

Enantioselective 1,3-Dipolar Cycloaddition of Nitrile Imines to α -Substituted and α,β -Disubstituted α,β -Unsaturated Carbonyl Substrates: A Method for Synthesizing Dihydropyrazoles Bearing a Chiral Quaternary Center

Mukund P. Sibi,^{a,*} Levi M. Stanley,^a and Takahiro Soeta^a

^a Department of Chemistry and Molecular Biology, North Dakota State University, Fargo, North Dakota 58105, USA
Fax: (+1)-701-231-8831; e-mail: mukund.sibi@ndsu.edu

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Abstract: Dihydropyrazoles bearing a chiral quaternary center at the 5-position have been prepared by enantioselective 1,3-dipolar cycloaddition of nitrile imines to α -substituted- and α,β -disubstituted- α,β -unsaturated carbonyl substrates. Use of α,β -unsaturated carbonyl substrates with a 1-benzyl-5,5-dimethylpyrazolidin-3-one auxiliary in conjunction with MgI_2 and a bisoxazoline ligand derived from (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol **6** proved optimal to obtain chiral dihydropyrazoles with high enantioselectivity (up to 99% *ee*).

Keywords: asymmetric synthesis; dihydropyrazoles; 1,3-dipolar cycloadditions; nitrile imines; pyrazolidinones

Control of rotamer geometry is critical for enantioselective addition reactions to α,β -unsaturated carbonyl compounds.^[1] Successful examples of chiral Lewis acid catalysis have been developed for α -unsubstituted substrates using oxazolidinone as an achiral template. Substrates such as **1** are ideal for chiral Lewis acid catalysis as they lead to organized chelation and exclusive reaction through the *s-cis* rotamer.^[2] In contrast, solutions with broad applicability for enantioselective addition to substrates with substitution on the α -carbon are limited.^[3,4] Our group has previously described the use of α,β -disubstituted acrylamides **2** as a general solution to control rotamer geometry, relieve $A^{1,3}$ strain, reduce twisting, restore conjugation, and improve reactivity in a variety of reactions.^[5] We now wish to report the use of α -substituted and α,β -disubstituted pyrazolidinone templates **3** as additional substrates capable of rotamer geometry control in enantioselective nitrile imine cycloadditions. A

number of enantioselective addition reactions utilizing unsubstituted and/or β -substituted pyrazolidinone templates have been reported (Figure 1).^[6] However,

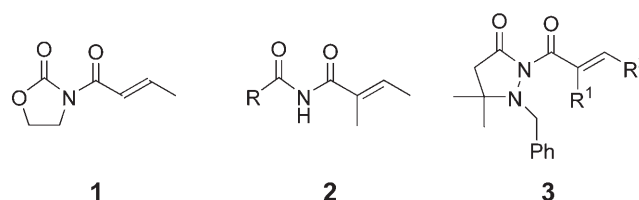
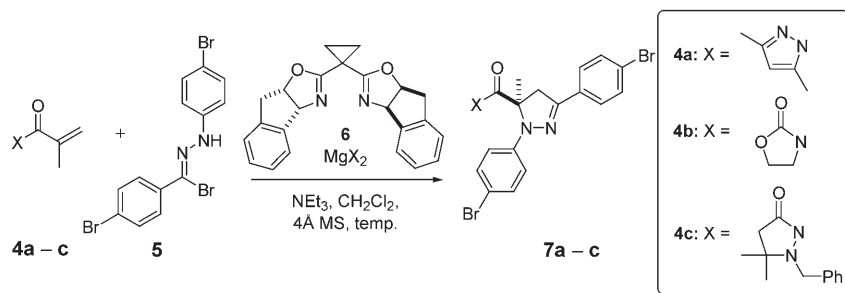


Figure 1. Common templates for enantioselective addition reactions.

the ability of pyrazolidinones to control rotamer geometry in α -substituted and α,β -disubstituted substrates has not been thoroughly examined.

We have previously reported enantioselective nitrile imine cycloadditions utilizing β -substituted α,β -unsaturated oxazolidinone amides as dipolarophiles.^[7] The resulting 4,5-dihydropyrazole products are of significant interest as chiral building blocks. However, we were further interested in the development of a method for the preparation of chiral dihydropyrazoles bearing a quaternary chiral center at the 5-position. Such a method would potentially allow control of the requisite *tert*-alkylamino chiral quaternary center present in a number of natural products.^[8] We initially chose to evaluate methacrylate substrates in room temperature reactions catalyzed by $\text{Mg}(\text{NTf}_2)_2/\mathbf{6}$. Substrates with 3,5-dimethylpyrazole and oxazolidinone auxiliaries gave products in low enantioselectivity (Table 1, entries 1 and 2). We attribute the low selectivity to a lack of rotamer control using these templates since face shielding of α -unsubstituted- β -substituted oxazolidinones is high even at room temperature. We were pleased to see significant enantioselectivity

Table 1. Template and chiral Lewis acid optimization for 1,3-dipolar cycloaddition of **5** to methacrylate substrates **4a–c**.^[a]

Entry	Substrate	Lewis Acid	mol % CLA*	Temp [°C]	Product	Yield [%]	ee [%]
1	4a	$\text{Mg}(\text{NTf}_2)_2$	30	rt	7a	88	0
2	4b	$\text{Mg}(\text{NTf}_2)_2$	30	rt	7b	78	22
3	4c	$\text{Mg}(\text{NTf}_2)_2$	30	rt	7c	67	70
4	4c	$\text{Mg}(\text{NTf}_2)_2$	30	−78	7c	97	77
5	4c	$\text{Mg}(\text{ClO}_4)_2$	30	rt	7c	63	36
6	4c	$\text{Mg}(\text{ClO}_4)_2$	30	−78	7c	80	87
7	4c	MgI_2	30	rt	7c	79	74
8 ^[b]	4c	MgI_2	30	−78	7c	82	98
9 ^[b]	4c	MgI_2	20	−78	7c	80	99
10 ^[b]	4c	MgI_2	10	−78	7c	69	94

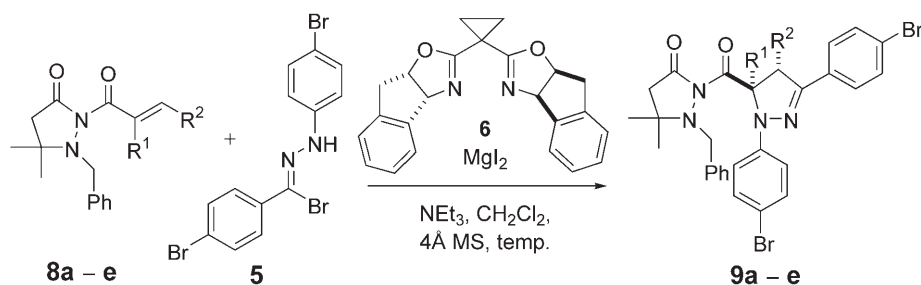
^[a] Typical reactions were run for 2–4 h with 1.5 equivs. **5** and 1.5 equivs. NEt_3 .

^[b] 1.2 equivs. **5** and 1.2 equivs. NEt_3 were employed.

tivity (70 % *ee*) when a substrate bearing a pyrazolidinone template was employed (entry 3). Use of $\text{Mg}(\text{ClO}_4)_2$ led to a decrease in enantioselectivity (36 % *ee*) and isolated yield (entry 5). MgI_2 proved to be the optimal Lewis acid for pyrazolidinone substrates, providing **7c** in 74 % *ee* (entry 7). Significant increases in enantioselectivity were observed when $\text{Mg}(\text{NTf}_2)_2$, $\text{Mg}(\text{ClO}_4)_2$, and MgI_2 catalyzed reactions were conducted at −78 °C (entries 4, 6 and 8), giving product in 77, 87, and 98 % *ee* respectively. Given the optimal yield and enantioselectivity observed in reactions catalyzed by 30 mol % $\text{MgI}_2/\mathbf{6}$, we were interested in the possibility of lowering catalytic loading. Catalyst loading of 20 mol % gave product in 80 % yield and 99 % *ee* (entry 9), essentially identical results to the 30 mol % experiment. Isolated yields were slightly lower when 10 mol % of the catalyst was employed (entry 10), but enantioselectivity remained high (94 % *ee*). Overall, these results suggest that a combination of $\text{MgI}_2/\mathbf{6}$ and the pyrazolidinone substrate **4c** provides effective control of rotamer geometry in α -substituted α,β -unsaturated carbonyl systems.

With an optimal chiral Lewis acid/template system in hand, we were interested in evaluating whether this system would be effective when α,β -disubstituted α,β -unsaturated carbonyl compounds were used as dipolarophiles. Results in Table 2 clearly demonstrate that the pyrazolidinone template functions well with α,β -

disubstituted carbonyl compounds also. The reaction of tiglate substrate **8a** catalyzed by 30 mol % $\text{MgI}_2/\mathbf{6}$ provided cycloadduct in 97 % yield and 99 % *ee* (entry 1). Furthermore, catalyst loading of 10 mol % led to no loss of selectivity although the isolated yield was lowered to 65 % (entry 2). Product **9b**, where $\text{R}^2 = \text{Et}$, was obtained in 99 % *ee* (entry 3) when 30 mol % catalyst was employed at −78 °C. However, yields were moderate at −78 °C. Therefore, the reaction temperature was elevated to −20 °C (entry 4) resulting in a modest increase in isolated yield and no loss of enantioselectivity. As seen with tiglate **8a**, reactivity is diminished significantly when 10 mol % catalyst is used in combination with **8b** (entry 5). In this case cycloadduct was isolated in 44 % yield with 98 % *ee*. α -Methyl cinnamate **8c** proved to be more challenging in terms of reactivity. Optimal results were obtained in the presence of 30 mol % catalyst by conducting the reaction at −20 °C for 24 h, providing product in 56 % yield and 99 % *ee* (entry 6). Reactions carried out at lower temperatures led to very minimal amounts of cycloaddition, while reactions at elevated temperatures led to significant dipole dimerization and lower yields of the desired product **9c**. Cycloadditions to cycloalkene substrates **8d** and **8e** gave cycloadducts in 98 % and 99 % *ee*, respectively (entries 7 and 8). Enantioselectivity remains high (99 % *ee*) in cycloaddition to **8e** when 10 mol % chiral Lewis

Table 2. 1,3-Dipolar cycloaddition of **5** to α,β -disubstituted substrates **8a–e**.^[a]

Entry	Substrate	R ¹	R ²	mol % CLA*	Temp [°C]	Product	Yield [%]	ee [%]
1	8a	Me	Me	30	−78	9a	97	99
2	8a	Me	Me	10	−78	9a	65	99
3	8b	Me	Et	30	−78	9b	69	99
4	8b	Me	Et	30	−20	9b	75	99
5	8b	Me	Et	10	−78	9b	44	98
6 ^[b]	8c	Me	Ph	30	−20	9c	56	99
7	8d	−(CH ₂) ₃ −		30	−78	9d	83	98
8	8e	−(CH ₂) ₄ −		30	−20	9e	63	99
9	8e	−(CH ₂) ₄ −		10	−78	9e	33	99

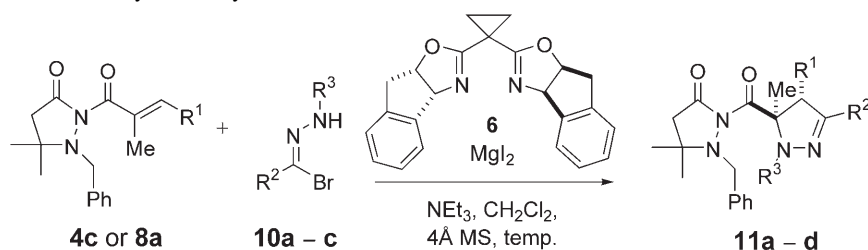
^[a] Typical reactions were run for 2–4 h with 1.2 equivs. **5** and 1.2 equivs NEt_3 .

^[b] Reactions were run for 24 h.

acid is employed, but a large decrease in yield (33%) was observed (entry 9). This trend is interesting as 10 mol % chiral Lewis acid experiments with cyclopentene **8d** resulted in high yields, but a noticeable loss of enantioselectivity.^[9] At this time we believe the uncatalyzed background reaction between the nitrile imine generated from **5** and substrate **8d** to be significant, while the background reaction with other α,β -disubstituted substrates screened is negligible.^[10] Thus, the drop in selectivity is a result of racemic back-

ground reaction, not because of a lack of rotamer geometry control.

To further evaluate the utility of the pyrazolidinone template/chiral Lewis acid system in nitrile imine cycloadditions, we chose to screen three additional hydrazonoyl bromides (Table 3). Reactions of nitrile imine derived from **10a** to substrates **4c** and **8a** gave cycloadducts in very high enantioselectivities (93–99% *ee*) and yields (92–96%), even when chiral Lewis acid loadings were lowered to 10 mol % (en-

Table 3. Reactions of additional hydrazonoyl bromides with substrate **4c** or **8a**.^[a]

Entry	Substrate	R ¹	Dipole	R ²	R ³	mol % CLA*	Temp [°C]	Product	Yield [%]	ee [%]
1	4c	H	10a	Ph	4-BrC ₆ H ₄	30	−78	11a	93	99
2	4c	H	10a	Ph	4-BrC ₆ H ₄	10	−78	11a	92	93
3	8a	Me	10a	Ph	4-BrC ₆ H ₄	30	−78	11b	96	99
4	8a	Me	10a	Ph	4-BrC ₆ H ₄	10	−78	11b	96	99
5	4c	H	10b	BnOCH ₂ −	4-MeOC ₆ H ₄	30	−78	11c	48	80
6	4c	H	10b	BnOCH ₂ −	4-MeOPh	30	−20	11c	61	79
7 ^[b]	4c	H	10c	Ph	Bn	30	−20	11d	67	67

^[a] Typical reactions were run for 2–4 h with 1.2 equivs. **10a–c** and 1.2 equivs. NEt_3 .

^[b] Phosphazene base P₁-*t*-Bu [*tert*-butylimino-tris(dimethylamino)phosphorane].

tries 1–4). Hydrazonoyl bromide **10b** derived from benzyloxyacetaldehyde and 4-methoxyphenylhydrazine gave product in 48% yield and 80% *ee* when reactions were conducted at -78°C (entry 5). A modest increase in yield with little loss of selectivity was observed when this reaction was carried out at -20°C (entry 6). Results with hydrazonoyl bromide **10c** derived from benzylhydrazine and benzaldehyde were disappointing, providing product with only 67% yield and 67% *ee* (entry 7).

In many cases the use of hydrazonoyl chlorides in place of hydrazonoyl bromides is desirable due to their increased stability and ease of preparation in selected cases. As such, we evaluated a number of hydrazonoyl chlorides in nitrile imine cycloadditions to substrate **4c** (Table 4). Our previous work suggested dehydrohalogenation of hydrazonoyl chlorides with common tertiary amine bases was inefficient at -78°C , but proceeds at -20°C with Et_3N . In fact, cycloaddition of the nitrile imine derived from **12a** gave product in 77% yield and 93% *ee* (entry 1). Use of P_1 -*t*-Bu phosphazene base at -20°C led to decrease in both isolated yield and enantioselectivity (entry 2).^[11] However, use of P_1 -*t*-Bu phosphazene base at -78°C provided product **13a** in 96% and 96% *ee* (entry 3). These results are comparable to those obtained for cycloaddition of **5** to **4c**. A similar trend was observed in cycloadditions of nitrile imine derived from **12b** (entries 4 and 5). P_1 -*t*-Bu phosphazene base at -78°C once again provided optimal results with product **13b** isolated in 94% yield and 95% *ee*, marking a drastic increase in yield versus the cor-

responding experiment with Et_3N . This trend is further demonstrated when hydrazonoyl chloride **12c** derived from cinnamaldehyde is employed (entries 6 and 7). Results with P_1 -*t*-Bu phosphazene base at -78°C illustrate the dramatic increase in both yield and selectivity observed under these conditions. Finally, cycloaddition of nitrile imine derived from benzyloxyacetaldehyde with Et_3N gave cycloadduct **13d** in 64% yield and 91% *ee*.

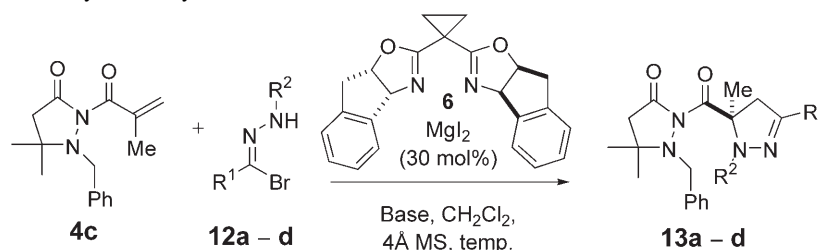
In summary, we have demonstrated a pyrazolidinone template/chiral Lewis acid combination that effectively controls rotamer geometry in nitrile imine cycloadditions to α -substituted α,β -unsaturated and α,β -disubstituted α,β -unsaturated substrates. This Lewis acid/template combination provides dihydropyrazole cycloadducts containing a chiral quaternary center at the 5-position in moderate to high yields (up to 97%) and excellent enantioselectivity (up to 99% *ee*). Further applications of rotamer geometry control with these systems and applications to natural product targets are currently in progress in our laboratory.

Experimental Section

Representative Procedure for Enantioselective Cycloaddition of Nitrile Imines (Table 2, Entry 1)

Substrate **8a** (0.0573 g, 0.2 mmol), MgI_2 (0.0167 g, 0.06 mmol), ligand **6** (0.024 g, 0.066 mmol), and 4 Å molecular sieves (0.10 g) were dissolved in CH_2Cl_2 (2 mL) and allowed to stir at room temperature for 30–60 min. The substrate/chiral Lewis acid complex was cooled to -78°C in a

Table 4. Reactions of various hydrazonoyl chlorides with **4c**.^[a]



Entry	Dipole	R ¹	R ²	Base	Temp [°C]	Product	Yield [%]	<i>ee</i> [%]
1	12a	Ph	Ph	Et_3N	-20	13a	77	93
2	12a	Ph	Ph	P_1 - <i>t</i> -Bu ^[b]	-20	13a	64	83
3	12a	Ph	Ph	P_1 - <i>t</i> -Bu ^[b]	-78	13a	96	96
4	12b	Ph	4-MeOC ₆ H ₄	Et_3N	-20	13b	47	91
5	12b	Ph	4-MeOC ₆ H ₄	P_1 - <i>t</i> -Bu ^[b]	-78	13b	94	95
6	12c	PhCH=CH-	Ph	Et_3N	-20	13c	39	89
7	12c	PhCH=CH-	Ph	P_1 - <i>t</i> -Bu ^[b]	-78	13c	78	94
8	12d	BnOCH ₂ -	Ph	Et_3N	-20	13d	64	91

^[a] Reactions using Et_3N to generate the nitrile imine were run for 24 h with 1.5 equivs. **12a–d** and 1.5 equivs. NEt_3 . Reactions using P_1 -*t*-Bu base to generate the nitrile imine were run for 2–4 h with 1.5 equivs. of **12a–c** and 1.5 equivs. of P_1 -*t*-Bu base.

^[b] Phosphazene base P_1 -*t*-Bu [*tert*-butylimino-tris(dimethylamino)phosphorane].

dry ice/acetone bath. Following cooling for 5 min, hydrazonoyl bromide **5** (0.1039 g, 0.24 mmol) in CH₂Cl₂ (2 mL) was added to the reaction. After an additional 5 min NEt₃ (0.34 mL, 0.24 mmol) was added to the reaction. The reaction was allowed to stir for 2–4 h or until starting material was consumed (TLC). Following completion of the reaction, 4 Å molecular sieves were removed by filtration through a short pad of Celite. The reaction mixture was concentrated onto silica gel (2 g) and purified by column chromatography on an ISCO Combiflash system (100% hexanes to 40% EtOAc/hexanes gradient) to furnish **9a** as a tan foam; yield: 0.1241 g (0.194 mmol, 97%); mp 84–86 °C; The enantiomeric purity was determined by HPLC analysis (254 nm, 25 °C) t_R = 11.2 min (major); t_R = 18.6 min (minor) [Chiracel AD-H (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL min⁻¹] as 99% *ee*. [α]_D²⁵: –3.68 (*c* 0.54, CHCl₃); ¹H NMR (CDCl₃, 500 MHz): δ = 1.14 (s, 3H), 1.25 (s, 3H), 1.26 (d, *J* = 7.0 Hz, 3H), 2.42 (d, *J* = 17.5 Hz, 1H), 2.69 (d, *J* = 17.5 Hz, 1H), 4.06 (d, *J* = 14.0 Hz, 1H), 4.08 (q, *J* = 7.0 Hz, 1H), 4.19 (d, *J* = 14.0 Hz, 1H), 6.93 (d, *J* = 9.5 Hz, 2H), 7.25–7.30 (m, 5H), 7.41–7.43 (m, 2H), 7.50–7.56 (m, 4H); ¹³C NMR (125 MHz, CDCl₃): δ = 12.3, 15.6, 25.7, 27.6, 44.0, 47.8, 57.0, 61.3, 75.1, 112.6, 117.5, 122.7, 127.8, 128.1, 128.5, 129.2, 131.2, 131.8, 131.9, 137.5, 142.5, 150.2, 169.8, 173.9; exact mass calcd. for C₃₀H₃₀Br₂N₄O₂Na⁺: 659.0628, found: 659.0622.

Acknowledgements

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- [9] Reactions utilizing substrate **8d** in place of substrate **8e** under conditions identical (10 mol% chiral Lewis acid) to those used in Table 2, entry 9 gave product in 63% yield and 48% *ee*.
- [10] Reaction of nitrile imine derived from **5** to substrate **8d** at –78 °C with no chiral Lewis acid present showed > 50% conversion by ¹H NMR, while an identical reaction with substrate **8e** showed < 5% conversion.
- [11] Although isolated yields are lower in this case, no starting material remains.