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Amino acid salt catalyzed intramolecular Robinson annulation†,‡

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Abstract

The silica gel absorbed amino acid salt catalyzed asymmetric intramolecular Robinson annulation reaction has been developed; up to 97% ee was obtained with this readily recoverable organocatalyst.

Organocatalysis has emerged as an important method for asymmetric syntheses of chiral molecules.¹ While the majority of current research efforts are directed toward providing useful synthetic building blocks, more and more applications for tandem reaction sequences and complex molecular constructions have recently appeared.²

We have previously reported the application of proline mediated intramolecular Robinson annulation for the asymmetric formal synthesis of a novel antibiotic agent platensimycin.³ The current communication documents the development of an amino acid salt catalyzed asymmetric intramolecular Robinson annulation,⁴ which provides a convenient route to a tricyclic ring structure resembling platencin, another antibiotic agent.⁵

The Robinson annulation precursor is synthesized *via* a straightforward sequence (Scheme 1) starting from *trans*-1,4-cyclohexanedimethanol. Formation of the mono-TBS ether, and then the tosylate, substitution to give a cyanide, and then DIBAL-H reduction, provides an aldehyde intermediate. Wadsworth–Emmons reaction gives the unsaturated ketone. Deprotection of silyl ether, followed by oxidation, then furnishes the desired compound **1**.

We then started screening the optimal organocatalysts for converting compound **1** to the Robinson annulation product **2**. Some representative results are shown in Scheme 2. While proline and its derivatives provided poor yields and ee's, the combination of a catalytic amount of trifluoroacetic acid and a stoichiometric amount of prolinol TBS ether gave better results (79% ee). Higher conversion (63% yield) was also obtained when a catalytic amount of chiral phosphoramidate⁶ and a stoichiometric amount of pyrrolidine were used. It should be noted that when sterically more bulky pyrrolidine derivatives, including the widely employed α,α -diphenylprolinol TMS ether,⁷ were used, no reaction took place. Optimization of these catalyst systems turned out to be fruitless. Considering that our substrate contains the α -branched aldehyde moiety, which is relatively poor for enamine formation, and the β -substituted α,β -unsaturated ketone as a poor electrophile, these unsatisfactory results were not so unexpected.⁸

At this point, our attention turned to alkali metal/quaternary ammonium salts of primary amino acids. These catalysts were initially studied by Yamaguchi and co-workers for the conjugate addition of malonates to α,β -unsaturated ketones or α,β -unsaturated aldehydes;⁹ later, by Feng

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and co-workers for cyanosilylation of ketones;¹⁰ and more recently, by Yoshida and co-workers for conjugate addition of isobutyraldehyde to β -nitroalkenes.¹¹ It was expected that enamine activation of an α -branched aldehyde could be easier with primary amines, while Lewis acid activation of α,β -unsaturated ketone moiety was expected from either alkali metal or quaternary ammonium cations. If such intramolecular dual activation is in operation, high enantioselectivity of this Robinson annulation reaction should be expected.

We were thus very pleased to find that while the parent amino acid phenylalanine did not promote the reaction (Table 1, entry 1), good to excellent ee's were obtained with those alkali metal/quaternary ammonium salt catalysts. Aromatic substituted alanine derived salt provided the best results (entries 2–10); leucine derived lithium salt was also active (entry 11), while *tert*-leucine (entry 12) and tryptophan (entry 13) derived lithium salt gave no conversion. Ether-type solvents were found to give the highest yields and ee's, while the enantioselectivity varied when different counter cations were used (entries 2–7), suggesting that Lewis acid strength and steric effects of corresponding solvated cations are important factors for asymmetric induction. The yield of this reaction was significantly improved (84% yield, 97% ee) when amino acid salt catalysts were absorbed on silica gel (entry 7). More importantly, such silica gel absorbed catalysts could be recovered very easily by filtration or centrifugation/decantation, and reused for three repeated runs without significant loss of catalytic activity or enantioselectivity (entry 7, 1st run, 84% yield, 97% ee; 2nd run, 71% yield, 96% ee; 3rd run, 80% yield, 96% ee). This merit should be attributed to the ionic nature of these amino acid salt catalysts, making it readily separable along with the absorbent silica gel from the organic reaction mixture.¹²

In summary, an amino acid salt catalyzed intramolecular Robinson annulation reaction has been developed, which provides a simple route to a tricyclic ring structure resembling the important antibiotic compound platencin. By using silica gel as absorbent, this type of catalyst is readily recoverable and reusable. We believe this type of silica gel absorbed amino acid salt catalyst could find lots of applications in organocatalytic reactions. Research along these lines, as well as the application of current methodology to the asymmetric synthesis of platencin, is currently underway in this laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Synthesis of Robinson annulation precursor **1**.

Scheme 2.

Selected organocatalysts from preliminary screening.

Table 1

Amino acid salt catalyzed intramolecular Robinson annulation

Entry	Catalyst	Yield ^a (%)	ee ^b (%)
1 ^c		NR ^d	—
2	M = Li	23	91
3	M = Li	54 ^e	96 ^e
4	M = Na	38	91
5	M = K	14	70
6	M = Rb	17	92
7	M = Cs	50	94
8 ^e	M = Cs	29 ^e	96 ^e
9 ^e	M = N ⁺ Bu ₄	31	97
	M = N ⁺ Bu ₄	84 ^f	97 ^f
	M = N ⁺ Bu ₄	71 ^g	96 ^g
	M = N ⁺ Bu ₄	80 ^h	96 ^h
		25	90
		36	94

Entry	Catalyst	Yield ^a (%)	ee ^b (%)
10 ^e		56	88
11 ^e		36	64

Entry	Catalyst	Yield ^a (%)	ee ^b (%)
12 ^e		NR ^d	—
13 ^e		NR ^d	—

^a Isolated yield.

^b Determined by HPLC on OJ-H column.

^c CH₂Cl₂ is used as solvent.

^d NR = no reaction.

^e Et₂O is used as solvent.

^f 1st run, 50 mol% silica gel absorbed catalyst is used.

^g 2nd run, using 50 mol% recovered silica gel absorbed catalyst from 1st run.

^h 3rd run, using 50 mol% recovered silica gel absorbed catalyst from 2nd run.