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Direct Catalytic Asymmetric α-Amination of Aldehydes

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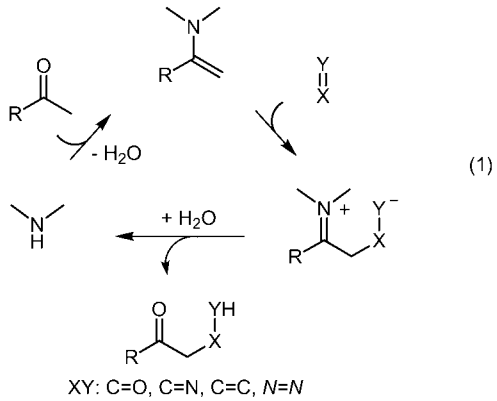
The electrophilic α-amination of carbonyl compounds is an unorthodox yet increasingly used method for the synthesis of nitrogenous molecules.[1] Several asymmetric variants have been proposed in recent years. For example, chiral auxiliary derivatized preformed enolates and enolethers react with azodicarboxylates to furnish α-amino acid derivatives in high stereoselectivities.[2] Catalytic enantioselective variants have also been developed and include metal-catalyzed reactions of enolsilanes with azodicarboxylates.[3] In addition to these indirect variants that require preformation of enolate equivalents, the α-amination has also been an early example of a catalyzed direct enantioselective enolate−electrophile-type bond construction.[4] A direct catalytic asymmetric α-amination of 2-keto esters with azodicarboxylates has recently been developed.[5] As part of our ongoing studies on enamine catalysis[6] we have explored the proline-catalyzed asymmetric α-amination of unmodified carbonyl compounds with azodicarboxylates. Our preliminary results culminating in the first highly efficient and enantioselective direct catalytic asymmetric α-amination of aldehydes are disclosed herein.

On the basis of a generalized enamine catalysis-cycle (eq 1) we expected dialkyl azodicarboxylates ($RO_2CN{=}NCO_2R$) to be useful



(1)

electrophiles in reactions with catalytically generated enamines.[7] We reasoned that these powerful aminating reagents might only react reversibly, if at all, with a nucleophilic aminocatalyst such as proline. Reversibility of such *parasitic equilibria* is imperative for multiple turnover in enamine catalysis and is most likely observed with other electrophiles, including aldehydes, imines, and activated olefins, in aldol, Mannich, and Michael reactions.

On the basis of the high reactivity of aldehydes we further hoped to conduct direct electrophilic α-aminations of aldehydes without having to use a large excess of the nucleophile.[8] The produced α-hydrazino aldehydes should be versatile precursors for diverse α-amino- and α-hydrazino acid derivatives.

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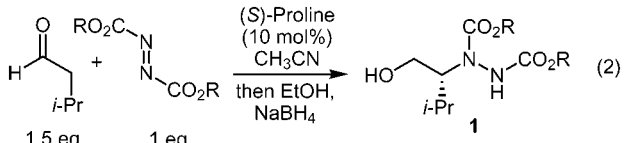
We found the proline-catalyzed reaction of aldehydes with azodicarboxylates to be a highly efficient and enantioselective process. For example, isobutyraldehyde (1.5 equiv) reacts with di-*tert*-butyl azodicarboxylate at room temperature to give the expected product in 97% yield and 92% ee (after in situ $NaBH_4$ reduction to the primary alcohol).[9] If dibenzyl azodicarboxylate was exposed to the same reaction conditions, the corresponding product was obtained in 99% yield and 86% ee. Cooling the reaction mixture to 0 °C further improved the enantioselectivity to 96% ee (eq 2).



(2)

R = *t*-Bu: 97% yield, 92% ee (20°C)
R = Bn: 99% yield, 86% ee (20°C)
99% yield, 96% ee (0°C)

We noticed the enantioselectivity of these reactions to be time dependent and longer reaction times to cause partial racemization. Interestingly, the endpoint of the reaction can easily be monitored by the disappearing yellow color of the azodicarboxylate. We made use of this observation and treated the reaction mixture immediately after its complete decolorization with sodium borohydride and ethanol to give the corresponding pure, crystalline, and configurationally stable 2-hydrazino alcohols in excellent yields.

Other azodicarboxylates (eq 2, R = *i*-Pr, Et) are efficiently processed under our reaction conditions and give the products in high yields and enantioselectivities. Nevertheless, we decided to use dibenzyl azodicarboxylate as the aminating reagent in the present study. Its advantages include the introduction of the easily removable Cbz-protecting group and of a benzene chromophore into the product, facilitating HPLC analysis. In addition to acetonitrile, we studied several other solvents (THF, EtOAc, CH_2Cl_2, dioxane) that, however, turned out to be less effective and to cause markedly decreased enantioselectivities (e.g. ca. 50% ee in dioxane).

We have studied proline-catalyzed reactions of five different aldehydes with dibenzyl azodicarboxylate and generally isolated the produced alcohols (**1**−**5**) in excellent yields and enantioselectivities after in situ $NaBH_4$ reduction (Table 1). In each case we prepared both enantiomers separately and determined the enantioselectivities by chiral-stationary phase HPLC analyses. The ee and absolute configuration of product **5** was determined via conversion into a known compound (vide infra). All products are crystalline solids and nonperfect ee values may be improved by recrystallization.

Among the potential applications of our new methodology, a short asymmetric synthesis of α-amino acid derivatives seemed attractive to us. As an illustration, alcohol (*R*)-**5** was hydrogenated

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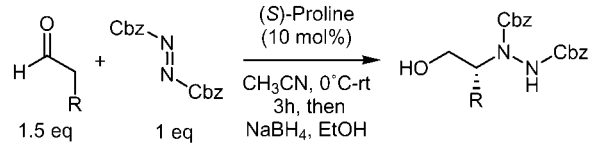
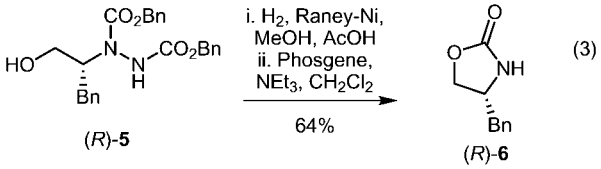
Table 1. Proline-Catalyzed Direct Asymmetric α-Amination of Aldehydes



product	R	yield, %	ee, %
1	*i*-Pr	99	96
2	*n*-Pr	93	>95
3	*n*-Bu	94	97
4	Me	97	>95
5	Bn	95	>95

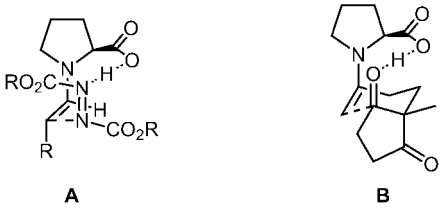
over Raney Nickel[10] and worked up with phosgene to furnish oxazolidinone (*R*)-**6**, a commercially available Evans auxiliary (eq 3).[11]



(3)

We expect this novel route to be useful for the synthesis of several other 4-substituted 2-oxazolidones, including various Evans auxiliaries in both enantiomeric forms. By measuring the optical rotation and ee of compound **6**, we could furthermore establish the (expected) absolute configuration and the ee of alcohol **5**.

The observed sterochemistry can be explained with a proline−enamine-involving transition state (**A**). The proposed model is based on Houk's calculated transition state of the Hajos−Parrish−Eder−Sauer−Wiechert reaction (**B**)[12] and is also consistent with our previously proposed transition states for intermolecular aldol and Mannich reactions.[6]



A **B**

In summary we have developed the first direct catalytic asymmetric α-amination of aldehydes. Among the unique features of this novel transformation, the folowing are emphasized: (1) The described reaction is the first direct α-amination of aldehydes. (2) The reaction furnishes crystalline products in excellent enantioselectivities and yields. (3) The products are useful precursors for 2-oxazolidinones and other natural and nonnatural α-amino and α-hydrazino acid derivatives.[13] (4) The operationally simple reactions are rapid, and require a relatively low amount of an inexpensive and nontoxic catalyst that is available in both enantiomeric forms.

Scope and application of this novel transformation are currently under active investigation in our laboratories and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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