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Highly Stereoselective Formal [3 + 3] Cycloaddition Reactions of Chiral Vinylogous Amides with α,β-Unsaturated Iminiums

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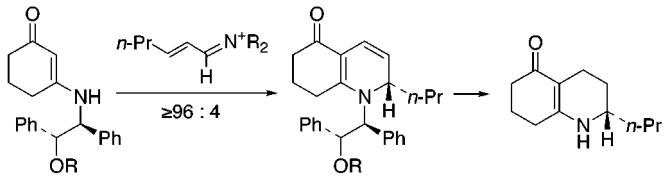
ABSTRACT



Highly stereoselective formal [3 + 3] cycloaddition reactions of chiral vinylogous amides with α,β-unsaturated iminiums are described. A mechanistic model is proposed to rationalize the observed stereoselectivity. The 6π-electron electrocyclic ring closure appears to be reversible, and a preferred rotation of the alkenyl group, one of the three 2π-components, during the ring closure step provides the thermodynamically favored diastereomer as the major product.

We have been exploring reactions of α,β-unsaturated iminiums with 1,3-dicarbonyl equivalents to construct heterocyclic structures.[2−4] These reactions involve a sequence that consists of a Knoevenagel condensation [an amine-assisted C-1,2-addition−reversible β-elimination] followed by a 6π-electron electrocyclic ring closure [Figure 1].[2a,5,6] This process constitutes a stepwise formal [3 + 3] cycloaddition protocol[7] useful for synthesis of complex heterocycles. The net result of this process is the formation of two σ-bonds in addition to a new stereocenter adjacent to the heteroatom. This formal

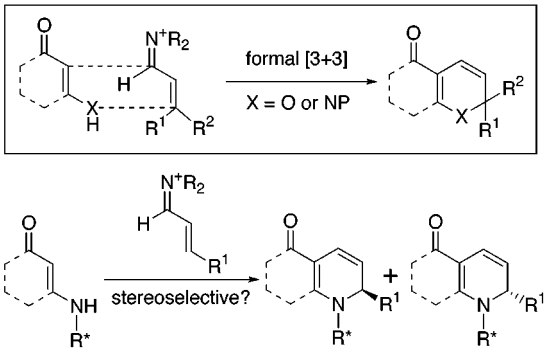


Figure 1. Chiral vinylogous amide approach.

(1) UMN Undergraduate Research Participants: 1998−1999. Recipients of 1998 and 1999 LANDO-NSF REU Fellowships.

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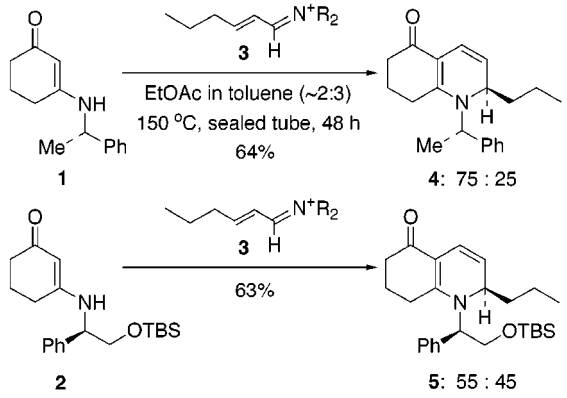
[3 + 3] cycloaddition method can be classified as a sequential anionic−pericyclic strategy for which the significance in natural product synthesis has been elegantly summarized by Tietze.[8]

Our recent work using vinylogous amides has rendered this strategy attractive for synthesis of piperidinyl heterocycles.[3] Having established its synthetic feasibility, we have been exploring an asymmetric variant of this formal cycloaddition method. Specifically, we are interested in using chiral vinylogous amides to control the stereocenter adjacent to the nitrogen atom [Figure 1].[9] We report here our first realization of stereoselective formal [3 + 3] cycloaddition reactions of chiral vinylogous amides with α,β-unsaturated iminiums.

Our initial choices of chiral vinylogous amides were compounds **1** and **2** as shown in Scheme 1 because of their

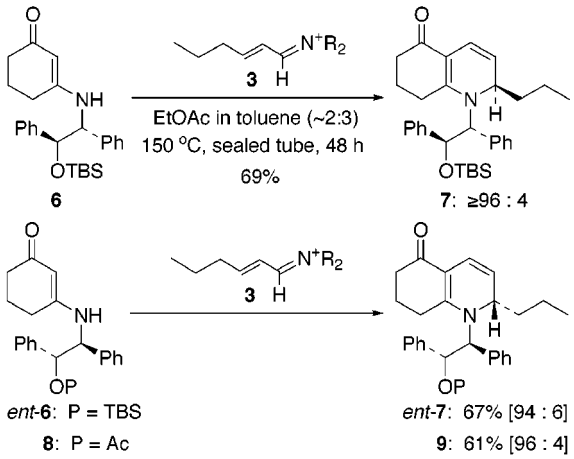
Scheme 1



synthetic accessibility from simple condensation of the corresponding chiral amines with 1,3-cyclohexanedione. When the vinylogous amide **1** was reacted with α,β-unsaturated iminium **3** [derived from 2-hexenal] at 150 °C for 48 h, the desired formal cycloadduct **4**[10] was obtained in 64% with a diastereomeric ratio of 75:25. On the other hand, the reaction of the vinylogous amide **2** with **3** was completely stereorandom, leading to the cycloadduct **5** in 63% yield but with a ratio of 55:45.

Uncertain of the mechanistic source of stereoinduction or lack thereof, we screened several chiral vinylogous amides, and compound **6** provided the best stereoselectivity [Scheme 2]. The reaction of **6** with α,β-unsaturated iminium **3** at 150

Scheme 2



°C for 48 h afforded the desired cycloadduct **7** in 69% yield as a single diastereomer. It is noteworthy that compound **7** possessed an unusually high specific optical rotation of −610. Compound **7** could be readily desilylated using TBAF [80% yield], leading to a crystalline alcohol intermediate that was suitable for X-ray diffraction. The X-ray crystal structure of desilylated **7** [Figure 2] revealed its absolute configuration as shown in Scheme 2.

Under the same reaction conditions, the enantiomer of **6** provided *ent*-**7** in 67% yield with an almost equally high

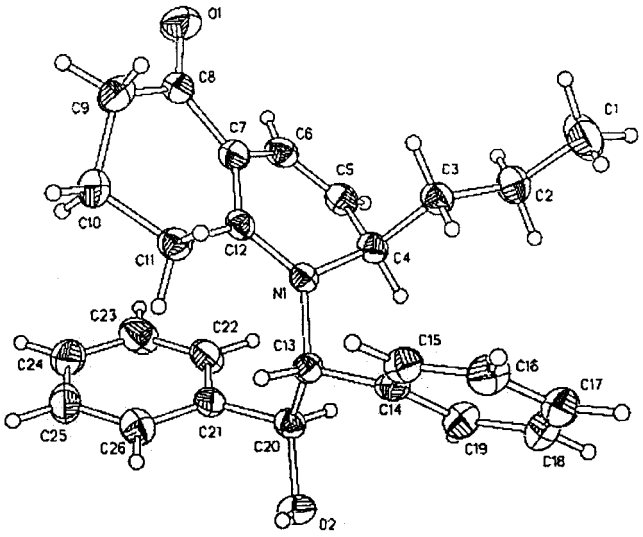


Figure 2. X-ray structure of desilylated **7**.

(5) For earlier studies in this area, see: (a) Hua, D. H.; Chen, Y.; Sin, H.-S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J.-P.; Chiang, P. K. *J. Org. Chem.* **1997**, *62*, 6888. (b) Jonassohn, M.; Sterner, O.; Anke, H. *Tetrahedron* **1996**, *52*, 1473.

(6) (a) de March, P.; Moreno-Mañas, M.; Casado, J.; Pleixats, R.; Roca, J. L.; Trius, A. *J. Heterocycl. Chem.* **1984**, *21*, 1369. (b) Tietze, L. F.; Kiedrowski, G. v.; Berger, B. *Synthesis* **1982**, 683. (c) de Groot, A.; Jansen, B. J. M. *Tetrahedron Lett.* **1975**, 3407.

(7) Examples of [3 + 3] cycloaddition reactions in the truest sense are extremely scarce, and there are only limited examples of metal-mediated [3 + 3] cycloaddition reactions. For recent reviews, see: (a) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(8) For a review on synthetic methods involving sequential transformations, see: Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.

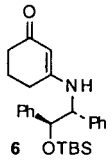
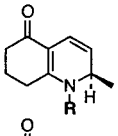
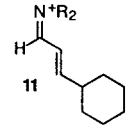
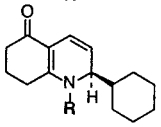
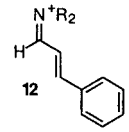
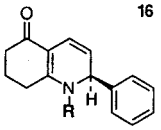
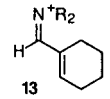
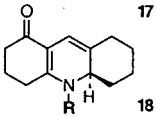
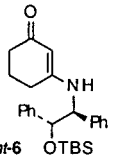
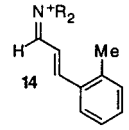
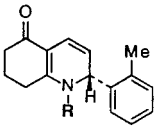
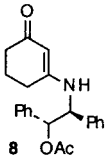
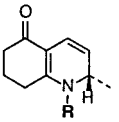
(9) For a recent elegant study using chiral vinylogous amides to control stereochemistry of a quaternary center using aza-annulation chemistry, see: Benovsky, P.; Stephenson, G. A.; Stille, J. R. *J. Am. Chem. Soc.* **1998**, *120*, 2493.

(10) All new compounds are characterized by ^{1}H NMR, ^{13}C NMR, FTIR, and mass spectroscopy. Details may be obtained from the Supporting Information.

diastereoselectivity. The type of protecting group on the oxygen does not appear to affect the stereoselectivity of this formal cycloaddition reaction. For example, the reaction of chiral vinylogous amide **8**, containing an acetyl group, led to the desired heterocycle **9** in comparable yield and stereoselectivity [Scheme 2].

Having established the stereochemical assignment as well as the synthetic feasibility of this stereoselective reaction, reactions of **6**, *ent*-**6**, or **8** with a variety of α,β-unsaturated iminiums **10**−**14** were carried out. These reactions led to the preparation of compounds **15**−**20** in good yields as well as high stereoselectivity [Table 1]. Again, unusually high

Table 1. Generality of the Stereoselective [3 + 3] Cycloaddition

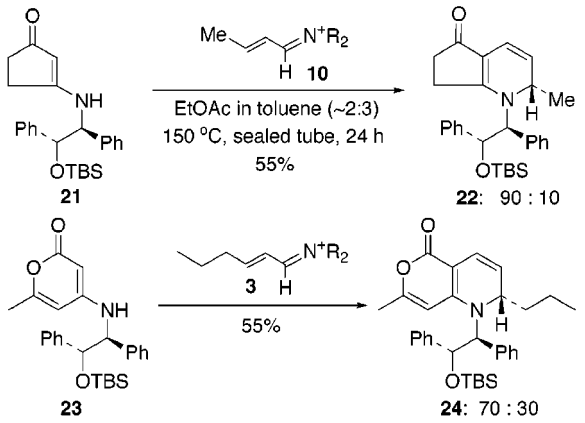
entry	chiral amide	iminium[a]	product[b]	yield[c]	*d.r.*[d]
1	 **6**	 **10**	 **15**	79 %	90 : 10
2	**6**	 **11**	 **16**	79	83 : 17
3	**6**	 **12**	 **17**	55	85 : 15
4	**6**	 **13**	 **18**	45	93 : 7
5	 *ent*-**6**	 **14**	 **19**	54	87 : 13
6	 **8**	 **10**	 **20**	84	93 : 7

a. Iminiums are generated from 1.0 eq of piperidine and 1.0 eq Ac_2O in anhydrous EtOAc at 85 °C for 1 h. All reactions were carried out in EtOAc/toluene [3:2] at 150 °C in a sealed tube, and 0.5 eq of the chiral amide was used. b. The **R** group represents the corresponding chiral group in the starting amide. c. All yields are isolated yields. d. All ratios are determined by ^1H NMR and/or ^{13}C NMR.

specific optical rotations were also obtained for the major isomers. It is noteworthy that tricycle **18** could also be obtained with high stereoselectivity using the α,β-unsaturated iminium derived from cyclohexencarboxaldehyde, albeit in a slightly lower yield.

Reactions of chiral vinylogous amide **21** with α,β-unsaturated iminium **10** also provided comparable stereoinduction, leading to the formal cycloadduct **22** in 55% with a ratio of 90:10 [Scheme 3]. However, the reaction of **23** with **3** led to **24** in similar yields but with a much depreciated

Scheme 3



diastereomeric ratio. These comparisons, along with those unsuccessful examples shown in Scheme 1, prompted us to explore a possible mechanistic model for this stereoselective reaction. However, we first examined whether the observed diastereoselectivity is a result of thermodynamic or kinetic control, thereby providing insight into an important mechanistic point regarding the reversibility of the 6π-electron electrocyclic ring closure.

Toward this goal, we heated samples of the pure major isomer of **5** [≥95:5 major to minor] and an enriched minor isomer of **7** [28:72 major to minor] at 150 °C in d_8-toluene for 36 h. The final isomeric ratios for **5** and **7** were 59:41 and 93:7, respectively. These experiments suggest that the diastereoselectivity observed for these reactions is a result of a thermodynamic control, and that the 6π-electron electrocyclic ring closure step appears to be reversible.[11] The isomeric ratios were not affected when **5** and **7** were heated at 85 °C for 10−15 h, and the ratios do not improve upon heating at 240 °C for 24 h.

On the basis of these experiments, we proposed a mechanistic model which is shown in Figure 3. The X-ray

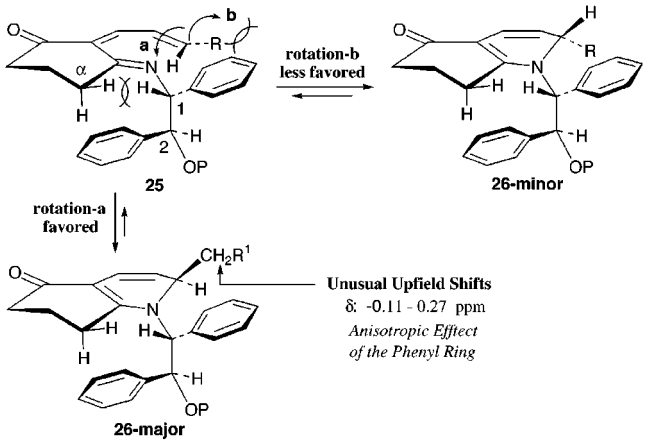


Figure 3. Proposed mechanistic model.

structure of desilylated **7** [Figure 2] reveals an interesting conformational preference or orientation for the chiral groups tethered to the nitrogen atom. That is, the two phenyl groups are completely *anti* to one another and the one at C-1 appears to π-stack with the vinyl carbon bearing the R group. In addition, the imine nitrogen atom and the oxygen atom are also *anti* to one another. If such a conformational preference is viable prior to an electrocyclic ring closure, then there can be two possible rotations for the vinyl strand of imine intermediate **25** during the ring closure.[12,13]

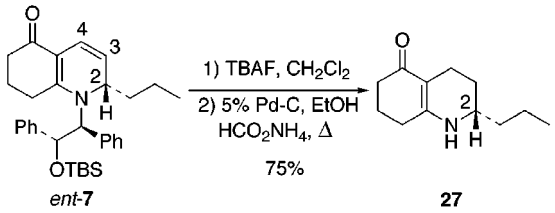
The rotation-a of the vinyl strand should be favored leading to the major isomer with the correct stereochemical assignment, while the rotation-b is less favored owing to the severe steric interaction between the R and phenyl groups. This rotational preference essentially leads to the major product with the least amount of steric congestion between the R and phenyl groups, and thus, the major isomer of **26** is also the thermodynamically more stable one. The reversibility of the ring closure would allow the minor isomer of **26** to revert back to the intermediate **25**, and again through the more favored rotation-a, the final diastereomeric ratio may be attained. While this model appears to be suitable to the observed diastereoselectivity, it does not fully compliment with the result in which a relatively lower diastereoselectivity was observed for larger R groups [entries 1 and 6 versus entries 2, 3, and 5 in Table 1].

The proposed conformational preference is the key to the observed stereoselectivity and unique to this particular chiral vinylogous amide in which the phenyl ring at C-1 can reside close to the vinyl strand bearing the R group, thereby ensuring the rotational preference.[14] To support the close proximity of the C-1 phenyl group to the R group, we observed in ^{1}H NMR that, when applicable, resonance of the methyl, methylene, or methine protons of formal cycloadducts are shifted toward high field in an unusual manner [−0.11 to 0.27 ppm], presumably owing to the anisotropic effect of the phenyl ring. Hence, perturbations of this conformational preference may lead to loss of stereoselectivity as demonstrated in reactions of **1** and **2**.

In addition, the carbon α to the imine group in **25** may also play a role in providing the required conformation. The phenyl group at C-1 would likely prefer to be far away from this sp^3 methylene unit to avoid potential steric interaction. However, in compound **23**, this carbon is sp^2, thereby providing less steric interaction with the C-1 phenyl group. Thus, reactions of **23** also led to lower diastereoselectivity. We are currently pursuing calculations to determine whether any $\pi-\pi$ interactions may exist between the phenyl ring at C-1 and the vinyl strand bearing the R group.

Finally, the chiral-inducing unit tethered to the nitrogen atom can be removed efficiently using hydrogenation protocols. Compound *ent*-**7** was first desilylated quantitatively using TBAF in CH_2Cl_2, and the corresponding desilylated product was subsequently refluxed with ammonium formate and 5% Pd−C in EtOH to provide heterocycle **27** in 75% yield [Scheme 4]. The stereochemical

Scheme 4



ent-**7** **27**

integrity at C-2 in **27** was not eroded because hydrogenation occurred readily for the olefin at C3−C4, preventing any electrocyclic ring opening to occur. Since the stereochemistry at C-2 of **27** is the same as the corresponding one in pumilotoxin C,[15] we are pursuing an asymmetric synthesis of members of the pumiliotoxin family of alkaloids using this methodology.[16]

We have described here the first highly stereoselective reactions of chiral vinylogous amides with α,β-unsaturated iminiums. We have also proposed a mechanistic model that would rationalize the observed stereoselectivity as a result of a preferred rotation during a reversible electrocyclic ring closure step, leading to the thermodynamically more stable product. Studies related to reactions of other chiral vinylogous amides as well as synthetic applications of this stereoselective reaction are currently underway.

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Supporting Information Available: General procedures and characterization data for all new compounds and ^{1}H NMR [13 pages]. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For another precedent, see: Moorhoff, C. M. *Synthesis* **1997**, 685.
(12) We are assuming that the imine nitrogen rather than an iminium species is involved in the ring closure because of the presence of excess piperidine. For a related reference, see: Kametani, T.; Kajiwara, M.; Fukumoto, K. *Tetrahedron* **1974**, *30*, 1053.
(13) Shishido, K.; Ito, M.; Shimada, S.-I.; Fukumoto, K.; Kametani, T. *Chem. Lett.* **1984**, 1943.
(14) For a related example of such a rotational preference during a 6π-electron electrocyclic ring closure, see: Hsung, R. P.; Quinn, J. F.; Weisenberg, B. A.; Wulff, W. D.; Yap, G. P. A.; Rheingold, A. L. *J. Chem. Soc., Chem. Commun.* **1997**, 615.
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