ORGANIC LETTERS

2003
Vol. 5, No. 14
2559−2561

Asymmetric Michael Addition of α-Hydroxyketones to Nitroolefins Catalyzed by Chiral Diamine

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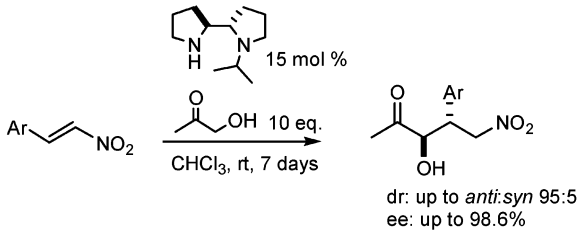
Received May 20, 2003

ABSTRACT



The regio-, stereo-, and enantioselective direct Michael addition of α-hydroxyketones to *β*-arylnitroolefins catalyzed by *N*-*i*Pr-2,2′-bipyrrolidine is described. The formation of an internal hydrogen bond between the OH group of α-hydoxyacetone and the tertiary nitrogen of the catalyst leads to the formation of a rigid *cis* enamine intermediate that explains the inversion of the expected diastereoselectivity and the very high ee's.

The development of nonmetallic asymmetric catalysis has received much attention since its rediscovery in the beginning of the 21st century.[1] Indeed, following the famous asymmetric annulation catalyzed by L-proline in the 1970s,[2] reported by Hajos et al. and Wiechert et al., almost nothing new was published. Only recently have many examples of reactions catalyzed by L-proline been reported, such as aldol reactions, Mannich reactions, conjugate additions, or α-aminations.[3] At the same time, new amines were developed as catalysts and were also used in aldol reactions,[4] Mannich reactions,[5] and conjugate additions.[6] All of these reactions are known under the neologism of organocatalysis.

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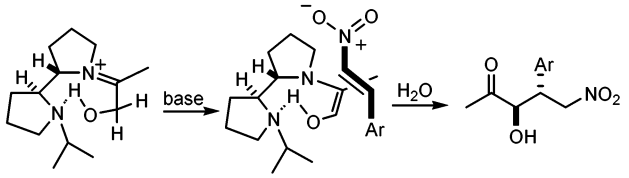
10.1021/ol0348755 CCC: $25.00
Published on Web 06/10/2003

We[7] and others,[3m,n,6f] have recently reported the organocatalyzed conjugate addition of aldehydes and ketones to nitrostyrene. It was shown that L-proline was not very efficient (lower yields and ee's) compared to diamines. One of the problems we met for nonsymmetrical ketones was the regioselectivity. Therefore, we decided to test α-alkoxycarbonyl compounds to see if the regioselectivity of the reaction could be controlled. Indeed, it is commonly accepted that, in the catalytic cycle, an iminium is formed before being deprotonated to the reactive nucleophilic enamine. The difference of acidity between the α and α′ protons leads exclusively to the enol/enamine intermediate (Scheme 1).

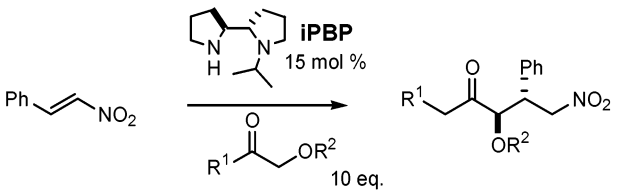
Scheme 1. Proposed Mechanism for Diamine-Catalyzed Michael Addition



The use of α-alkoxycarbonyls has already been described in aldol reactions[8] and Mannich reactions,[9] catalyzed by L-proline, with very high stereoselectivities and regioselectivities. In this communication, we report the first asymmetric organocatalyzed conjugate addition of α-hydroxyketones to nitroolefins.

We have first performed the racemic version by using pyrrolidine as catalyst for the addition of α-methoxyacetone and α-hydroxyacetone to nitrostyrene. The reaction is fully regioselective, and the racemic adduct was obtained in both cases in favor of the *syn* isomer as predicted. The asymmetric version was carried out with our previously reported diamine, (*S*,*S*)-*N*-*i*Pr-2,2′-bipyrrolidine (**iPBP**);[7] The results are summarized in Table 1. The addition of α-methoxyacetone in chloroform provided, as expected, the desired product (entry 1) with a good selectivity (69% ee, *anti*/*syn* 17:83), but surprisingly, the addition of α-hydroxyacetone (entry 2), under the same conditions as above, led to the opposite diastereomer (*anti*/*syn* 83:17) with a very high enantiocontrol (98% ee). This result, with diamine **iPBP**, was much better than the one obtained in a preliminary attempt using L-proline as chiral catalyst. L-Proline, one of the most widely used organocatalysts, gave after 4 days, in methanol, the addition product of α-hydroxyacetone to nitrostyrene, with a very poor stereo- and enantiocontrol (67% yield, 11% ee (*syn*), *anti*/*syn* 30:70). It is interesting to note that the major diastereomer is the *syn* adduct (entry 10).

Table 1. Asymmetric Addition of α-alkoxycarbonyl Compounds to Nitrostyrene, Catalyzed by Diamine **iPBP**



entry	R^1	R^2	solvent	reaction conditions	dr[a] *anti*/*syn*	yield[b] (%)	ee[c] (%)
1	Me	Me	$CHCl_3$	rt, 2 days	17:83	75	69
2	Me	H	$CHCl_3$	rt, 7 days	83:17	79	97.6
3	*n*-Pr	H	$CHCl_3$	60 °C, 7 d	92:8	21	98.4
4	Me	H	CH_2Cl_2	rt, 7 days	82:18	68	98.3
5	Me	H	Et_2O	rt, 7 days	70:30	60	81
6	Me	H	THF	rt, 7 days	60:40	37	73
7	Me	H	MeOH	rt, 2 days	75:25	53	93
8	Me	H	*i*PrOH	rt, 4 days	68:32	48	75
9	Me	H	DMF	rt, 7 days		0[d]	
10[e]	Me	H	MeOH	rt, 4 days	30:70	67	11

[a] Determined by ^{1}H NMR or SFC of the crude product. [b] Isolated yield after column chromatography. [c] Determined by chiral GC or SFC of the purified product (major diastereomer). [d] Decomposition of the starting marterial. [e] With L-proline as chiral catalyst.

Screening of different solvents has shown that chlorinated solvents, $CHCl_3$ (entry 2) and CH_2Cl_2 (entry 4), gave higher yields and stereoselectivities. We have then tested 1-hydroxypentan-2-one, which gave the adduct after 7 days at 60 °C with a very high stereoselectivity but low yield (entry 3), probably because of the thermal instability of the adduct.

We explain the inversion of diastereoselectivity, between the pyrrolidine catalysis and the chiral bipyrrolidine derivatives **iPBP**, by the presence of a second nitrogen that fixes the conformation via a hydrogen bond to give the *cis* enamine instead of the *trans* one. Thus, the high enantioselectivities obtained are due to the resulting rigid reactive intermediate (Scheme 1). The relative approach of the reactants should follow Seebach's model, who explained the selectivity by an acyclic synclinal model.[10]

In a second step, the addition of α-hydroxyacetone to different *β*-arylnitroolefins **1**−**10a** was tested, and the results are summarized in Table 2. All reactions were carried in chloroform with 15% catalyst and 10 equiv of ketone for a duration of 7 days.

We have observed only little differences in enantioselectivity between the adducts **1b**−**10b**. Generally speaking, electron-withdrawing groups on the aryl moiety gave slightly higher yields and stereoselectivities. Unfortunately, nonaromatic nitroolefins, such as *β*-cyclohexylnitroethene or *β*-(*n*-butyl)-nitroethene, did not react with α-hydroxyacetone. This was presumably due to the faster addition of the catalyst to nitroolefin than to ketone.

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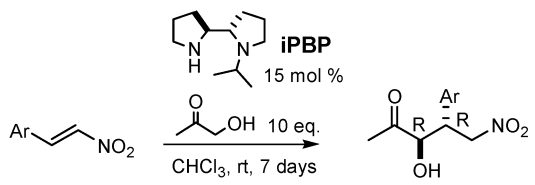
Table 2. Asymmetric Addition of α-Hydroxyacetone to Nitroolefins, Catalyzed by Diamine **iPBP**, in Chloroform



entry/product	Ar	dr[a] *anti/syn*	yield[b] (%)	ee[c] (%)
1	Ph	83:17	79	97.6
2	4-MePh	84:16	68	97.6
3	4-MeOPh	81:19	65	97.3
4	4-Cl-Ph	87:13	81	97.8
5	2-CF_3Ph	95:5	84	98.5
6	2,6-Cl_2Ph	84:16	83	98.1
7	3,4-Cl_2Ph	88:12	66	98.1
8	2,4-Cl_2Ph	91:9	85	98.6
9	1-naphthyl	78:22	68	98.3
10	2-thienyl	78:22	66	96.3

[a] Determined by ^{1}H NMR or SFC of the crude product. [b] Isolated yield after column chromatography. [c] Determined by chiral SFC of the purified product.

The relative configuration of the adduct **5b** was determined by X-ray diffraction[11] of its Mosher ester **5c** (Figure 1). The absolute configuration of center C2′ (*R*) being known, we deduced the absolute configuration of adduct **5b** (*R*,*R*). It

(11) X-ray data for **5c** were collected at 200 K on a Stoe IPDS diffractometer with Mo Kα radiation. $C_{22}H_{19}NO_6F_6$, M = 507.4; orthorhombic, $P2_12_12_1$, Z = 4, a = 9.8059(4), b = 11.3493(7), c = 20.3434(11) Å, V = 22264.0(2) Å^3, R = 0.030, ωR = 0.031 (See Supporting Information for further details).

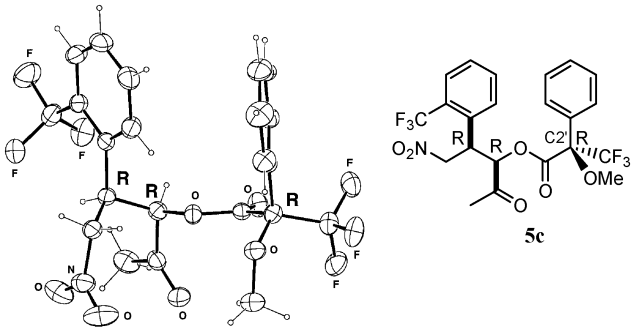


Figure 1. Ortep view of the X-ray crystal structure of **5c**. Ellipsoids are represented with 40% probability.

may be considered that the configuration of the others adducts **1b**−**10b** is the same.

In summary, we have demonstrated that L-proline is not a universal oganocatalyst. For addition reactions to nitroolefins, chiral diamines seem to be more selective. This is particularly the case for the addition of α-hydroxyketones, which allow, through a rigid transition state, an *anti* selectivity, with a very high enantioselectivity.

Acknowledgment. We thank the Swiss National Science Foundation (grant 20-61891-00) for financial support.

Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C spectra and chiral separations for compound **1b**−**10b**; tables of crystal data, atomic coordinates, bond lengths and angles, anisotropic displacements parameters for **5c**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0348755