ORGANIC
LETTERS

2005
Vol. 7, No. 12
2349−2352

# Enantioselective Cycloadditions with α,*β*-Disubstituted Acrylimides

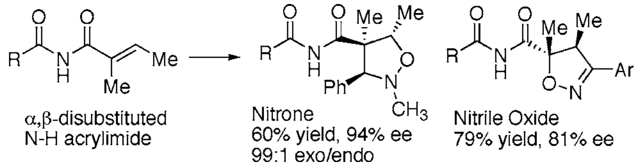
**Mukund P. Sibi,* Zhihua Ma, Kennosuke Itoh, Narayanasamy Prabagaran, and Craig P. Jasperse**

*Department of Chemistry, North Dakota State University,
Fargo, North Dakota 58105-5516*

*mukund.sibi@ndsu.edu*

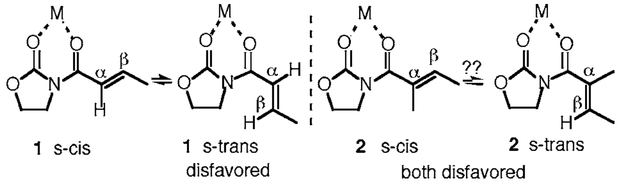
**Received March 18, 2005**

## ABSTRACT



**The use of N-H imide templates provides a solution to the problem of rotamer control in Lewis acid catalyzed reactions of α,*β*-disubstituted acryloyl imides. Reactions proceed through the s-cis rotamer and with improved reactivity because $A^{1,3}$ strain is avoided. Enantioselective nitrone, nitrile oxide, and Diels−Alder cycloadditions demonstrate the principle.**

Rotamer control is a central requirement for enantioselective addition reactions involving α,*β*-unsaturated carbonyl compounds.[1] Many successful reactions using chiral Lewis acid catalysis have been developed for situations when the α-carbon of the substrate is unsubstituted (e.g., crotonate **1**). Traditional templates such as oxazolidinone are well-suited for crotonates because they provide organized chelation such that substrates **1** react exclusively via the s-cis rotamer.[2] However, no general solution for α,*β*-disubstituted substrates such as tiglate **2** has been developed.[3,4] In substrate **2**, the use of traditional auxiliaries results in problematic $A^{1,3}$ interactions for both the s-cis and the s-trans rotamers. To relieve strain, the C−C bond of the enoyl group twists. This twisting not only leads to ill-defined conformations unsuited for enantioselective reactions but also breaks conjugation, contributing to greatly diminished reactivity at the *β*-carbon. Thus although $A^{1,3}$ interactions may be desirable with α-unsubstituted substrates **1**, they are undesirable when α-substituted substrates **2** are used.



We reasoned that the simple use of N-H imide templates[5] (**3**) would relieve $A^{1,3}$ strain, reduce twisting, restore conjugation, and improve reactivity. However, whether there would be useful levels of s-cis/s-trans rotamer control in the

---

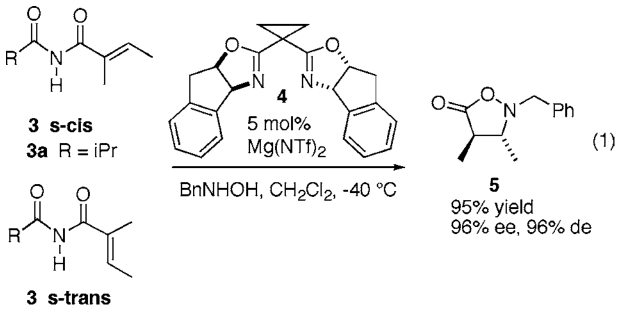
(1) For a general discussion, see: *Principles of Asymmetric Synthesis*; Gawley, R. E.; Aube, J. Pergamon: Oxford, 1996. Also see: (a) Nishimura, K.; Tomioka, K. *J. Org. Chem.* **2002**, *67*, 431. (b) Hawkins, J. M.; Nambu, M.; Loren, S. *Org. Lett.* **2003**, *5*, 4293. (c) Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127. (d) Sibi, M. P.; Sausker, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 984. (e) Avalos, M.; Babiano, R.; Brao, J. L.; Cintas, P.; Jimenez, J. L.; Palacios, J. C.; Silva, M. A. *J. Org. Chem.* **2000**, *65*, 6613.

(2) (a) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559. (b) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582. (c) Castellino, S. *J. Org. Chem.* **1990**, *55*, 5197.

(3) For diastereoselective reactions with Oppolzer's sultam as chiral auxiliary and related work on tiglates and cycloalkenes, see: (a) Oppolzer, W.; Kingma, A. J. *Helv. Chim. Acta* **1989**, *72*, 1337. (b) Oppolzer, W.; Kingma, A. J.; Poli, G. *Tetrahedron* **1989**, *45*, 479. (c) Niu, D.; Zhao, K. *J. Am. Chem. Soc.* **1999**, *121*, 2456. (d) Karlsson, S.; Hoegberg, H.-E. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1076. (e) Davies, S. G.; Epstein, S. W.; Garner, A. C.; Ichihara, O.; Smith, A. D. *Tetrahedron: Asymmetry* **2002**, *13*, 1555. (f) Adam, W.; Degen, H.-G.; Krebs, O.; Saha-Mller, C. *J. Am. Chem. Soc.* **2002**, *124*, 12938. (g) Lee, W.-D.; Chiu, C.-C.; Hsu, H.-L.; Chen, K. *Tetrahedron* **2004**, *60*, 6657. (h) Dieter, R. K.; Lu, K.; Velu, S. E. *J. Org. Chem.* **2000**, *65*, 8715.

10.1021/ol050599d CCC: $30.25

absence of $A^{1,3}$ interactions remained unclear. Our initial study involving hydroxylamine additions to α,*β*-disubstituted N-H acrylimides **3** was reported recently (eq 1).[6] The additions were highly enantio- and diastereoselective. The level of selectivity suggested that high rotamer control was involved, and the absolute configuration of the products **5** suggested that the reaction proceeded via the s-cis rotamer of **3**. Whether reaction involved the s-cis rotamer because the population of the s-trans complex was minimal or because both rotamers were in equilibrium but the s-cis rotamer reacted selectively (Curtin-Hammett principle) was unclear. As expected, the reactivity with N-H imide templates **3** was dramatically higher than with $A^{1,3}$ templates such as oxazolidinone or *N*-methylbenzimide. Intermolecular radical additions to substrates **3** mediated by $MgI_2$-**4** also proceed with good yield and high diastereo- and enantioselectivity (maximal dr 99:1, 94% ee) and proceed via the s-cis rotamer.[7]

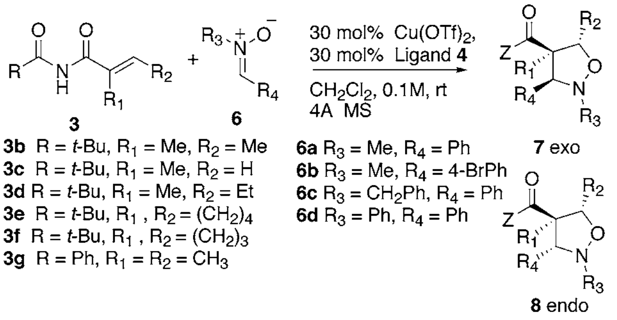


Following the success of our initial studies, we have now investigated additional types of addition reactions in order to assess whether useful s-cis rotamer control is general in Lewis acid activated reactions of substrates **3**. In this paper we report our results involving nitrone, nitrile oxide, and Diels−Alder cycloadditions to α,*β*-disubstituted acrylimides **3**. The results show improved reactivity and good to high enantioselectivity in each case, suggesting that the N-H imide solution to the α,*β*-disubstitution problem may have considerable generality.

A number of catalysts have been reported for enantioselective nitrone additions to α-unsubstituted acrylate and crotonate type substrates with varying templates.[8] However, enantioselective nitrone additions to α,*β*-disubstituted substrates are rare, presumably because of low reactivity.[9] We recently reported a chiral $Cu(OTf)_2$-ligand **4** catalyst that gives highly exo- and enantioselective nitrone additions to pyrazolidinone crotonates and cinnamates.[10] As expected, however, when oxazolidinone tiglate **2** was tested under analogous reaction conditions, conversion was negligible.

Our results using the same $Cu(OTf)_2$-**4** Lewis acid with α,*β*-disubstituted N-H imide substrates **3** are shown in Table 1. Entries 1−5 show additions of *N*-methylnitrone **6a** to imides **3** with varying α,*β*-substituents. In each case the regioselectivity is very high, with only products forming in which the oxygen end of the dipole adds to the *β*-carbon of the acceptor. With the exception of *β*-unsubstituted acrylamide **3c**, the diastereoselectivity is outstanding, strongly favoring the **7-exo** products over the **8-endo** products.[11] Most importantly, enantioselectivity is consistently excellent, around 90% or above. The one limitation evident in entries 1−5 is that of reactivity. Even with long reaction times,

**Table 1.** Nitrone Cycloadditions



| entry | SM | nitrone | time (days) | % yield (SM)[a,b] | ee (%)[cb] | **7/8** |
|---|---|---|---|---|---|---|
| 1 | **3b** | **6a** | 7 | 60(30) | 94 | 99/1 |
| 2 | **3c** | **6a** | 7 | 57 | 89 | 81/19 |
| 3 | **3d** | **6a** | 10 | 63(25) | 91 | 99/1 |
| 4 | **3e** | **6a** | 10 | <15 | | |
| 5 | **3f** | **6a** | 7 | 82 | 92 | 99/1 |
| 6 | **3f** | **6b** | 7 | 89 | 97 | 99/1 |
| 7 | **3f** | **6c** | 10 | 89 | 94 | 99/1 |
| 8 | **3f** | **6d** | 5 | 77 | 89 | 94/6 |
| 9 | **3b** | **6d** | 7 | 50 | 86 | 85/15 |
| 10 | **3b** | **6b** | 7 | 62(34) | 98 | 99/1 |

[a] For reaction conditions see Supporting Information. [b] Recovered starting material following chromatography in parentheses. [c] Chiral HPLC analysis.

---

(4) (a) For enantioselective conjugate addition to tiglates see: Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.-i.; Tomioka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2886−2887. Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.-i.; Tomioka, K. *Chem. Commun.* **2004**, 1850. (b) For an example of organocatalysis in nitrone cycloaddition to cyclopentene carboxylic acid esters, see: Karlsson, S.; Hgberg, H.-E. *Eur. J. Org. Chem.* **2003**, 2782.

(5) For pioneering work on the use of imide-unsubstituted substrates in conjugate additions, see: (a) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959 and (b) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442 and references therein.

(6) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796.

(7) Sibi, M. P.; Petrovic, G.; Zimmerman, J. *J. Am. Chem. Soc.* **2005**, *127*, 2390.

(8) For recent reviews, see: (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley and Sons: Hoboken, NJ, 2003. (b) Gothelf, K. V.; Jrgensen K. A. *Chem Commun.* **2000**, 1449. (c) Gothelf, K. V.; Jrgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. Also see: (d) Gothelf, K. V.; Thomsen, I.; Jrgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59. (e) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (f) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355. (g) Desimoni, G.; Faita, G.; Mortoni, A.; Righetti, P. *Tetrahedron Lett.* **1999**, *40*, 2001. (h) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227. (i) Suga, H.; Kakehi, A.; Ito, S.; Sugimoto, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 327.

(9) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett.* **2002**, *4*, 2457. Also see ref 4b.

(10) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718−719.

(11) Use of the same $Cu(OTf)_2$-**4** Lewis acid in our previous study (ref 10) also gave strong exo selectivity for crotonate and cinnamate substrates, but the exo/endo selectivity with α,*β*-disubstituted substrates **3** is significantly higher.

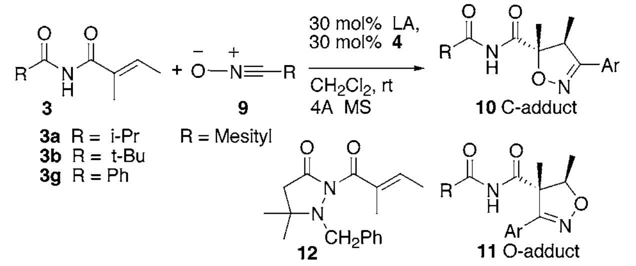
yields are generally modest and some starting material is often recovered. The relative reactivities of cyclopentene and cyclohexene substrates **3f** and **3e** are interesting. Cyclopentene substrate **3f** showed unusually good reactivity (entry 5), whereas cyclohexene analogue **3e** had unusually poor reactivity (entry 4). Entries 5−8 screen the influence of the nitrone substituents. Results are consistently excellent with *N*-alkyl nitrones (entries 5−7), including the *N*-benzyl nitrone **6c** (89% yield, 94% ee, 99:1 exo/endo). The *N*-phenyl nitrone **6d** shows somewhat reduced enantio- and diastereoselectivity with both cyclopentene substrate **3f** (entry 8) and tiglate **3b** (entry 9).

One other set of results not shown in the Table 1 also bears comment. A brief screening of the impact of the imide R group, using *tert*-butyl imide **3b**, isopropyl imide **3a**, and benzimide **3g**, showed significant dependence on the imide R group. The alkyl imides **3a** and **3b** showed much better reactivity than the benzimide **3g**, with the bulkier *tert*-butyl imide **3b** providing optimal yield, enantioselectivity, and diastereoselectivity. That the nature of the R group can be adjusted to optimize chemistry when N-H imides are used is an important variable to keep in mind.[12]

The absolute and relative configuration of the exo cycloadduct from cyclopentene **3f** and nitrone **6b** (entry 6) was established by X-ray crystallography. The absolute configuration suggests reaction via the s-cis rotamer, since the configuration of the *β*-carbon in the product is the same as when nitrones or radicals add to α-unsubstituted oxazolidinone and pyrazolidinone crotonates and cinnamates under the influence of the same Cu(OTf)$_2$-**4** Lewis acid.[13] The regioselectivity and relative configuration of the racemic cycloadduct from tiglate **3b** and nitrone **6b** (entry 10) was also established by X-ray crystallography.

The nitrone cycloaddition results in Table 1 confirm two important points. First, rotamer control for α,*β*-disubstituted acrylamides with N-H imide templates is again very high. Enantioselectivities as high as 97% (entry 6) and 98% (entry 10) would be impossible without strong s-cis/s-trans rotamer control. Second, the yields with the N-H imide template as compared to the A$^{1,3}$ oxazolidinone template (negligible conversion for substrate **1**) confirm that use of N-H imides greatly improves reactivity for α,*β*-disubstituted substrates.

**Table 2.** Nitrile Oxide Cycloadditions



| entry | SM | LA | time (days) | % yield[a] | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | **3g** | MgI$_2$ | 2 | 82 | 65 |
| 2 | **3g** | Mg(ClO$_4$)$_2$ | 2 | 79 | 81 |
| 3 | **3g** | Mg(NTf$_2$)$_2$ | 2 | 51 | 82 |
| 4 | **3g** | Ni(ClO$_4$)$_2$ | 4 | 99 | 77 |
| 5 | **3g** | Ni(SbF$_6$)$_2$ | 4 | 74 | 37 |
| 6 | **3a** | Mg(ClO$_4$)$_2$ | 7 | 56 | 83 |
| 7[c] | **3b** | Mg(ClO$_4$)$_2$ | 7 | *c* | |
| 8[d] | **12** | Mg(ClO$_4$)$_2$ | 7 | 12 | 95 |

[a] For reaction conditions see Supporting Information. Isolated yield after column purification. [b] Chiral HPLC analysis. [c] A complex mixture formed. [d] A complex mixture of side products formed.

We have recently reported that both MgX$_2$-**4** and NiX$_2$-**4** complexes catalyze highly enantioselective and regioselective nitrile oxide additions to pyrazolidinone crotonates.[14] We have now screened these same Lewis acids for their ability to catalyze nitrile oxide additions to α,*β*-disubstituted acrylimides **3** (Table 2). As shown in entries 1−5, Ni(ClO$_4$)$_2$, Mg(ClO$_4$)$_2$, and MgI$_2$ all provide good catalysis, resulting in yields of 79−99% (entries 1, 2, and 4). Mg(ClO$_4$)$_2$ gave slightly higher ee's than Ni(ClO$_4$)$_2$ did (81% versus 77%, entries 2 and 4). All of these reactions were completely regioselective for the C-adduct **10**, in which the carbon terminus of the dipole adds to the *β*-carbon of the acceptor, to the exclusion of *O*-adduct **11**. The reaction using Mg(ClO$_4$)$_2$ shows a surprising sensitivity to the imide R group, with imides **3g** and **3a** reacting much more cleanly than imide **3b** (compare entries 2, 6, with 7). This is in curious contrast to the nitrone reactions, in which benzimide **3g** showed inferior reactivity.[12]

Entry 8 shows a comparison reaction involving a substrate **12** with a pyrazolidinone template rather than an N-H imide template.[15] The reactivity is very low. This again demonstrates the superior reactivity with N-H imide templates as compared to A$^{1,3}$ templates, and once again the reasonably good enantioselectivities (77−83% ee, entries 2−4 and 6) indicate a reasonable level of rotamer control.

A host of catalysts have been developed for enantioselective Diels−Alder additions, such that the ability to catalyze cyclopentadiene addition to crotonate acceptors is a standard benchmark for new chiral Lewis acids. However, enantioselective Diels−Alder addition to α,*β*-disubstituted acrylimides remains an unsolved problem, particularly when neither substituent has electron-withdrawing character to improve reactivity.[16] Our results on Diels−Alder reaction of α,*β*-alkyldisubstituted N-H acrylimides **3** are shown in Table 3. The Lewis acids MgI$_2$-**4** and Cu(OTf)$_2$-**4** that catalyzed the

---

[12] Sensitivity to the imide R group was also observed in amine and radical additions, see refs 6 and 7.

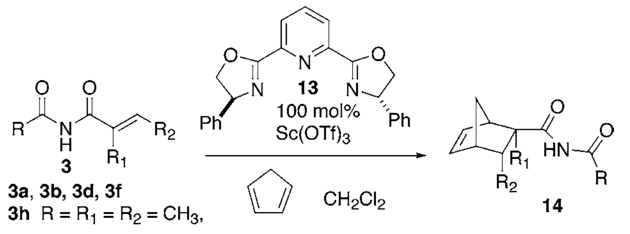
[13] (a) Addition of nitrones to pyrazolidinone crotonates/cinnamates: ref 10. (b) Addition of radicals to oxazolidinone crotonates/cinnamates: Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472−9473. (c) Addition of radicals to pyrazolidinone crotonates/cinnamates: Sibi, M. P.; Prabagaran, N. *Synlett* **2004**, *13*, 2421−2424. Each of these reactions occurs via s-cis rotamers.

[14] Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366−5367.

[15] This pyrazolidinone template was very effective in our previous nitrile oxide additions to crotonates and cinnamates; see ref 14.

[16] For the use of tiglates as dienophiles, see: (a) de Miranda, D. S.; da Conceicao, G. J. A.; Zukerman-Schpector, J.; Guerrero, M. C.; Schuchardt, U.; Pinto, A. C.; Rezende, C.; Marsaioli, A. J. *J. Braz. Chem. Soc.* **2001**, *12*, 391. (b) Dogan, O.; Oppolzer, W. *Turk. J. Chem.* **2001**, *25*, 273. (c) Paczkowski, R.; Maichle-Mossmer, C.; Maier, M. E. *Org. Lett.* **2000**, *2*, 3967. (d) Liu, W.-C.; Liao, C.-C. *Synlett* **1998**, 912.

**Table 3.** Diels−Alder Cycloadditions



| entry | SM | temp, time (h) | % yield$^{a,b}$ | ee (%)$^c$ | dr$^d$ |
|---|---|---|---|---|---|
| 1 | **3b** | −40°, 24 | 71 | 80 | 84:16 |
| 2 | **3d** | −20°, 24 | 53 | 80 | 71:29 |
| 3 | **3f** | −20°, 24 | 70 | 65 | 73:27 |
| 4 | **3a** | −40°, 24 | 67 | 65 | 60:40 |
| 5 | **3h** | −40°, 24 | 78 | 70 | 81:19 |

[a] For reaction conditions see Supporting Information. [b] Isolated yield after column purification. [c] Chiral HPLC analysis. [d] NMR analysis.

nitrone and nitrile oxide cycloadditions were too weak to catalyze cyclopentadiene addition. The stronger 3+ Lewis acid Sc(OTf)$_3$ in conjunction with chiral pybox ligand **13** did provide enough reactivity to give modest yields. Entries 1−3, in which the α- and β-alkyl substituents vary, show modest yields, enantioselectivity, and diastereoselectivity. Of several imide R groups tested (entries 1, 4, and 5), the larger *tert*-butyl group gives optimal enantio- and diastereoselectivity (80% ee, 84:16 dr, entry 1). Enantioselectivity drops sharply with less than 50% Lewis acid (70%, 60%, and 12% ee with 100%, 50%, and 30% catalyst, respectively, in additions to substrate **3h**). Most likely the enantioselectivity in these reactions is limited not by a lack of rotamer control but rather by the Sc(OTf)$_3$-**13** Lewis acid.

The results in this paper demonstrate that nitrones, nitrile oxides, and dienes can all add to α,β-disubstituted acrylimides in good-to-excellent yields, with good-to-excellent regio- and diastereoselectivities, and with good-to-excellent enantioselectivities. This is true even when neither the α- nor β-substituents are electron-withdrawing. Two new stereocenters including chiral quaternary carbons are formed in each case.

Reactivities of α,β-dialkylated substrates in these reactions are consistently much higher with N-H imide templates than when traditional oxazolidinone templates or other A$^{1,3}$ templates are used, just as was true in our hydroxylamine and radical additions.[6,7] The diminished reactivity of α-substituted systems as compared to α-unsubstituted analogues is not eliminated entirely. Even in the absence of A$^{1,3}$ strain, electron-donating α-alkyl substituents still have a rate-retarding electronic effect associated with a higher LUMO, and in the case of concerted cycloadditions also have a steric effect. Nevertheless, while the use of N-H imide templates does not bring the reactivity of α,β-dialkylated acrylamides all the way back up to the level of α-unsubstituted analogues, it appears general that the use of these templates goes a long way toward lessening reactivity problems.[17] Given that both nitrone and Diels−Alder cycloadditions are relatively slow in general, the fact that these cycloadditions proceed in useful yields using α,β-dialkylated substrates **3** is impressive.

The enantioselectivities in this paper, combined with our previously reported hydroxylamine[6] and radical[7] additions, clearly demonstrate that useful levels of rotamer control exist when α,β-disubstituted N-H acrylimides are activated by Lewis acids. Calculations by Houk on electrophilic reactions of α,β-unsaturated carbonyls predict an inherent electronic reactivity preference for s-cis conformations.[1c] In our reactions it is unclear whether the s-cis rotamer of **3** reacts preferentially because the ground-state population of s-trans rotamer is minimal, or because both rotamers are in equilibrium with the s-cis rotamer reacting selectively (Curtin−Hammett principle), or both. Nevertheless, rotamer preference appears to be usefully high for five different types of addition reactions (hydroxylamine,[6] radical,[7] nitrone, nitrile oxide, and Diels−Alder). The rotamer preference also appears to be high using four metal cations (CuX$_2$, MgX$_2$, NiX$_2$, ScX$_3$) with widely differing Lewis acidities and coordination environments. Whatever the origins, our results suggests that useful levels of rotamer control is likely to be fairly general when α,β-disubstituted N-H acrylimides are activated by Lewis acids.

**Acknowledgment.** We thank the National Science Foundation (NSF-CHE-0316203) for financial support.

**Supporting Information Available:** Characterization data for compounds and experimental procedures; crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050599D

---

(17) The enhanced reactivity with N-H imide templates is not unique to α,β-dialkylated substrates. We have also observed in several reactions that crotonates and cinnamates with N-H imide templates are more reactive than with oxazolidinone templates. Presumably the use of N-H imides provides an electronic advantage apart from the differing sensitivity to A$^{1,3}$ strain.