arise from either poor enantiomer discrimination (as a function of nucleophile identity) or inefficient racemization relative to annulation. We sought to determine the degree of enantiodifferentiation of the *R* and *S* enantiomers of **1** by (*Z*)-aldimine **2n** (eq 5). Because of its low rate of enantiomer interconversion, cyclopropane **1f** bearing a phenyl donor group is a substrate for simple kinetic resolution under the (pybox)MgI_2 reaction conditions. Reaction of *rac*-**1f** and **2n** was carried to partial conversion to furnish pyrrolidine **3fn** as the *trans* isomer with a moderate level of enantioenrichment. The recovered **1f** was highly enriched in the *R* enantiomer. These results indicate that **2n** is selective for reaction with (*S*)-**1f**.



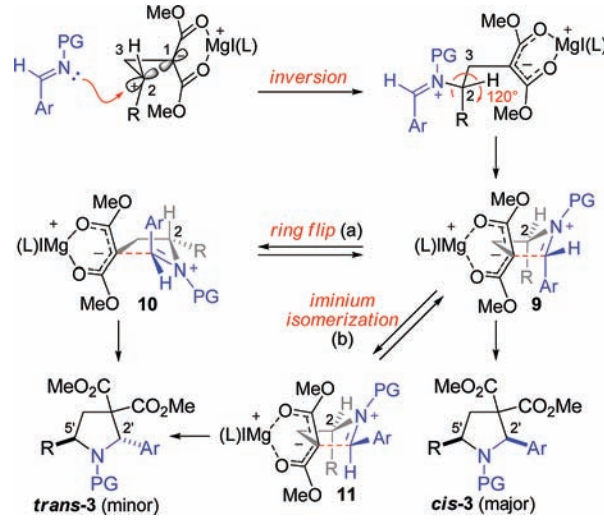
The results of eqs 3 and 5 may be collectively understood in terms of the relative rate constants illustrated in Scheme 3. A

(15) CCDC 773308 and CCDC 773309 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 3. Summary of Observed Substituent and Geometric Effects in Enantioselective Cyclopropane/Aldehyde Annulation



Scheme 4. Mechanistic Proposal for the Formation of 2,5-*cis*-Pyrrolidines via Annulation of **1** with (*E*)-Aldimines



(*Z*)-aldimine is expected to exhibit greater nucleophilicity than the *E* isomer because of steric effects. In the reaction of *rac*-**1a** with **2n**, this enhanced nucleophilicity means that both (*S*)-**1a** and (*R*)-**1a** undergo annulation faster than the enantiomers can interconvert [$k_{(S)}$, $k_{(R)} > k_{int}$, k_{int}']. The results of eq 5 intimate that the inherent preference exhibited by **L2**·MgI_2 for the (*S*)-malonyl cyclopropanes is preserved regardless of the aldimine geometry [$k_{(S)} > k_{(R)}$]; therefore, the poor enantioselectivity in the formation of **3an** is a consequence of noncompetitive substrate racemization rather than poor enantiomer discrimination.

A unified least-motion model for the stereoselective (3 + 2) annulation of **1** and (*E*)-aldimines is presented in Scheme 4. An attack trajectory that minimizes steric interactions and maximizes orbital overlap is analogous to that of the (*Z*)-aldimine. In contrast to reactions with aldehydes, the nucleophilic lone pair is oriented *syn* to the Ar group. Counter to the annulation of **1** with **2n**, a 120° rotation of the C2−C3 bond places both R and Ar in pseudoaxial orientations within the envelope transition state (**9**), presumably minimizing steric penalties associated with structures **10** (R ↔ PG) and **11** (Ar ↔ PG). These structures are in accord with precedent provided by related cyclizations of *N*-acyl iminium ions.[16]

(16) Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397.

Ring closure provides the major 2,5-*cis*-disubstituted pyrrolidines *cis*-**3**. Formation of the minor *trans* adducts (*trans*-**3**) may arise from several as yet indistinguishable pathways: aldimine isomerization to (*Z*)-**2** prior to alkylation and ring flip (path a) or iminium isomerization (path b) after alkylation but prior to ring closure.

Conclusion

In summary, we have developed an enantioselective synthesis of 2,5-*cis*-disubstituted pyrrolidines through a dynamic kinetic asymmetric (3 + 2) annulation of racemic cyclopropanes and (*E*)-aldimines. Careful selection of the substituted *N*-benzyl protecting group of the aldimine allowed for an increase in enantioselectivity as well as selective deprotection of the pyrrolidine cycloadduct in the presence of other electron-rich benzyl substituents. Simple mechanistic studies and stereochemical observations suggest that the aldimine dipolarophiles react through the *E* geometry via the unusual diaxial transition state **9**. Experiments that probe the structure of the cyclopropane/Lewis acid complex and extend the scope of this reaction family are underway.

Acknowledgment. This work was supported by the NSF (CHE-0749691) and Novartis. We thank Dr. Peter S. White for X-ray crystallographic analysis.

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

JA1032277