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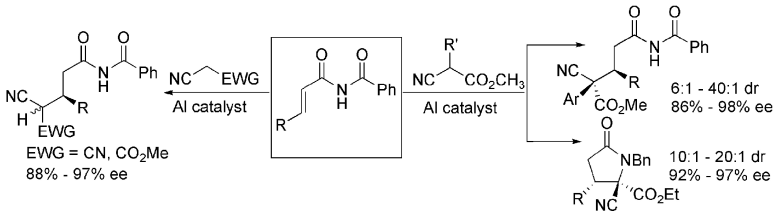

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Enantioselective Michael Additions to α,β-Unsaturated Imides Catalyzed by a Salen−Al Complex

Mark S. Taylor and Eric N. Jacobsen*

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

Received July 9, 2003; E-mail: jacobsen@chemistry.harvard.edu

The conjugate addition of carbon-based nucleophiles to α,β-unsaturated carbonyl compounds is one of the classical methods for C−C bond construction, and the development of asymmetric catalytic versions of this type of transformation has been the subject of intensive research over the past several years.[1] An attractive approach to this problem involves the generation of nucleophilic species by in situ deprotonation of acidic hydrocarbons. In principle, direct Michael additions with such nucleophiles may form the basis for operationally simple, atom economical, and functional group-tolerant methods. Although substantial progress has been realized in the development of asymmetric Michael addition reactions, the nucleophiles employed generally have been limited to β-dicarbonyl compounds[2] and nitroalkanes.[3] Furthermore, general methods for addition to unsaturated carboxylic acid derivatives have not yet been developed. Expanding the scope of the asymmetric Michael reaction with respect to both the electrophile and the nucleophile would represent an important advance. Herein, we report highly enantioselective conjugate additions of electron-deficient nitrile derivatives to acyclic α,β-unsaturated imides catalyzed by a chiral (salen)aluminum complex. The scope of useful nucleophiles includes trisubstituted nitriles, allowing diastereo- and enantioselective access to carbon- and heteroatom-substituted quaternary stereocenters.

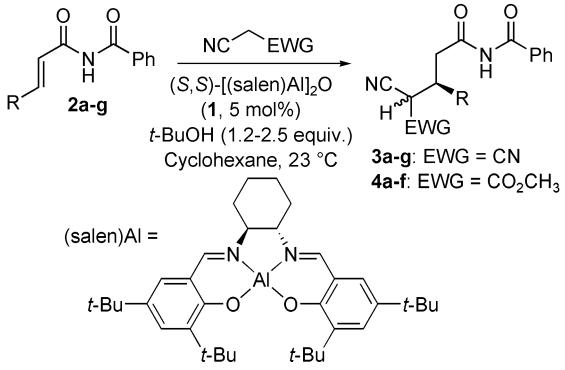
Aluminum salen complexes have been identified recently as effective catalysts for asymmetric conjugate addition reactions.[4] A screen of acidic hydrocarbons as potential nucleophiles[5] revealed that μ-oxo dimer **1**[6] catalyzes the addition of malononitrile and methyl cyanoacetate to imides **2** with high enantioselectivity and in the absence of Brönsted base (Table 1). The scope of the reaction proved to be quite broad with respect to β-substitution on the electrophile: alkyl groups with widely varying steric properties, as well as aryl groups (with the exception of electron-rich derivatives such as *p*-methoxyphenyl, for which the malononitrile addition product was obtained in only 44% ee), were tolerated. The use of nonpolar solvents led to increased enantioselectivity, with cyclohexane affording optimal results. This improvement was accompanied by decreases in reaction rate; however, useful reactivity could be restored by the addition of *tert*-butyl alcohol (1.2 equiv relative to substrate).[7] The absolute configuration of adducts **3** and **4** prepared using (*S*,*S*)-**1** is consistent with earlier observations in conjugate additions of azide and cyanide.[4a,b]

Although the conjugate addition of methyl cyanoacetate generates two stereocenters, the α-cyano ester stereocenter is readily epimerizable, and the adducts were obtained as roughly 1:1 mixtures of diastereomers. The use of substituted cyanoacetate derivatives offers the possibility of generating a configurationally stable quaternary stereocenter under kinetic control.[8] Upon screening such nucleophiles, we found that methyl phenylcyanoacetate added to imide **2e** to afford adduct **5a** with 14:1 diastereoselectivity and 97% enantiomeric excess (Table 2).

A variety of aryl and heteroaryl cyanoacetates, as well as a number of imides bearing unbranched alkyl substitutents at the β position, were found to be effective reacting partners in the conjugate addition. In addition to products bearing carbon-substituted quaternary stereocenters, diastereomerically and enantiomerically enriched quaternary amino nitriles were also prepared in a selective fashion by conjugate addition of ethyl (*N*-benzylamino)cyanoacetate, followed by cyclization to the γ-lactam. X-ray crystallographic analysis served to elucidate the relative configuration of **5b** and **6d**.

This new method provides access to useful building blocks for organic synthesis (Scheme 1). Methyl cyanoacetate adducts undergo clean demethoxycarboxylation under Krapcho conditions[9] to provide the 3-substituted 4-cyanobutyrate derivatives (**7**). Regioselective cleavage of the imide functional group occurs smoothly to furnish a variety of carboxylic acid derivatives under mild conditions;

Table 1. Conjugate Addition of Malononitrile and Methyl Cyanoacetate to Imides **2a**−**g**



product	R	EWG	time	yield (%)[a]	ee (%)[b]
3a	Ph[c]	CN	28 h	87	90
3b	*p*-FC_6H_4[c,j]	CN	36 h	88	93
3c	*p*-ClC_6H_4[c]	CN	38 h	99	92
3d	Me[c,d]	CN	20 h	89	96
3e	*n*-Pr[c,d]	CN	20 h	95	97
3f	*i*-Pr[c]	CN	36 h	91	96
3g	*t*-Bu[c]	CN	48 h	88	97
4a	Ph[e]	CO_2CH_3	40 h	98	88[f]
4b	*p*-FC_6H_4[e,g,k]	CO_2CH_3	54 h	94	89[f]
4c	*p*-ClC_6H_4[e]	CO_2CH_3	56 h	99	89[f]
4d	Me[e]	CO_2CH_3	48 h	96	86[f,h]
4e	*n*-Pr[e]	CO_2CH_3	40 h	88	90[f]
4f	*i*-Pr[i]	CO_2CH_3	6 d	89	95[f]

[a] Isolated yield, after chromatography, from reactions carried out on 0.50 mmol scale. Unpurified commercial solvents were used, without inert atmosphere techniques. [b] Determined by chiral HPLC of the adduct, unless noted otherwise (see Supporting Information for full details). [c] 1.2 equiv of nucleophile was used. [d] 2.5 mol % catalyst was used. [e] 2.5 equiv of nucleophile was used. [f] Enantiomeric excess values represent the 3*R*/3*S* ratio. [g] Reaction carried out on 25 mmol scale. [h] Determined by chiral GC analysis after hydrogenation and cyclization to the δ-lactam. [i] 5.0 equiv of nucleophile was used. [j] Absolute configuration determined by imide methanolysis and decyanation to **7**. [k] Absolute configuration determined by derivitization to (−)-paroxetine (see text).

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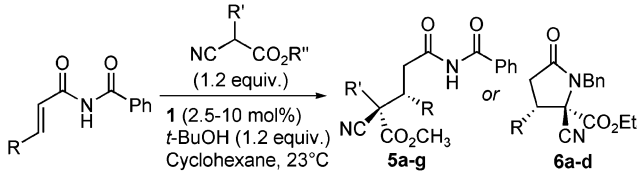
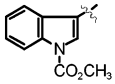
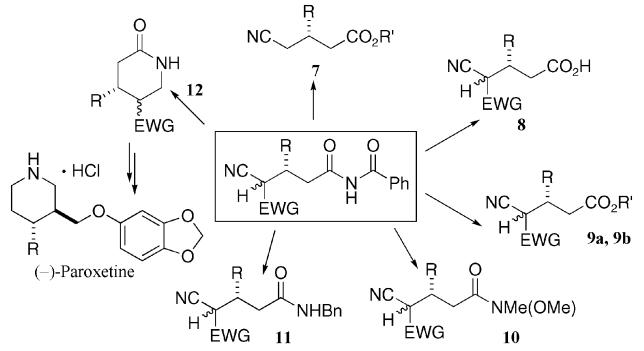
Table 2. Diastereo- and Enantioselective Conjugate Addition of Trisubstituted Cyanoacetate Derivatives



product	R	R′	time	yield (%)[a]	ee (%)[b]	dr[c]
5a[d,f]	*n*-Pr	Ph	19 h	98	97	14:1
5b[d,f]	*n*-Pr	*m*-$CF_3C_6H_4$	15 h	96	98	35:1
5c[d,g]	*n*-Pr	*p*-$MeOC_6H_4$	38 h	94	95	6:1
5d[d,g]	*n*-Pr		51 h	79	95	14:1
5e[d,g]	*n*-Pr	2-thiophenyl	4 d	76	91	14:1
5f[d,f]	Me	Ph	24 h	95	86	5:1
5g[d,g]	*i*-Bu	Ph	24 h	96	96	16:1
6a[e,f]	Me	NHBn	26 h	74	92	10:1
6b[e,g]	*n*-Pr	NHBn	23 h	92	91	14:1
6c[e,g]	*i*-Bu	NHBn	60 h	89	97	13:1
6d[e,h]	Ph	NHBn	54 h	68	96	20:1

[a] Isolated yield, after chromatography, from reactions carried out on 0.50 mmol scale. [b] Of major diastereomer, determined by chiral HPLC. [c] Determined by ^{1}H NMR. [d] Reaction carried out using (*R*,*R*)-**1**. [e] Reaction carried out using (*S*,*S*)-**1**. [f] Reaction carried out using 2.5 mol % catalyst. [g] Reaction carried out using 5.0 mol % catalyst. [h] Reaction carried out with 10 mol % catalyst and 2.5 equiv of *t*-BuOH.

Scheme 1. Regioselective Cleavage of Imides **3b** and **4b**[a]



[a] R = *p*-FC_6H_4, R′ = Me, allyl. For reagents and conditions, see Supporting Information.

carboxylic acids[6a] (e.g., **8**), esters[10] (e.g., **9a**, **b**), Weinreb amides[11] (e.g., **10**), and *N*-benzyl amides (e.g., **11**) are obtained without loss of enantiopurity. Reduction of the nitrile group results in intramolecular aminolysis, delivering the δ-lactam **12** as a 2:1 mixture of diastereomers. Such δ-lactams are useful intermediates for the synthesis of piperidines, ubiquitous structures in natural products and pharmaceutically active compounds.

As an illustration of the utility of the latter methodology, paroxetine (Paxil), a serotonin reuptake inhibitor used widely for the treatment of anxiety, was prepared from **12** (R = 4-FC_6H_4) in six steps, following a synthesis developed at Sumigo Fine Chemicals.[12] Starting with **2b** and through the intermediacy of **4b** obtained in 96% ee by recrystallization from ethanol (77% recovery), (−)-paroxetine was obtained in a total yield of 47% over seven steps.[13,14]

We have demonstrated that the aluminum complex **1** is an efficient catalyst for the conjugate addition of di- and trisubstituted nitriles to a wide range of acyclic alkyl- and aryl-substituted α,β-unsaturated imides. This new methodology provides access to multifunctional compounds that, to date, have not been readily accessible in enantioenriched form. Synthetic applications of these products include the preparation of enantiomerically enriched piperidines, as exemplified by an expedient asymmetric catalytic synthesis of (−)-paroxetine. Studies are underway to expand the scope and synthetic utility of this new reaction, as well as to glean insight into its mechanism.

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Supporting Information Available: Complete experimental procedures, characterization data, and chiral chromatographic analyses of racemic and enantiomerically enriched products (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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