Catalytic Enantioselective Conjugate Addition of 1,3-Dicarbonyl Compounds to Nitroalkenes

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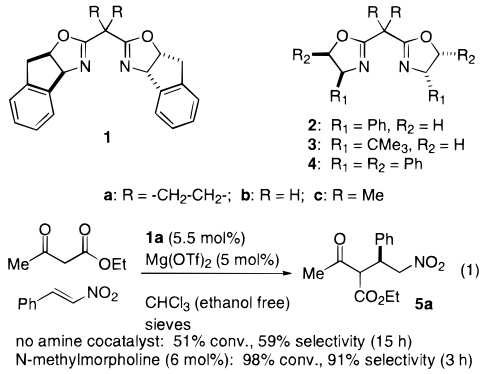
In recent years, catalytic enolate bond constructions have emerged as powerful methods for asymmetric synthesis.[1,2] However, with few exceptions, it has not been possible to accomplish these bond constructions in a manner in which enolization is incorporated into the catalytic cycle. In general, catalytic enolate bond constructions have required the formation of a stable activated enolate surrogate, most generally a silyl ketene acetal or silyl enol ether, which reacts with an electrophile mediated by a Lewis acid catalyst.[2] Notable exceptions include the gold-catalyzed aldol reactions of Ito and Hayashi,[1] the proline−rubidium catalyst system of Yamaguchi,[3] the magnesium sulfonamide-catalyzed amination of Evans and Nelson,[4] and particularly the mixed-metal systems of Shibasaki.[5]

The conjugate addition of enolates to activated olefins remains an active field of research. Indeed, substantial effort has gone into the investigations of enantioselective versions of this reaction,[6] though highly selective variants are rare.[5c,d] Nitroolefins have shown limited success in enantioselective Michael additions. Due to their multiple reactivities, nitro compounds remain important intermediates in organic synthesis.[7] Here, we report the first highly enantioselective catalytic asymmetric conjugate addition of ketoesters and malonates to nitroolefins.[8] This reaction is catalytic in ligand−metal complex and employs an amine cocatalyst. It is particularly interesting because it controls absolute stereochemistry at the β-carbon of the conjugate acceptor.

When ethyl acetoacetate and nitrostyrene were combined in hydrocarbon-stabilized $CHCl_3$ in the presence of 5 mol % of the preformed complex of magnesium triflate and bis(oxazoline) ligand **1a**,[9,10] the Michael addition proceeded to 51% conversion after 15 h; the phenyl-bearing stereocenter of nitroketone **5a** was formed with 59% selectivity (eq 1), indicating enantioselective attack on nitrostyrene.[11] When a small amount (6 mol %) of *N*-methylmorpholine (NMM) was added as cocatalyst, the reaction proceeded to completion in 3 h, with a selectivity of 91%.[12]



The effect of ligand structure on the course of the reaction was investigated (Table 1, eq 2). The unsubstituted aminoindanol-derived ligand **1b** resulted in low conversion, with low selectivity (entry 2), as did dimethyl-substituted derivative **1c** (entry 3).[13] Ligands derived from other amino alcohols were also investigated. While phenyl- and *tert*-butyl ligands **2c** and **3c** provided generally low selectivities (entries 4 and 5), cyclopropyl-bridged diphenyl bis(oxazoline) **4a** did provide excellent reactivity, though only 82% selectivity. Notably, in the absence of ligand, the reaction did not proceed.

Magnesium salts with more coordinating counterions (I, Br, Cl) gave uniformly lower rates and selectivities. Calcium triflate and samarium triflate both provided fair reaction rates but very low selectivities. Copper triflate and zinc triflate were unable to promote the reaction at reasonable rates. The structure of the amine was relatively unimportant, as others also provided good selectivity (morpholine, 86%; *N*-ethylpiperidine, 86%; 5,6-dimethylbenzimidazole, 87%). However, stronger bases, such as triethylamine and Hunig's base, gave somewhat inferior results, presumably due to background reaction. Other solvents have been

(1) Sauamura, M.; Ito, Y. Asymmetric Aldol Reactions. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 7.2, pp 367−388.

(2) For a review of Lewis acid-catalyzed additions of enolate surrogates to electrophiles, see: Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357−389. See also: Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120.

(3) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520−3530 and references therein.

(4) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452−6453.

(5) (a) Shibasaki, M.; Sasai, H.; Arai, T.; Iida, T. *Pure Appl. Chem.* **1998**, *70*, 1027−1034 and references therein. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168−4178. For leading references on Michael additions catalyzed by heterobimetallic complexes, see: (c) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104−106. (d) Funabashi, K.; Saida, Y.; Kanai, M.; Arai, T.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7557−7558.

(6) For an early example of a highly selective catalyzed reaction, see: (a) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625−628. For a recent example of a highly selective Mukaiyama Michael reaction, see: (b) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994−1995. For a review of catalyzed conjugate addition reactions, see: (c) Ferigna, B. I.; de Vries, A. H. M. *Advances in Catalytic Processes*; JAI Press: London, 1995; pp 151−192.

(7) For recent reviews, see: (a) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423−434. (b) Fuji, K.; Node, M. *Synlett* **1991**, 603. (c) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833−847.

(8) The addition of 1,3-dicarbonyl compounds to nitrostyrene has been reported to be promoted by chiral alkaloid catalysts in up to 43% ee. Brunner, H.; Kimel, B. *Monatsh. Chem.* **1996**, *127*, 1063−1072.

(9) Davies, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 1145. For a review of the use of C_2-symmetric bis(oxazoline) ligands in asymmetric catalysis, see: Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45.

(10) For examples of the use of bis(oxazoline)magnesium complexes in catalysis, see the following. Conjugate additions of *O*-benzylhydroxylamine to unsaturated amides: (a) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615−6616. Radical additions to α,β-unsaturated imides: (b) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800. Diels−Alder reaction: (c) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074−3088. (d) Carbone, P.; Desimoni, G.; Faita, G.; Filippone, S.; Righetti, P. *Tetrahedron* **1998**, *54*, 6099−6110. (e) Desimoni, G.; Faita, G.; Invernizzi, A. G.; Righetti, P. P. *Tetrahedron* **1997**, *53*, 7671−7688. (f) Takacs, J. M.; Quincy, D. A.; Shay, W.; Jones, B. E.; Ross, C. R., III. *Tetrahedron: Asymmetry* **1997**, *8*, 3079−3087. (g) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807−6810. Nitrone 1,3-dipolar cycloadditions: (h) Gothelf, K. V.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **1998**, *53*, 5483−5488.

(11) The adducts of β-ketoesters with nitrostyrenes are formed as 1:1 mixtures of compounds diastereomeric at the product ketoester α-position due to rapid equilibration under the reaction conditions. By NMR, the enol tautomer is also observed sometimes. See Supporting Information.

(12) In a typical experiment, $Mg(OTf)_2 \cdot 4H_2O$ (19.6 mg, 0.05 mmol, 0.05 equiv) and ligand **1c** (20.1 mg, 0.055 mmol, 0.055 equiv) are combined in the reaction vessel. One milliliter of $CHCl_3$ is added, and the mixture is stirred for 1 h. Four milliliters of $CHCl_3$ is added, followed by 200 mg of 4-Å molecular sieves, and the resulting mixture is stirred for an additional 90 min. Following this, nitrostyrene (149 mg, 1 mmol, 1 equiv) is added, followed by ethyl acetoacetate (0.15 mL, 1.2 mmol, 1.2 equiv) and *N*-methylmorpholine (6.6 μL, 0.06 mmol, 0.06 equiv). Conversion and selectivity are determined by HPLC analysis. See the Supporting Information for details.

(13) For a computational study of the effect of the bridge substituents on the Diels−Alder reaction catalyzed by bis(oxazoline)copper complexes, see: Davies, I. W.; Deeth, R. J.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **1999**, *40*, 1233−1236. See also ref 9.

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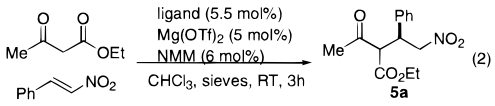
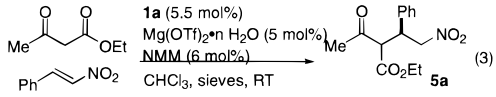
Table 1. Effect of Ligand in the Michael Addition



entry	ligand	selectivity[11] (%)	conversion (%)
1	**1a**	91	96
2	**1b**	65	33
3	**1c**	77	44
4	**2c**	58	9
5	**3c**	0	7
6	**4c**	76	15
7	**4a**	82	99

Table 2. Effect of Water on the Michael Addition



entry	*n*[a]	added water	sieves[b]	selectivity[11] (%)	conversion (%) (2 h)
1	4	0	yes	90	91
2	4	0	no	73	60
3	0.25	0	yes	90	64
4	0.25	4 equiv[c]	yes	91	91

[a] The extent of salt hydration was determined by KF coulometry. [b] 200 mg of powdered 4-Å sieves/mmol of nitrostyrene was employed. [c] Water was added to the dry $Mg(OTf)_2$ before complexation.

investigated, including toluene (86% selectivity), CH_2Cl_2 (81% selectivity), THF (58% selectivity), and DMF (0% selectivity); chloroform and toluene have proven to be optimal for this reaction. In particular, coordinating solvents lower selectivity and reactivity.

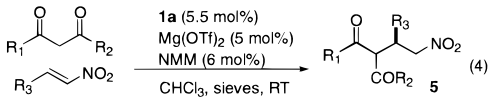
The effect of water on the reaction is illustrated in Table 2 (eq 3). The data indicate that it is necessary to have hydrated $Mg(OTf)_2$ present during ligand−metal complexation (entries 3 and 4);[12] however, the catalytic Michael addition proceeds more effectively in an anhydrous reaction mixture. Practically, the catalyst formation is conducted with $Mg(OTf)_2 \cdot 4H_2O$, and then molecular sieves are added, and the mixture is stirred for 90 min prior to addition of the reactants. The presence of sieves during the catalytic reaction increases both the rate and selectivity of the reaction (entries 1 vs 2).[14]

The rate and selectivity of the Michael addition are influenced by the size of the ester group (Table 3, eq 4). *iso*-Butyl acetoacetate reacts with nitrostyrene with 88% selectivity (entry 2), but the larger *tert*-butyl ester reacts slowly and with only 29% selectivity (entry 3). However, substitution on the ketone moiety is accommodated, as in the cases of ethyl isobutyryl acetate (94% selectivity, entry 4) and the still bulkier 2,2-dimethylpentyl derivative (≥88% selectivity, entries 5 and 6). 2-Alkylated ketoesters were unreactive under the reaction conditions.

The reaction has been further extended to the addition of malonates to nitroalkenes. These reactions are generally faster and less sensitive to reaction conditions. In particular, reactions in toluene provide excellent levels of selectivity (entries 8 and 12). The steric bulk of the ester affects rates and selectivities in a manner similar to that observed in ketoester reactions (entries 7−10). A number of nitroalkenes have been found to undergo the reaction with high yields and selectivities. Electron-poor (entry 11) and -rich (entry 12) nitrostyrenes react with equal facility. Additionally, alkyl-substituted nitroolefins (entries 13 and 14) undergo clean and selective reaction.

(14) The effect of water on magnesium bis(oxazoline)-catalyzed reactions has been documented in other cases (refs 10d,e,h). See the Supporting Information for an investigation of this effect.

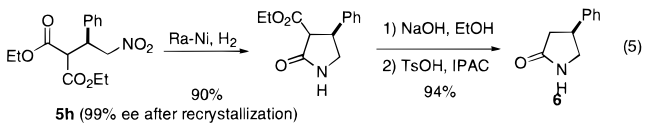
Table 3. Scope of the Asymmetric Addition of 1,3-Dicarbonyl Compounds to Nitroalkenes



entry	R_1	R_2	R_3	adduct	select-ivity[11] (%)	yield (%)
1	Me	OEt	Ph	**5a**	90	95
2	Me	O*i*-Bu	Ph	**5b**	88	92
3	Me	O*t*-Bu	Ph	**5c**	29	94
4	$CHMe_2$	OEt	Ph	**5d**	94	90
5		OEt	Ph	**5e**	92	95
6		OEt	3-MeO-4,5-OCH_2O-Ph	**5f**	88[a]	89[a,b]
7	OMe	OMe	Ph	**5g**	93	96
8	OEt	OEt	Ph	**5h**	95 (93)[c]	92 (93)[c]
9	$OCHMe_2$	$OCHMe_2$	Ph	**5i**	94	92
10	$OCMe_3$	$OCMe_3$	Ph	**5j**	33	88
11	OEt	OEt	*p*-F-Ph	**5k**	90	90
12	OEt	OEt	2,6-$(MeO)_2$-Ph	**5l**	97 (97)[c]	93 (95)[c]
13	OEt	OEt	*n*-C_5H_{11}	**5m**	89	93
14	OEt	OEt	Me_2CHCH_2	**5n**	90	88

[a] Reaction run at 35 °C. [b] HPLC yield. [c] Numbers in parentheses refer to reactions in toluene.

Adduct **5h** can be recrystallized to 99% ee (88% recovery). This has been converted in three steps (85% yield) to (*R*)-4-phenyl-2-pyrrolidinone (**6**), establishing the sense of induction of these reactions and demonstrating the utility of the adducts in forming substituted pyrrolidinones (eq 5).[15]



The experimental results to date, including a kinetic analysis which will be reported later, support a mechanism in which the amine deprotonates the catalyst-bound dicarbonyl compound. The resulting chiral enolate complex, which is a long-lived intermediate, adds diastereoselectively to the nitroalkene.[16]

In summary, we have developed a catalyst system for the conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes. These reactions proceed with low catalyst loading and excellent facial selectivities at the conjugate acceptor. The products of these reactions are important intermediates for the syntheses of 4-substituted pyrrolidines. Further investigations, including mechanistic studies, will be reported shortly.

Acknowledgment. We gratefully acknowledge Michael Fitzgerald for assistance in the development of many of the chiral assays for this project.

Supporting Information Available: General experimental and characterization details of Michael adducts **5a**−**n** and proofs of induction of adducts **5f** and **5m** and possible transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Raney nickel hydrogenation was followed by saponification and decarboxylation, see: Petzoldt, K.; Schmiechen, R.; Hamp, K.; Gottwald, M. U.S. Patent 553911, 1996. Mulzer, *J. Prakt. Chem.* **1994**, *336*, 287. (*R*)-4-Phenylpyrrolidinone (**6**) thus obtained had a rotation of $[\alpha]^{25}_D = +35.2$ (*c* 1.02 MeOH) (lit. $[\alpha]^{25}_D = -33.8$ (*c* 0.89 MeOH) for the (*S*)-isomer: Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36−42).

(16) See Supporting Information for a description of possible transition states.