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Enantioselective catalytic addition of nitroesters to *N*-carboalkyloxy imines: a route to quaternary stereocenters

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ABSTRACT

A readily available, low cost bifunctional organic catalyst promoted the addition of nitroesters to imines; in the reaction between 2-nitropropionates and *N*-Boc protected aldehyde-imines the product bearing a new quaternary stereocenter was obtained in up to 81% ee. The positively charged catalyst was postulated to control the attack of the enolic form of nitroester to imine through a hydrogen bonding network.

The stereoselective carbon-carbon bond formation promoted by a chiral catalyst is an area of major interest in asymmetric catalysis.[1] In this field, the stereoselective construction of quaternary stereocenters is one of the most challenging topics of the modern organic chemistry.[2] The concurrent synthesis of adjacent quaternary and tertiary stereogenic centers is even more appealing since it allows the assembly of highly functionalized molecules; such possibility is specially intriguing in the case of chiral 1,2-diamino acids, which are structures of extreme value for their relevance in biological active compounds.[3]

Among the possible methods for the preparation of α,β-diamino acids the Mannich addition to imines[4] represents a viable approach that has been recently explored.[5] An alternative approach is represented by the addition to imines of nitroester, pioneered a few years ago by Johnston.[6] However, the synthesis of α-tetrasubstituted diamino acids, that requires the use of α-substituted nitroesters, remained an elusive goal[7] that only very recently has been positively addressed by three different groups, either by employing an organometallic catalyst[8] or organocatalysts, namely, a chiral ammonium betaine[9] or a sterically hindered bifunctional proton complex[10] in reactions with very bulky nitroesters.

We thought that the use of a new and easily prepared bifunctional catalyst in this very challenging reaction would have been amenable. Prompted by a recent report where the use of chiral 1,2-diphenylethylenediamine, a commercially available, although expensive diamine, as scaffold in a bifunctional thiourea/amine organocatalyst was described[11] we wish to report our preliminary results in the field.

In our previous work a chiral bifunctional thiourea catalyst derived from *t*-leucine was developed and successfully employed in the stereoselective addition of activated nucleophiles to imines.[12] Compound **1** (Fig. 1) was easily prepared in five steps using a straightforward general procedure: the condensation of *N*-methyl benzylamine with N-protected Boc (*S*)-*t*-leucine afforded in quantitative yield *N*-benzyl, *N*-methyl amide of (*S*)-*t*-leucine, that was converted in the corresponding isothiocyanate and immediately reacted with (1*R*,2*R*)-1,2-diamino cyclohexane to afford the bifunctional amino thiourea in 65% yield. Finally reductive amination with formaldehyde and sodium borohydride, followed by treatment with acetic acid allowed to isolate *N*,*N*-dimethyl amino derivative **1** in 61% yield after chromatographic purification.

On the basis of our work[12] and with the aim of mimicking Johnston's proton complex[10] we decided to protonate compound **1** with acetic acid to afford catalyst **1/H$^+$**, which was fully characterized by mass spectrometry and NMR spectroscopy. The addition of ethyl 2-nitro propionate to *N*-Boc benzaldehyde imine was used as model reaction to test the catalytic activity of **1** and **1/H$^+$**; the results are collected in Table 1. In a typical experimental procedure, to a 1-mL dichloromethane solution of the catalyst (0.02 mmol), cooled to 0 °C, under nitrogen atmosphere, 1 mL dichloromethane solution of *N*-Boc benzaldehyde imine (0.2 mmol) was added, followed by injection of ethyl 2-nitro propionate (0.21 mmol). The reaction mixture was allowed to stir for 18 h at 0 °C, then it was concentrated under vacuum and purified by flash chromatography (hexane–ethyl acetate 85:15) (Scheme 1).

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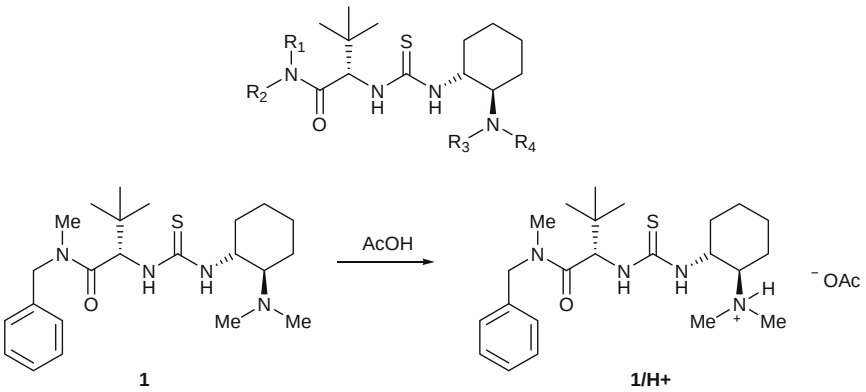
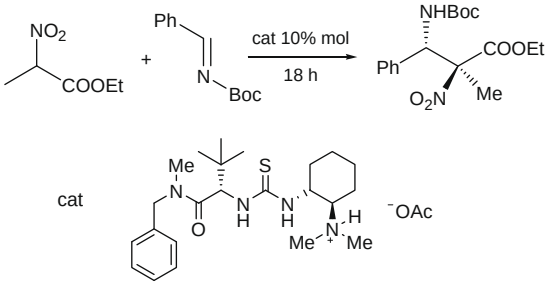


Figure 1. Bifunctional organic catalysts employed in the enantioselective addition of nitroesters to imines.

Table 1
Enantioselective addition of ethyl nitropropionate to *N*-Boc benzaldehyde imine catalyzed by catalyst **1/H⁺** Scheme 1

Entry	Solvent	Temperature (°C)	Yield[a] (%)	ee[b] (%)
1	DCM	25	71	70
2	DCM	0	81	81
3	Et_2O	25	72	73
4	Et_2O	0	41	81
5	Toluene	0	88	60
6	DCM	−20	47	77
7[c]	DCM	0	89	59

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess of anti isomer determined by HPLC (Chiracel OD).
[c] Reaction run with neutral catalyst **1**.



Scheme 1. Addition of 2-nitropropionate to *N*-Boc imine.

Catalyst **1/H⁺** worked well both in dichloromethane and diethyl ether at room temperature, affording the (*S*, *S*)-*anti*-product in good yield and 70–73% enantiomeric excess (entries 1 and 3) although with no diastereoselectivity (*syn*/*anti* ratio was about 1/1).[13] The (*S*,*S*)-*anti* configuration was determined on the basis of literature data. Lowering the reaction temperature was beneficial both in terms of yield and enantiomeric excess in DCM (entry 2): the product was obtained in 81% yield and 81% ee.

In diethyl ether the ee was improved while the yield was not completely satisfactory (entry 4). The use of toluene as solvent allowed isolating the product in 88% yield and 60% ee (entry 5). A further lowering of the reaction temperature did not bring any increase in the enantioselectivity. As expected, the use of protonated catalyst[14] proved to be necessary to obtain a good level of enantioselectivity: compound **1** afforded the desired product in 89% yield and 59% ee in DCM at 0 °C (entry 7). We believe that the proton on the amine moiety allows the coordination of the imine to the catalyst, thus playing a crucial role in determining the stereochemical outcome of the reaction, as it will be discussed later.

The scope of the reaction was extended to differently substituted imines, as illustrated in Table 2. A coordinating protective group on the imine nitrogen (R″ = Cbz, COOMe) is necessary to achieve a good level of stereocontrol (entries 1 and 2). *N*-Acyl imines reacted in slightly lower yield and enantioselectivity. Having established *t*-butyloxycarbonyl as the nitrogen protecting group of choice[15] a variation of the aldehydic substrates was studied. It was found that electron-withdrawing group on the aldehyde ring is better tolerated than electron-donating group (entry 5 vs entry 6).

It is worth mentioning that an imine bearing a coordinating group on the aldehydic part, such as the *N*-4-methoxyphenyl imine of ethyl glyoxylate leads to the product in high yield but low enantioselectivity (entry 7), as further indication of the decisive role played by the Boc group of the imine in controlling the stereoselection of the process (Scheme 2).

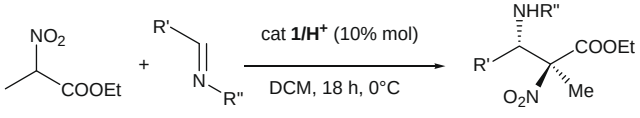
Substitution at the nitroester was also tested: the addition of ethyl-2-nitrobutanoate to *N*-Boc benzaldehyde imine promoted by **1/H⁺** afforded the expected product in 60% yield and 72% ee in DCM at 0 °C (Scheme 3).[16]

The stereochemical outcome of the reaction finds a nice theoretical rationale in a very preliminary semiempirical (AM1) evaluation of the complexes between **1/H⁺** with the two reactants. Due to acidic reaction conditions, calculations were performed on the (*E*)-enolic form of ethyl 2-NO_2 propionate, that coordinates at **1/H⁺** via a hydrogen-bonding network involving NO_2 (with the

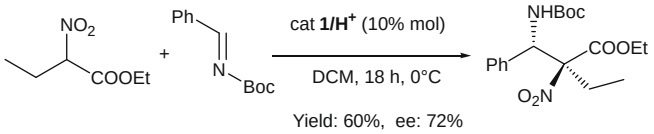
Table 2
Enantioselective addition of ethyl 2-nitro propionate to different imines Scheme 2

Entry[a]	R′	R″	Yield[b] (%)	ee[c] (%)
1	Ph	Cbz	48	65
2	Ph	COOMe	66	58
3	Ph	COPh	55	54
4	Ph	Boc	81	81
5	4-OMe-Ph	Boc	74	27
6	4-Cl-Ph	Boc	73	67
7	COOEt	4-OMe-Ph	77	37

[a] Reaction run in DCM at 0 °C.
[b] Yields determined after chromatographic purification.
[c] Enantiomeric excess determined by HPLC.



Scheme 2. Addition of nitropropionate to different imines.



Scheme 3. Addition of 2-nitrobutanoate to *N*-Boc imine.

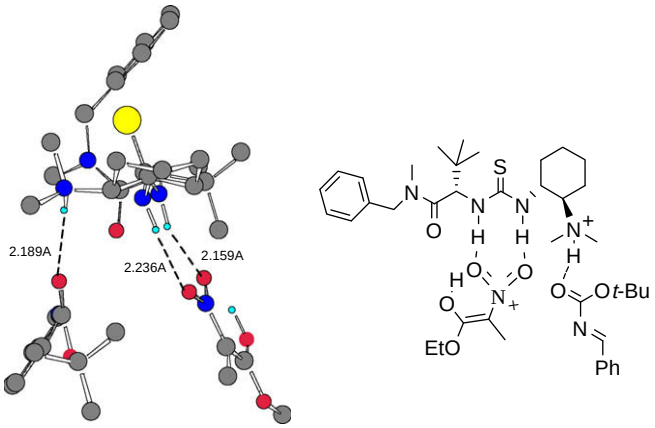


Figure 2. Minimum energy complex between **1/H**$^+$ and reactants. Non-acidic hydrogens are removed for sake of clarity. Distances between hydrogen-bonded atoms are reported.

thioureic NH hydrogens) and enolic OH (with the amidic C=O). The insertion of the imine slightly modifies this pattern: the nitroenolate is still hydrogen-bounded to the two NH of the thiourea, while *N*-Boc benzaldehyde imine is held in place via an hydrogen bond between the amidic C=O and the protonated amine of the ligand.[17] All the possible four complexes were fully optimized and characterized as minima,[18] the structure of the lowest energy one—leading to the major, (*S*,*S*) diastereoisomer—is shown in Figure 2. The calculated ee (88% at 0 °C) is in nice agreement with the experimental results.

We believe that the extremely simple catalyst synthesis, as well as the possibility of a modular approach for developing new and more efficient metal-free promoters for a relatively unexplored field like the nitroester reactions makes the present methodology very attractive.[19]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.036.

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13. Enantiomeric excess of *syn* diastereoisomer was lower than 50% under any reaction conditions.
14. The use of different protic acids (trifluoroacetic acid, trifluoromethane sulfonic acid, and methane sulfonic acid) resulted in high enantiomeric excess but low reproducibility. According to a referee's suggestion the reaction promoted by the pivalate salt of catalyst **1** was studied, in order to explore the use of a more basic carboxylate anion; by running the reaction in DCM at 0 °C for 18 h, the product was obtained in 71% yield, 55/45 dr and 57% ee for the major diastereoisomer.
15. It must be noted that Boc residue maybe the easier protecting group to remove; for synthetic transformations of α-nitro, β-amino ester see Refs.[6,10,11]
16. Attempts at improving the diastereoselectivity of the reaction, for example, by using bulkier esters (see Ref. 10) gave no satisfactory results.
17. The coordination of *t*-butyloxy carbonyl of imine to the thiourea and of the nitro ester to the RMe_2NH^+ group of diaminocyclohexane is also possible; however, from our preliminary calculations such arrangement does not allow to establish a favorite mode of reaction of the two reagents.
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