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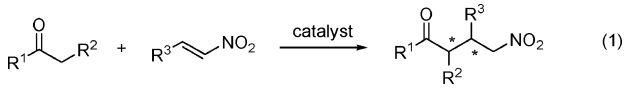
Highly Enantioselective Direct Conjugate Addition of Ketones to Nitroalkenes Promoted by A Chiral Primary Amine−Thiourea Catalyst

Hongbing Huang and Eric N. Jacobsen*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

Received March 27, 2006; E-mail: jacobsen@chemistry.harvard.edu

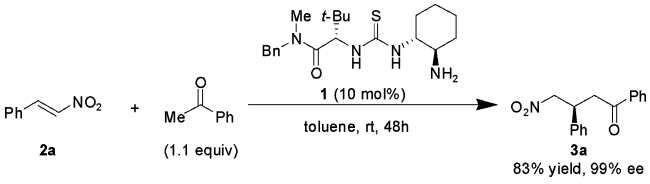
The importance of nitroalkanes in organic synthesis is tied to their propensity to undergo facile α-alkylation reactions and interconversions to other important organic functional groups.[1] Conjugate addition of carbon-centered nucleophiles to nitroalkenes represents a direct and most appealing approach to chiral nitroalkanes, and development of asymmetric catalysts for such processes has been the focus of important recent research effort.[2] Among the variants of this strategy, direct Michael addition of carbonyl compounds to nitroalkenes offers a particularly attractive approach, affording versatile difunctional products in an atom-economical manner (eq 1). Impressive progress has been made recently in the development of bifunctional organic catalysts for the enantioselective addition of malonate derivatives[3] or simple aldehydes and ketones to nitroalkenes.[4] Nonetheless, identification of new catalyst systems with broad substrate scope with respect to both nucleophilic and electrophilic reacting partners remains an important challenge. Herein, we describe a new catalyst (**1**) for asymmetric conjugate additions of ketones to nitroalkenes. The notable features of this system include high enantioselectivities across a broad range of substrates, as well as high diastereo- and regioselectivities resulting directly from the unusual structural features of the catalyst.[5]



(1)

Inspired by the proven ability of thiourea derivatives to serve as effective general acid catalysts in asymmetric addition reactions,[6] we undertook a systematic investigation of members of this compound class as potential catalysts for the model reaction of acetophenone with nitrostyrene (Scheme 1). In particular, we

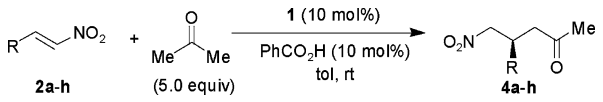
Scheme 1. Model Reaction[11]



performed an extensive screen of chiral thiourea frameworks incorporating additional amine functionality for cooperative enamine generation, and this led to the identification of primary amine **1** as a promising catalyst.[7,8] Among the standard reaction parameters, solvent choice and reagent concentration proved particularly important. While reactions carried out in highly polar and/or protic solvents were impractically slow, those run in nonpolar solvents, such as toluene or CH_2Cl_2, proceeded with useful rates along with high enantioselectivity (up to 99% ee). Reactions carried out at $[\mathbf{2a}]_0 = 0.3$ M in dichloromethane required use of 2-fold excess acetophenone and stalled at 40% conversion after 96 h. However, at higher concentration (2 M), complete conversion was achieved after 48 h. Further increase of the concentration to 5 M allowed generation of Michael adduct **3a** in 83% yield and 99% ee using only a small excess of acetophenone (1.1 equiv).

With optimized conditions established for the model reaction of acetophenone with nitrostyrene, we explored the scope of useful nitroalkene substrates using acetone as a more challenging reacting partner.[4b−f] Although reaction of acetone with nitrostyrene afforded the desired Michael adduct **4a** in 99% ee, yield was compromised due to formation of bisalkylation byproduct (40% yield). However, this side reaction was suppressed completely and without erosion of enantioselectivity by the addition of catalytic amounts of weak acids, such as benzoic acid. Under these conditions, a wide range of aromatic and heteroaromatic nitroalkenes underwent reaction with acetone in high yields and enantioselectivities (Table 1, entries a−e).

Table 1. Enantioselective Addition of Acetone to Nitroalkenes



entry	R	yield (%)[a]	ee (%)[b]
a	Ph	93	99
b	4-$MeOC_6H_4$	88	99
c	4-MeC_6H_4	87	97
d	2-furyl	88	99
e	2-thienyl	94	96
f[c]	Me	70	98
g[c]	*n*-Bu	78	95
h[c]	*i*-Bu	81	94

[a] Isolated yield of purified **4**. [b] Determined by HPLC analysis (see Supporting Information). [c] Results obtained using 15 mol % of **1** and 2 mol % of $PhCO_2H$.

Perhaps more significant, nitroalkenes bearing aliphatic β-substituents proved to be viable electrophilic reacting partners in the presence of added benzoic acid.[9] Highly reactive 1-(*E*)-nitropropene provided the Michael adduct with excellent enantioselectivity (98% ee, entry f). Nitroalkenes bearing more sterically demanding aliphatic substituents underwent reaction in high enantiomeric excesses along with improved yields (entries g and h).

Catalyst **1** displayed a marked bias toward activation of ethyl ketones, allowing regio- and diastereoselective formation of a variety of branched products bearing contiguous tertiary stereocenters (**5a**−**e**, Chart 1). Methyl ethyl ketone underwent reaction with nitrostyrene with modest 2:1 regioselectivity, favoring branched product **5a** over its chromatographically separable regioisomer, with both generated with high enantioselectivities (97 and 95% ee, respectively). Furthermore, the branched product **5a** was generated with high (15:1) selectivity favoring the anti diastereomer.[12] Higher *n*-alkyl ethyl ketones afforded Michael adducts with complete regioselectivity, high enantiomeric excess (98−99% ee), and diastereoselectivity favoring the anti isomers (11−20:1 dr). No

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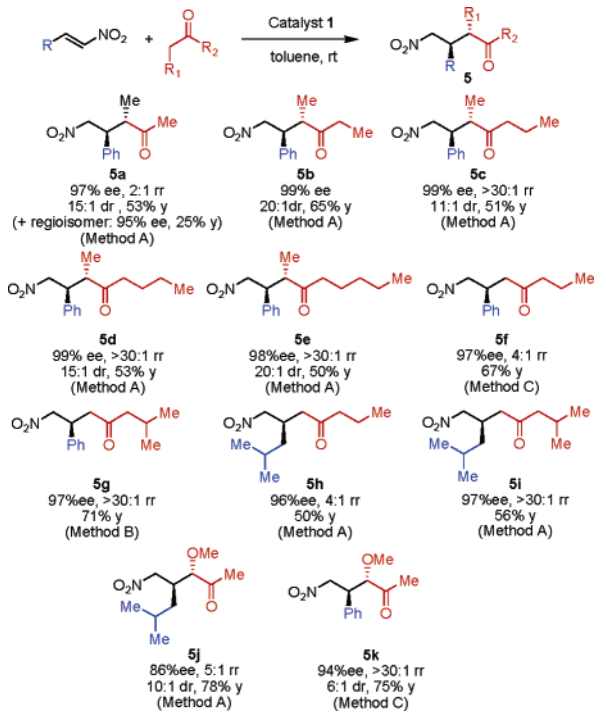
Chart 1. Diastereo- and/or Regioselective Asymmetric Additions of Ketones to Nitroalkenes[a]



[a] rr = regioisomer ratio. Method A: 20 mol % of **1**, 2 mol % of $PhCO_2H$, 1.5−5.0 equiv of ketone. Method B: 10 mol % of **1**, 1.5 equiv of ketone. Method C: 20 mol % of **1**, 2.0 equiv of ketone.

soluble byproducts were detected, and the moderate product yields (50−65%) appear to reflect formation of small amounts of insoluble polymeric materials. The observed sense of relative stereoinduction stands in contrast to results obtained with secondary amine catalysts, which lead to selective formation of the syn diastereomers.[4,13] As might be anticipated from the results leading to **5a**−**e**, additions of methyl propyl ketone provided linear products (**5f**, **5h**) with modest (4:1) regioselectivity and excellent enantioselectivity, while the more sterically demanding methyl isopropyl ketone afforded linear products (**5g**, **5i**) exclusively. However, branched products (**5j**, **5k**) were obtained with methoxyacetone as the Michael donor.

A bifunctional mechanism involving enamine catalysis is clearly indicated in Michael reactions promoted by catalyst **1**. The observed anti diastereoselectivity suggests participation of a *Z*-enamine intermediate (Figure 1), given the complementary diastereoselectivity obtained in analogous reactions involving *E*-enamines generated from secondary amine catalysts.[14,15] The utility of bifunctional primary amine catalysts in other valuable organic transformations is under active investigation.[16]

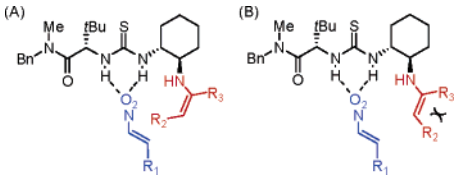


Figure 1. Proposed intermediates in Michael reactions catalyzed by **1**. (A) Favored *Z*-enamine. (B) Disfavored *E*-enamine.

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Supporting Information Available: Catalysts screening studies, experimental procedures, analytical data, and chiral chromatographic analysis of racemic and enantiomerically enriched products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Results obtained with representative catalyst structures are provided as Supporting Information.

(9) To our knowledge, these represent the first examples of highly enantioselective asymmetric addition of ketones to aliphatic nitroolefins. For earlier efforts, see ref 4g.

(10) Added benzoic acid leads to increased product yield, but does not affect the enantioselectivity of these reactions. Therefore, it is likely not involved in the ee-determining conjugate addition step, but rather only in minimizing byproduct formation by accelerating the delicate balance of imine and enamine formation and imine hydrolysis steps in the desired catalytic pathway. No beneficial effect of added acid was observed for certain substrate combinations (see Chart 1).

(11) The absolute configuration of **3a** was established by comparison of the rotation value with published data: Seebach, D.; Lyapkalo, I. M.; Dahinden, R. *Helv. Chim. Acta* **1999**, *82*, 1829−1842.

(12) The relative configuration was assigned by comparison with published data: Yamamoto, Y.; Nishii, S. *J. Org. Chem.* **1988**, *53*, 3597−3603.

(13) Alexakis et al. have reported an anti-selective Michael addition using α-hydroxyacetone, but only this particular substrate afforded anti product. Other substituted ketones afforded syn Michael adducts. See ref 4b and (a) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559−2561. (b) Andrey, O.; Alexakis, A. G. *Org. Lett.* **2002**, *4*, 3611−3614.

(14) Consistent with this hypothesis, cyclic ketones capable only of forming *E*-enamines afford syn products. See also ref 5.

(15) The precise mode of nitroalkene binding to the thiourea is not known. Ground state structures determined both experimentally (Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415−8426) and computationally (Zuend, S.; Jacobsen, E. N., unpublished) point to an in-plane arrangement with each thiourea hydrogen bound to one oxygen of the nitro group as most stable. However, modeling studies suggest that an out-of-plane binding geometry, wherein only one of the nitro group oxygens is engaged by the thiourea, may be required for intramolecular reaction with the enamine.

(16) For example, aldehydes participate in highly enantioselective additions to nitroalkenes with primary amine−thiourea catalysts closely related to **1**: Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. work in progress.

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