ORGANIC LETTERS

2002
Vol. 4, No. 9
1415−1418

Modular Evolution of a Chiral Auxiliary for the 1,3-Dipolar Cycloaddition of Isomünchnones with Vinyl Ethers

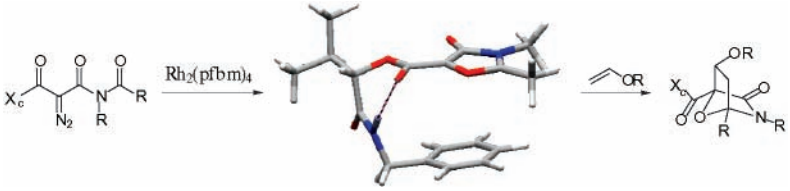
Sergey N. Savinov and David J. Austin*

Department of Chemistry, Yale University, New Haven, Connecticut 06511

david.austin@yale.edu

Received December 19, 2001 *(Revised Manuscript Received March 19, 2002)*

ABSTRACT

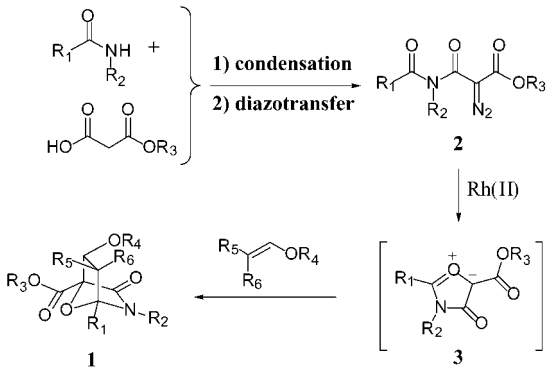


The 1,3-dipolar cycloaddition reaction has long been recognized as a powerful methodology in organic synthesis. More recently, this reaction has become a popular manifold for the construction of chemical diversity. Herein, we report the development of a chiral template for the facially selective cycloaddition of isomünchnones, a common class of 1,3-dipoles. The modular format of the asymmetric unit allowed a systematic optimization of selectivity. In addition, the chiral auxiliary was removed through an unusually facile ester aminolysis.

Since its introduction, the 1,3-dipolar cycloaddition has become an important reaction for the synthesis of heterocyclic molecules.[1] We utilize this approach for the construction of bicyclic diversity scaffold **1**, which can serve as a small-molecule probe for the chemical investigation of cellular targets.[2] To this end, we have previously reported the *endo* diastereoselective 1,3-dipolar cycloaddition of isomünchnones with vinyl ethers.[3] Herein we report the design and optimization of a chiral auxiliary for their enantioselective cycloaddition. The diastereomeric excess (de) obtained with the optimized auxiliary exceeds 95%. In addition, the auxiliary is efficiently removed under mild aminolysis, furthering the synthetic utility of this approach.

Diazoimides such as **2** undergo chemoselective rhodium(II) perfluorobutyramidate [Rh_2(pfbm)$_4$] catalyzed cyclization to isomünchnone intermediates **3**, which upon treatment with a suitable dipolarophile undergoes a 1,3-dipolar cycloaddition, yielding bicyclic product **1** (Scheme 1).[3] To use this methodology for the synthesis of specific small-molecule probes, the bimolecular cycloaddition step must be both regio- and diastereoselective. Additionally, the methodology should involve an enantioselective process, since drug−biomolecule interactions are stereospecific,[4] and the use of

Scheme 1. Construction of the Diversity Scaffold (**1**)



(1) (a) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909. (b) Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, *2*, 123−41. (c) Padwa, A. *Trends Org. Chem.* **1993**, *4*, 139−60. (d) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vols. 1 and 2.

(2) (a) Savinov, S. N.; Austin, D. J. *Comb. Chem. High Throughput Screen.* **2001**, *4*, 593−7. (b) Sche, P. P.; McKenzie, K. M.; White, J. D.; Austin, D. J. *Chem. Biol.* **1999**, *6*, 707−716. (c) Sche, P. P.; McKenzie, K. M.; White, J. D.; Austin, D. J. *J. Chem. Biol.* **2001**, *8*, 399−400.

(3) Savinov, S. N.; Austin, D. J. *J. Chem. Commun.* **1999**, 1813−4.

10.1021/ol017263y CCC: $22.00
Published on Web 03/30/2002

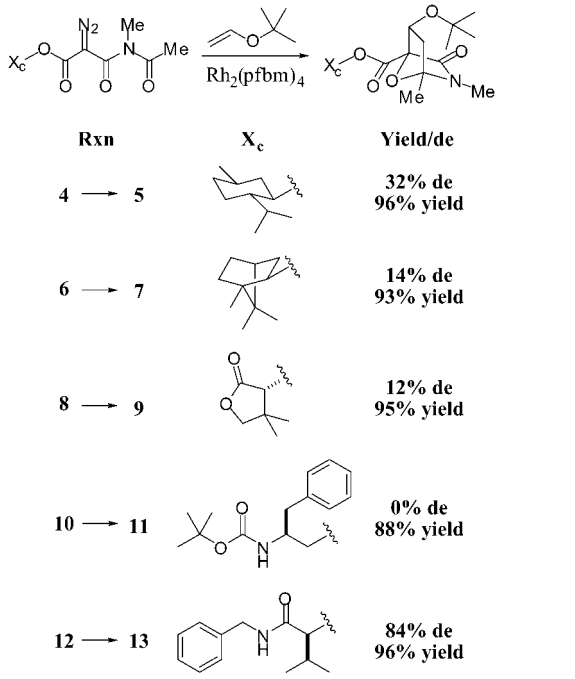
mirror-image related molecules is one of the best methods for assessing affinity-independent specificity.[5]

Both the regio- and diastereoselective applications of this method are accomplished by exploiting primary[6] and secondary[7] orbital effects, furnishing exclusively bicyclic constructs of *syn*/*endo* topology.[3] Therefore, manipulation of absolute stereochemistry remains a challenge for the synthesis of these molecules in a *stereoselective* manner.

The catalytic enantioselective cycloaddition of some 1,3-dipoles, such as nitrones, has been reported.[8] The application of a chiral rhodium(II) catalyst for the asymmetric induction of a carbonyl ylide cycloaddition has also been reported with moderate selectivity (ca. 50% ee).[9] This low enantioselectivity, in conjunction with the evidence of metal-free dipoles,[10] indicates the transient nature of metal coordination with the isomünchnone dipole. While several diastereoselective cycloadditions with chiral isomünchnones have been reported,[11] the stereogenic center was an integral part of the molecule, not allowing use as a removable auxiliary.

To fulfill the criteria for the stereospecific construction of scaffold **1**, we required a removable enantioselective 1,3-dipolar cycloaddition auxiliary. By incorporating a chiral substituent at the ester position of the dipole (OR_3, Scheme 1), we hoped to create an inductive effect that would be proximal to the dipole to induce facial selectivity, yet sensitive enough for subsequent removal. A variety of potential auxiliaries were evaluated by coupling the corresponding chiral malonic acid ester with methylacetamide.[12] Diazotransfer subsequently furnished the 1,3-dipole precursors **4**, **6**, and **8**, derivatized with (−)-menthol, (−)-borneol, and (*R*)-(-)-pantalactone respectively (Scheme 2). Treatment of α-diazoimides **4**, **6**, and **8** with a catalytic amount of $Rh_2(pfbm)_4$ in the presence of *tert*-butyl vinyl ether led to formation of the corresponding cycloadducts **5**, **7**, and **9** in good to excellent yield. While each chiral dipole underwent efficient cycloaddition, the terpene-based chiral auxiliary failed to exert the required π facial bias and provided only a modest level of selectivity.[13] Despite low diastereoselectivity, these preliminary results were encouraging enough to warrant further exploration of this approach. An amino acid based chiral auxiliary would allow the introduction of stereoelectronic bias,[14] while providing a modular design for

Scheme 2. Facial Selectivity at the Dipole Ester



systematic optimization. In addition, amino acids afford a diverse array of functionality and are available in enantiomeric pairs.

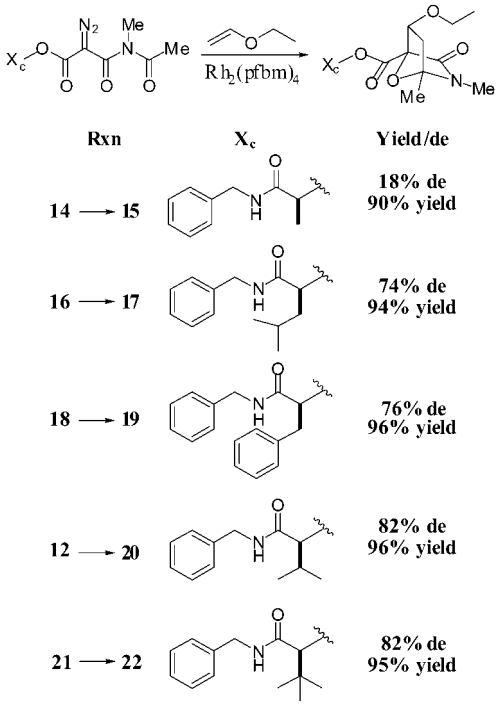
α-Diazoimide **10** was synthesized with a phenylalanine-based chiral auxiliary. Interestingly, upon exposure to $Rh_2(pfbm)_4$ in the presence of *tert*-butyl vinyl ether, L-phenylalanine derivative **10** led to a 50:50 mixture of bicyclic adducts (2*R*,5*S*)-**11** and (2*S*,5*R*)-**11**. It was postulated that the lack of selectivity was due to the flexibility of the methylene spacer between the dipole and the chiral center. α-Diazoimide **12** contains a more sterically demanding *β*-branched isopropyl group, thereby limiting flexibility adjacent to the dipole. Treatment of α-diazoimide **12** with $Rh_2(pfbm)_4$ in the presence of *tert*-butyl vinyl ether provided cycloadduct **13** in a 84% de in excellent yield. The absolute stereochemistry of the major isomer was determined via single-crystal X-ray analysis, which identified the (2*Re*-5*Re*) face of the dipole as the preferred approach of dipolarophile. Fortunately, both the *syn*-regiocontrol and *endo*-diastereocontrol were maintained, despite the added steric congestion from the auxiliary.

To better understand how amino acid substitution affects the level of diastereofacial induction, a series of α-hydroxy acids, readily accessible from their corresponding α-amino acids,[15] were used to construct α-diazoimides with incremental substitution. In analogy with the parent system **12**, four diazo substrates, **14**, **16**, **18**, and **21**, were prepared from

(4) The importance of chirality in drug design has been recently reviewed: Beroza, P.; Suto, M. J. *Drug Discovery Today* **2000**, *5*, 364.
(5) Liu, F.; Johnson, E. F.; Austin, D. J.; Anderson, K. F. Submitted.
(6) Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, 123.
(7) Savinov, S. N. Ph.D. Dissertation, Yale University, New Haven, CT, 2000.
(8) (a) Gothelf, K. V.; Jorgensen, K. A. *Chem. Commun.* **2000**, *16*, 1449−58. (b) Jensen, K. B.; Roberson, M.; Jorgensen, Karl A. *J. Org. Chem.* **2000**, *65*, 9080−4.
(9) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Tetrahedron Lett.* **1997**, *38*, 6471.
(10) Padwa, A.; Snyder, J. P.; Curtis, E. A.; Sheehan, S. M.; Worsencroft, K. J.; Kappe, C. O. *J. Am. Chem. Soc.* **2000**, *122*, 8155−67.
(11) (a) Padwa, A.; Prein, M. *J. Org. Chem.* **1997**, *62*, 6842. (b) Padwa, A.; Prein, M. *Tetrahedron* **1998**, *54*, 6957. (c) Angell, R.; Fengler-Veith, M.; Finch, H.; Harwood, L. M.; Tucker, T. T. *Tetrahedron Lett.* **1997**, *38*, 4517.
(12) Rigo, B.; Fasseur, D.; Cauliez, P.; Couturier, D. *Tetrahedron Lett.* **1989**, *30*, 3073.
(13) The percent diastereoselectivity (% de) was determined by ^{1}H NMR integration of the diastereomeric pairs.
(14) A π-complex is a feature common to many diastereofacially robust chiral auxiliaries: (a) Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *J. Org. Chem.* **1998**, *63*, 8397. (b) Mezrhab, B.; Dumas, F.; d'Angelo, J.; Riche, C. *J. Org. Chem.* **1994**, *59*, 500. (c) Maddaluno, J. F.; Gresh, N.; Giessner-Prettre, C. *J. Org. Chem.* **1994**, *59*, 793.
(15) Johnson, R. L. *J. Med. Chem.* **1980**, *23*, 666.

L-alanine, L-leucine, L-phenylalanine, and L-*tert*-leucine, respectively.[16] Ethyl vinyl ether-derived cycloadducts **15**, **17**, **19**, **20**, and **22** were obtained in good yield from the corresponding α-diazoimides through $Rh_2(pfbm)_4$-catalyzed cyclization−cycloaddition, with the favored (2*Re*-5*Re*) approach in each case (Scheme 3).

Scheme 3. Facial Selectivity at the Amino Acid Site



Although the level of diastereoinduction varied widely, it could be correlated with the level of substitution. L-Alanine derivative **14** gave the lowest diastereofacial selection, while both the L-isoleucine **16** and L-phenylalanine **18** auxiliaries provided a significantly higher level of induction, presumably due to the bulkier isobutyl and benzyl substituents. However, the diastereofacial bias appeared to reach saturation with isopropyl derivative **20**, since no additional effect was observed with *tert*-butyl derivative **22**.

A crystal structure of cycloadduct **13**[17] confirmed the absolute stereochemistry of the cycloaddition. A molecular mechanics (MM2 force field)[18] based Monte Carlo[19] conformational search, using the Macromodel[20] software package, was used to establish the preferred structural arrangement in the dipole. The auxiliary of **12** was conformationally sampled (i.e., the geometry-optimized dipole was fixed), with charges localized at N ("+") and exocyclic O ("−").

The computational analysis predicts a hydrogen-bonded seven-membered ring conformation (Figure 1). The aromatic

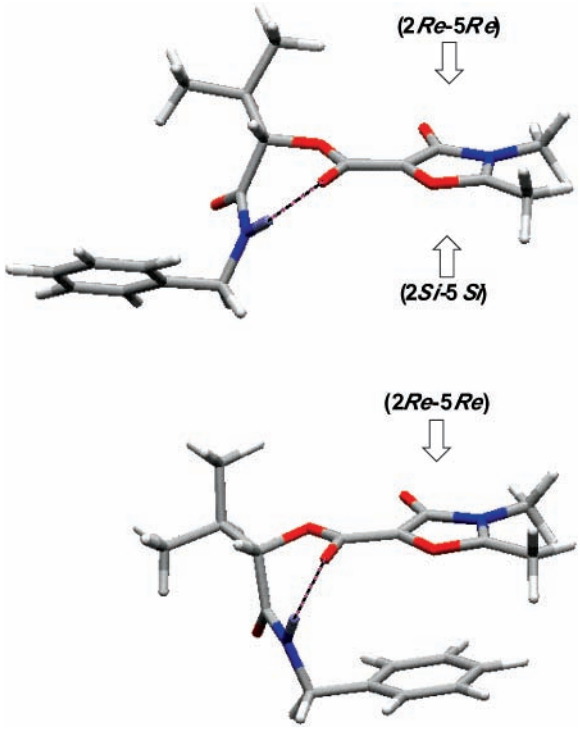


Figure 1. Computational models for the 1,3-dipole.

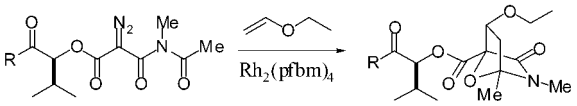
group is allowed free rotation, as noted in the existence of two low-energy structures, with the aromatic moiety either engaged in a π-stacking interaction with the dipole or projected away. In one conformation the (2*Si*-5*Si*)-face is blocked, while the second conformation leaves the dipole free, allowing cycloaddition from the less favored (2*Si*-5*Si*)-face.

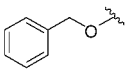
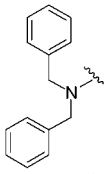
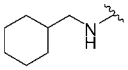
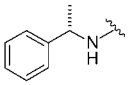
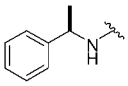
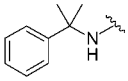
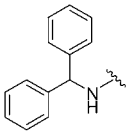
The importance of hydrogen bond-mediated organization was confirmed by screening substrates **23** and **25**, which lack the amide N−H (Scheme 4); in both cases the stereoselection was greatly compromised. The contribution of π-stacking toward selectivity is questionable, as shown by the similar, if somewhat diminished, diastereoselectivity noted in **27** (cf. **12**). Attempts to further probe the contribution of π-stacking and to favor the blocked conformation (Figure 1, bottom) α-diazoimides **29**, **31**, and **33** were constructed. As expected, the absolute configuration of the benzylic center produced little influence on either the sense or extent of the facial selectivity. When treated with $Rh_2(pfbm)_4$ in the presence of ethyl vinyl ether, α-diazoimide **35** provided the single cycloadduct **36**, with a de greater than 95%. This improved diastereoselectivity is presumably due to the degenerate nature of the possible conformations.

Substituents on the dipolarophile were found to have a minimal effect on the overall facial selectivity. As shown in Scheme 5, good yields and selectivities were observed for bicyclic constructs **37**−**40**, regardless of substitituion of the

(16) (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196. (b) Konradi, A. W.; Kemp, S. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1994**, *116*, 1316.
(17) See Supporting Information.
(18) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
(19) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.
(20) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

Scheme 4. Facial Selectivity at the Auxiliary Amine



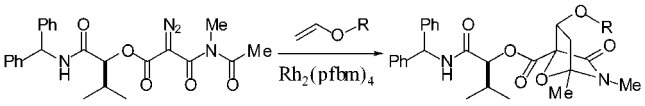
Rxn	R	Yield/de
23 → 24		12%de 85% yield
25 → 26		18% de 89% yield
27 → 28		78% de 88%yield
29 → 30		90% de 93% yield
31 → 32		92% de 93% yield
33 → 34		94%de 91% yield
35 → 36		>95% de 92% yield

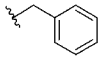
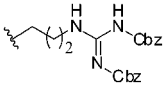
vinyl ether dipolarophile. Notably, both a sterically demanding *tert*-butyl vinyl ether and a hydrogen-bond donor (guanidine) provided cycloadducts **37** and **40**, respectively, in excellent yield and high diastereofacial selectivity.

Removal of the chiral auxiliary can be achieved under surprisingly mild conditions by treatment with primary amines. Cleavage of cycloadducts **36**−**40** with methylamine furnished amides **41**−**45**, in excellent yield (Scheme 6). Dimethylamine failed to cleave the auxiliary, even under elevated temperature.

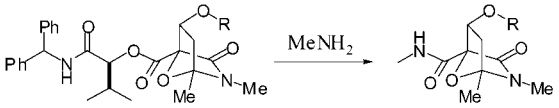
In conclusion, we have presented the systematic optimization of a chiral auxiliary for diastereofacially selective 1,3-dipolar cycloaddition in the presence of a variety of dipolarophiles. This diastereofacial selectivity, when coupled with the previously established regioselectivity and *endo*-selectivity of this cycloaddition, ensures that only one of the eight possible products is formed. In addition, the structure−selectivity relationship established during the course of this study demonstrates the power and flexibility of a modular auxiliary design. The use of this methodology for the construction of chemically diverse libraries is currently under investigation.

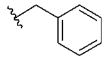
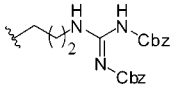
Scheme 5. Effect of Dipolarophile on Facial Selectivity



Rxn	R	Yield/de
35 → 37		>95% de 95% yield
35 → 38		>95% de 92% yield
35 → 39		>95% de 88% yield
35 → 40		>95% de 86% yield

Scheme 6. Removal of the Chiral Auxiliary



Rxn	R	Yield
36 → 41		95% yield
37 → 42		89% yield
38 → 43		92% yield
39 → 44		95% yield
40 → 45		88% yield

Acknowledgment. The authors thank Susan de Gala for X-ray structure analysis, Wolfgang Hinz and Viet-Anh Nguyen for helpful discussion, and the National Institutes of Health (R01 GM59673) for financial support. D.J.A. is the recipient of an Alfred P. Sloan Foundation Fellowship.

Supporting Information Available: Experimental details and characterization of compounds **4**−**45**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL017263Y