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Published on Web 12/18/2004

Catalytic Enantioselective Conjugate Addition of Cyanide to α,β-Unsaturated *N*-Acylpyrroles

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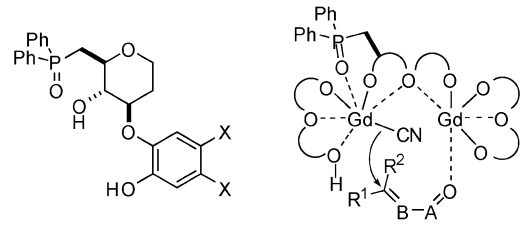
The conjugate addition of cyanide to α,β-unsaturated carboxylic acid derivatives is one of the most useful reactions in organic chemistry. The resulting β-cyano adducts can be converted to γ-aminobutyric acids (GABA analogues) under reducing conditions, 1,2-dicarboxylic acids via hydrolysis, and β-amino acids via Curtius rearrangement. Specifically, the catalytic enantioselective version of this reaction provides very important chiral building blocks for pharmaceuticals. Up to now, only one catalytic enantioselective conjugate addition of cyanide has been reported; Jacobsen's group obtained excellent enantioselectivity from β-aliphatic-substituted α,β-unsaturated imides using the chiral salen−Al complex as a catalyst.[1] On the other hand, substrates with a β-aryl or β-vinyl substituent were unreactive in their system. Thus, there is high demand for a reaction with broader substrate generality. In this communication, we report the catalytic enantioselective conjugate addition of cyanide to various β-substituted α,β-unsaturated *N*-acylpyrroles, including β-aryl, β-vinyl, and α,β-disubstituted derivatives, using a chiral gadolinium complex.

We recently developed a catalytic enantioselective Strecker reaction of *N*-phosphinoyl ketoimines using a chiral gadolinium complex prepared from $Gd(O^iPr)_3$ and ligand **2** in a 1:2 ratio.[2] Both catalyst activity and enantioselectivity were significantly improved in the presence of protic additives, such as 2,6-dimethylphenol or HCN. Structural information of the asymmetric catalyst suggested that the active catalyst is a proton-containing 2:3 complex of Gd and **2**,[2] and the reaction would proceed through an intramolecular cyanide transfer to an activated imine from the gadolinium cyanide (**3**).[3] Because of the topologic analogy of the reaction pattern (1,4-addition), we planned to extend our catalysis to the conjugate addition of cyanide to α,β-unsaturated carboxylic acid derivatives (**4**).

Targeting cinnamic acid derivatives as substrates, we started our optimization using 5 mol % catalyst, 1.5 equiv of TMSCN, and 1 equiv of 2,6-dimethylphenol, observing the effects of the carbonyl substituents of the substrates (Y in Table 1) on the reactivity and enantioselectivity (entries 1−6). Although ethyl cinnamate and cinnamoyl imidazolide did not produce any products, benzylidene malonate **5**, oxazolidinone **6**, and *N*-acylpyrrole **7a**[4] produced the corresponding adducts at ambient temperature, albeit with low to moderate enantioselectivity. When the reaction temperature was decreased to −20 °C, the enantioselectivity of the product from *N*-acylpyrrole **7a** was significantly improved to 74% ee, with diminishing chemical yield (entry 6). Higher enantioselectivity (81% ee) was produced using a catalyst derived from the electronically tuned **2**, although the yield was still moderate (entry 7). Finally, HCN was determined to be a better protic additive than 2,6-dimethylphenol; high chemical yield and enantioselectivity were obtained using 10 mol % catalyst, 1 equiv of TMSCN, and 2 equiv of HCN (entry 8).[5]

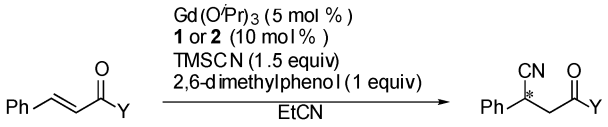


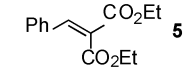
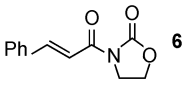
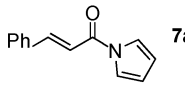
1: X = H
2: X = F

3: A = PPh_2, B = N
4: A = CY, B = CR^3

Figure 1. Chiral ligands (**1** and **2**) and the working hypothesis for the transition-state model of the Strecker reaction (**3**) and the conjugate addition (**4**).

Table 1. Optimization of the Reaction Conditions



entry	substrate	ligand	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	 **5**	**1**	r.t.	45	39	25
2		**1**	–20	44	4	4
3	 **6**	**1**	r.t.	26	27	52
4		**1**	–20	113	16	65
5	 **7a**	**1**	r.t.	14	96	0
6		**1**	–20	43	34	74
7		**2**	–20	40	34	81
8[c]		**2**	–20	98	90	91

[a] Isolated yield. [b] Determined by chiral HPLC. [c] With 10 mol % catalyst, 1 equiv of TMSCN, and 2 equiv of HCN (instead of 2,6-dimethylphenol).

The optimized reaction conditions were applied to other substrates containing β-aryl, vinyl, and alkyl substituents (Table 2). Excellent enantioselectivity was obtained from a wide range of α,β-unsaturated *N*-acylpyrroles.[6] The reaction also proceeded from α,β-disubstituted substrate **7i** with high enantioselectivity, although diastereoselectivity requires further improvement.[7] Thus, this reaction significantly expanded the substrate generality of the catalytic enantioselective conjugate addition of cyanide to α,β-unsaturated carboxylic acid derivatives.

Because of the synthetic versatility of the cyanide and *N*-acylpyrrole,[4] short-step synthesis of a broad range of chiral pharmaceuticals should become possible using this reaction as a key step. Selected examples are shown in Scheme 1. First, a β-phenyl-substituted GABA analogue,[8] which has inhibitory activity

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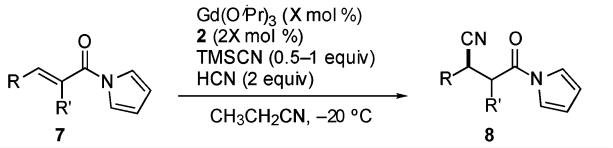
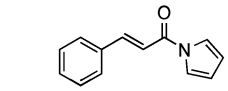
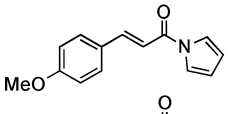
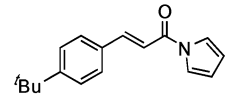
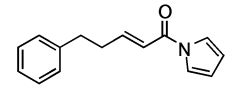
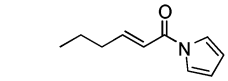
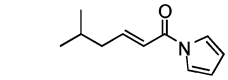
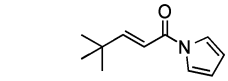
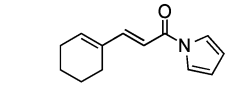
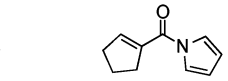
10.1021/ja043424s CCC: $30.25

Table 2. Catalytic Enantioselective Conjugate Addition of Cyanide to α,β-Unsaturated *N*-Acylpyrroles



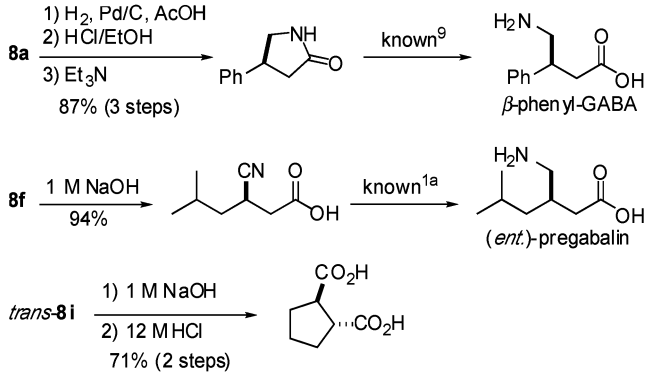
entry	substrate		catalyst (X mol %)	time (h)	yield (%)[a]	ee (%)[b]
1[c]		**7a**	10	98	90	91[g]
2[c]		**7b**	10	98	85	90
3[c]		**7c**	10	88	91	89
4[d]		**7d**	5	43	92	96
5[d]		**7e**	5	42	91	98[g]
6[d]		**7f**	5	42	89	97[g]
7[d]		**7g**	5	88	87	90
8[c]		**7h**	20	139	78	93
9[c,e]		**7i**	5	8	99 (1.1 / 1)[f]	88[h]/83[i]

[a] Isolated yield. [b] Determined by chiral HPLC. [c] With 1 equiv of TMSCN. [d] With 0.5 equiv of TMSCN. [e] The reaction experiment was performed at room temperature. [f] Ratio of trans/cis. [g] Absolute configuration was determined as shown in the above scheme. [h] Enantiomeric excess of trans isomer. The absolute configuration was determined to be (2*R*,3*R*). [i] Enantiomeric excess of cis isomer. The absolute configuration was determined to be (2*S*,3*R*).

in the nervous system, was synthesized in four steps from **8a** through hydrogenation of the cyanide and lactam formation.[9] Second, pregabalin,[10] an important anticonvulsant drug, was synthesized in two steps from **8f**. Third, *trans*-cyclopentanedicarboxylic acid, a useful chiral building block, was synthesized in two steps from *trans*-**8i**.

In conclusion, we developed a catalytic enantioselective conjugate addition reaction of cyanide to α,β-unsaturated *N*-acylpyrroles using the chiral gadolinium catalyst generated from Gd(O^{i}Pr)$_3$ and D-glucose-derived ligand **2**. This reaction expands the previous substrate scope significantly; substrates with β-aryl and β-vinyl substituents and α,β-disubstituted substrates can now be used. Using this reaction as a key step, short-step syntheses of several

Scheme 1. Conversion of the Products to Useful Compounds



pharmaceuticals and their lead compounds were achieved. Detailed mechanistic studies and efforts to further improve the efficiency are in progress.

Acknowledgment. Financial support was provided by Kuraray Co. Ltd., PRESTO of Japan Science and Technology Agency (JST), and Grant-in-Aid for Specially Promoted Research of MEXT. We thank Ms. Sugita, Mr. Qin, and Dr. Matsunaga for helpful advice regarding α,β-unsaturated *N*-acylpyrrole synthesis.

Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Catalysts prepared from other lanthanide alkoxides produced less satisfactory results.

(6) General Procedure: Gd(O^{i}Pr)$_3$ (0.2 M in THF, 75 μL, 0.015 mmol) was added to a solution of **2** (13.8 mg, 0.030 mmol) in THF (0.3 mL) at 0 °C. The mixture was stirred at 45 °C for 1 h, and then the solvent was evaporated at ambient temperature. After drying the resulting precatalyst under reduced pressure (<5 mmHg) for 1.5 h, substrate **7f** (53.1 mg, 0.30 mmol) in propionitrile (500 μL) was added at room temperature, then cooled to −20 °C. After 20 min, TMSCN (20 μL, 0.15 mmol) was added, and after 10 min, HCN (4 M in propionitrile stock solution, 150 μL, 0.60 mmol) was added to start the reaction.

(7) The cyanide addition proceeded with high enantioselectivity. Lack of the diastereoselectivity is due to the nonstereoselective protonation of the intermediate enolate.

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JA043424S