Highly Enantioselective, Catalytic Conjugate Addition of Cyanide to α,β-Unsaturated Imides

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While significant advances have been made in the development of catalyst systems for enantioselective 1,2-cyanations of aldehydes, ketones,[1] and imines,[2] no asymmetric catalysts for 1,4-additions to α,β-unsaturated carbonyl compounds have been identified to date. Such methodology would provide access to difunctional intermediates that are readily converted to a variety of useful chiral building blocks, including β-substituted-γ-aminobutyric acids and α-substituted-β-amino acids (Scheme 1). We describe here the application of readily available (salen)Al^{III} catalysts to the conjugate addition of hydrogen cyanide to α,β-unsaturated imides with high enantioselectivity.

We initiated the study with a screen of known chiral cyanation and conjugate addition catalysts in reactions of HCN or TMSCN with α,β-unsaturated acid derivatives. Chiral aluminum salen catalysts (e.g., **1a,b**) were of particular interest given their proven activity in the asymmetric cyanation of imines[3] and conjugate addition of HN$_3$ to α,β-unsaturated imides (Figure 1).[4] Using imide **2c** as a model substrate,[5] we found that complex **1a** promoted the conjugate addition of HCN in 90% ee, but with very low conversion (1−2 turnover numbers). Systematic variation of solvent, cyanide source, order of addition, and reaction temperature led to substantial improvement in reactivity,[6] with product **3c** generated in 90% isolated yield and 97% ee under optimal conditions.[7] The method used for generation of HCN proved to be a particularly important reaction parameter: no reaction was observed when HCN alone was used as a cyanide source, but good reactivity was obtained with HCN generated in situ from TMSCN and an alcohol such as 2-propanol[8] (vide infra).

Generally good results were obtained with imide substrates bearing aliphatic β-substituents (Table 1).[9] Enantioselectivity was found to be largely insensitive to the steric properties of the substituent, with products **3a** and **3g** generated in similar yield and ee. A significant substrate-dependence on reactivity was observed, however, and slower-reacting imides such as **2g** and **2h** required elevated temperatures and catalyst loadings to attain full conversion (method B). Imide derivatives bearing unsaturated β-substituents (R = aryl, vinyl, alkynyl) proved unreactive, even under forcing conditions.

This new methodology can be applied in a straightforward manner to the synthesis of pregabalin (**5**, (S)-3-isobutyl-γ-aminobutyric acid), an anticonvulsant drug that has been identified as a promising treatment for neuropathic pain.[12,13] In general, β-substituted-γ-amino acids are difficult to synthesize, with the current manufacturing process for pregabalin involving a racemic 1,4-cyanation followed by late-stage classical resolution.[14,15] Cyanide-adduct (S)-**3e** was prepared in 96% ee on the gram scale (Scheme 2). Selective imide hydrolysis provided carboxylic acid **4**, and nitrile reduction over platinum oxide afforded γ-amino acid **5** in excellent yield without deterioration of enantiomeric purity. The overall yield from commercially available materials was thus 62% over six steps.

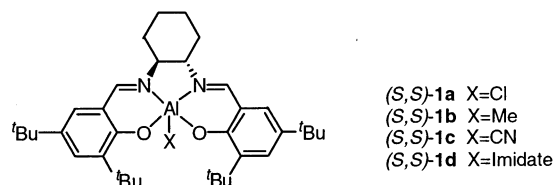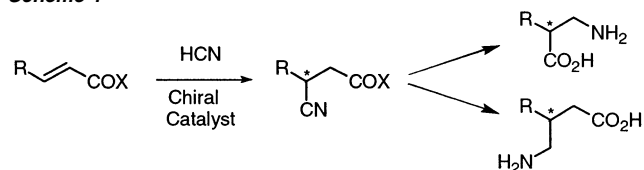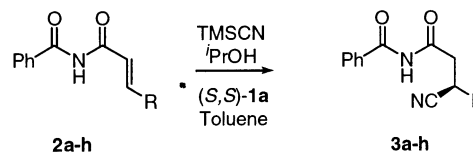Cyanide adducts (**3**) can also be applied toward the synthesis of

Figure 1.

(S,S)-**1a** X=Cl
(S,S)-**1b** X=Me
(S,S)-**1c** X=CN
(S,S)-**1d** X=Imidate

Scheme 1

Table 1. Conjugate Addition of TMSCN to α,β-Unsaturated Imides

product	R	method[a]	time (h)	isolated yield (%)	ee[b] (%)
3a	Me	A	26	92	98[c]
3b	Et	A	26	95	97
3c	^{n}Pr	A	26	90	97
3d	^{i}Pr	A	26	91	94
3e	^{i}Bu	A	26	93	96
3f	(CH$_2$)$_3$CHCH$_2$	A	48	96	95
3g	^{t}Bu	B	48	90	97
3h	CH$_2$OBn	B	48	70	87

[a] Reactions were carried out on a 0.5 mmol scale. Method A: 10 mol % (S,S)-**1a** (see ref 10), 2.5 equiv of TMSCN, 2.5 equiv of 2-propanol, 0.2 mL of toluene, 24 °C. Method B: 15 mol % (S,S)-**1a**, 4 equiv of TMSCN, 4 equiv of 2-propanol, 0.4 mL of toluene, 45 °C. [b] The ee was determined by chiral HPLC on a Pirkle L-Leucine column. [c] Absolute stereochemistry was determined by conversion of **3a** to the known γ-amino acid (ref 11).

enantioenriched α-substituted-β-amino acid derivatives (Scheme 3).[16] Compound **3c** was accessed by the catalytic, enantioselective addition of HCN to imide **2c**. Curtius rearrangement of the derived acid **6** was accomplished using diphenylphosphoryl azide (DPPA)[17] in *tert*-butyl alcohol to afford the Boc-protected cyano amide **7**. Hydrolysis of the nitrile in hydrochloric acid afforded the amino acid product in excellent yield and with minimal racemization.

Spectroscopic studies revealed that the chloride complex (**1a**) is converted to two distinct species under the reaction conditions. Upon addition of TMSCN, **1a** is transformed to a new complex that we hypothesize to be (salen)Al−CN complex **1c**.[18,19] Addition of imide to complex **1c** results in formation of a new (salen)Al−imidate complex (**1d**). Initial rate studies reveal a second-order kinetic

Scheme 2. Synthesis of Pregabalin (**5**)
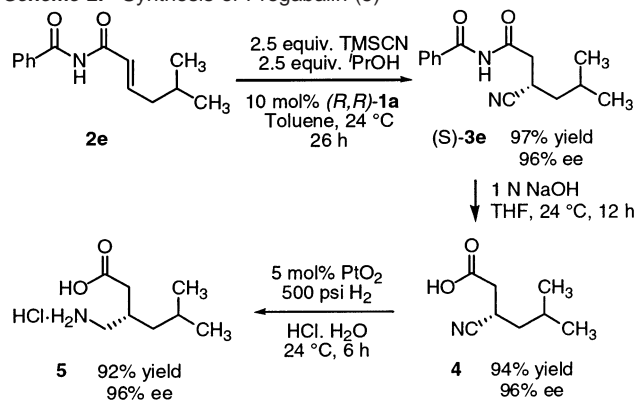
Scheme 3. Synthesis of α-Substituted-β-Amino Acid
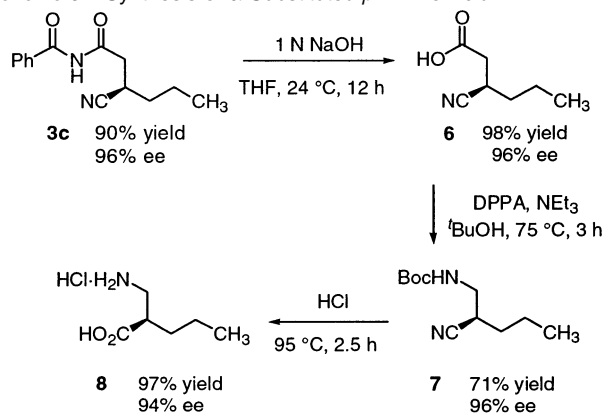
dependence on catalyst concentration.[20] Taken together, these preliminary data are consistent with a bimetallic, dual activation mechanism involving cyanide delivery from the complex (**1c**) to the electrophile bound as the imidate complex (**1d**).[21]

In summary, this represents the first example of asymmetric catalysis of cyanide conjugate addition reactions. The methodology has been applied successfully in the synthesis of important classes of chiral γ- and β-amino acids. Mechanistic data obtained thus far point to a cooperative bimetallic mechanism for nucleophile and electrophile activation. Current studies are being directed toward the development of more reactive and general systems through independent optimization of the nucleophile-delivery and Lewis acid activation functions of the catalyst system. Our results from these efforts will be reported in due course.

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

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(6) Best results were obtained through the use of concentrated toluene solutions. Similar enantioselectivities, but slower reaction rates, were obtained in TBME and chlorobenzene. Use of excess TMSCN (≥2.5 equiv) proved necessary for the attainment of complete conversion of the imide substrate, with improved rates and comparable enantioselectivities achieved with higher cyanide concentrations.

(7) General procedure (method A): Aluminum complex **1a** (60.7 mg, 0.1 mmol) and the imide **2** (1 mmol) were combined in a 25 mL Schlenk flask under N$_2$. Toluene (0.4 mL) and TMSCN (333 μL, 2.5 mmol) were added by syringe, and the mixture was heated gently until the yellow solution became homogeneous. The reaction flask was then placed in a water bath at ambient temperature, and 2-propanol (193 μL, 2.5 mmol) was added dropwise over 2 min. The system was sealed, and the mixture was stirred for the specified length of time. Solvents were removed in vacuo with a K$_2$CO$_3$ solution trap. The residue was purified by flash chromatography to afford pure product **3**.

(8) Comparable results were obtained using ethanol or *tert*-butyl alcohol.

(9) No reactivity was observed with imides bearing α-substitution.

(10) Best results were obtained when the catalyst was dried azeotropically with toluene prior to use.

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(18) Titration of a solution of (salen)Al−Cl with TMSCN led to formation of a precipitate, and TMSCl remained in solution. Direct characterization of the Al-containing product has been hampered by its low solubility.

(19) This complex does not form upon treatment of **1a** with HCN, consistent with the observation that the conjugate addition reaction does not take place with pregenerated HCN (vide supra). However, catalytic activity is restored if TMSCN (1 equiv relative to imide) is added.

(20) Spectroscopic and kinetic data are provided as Supporting Information.

(21) Closely analogous mechanisms have been revealed in epoxide ring-opening reactions catalyzed by metal salen complexes. See: Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421−431.

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