

An Entry to a Chiral Dihydropyrazole Scaffold: Enantioselective [3 + 2] Cycloaddition of Nitrile Imines

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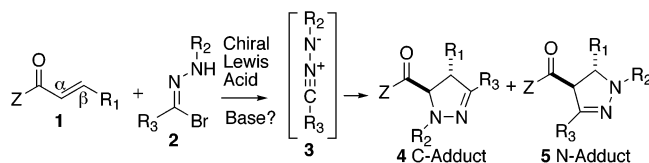
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Recently, a number of catalytic asymmetric [3 + 2] cycloadditions of 1,3-dipoles to olefins have been reported.^{1,2} In this context, nitrile imines are dipoles of interest, as the adducts obtained from their reaction with olefins, 4,5-dihydropyrazoles, have potential biological significance³ and the ability to serve as versatile chiral building blocks. Diastereoselective inter- and intramolecular cycloadditions of nitrile imines to olefins have been reported.⁴ However, there are currently no reports of catalytic enantioselective [3 + 2] cycloadditions of nitrile imines to olefins. In this manuscript, we report the first successful examples of highly regio- and enantioselective additions of nitrile imines to olefins using 10 mol % chiral Lewis acid catalysts. Furthermore, we also demonstrate that functional groups can be incorporated into both the dipole and/or the dipolarophile that are amenable for further manipulations.

We envisioned Lewis-acid-activated enantioselective cycloaddition of nitrile imines as shown in Scheme 1. Several features

Scheme 1



were required for success. First, the addition needed to be regioselective (adduct 4 vs 5). Second, we required selective coordination by the chiral Lewis acid to dipolarophile 1. Third, we wanted mild conditions for generation of the dipole.⁵ The use of solvents or amines that might coordinate Lewis acids and the need for high temperatures were undesirable, and the use of silver salts or ionic bases could prove to be detrimental due to interference with the chiral Lewis acid catalysis.

We decided to generate nitrile imines by dehydrohalogenation and set out to find a compatible amine base–chiral Lewis acid combination using oxazolidinone crotonate **1a** and hydrazonyl bromide **2a** (Table 1, entries 1–7). The noncoordinating diisopropylethylamine was used initially. Ligand **6** in combination with magnesium Lewis acids provided cycloaddition product **7a** in high yield and excellent enantioselectivity (entries 2–4).^{6,7} The reaction was completely regioselective, with the carbon end of the dipole adding to the β -terminus of the crotonate acceptor, in keeping with a dipole HOMO–dipolarophile LUMO process.⁸ Only the anti diastereomer **4a** was observed by ¹H NMR, suggesting a concerted reaction mechanism. By contrast, transition metal salts Cu(OTf)₂, Ni(ClO₄)₂, and Zn(NTf₂)₂ (entries 5–7) gave low enantioselectivity and activity. The poor results with some of these transition metal cations may result from adverse interaction between the Lewis acid and either the dipole or the amine base.

Enantioselectivity and yield were essentially uncompromised when the catalyst loading was reduced to 20 and 10 mol % but began to decline at 5% (Table 1, entries 3, 8, 9), presumably due

Table 1. Optimization of Reaction Conditions^a

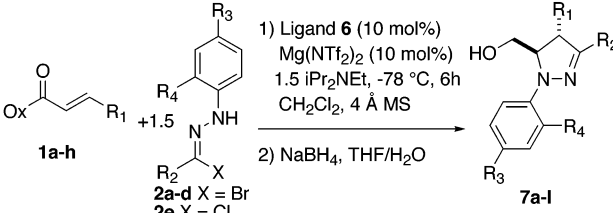
Chemical structures of 1a, 2a, 4a, and 7a, and the structure of Ligand 6 are shown. 1a is an oxazolidinone crotonate, 2a is a hydrazonyl bromide, 4a is a 4,5-dihydropyrazole, and 7a is a 4,5-dihydropyrazole derivative. Ligand 6 is a chiral Lewis acid catalyst.

| entry | Lewis acid | base | mol % CLA | temp (°C) | yield (%) ^{b,c} | ee (%) ^d |
|-------|------------------------------------|------------------------------|-----------|-----------|--------------------------|---------------------|
| 1 | | <i>i</i> Pr ₂ NEt | | −78 | 57 | |
| 2 | MgI ₂ | <i>i</i> Pr ₂ NEt | 30 | −78 | 91 | 98 |
| 3 | Mg(NTf ₂) ₂ | <i>i</i> Pr ₂ NEt | 30 | −78 | 93 | 99 |
| 4 | Mg(ClO ₄) ₂ | <i>i</i> Pr ₂ NEt | 30 | −78 | 92 | 96 |
| 5 | Cu(OTf) ₂ | <i>i</i> Pr ₂ NEt | 30 | −78 | 54 | 1 |
| 6 | Ni(ClO ₄) ₂ | <i>i</i> Pr ₂ NEt | 30 | −78 | 61 | 28 |
| 7 | Zn(NTf ₂) ₂ | <i>i</i> Pr ₂ NEt | 30 | −78 | 81 | 2 |
| 8 | Mg(NTf ₂) ₂ | <i>i</i> Pr ₂ NEt | 10 | −78 | 91 | 99 |
| 9 | Mg(NTf ₂) ₂ | <i>i</i> Pr ₂ NEt | 5 | −78 | 90 | 93 |
| 10 | Mg(NTf ₂) ₂ | <i>i</i> Pr ₂ NEt | 10 | −40 | 90 | 97 |
| 11 | Mg(NTf ₂) ₂ | <i>i</i> Pr ₂ NEt | 10 | 0 | 98 | 85 |
| 12 | Mg(NTf ₂) ₂ | Et ₃ N | 10 | −78 | 99 | 95 |
| 13 | Mg(NTf ₂) ₂ | NMM | 10 | −78 | 99 | 94 |
| 14 | Mg(NTf ₂) ₂ | DABCO | 10 | −78 | 51 | 98 |
| 15 | Mg(NTf ₂) ₂ | DBU | 10 | −78 | 60 | 80 |
| 16 | Mg(NTf ₂) ₂ | pyridine | 10 | −78 | 37 | 79 |

^a For reaction conditions, see Supporting Information. ^b Isolated yield of **7a**. ^c Regioisomeric and diastereomeric ratios were all >99:1 by ¹H NMR (500 MHz). ^d Determined by chiral HPLC.

to competing background reaction. Selectivity declined gradually as the temperature increased to 0 °C (entries 8, 10, 11). Tertiary amines Et₃N and NMM also gave excellent yields and selectivity (entries 12, 13). DABCO gave good selectivity but reduced yield (entry 14), while both yield and enantioselectivity were inferior with DBU and pyridine (entries 15, 16).⁹

With optimized conditions established, we evaluated the performance of other dipolarophiles (Table 2, entries 1–9). With R¹ = Me, Et, or Ph, the cycloadducts **5a–c** are isolated in high yields (>90%) and high enantioselectivities (97–99% ee, entries 1–3). Acceptors in which R¹ is functionalized also work very well (entries 4–7). Cycloaddition of benzoate substrate **1e** occurred without elimination, providing the corresponding diol **7e** in high selectivity following reduction (96% ee, entry 5). Enantioselectivity was slightly lower (91% ee) when R¹ = CO₂tBu (entry 6); increasing the catalyst loading to 20 mol % provides modest improvement (93% ee, entry 7). Yield and enantioselectivity were lower with acrylate **1g** (entry 8). While the yield improved to 95%

Table 2. Evaluation of Substrate Scope


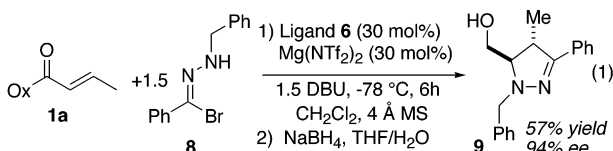
| entry | dipole | R ¹ | R ² | R ³ | R ⁴ | product | yield (%) ^a | ee (%) ^b |
|-----------------|--------|------------------------------|----------------|----------------|----------------|---------|------------------------|---------------------|
| 1 | 2a | Me | Ph | Br | H | 7a | 91 | 99 |
| 2 | 2a | Et | Ph | Br | H | 7b | 93 | 99 |
| 3 | 2a | Ph | Ph | Br | H | 7c | 95 | 97 |
| 4 | 2a | 2-furyl | Ph | Br | H | 7d | 94 | 99 |
| 5 ^c | 2a | OBz | Ph | Br | H | 7e | 97 | 96 |
| 6 | 2a | CO ₂ <i>t</i> -Bu | Ph | Br | H | 7f | 92 | 91 |
| 7 ^d | 2a | CO ₂ <i>t</i> -Bu | Ph | Br | H | 7f | 90 | 93 |
| 8 | 2a | H | Ph | Br | H | 7g | 82 | 79 |
| 9 ^d | 2a | H | Ph | Br | H | 7g | 95 | 84 |
| 10 | 2b | Me | <i>i</i> Pr | Br | H | 7h | 98 | 99 |
| 11 ^e | 2e | Me | Ph | H | H | 7i | 92 | 95 |
| 12 ^e | 2e | 3-Br-Ph | Ph | H | H | 7j | 97 | 97 |
| 13 | 2c | Me | 4-Br-Ph | Br | H | 7k | 95 | 95 |
| 14 | 2d | Me | Ph | OMe | Br | 7l | 96 | 96 |

^a Isolated yield. ^b Determined by chiral HPLC. ^c Upon treatment with NaBH₄, the benzoate is cleaved to yield the corresponding diol. ^d Performed with 20 mol % Mg(NTf₂)₂-6. ^e Et₃N as the base, 30 mol % Mg(NTf₂)₂-6, -20 °C, 48 h.

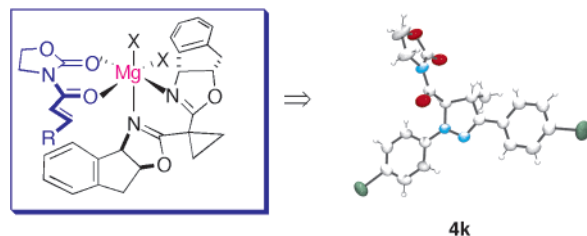
with 20 mol % catalyst loading, the enantioselectivity improved only marginally (entry 9).

Entries 10–14 show results using different hydrazonoyl halides. The bromide **2b** derived from an enolizable aliphatic aldehyde performs well (99% ee, entry 10), providing a product with an alkyl R² group. Entries 11 and 12 demonstrate the suitability of a hydrazonoyl chloride **2e** as the nitrile imine precursor. However, dehydrochlorination of **2e** to form the nitrile imine was more difficult.¹⁰ Et₃N proved to be more reactive than *i*Pr₂NEt and, under optimized reaction conditions (30 mol % CLA, Et₃N, -20 °C, 48 h), gave cycloadducts **7i** and **7j** in good yields and very high enantioselectivity (>90% yields, >95% ee; entries 11, 12). The use of the strong but nonnucleophilic (*tert*-butylimino)tris(dimethylamino) phosphorane as the base gave product **7i** in 93% yield and 94% ee under the normal -78 °C, 6 h, 10% catalyst conditions. Entry 14 shows that a *p*-methoxybenzene substituent can be used on nitrogen, which provides a potential handle for nitrogen deprotection. Entries 1–10 and 12–14 demonstrate that Br can be selectively located in the R¹, R², or nitrogen aryl groups. We thus have a versatile scaffold for potential elaboration via cross-coupling.

Dehydrobromination of *N*-benzyl bromide **8** did not proceed under standard conditions (*i*Pr₂NEt, -78 °C).¹¹ Use of DBU did enable dipole formation, giving cycloaddition product **9** in reasonable yield and 94% ee (eqn 1).^{9,11} The *N*-benzyl group provides another useful handle for nitrogen deprotection.



A crystal structure was obtained for cycloadduct **4k** (see Table 2, entry 13). The absolute stereochemistry was found to be (4*S*,5*R*)- (Figure 1).¹² This is consistent with a *cis*-octahedral model and also

**Figure 1.** Model to explain enantioselectivity and absolute stereochemistry.

with the sense of induction in other reactions catalyzed by magnesium Lewis acids and ligand **6**.¹³

In conclusion, we have developed a versatile strategy to access dihydropyrazoles in highly enantioenriched form. Application of the cycloaddition methodology in the synthesis of biologically active targets and post modification of the dihydropyrazoles¹⁴ is underway.

Acknowledgment. We thank Merck Pharmaceuticals for financial support.

Supporting Information Available: Experimental procedures and characterization data including NMR spectra for selected compounds (PDF). Crystal information files (CIF) for compound **4k**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Reduction of acyl oxazolidinone **4a** to the corresponding alcohol **7a** was not necessary, but the alcohol was more conducive to rapid chiral HPLC analysis.
- Use of molecular sieves was not essential with Mg(NTf₂)₂. With hygroscopic Lewis acids, however, the use of MS was beneficial for optimal and reproducible results, particularly at temperatures where water is more soluble in CH₂Cl₂. The sensitivity to water is probably acute because the basic conditions facilitate formation of Lewis acid hydroxide complexes.
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- We believe that addition to the hydrazonoyl halide may compete with nitrile imine formation when nucleophilic amines are used and that interaction with the Lewis acid (or the dipole itself) may also interfere.
- Use of DBU accelerated consumption of chloride **2e** but gave lower yield of the cycloadduct.
- Starting material **8** was recovered. Use of (*tert*-butylimino)tris(dimethylamino)phosphorane gave product **9** in 68% yield and 88% ee. Conditions were not optimized for any of the bases.
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