Methylene-Bridged Bis(imidazoline)-Derived 2-Oxopyrimidinium Salts as Catalysts for Asymmetric Michael Reactions
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Conjugate addition of glycinic-derived imine esters (1) to Michael acceptors can generate highly functionalized molecules with up to three contiguous stereogenic centers (Scheme 1), which is an attractive strategy for assembling molecular complexity from achiral precursors in a single step without byproducts.[1]

Presently, nonmetal-based phase-transfer catalysts (PTCs) and organocatalysts[2] have been deployed to great effect for these reactions.[3] Corey et al. first reported the conjugate addition of 1 to acrylates and enones with notable enantioselectivity (>90% ee) in the presence of an N-alkylated cinchonidine salt.[4] Subsequently, the scope of the reaction was expanded with other modified cinchona alkaloids[5] as well as new catalysts, comprising largely of reaction was expanded with other modified cinchona alkaloids[5] as well as new catalysts, comprising largely of molecular complexity from achiral precursors in a single step without byproducts.[1]#

Asymmetric Synthesis

Scheme 1. Conjugate addition of glycinic imine esters (1) to α,β-unsaturated carbonyl compounds.

Figure 1. Effective catalysts containing planar nitrogen atoms for asymmetric Michael reactions.

| Compound | Structure | Notes |
|----------|-----------|-------|
| 1        | ![Structure 1](image1) | (Ishikawa, 2001) |
| 2        | ![Structure 2](image2) | (Tan, 2011) |
| 3        | ![Structure 3](image3) | (Lambert, 2012) |
| 5        | ![Structure 5](image5) | (This work) |

The effectiveness of the pentanidium derivative 3 in the conjugate addition of 1a to vinyl ketone and chalcone derivatives.

The structure of 5 is derived from chiral methylene-bridged bis(imidazolines) (MBI), previously reported by Pfaltz and co-workers as a variant of bisoxazoline ligands for asymmetric catalysis.[13] The C2-symmetrical architecture was assembled in five steps from the N-Boc-protected amino acids 6a-c (Scheme 2): the MBIs 10a–j were prepared by a modified literature procedure, and subsequently treated with triphosgene to afford the 2-oxo-pyrimidinium salts 5. Single-crystal X-ray diffraction analysis of the n-butyl-substituted derivative 5b (Figure 2) revealed planar fused rings, corroborating a highly mesomeric tricyclic system.

The addition of the tert-butyl ester glycinate benzophene Schiff base 1a (Table 1) to MVK (11a) in the presence of 5a was chosen for reaction optimization, including extensive screening of solvent, dilution, inorganic base, catalyst loading, and stoichiometry (see Tables S1–S6, in the Supporting Information). Under phase-transfer conditions, the solvent exerted an important effect. When using Cs2CO3 as a base at a 5 mol% catalyst loading, the reaction was complete within an hour at ambient temperature in toluene or xylene, furnishing the Michael adduct 12a with greater than 80% ee (Table 1, entries 1 and 2). In comparison, the use which may account for the lack of development of this type of catalyst in the ensuing decade. However, two recent breakthroughs have rekindled interest in this area, with independent reports of the pentanidium derivative 3[11] and cyclopropanimine 4[12] (Figure 1), which can deliver very favorable catalytic turnovers and enantioselectivities between room temperature and −20 °C.

Herein, we describe the preparation of a family of structurally novel 2-oxopyrimidinium salts (5), and their performance as asymmetric PTCs in the conjugate addition of the glycinic imine ester 1a (R1= tBu) to vinyl ketone and chalcone derivatives.

Conjugate addition of glycine-derived imine esters (1) to Michael acceptors can generate highly functionalized molecules with up to three contiguous stereogenic centers (Scheme 1), which is an attractive strategy for assembling molecular complexity from achiral precursors in a single step without byproducts.[1]
of dichloromethane was detrimental for both productivity and enantiodiscrimination (entry 3).

As might be expected, variations in the structure of the catalyst have a profound effect on the reaction outcome. Extending the N-alkyl chain (from methyl to n-butyl and neopentyl) led to an increase in the product ee value to 88% (Table 1, entries 4 and 5), whereas the substitution with phenyl and bulky tert-butoyl groups has the opposite effect (entries 6 and 7). The level of enantioselectivity was restored with the N-benzyl derivative 5f, which also afforded a faster reaction (entry 8). In contrast, attempts to replace the phenyl substituents on the stereogenic centers of the catalyst with isopropyl (entries 9–11) or benzyl (entry 12) groups did not lead to any improvement. Concurrently, the study also revealed a highly synergistic relationship between the N and C substituents in determining the stereochemical outcome. For catalysts containing phenyl substituents at the stereogenic centers, the selectivity for the S isomer can be overturned by changing the N-alkyl substituent to a phenyl group (Table 1, entry 6 versus entries 1, 4, 5, 7, and 8). The same effect was also observed for the isopropyl-substituted series (entry 11 versus entries 9 and 10).

Eventually, the best yield and ee value were attained with 2 mol% of 5e within 2 hours at 0°C in toluene or o-xylene (Table 1, entries 11 and 15). Additional lowering of temperature led only to a slower reaction with no detectable improvement in the product ee value (entry 14). With these optimized reaction conditions in hand, five additional vinyl ketone substrates (11b–f) were evaluated (Table 2). In all cases, the product can be obtained with good to excellent yields and enantioselectivities, which compare favorably with previously reported systems.

Chalcone derivatives are a particularly challenging class of Michael acceptors. To date, only two catalysts have been reported to have broad generality for these substrates: a dimeric binol-derived (binol=2,2’-dihydroxy-1,1’-binaphthyl) N-spiroammonium salt (≤96% de, ≤93% ee)[21] and the pentanidium derivative 3 (100% de, ≤94% ee).[11a] Hence, we were delighted to find that 5c is not only

![Image](60x563 to 283x782)

**Figure 2.** Structure of (R,R)-5b as determined by single-crystal X-ray crystallography (nonstereogenic hydrogen atoms omitted).[37]

**Scheme 2.** Synthesis of chiral 2-oxopyrimidinium salts (5) from the N-Boc amino acids 6a–c: a) N-methylmorpholine, CIAO₂Bu, R’NHa (74–96%). b) AcCl, MeOH, 0°C–RT. c) LiAlH₄, THF, reflux (73–98% over 2 steps). d) CH₂C(OH)₂, 0°C–RT (84–93% over 2 steps). e) triphosgene, CH₂Cl₂, NEt₃, reflux, (65–100%). f) triphosgene, CH₂Cl₂, NEt₃, 0°C–RT (84–93% over 2 steps). Boc = tert-butoxycarbonyl.

| Entry | Catalyst[bd] | Solvent | T [°C] | t [min] | Yield [%][c] | ee [%][d] |
|-------|--------------|---------|--------|---------|-------------|----------|
| 1     | 5a (5)       | toluene | RT     | 65      | 82          | 81 (S)   |
| 2     | 5a (5)       | o-xylene| RT     | 45      | 78          | 82 (S)   |
| 3     | 5a (5)       | CH₄Cl₂ | RT     | 120     | 85          | 2 (S)    |
| 4     | 5b (5)       | toluene | RT     | 65      | 88          | 84 (S)   |
| 5     | 5c (5)       | toluene | RT     | 65      | 88          | 88 (S)   |
| 6     | 5d (5)       | toluene | RT     | 65      | 84          | 24 (R)   |
| 7     | 5e (5)       | toluene | RT     | 65      | 87          | 6 (S)    |
| 8     | 5f (5)       | toluene | RT     | 35      | 82          | 79 (S)   |
| 9     | 5g (5)       | toluene | RT     | 45      | 87          | 35 (R)   |
| 10    | 5h (5)       | toluene | RT     | 45      | 86          | 32 (R)   |
| 11    | 5i (5)       | toluene | RT     | 65      | 80          | 16 (S)   |
| 12    | 5j (5)       | toluene | RT     | 45      | 90          | 48 (R)   |
| 13    | 5c (2)       | toluene | 0      | 300     | 85          | 93 (S)   |
| 14    | 5c (2)       | toluene | −20    | 1440    | 76 (S)      | 93 (S)   |
| 15    | 5c (2)       | o-xylene| 0      | 300     | 79          | 93 (S)   |

[a] Reactions were performed using 1a (0.05 mmol), 11a (0.1 mmol), and Cs₂CO₃ (0.075 mmol) in 0.5 mL of solvent. [b] Catalyst loading is indicated within parentheses. [c] Yield of the isolated product after purification by column chromatography. Reactions were complete (TLC), unless otherwise indicated. [d] Determined by HPLC using a chiral stationary phase. Absolute configuration assigned by comparison with literature data. [e] 97% conversion (¹H NMR spectroscopy).

**Table 1:** Conjugate addition of tert-butyl glycinate benzophenone Schiff base (1a) to MVK (11a).[4]
Table 2: Addition of 1a to vinyl ketones catalyzed by 5c.[8]

| Entry | Ar     | Product | t [h] | Yield [%][b] | ee [%][b] |
|-------|--------|---------|-------|--------------|-----------|
| 1     | Me     | 12a     | 5     | 85           | 93        |
| 2     | Et     | 12b     | 10    | 92           | 90        |
| 3     | nPr    | 12c     | 3     | 95           | 92        |
| 4     | CH2CH2Ph | 12d  | 2     | 94           | 85        |
| 5     | Ph     | 12e     | 12    | 82           | 80        |
| 6     | 2-naphthyl | 12f | 24    | 76           | 83        |

[a] Reactions were performed using 1a (0.05 mmol), 11 (0.1 mmol), 5c (1 μmol), and Cs2CO3 (0.075 mmol) in toluene (0.5 mL) at 0°C. [b] Yield of the isolated product after purification by column chromatography.

[c] Determined by HPLC using a chiral stationary phase. Absolute stereochemistry established by comparison with literature data.

Table 3: Conjugate addition of 1a to chalcone derivatives 13.[9]

| Entry | Ar     | Product | t [h] | Yield [%][b] | ee [%][b] |
|-------|--------|---------|-------|--------------|-----------|
| 1     | Ph     | 14a     | 3     | 98           | 93        |
| 2     | 4-NO2C6H4 | 14b | 2     | 96           | 90        |
| 3     | 4-CIC6H4 | 14c     | 4     | 94           | 91        |
| 4     | 2-F-5-BrC6H4 | 14d | 5     | 94           | 93        |
| 5     | 4-CF3C6H4 | 14e     | 2     | 92           | 91        |
| 6     | 2-naphthyl | 14f | 4     | 96           | 85        |
| 7     | 2-pyridyl | 14g    | 3     | 96           | 93        |
| 8     | 3-pyridyl | 14h    | 3     | 98           | 93        |
| 9     | Ph     | 14i     | 6     | 88           | 85        |
| 10    | Ph     | 2-naphthyl | 14j | 6     | 92           | 86        |
| 11    | Ph     | 4-CIC6H4 | 14k     | 2     | 90           | 87        |
| 12    | Ph     | 2-furyl | 14l     | 3     | 87           | 90        |
| 13    | Ph     | 2-thienyl | 14m | 2     | 93           | 85        |
| 14    | Ph     | 4-CF3C6H4 | 14n    | 2     | 90           | 83        |
| 15    | Ph     | 4-pyridyl | 14o   | 3     | 96           | 88        |

[a] Reactions were performed using 1a (0.05 mmol), 13 (0.051 mmol), 5c (1 μmol) and Cs2CO3 (0.25 mmol) in mesitylene (0.5 mL) at −20°C for the indicated time. [b] Yield of the isolated product after purification by column chromatography. [c] HPLC using a chiral stationary phase. Absolute stereochemistry established by comparison with literature data.

The synthetic utility of the methodology was further demonstrated by the preparation of the novel proline/nicotine hybrid molecule (2S,3R,5S)-16,[14] containing three well-defined stereogenic centers, in just three steps (Scheme 4).

Scheme 3. Synthesis of chiral dihydropyrrole derivatives 15.

Scheme 4. Synthesis of the novel nicotine/proline hybrid (2S,3R,5S)-16. a) 1a, 5c (2 mol %), mesitylene, −20°C, 3 h. b) 1 N HCl, THF, 0°C, 1.5 h. c) NaBH4, MeOH, 0°C−RT, 24 h. THF = tetrahydrofuran.

Following the previous procedure, the dihydropyrrole intermediate 15c was obtained in good yield and selectivity. Reduction of the imine moiety with sodium borohydride furnished (2S,3R,5S)-16 as a single diastereoisomer with excellent optical purity (94% ee).[15]

In conclusion, a new family of 2-oxopyrimidinium salts has been shown to be highly effective catalysts for the asymmetric Michael addition of a glycine imine ester to vinyl ketones and chalcones under synthetically practical conditions. Although these catalysts contain only planar nitrogen moieties (Figure 2), they are entirely devoid of Brønsted basicity.[16] Thus, it is tantalizing to suggest that these first-in-class compounds may offer a greater reaction scope, particularly towards substrates with base-labile moieties. Future work will include delineating the mechanism of these reactions, and applications in other asymmetric processes.

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