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Asymmetric Conjugate Hydrocyanation of α,β-Unsaturated *N*-Acylpyrroles with the Ru(phgly)$_2$(binap)−CH$_3$OLi Catalyst System

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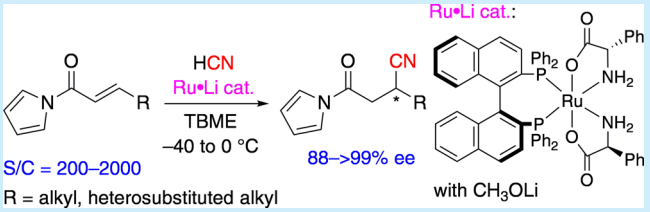
Supporting Information

ABSTRACT: Asymmetric conjugate hydrocyanation of α,β-unsaturated carboxylic acid derivatives catalyzed by a Ru[(*S*)-phgly]$_2$[(*S*)-binap]−CH$_3$OLi system was examined. The *N*-acylpyrrole gave the best result in terms of reactivity and enantioselectivity. A series of substrates with alkyl or heterosubstituted alkyl groups at the β-position reacted with a substrate-to-catalyst molar ratio of 200−2000 to afford the β-cyano products in the range of 88%−>99% ee. The mode of enantioselection in the hydrocyanation was proposed.



Enantioselective conjugate cyanation of α,β-unsaturated carboxylic acid derivatives is a reliable procedure for the production of optically active β-cyano compounds that can be readily converted to the biologically important β-substituted-γ-amino carboxylic acids.[1,2] A variety of chiral catalysts have been developed for this reaction based on the diverse array of potential unsaturated substrates and cyanide sources. The conjugate reaction of α,β-unsaturated imides and the (CH$_3$)$_3$SiCN/2-propanol system with chiral salen−Al or cooperative bimetallic catalysts afforded the β-cyano adducts in up to 98% enantiomeric excess (ee).[3,4] The turnover number (TON) of the catalyst was as high as 50. The chiral polymetallic Gd or Sr species catalyzed the reaction of α,β-unsaturated *N*-acylpyrroles with the trialkylsilyl cyanide/protic compound system (TON: up to 200; ee: up to 99%).[5] The use of trialkylsilyl cyanide is crucial to achieve high yield of products in both cases.[3,5] Chiral phase-transfer catalysts with the quinuclidine backbone promoted the conjugate addition of acetone cyanohydrin to α,β-unsaturated *N*-acylpyrroles (TON: up to 10; ee: up to 98%).[6] Alkylidenemalonates are cyanated in a conjugate manner with the ethyl cyanoformate/2-propanol system in the presence of chiral modular Ti catalysts (TON: up to 10; ee: up to 94%).[7] Chiral phase-transfer catalysts with the binaphthyl backbone promoted the reaction of alkylidenemalonates and KCN (TON: up to 320; ee: up to 95%).[8] All of the above reactions achieved high enantioselectivity, but there is room for improvement in the catalytic activity. Furthermore, no successful examples have been reported using HCN, the simplest cyanide source.

Recently, we reported asymmetric conjugate addition of HCN to α,β-unsaturated ketones catalyzed by the combined system of Ru(phgly)$_2$(binap) and C$_6$H$_5$OLi.[9−11] A series of aromatic, heteroaromatic, and aliphatic β-cyano ketones was obtained in high enantioselectivity. This observation prompted us to investigate asymmetric conjugate hydrocyanation of α,β-unsaturated carboxylic acid derivatives with our original chiral Ru−Li combined catalyst.[12]

The reaction of *N*-acylpyrrole derived from crotonic acid **1a** (1.0 mmol, 0.15 M)[13] and HCN prepared in situ by mixing (CH$_3$)$_3$SiCN (1.5 mmol) and CH$_3$OH (1.5 mmol) in *t*-C$_4$H$_9$OCH$_3$ at 25 °C proceeded smoothly in the presence of Ru[(*S*)-phgly]$_2$[(*S*)-binap][14] ((*S*$_A$,*S*$_P$)-**3**: 2.0 μmol; substrate-to-catalyst molar ratio (S/C) = 500) and CH$_3$OLi (0.10 M in CH$_3$OH, 2.0 μmol) to afford the β-cyano compound (*S*)-**2a** as a sole observable product in 98% yield and 88% ee in 2 h (Table 1, entry 1). The higher concentration of **1a** (0.30 M) resulted in the lower ee value of **2a** (83%). The enantioselectivity decreased when the reaction was conducted in *cyclo*-C$_5$H$_9$OCH$_3$ or (C$_2$H$_5$)$_2$O (entries 2 and 3). No conversion was observed in less polar toluene solution (entry 4). A higher enantioselectivity was achieved under the lower temperature conditions, although the reaction rate slowed down (entries 5 and 7). Thus, the ee value reached 96% at −20 °C. The reaction using isolated HCN[15] instead of HCN formed in situ proceeded smoothly to give **2a** in the same ee (entry 6 vs entry 5), suggesting that this reaction is the hydrocyanation without substantial influence from the existing silicone compounds.

The conjugate cyanation of the *N*-acyl-3,5-dimethylpyrazole analogue **1b** afforded the β-cyano adduct **2b** in high ee, but the moderate yield of 44% with an S/C of 200 at 0 °C for 15 h was not satisfactory (Table 1, entry 8). The unsaturated amide **1c** was feebly reactive (entry 9). The cyanation of the pyrrolidinone-derived imide **1d** with an S/C of 200 at 0 °C was completed in 24 h to give **2d** with a moderate ee of 61% (entry 10). The reaction of the oxazolidinone **1e**, the structure of which is similar to that of the imide **1d**, also proceeded

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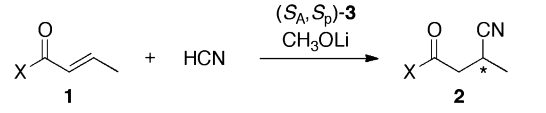
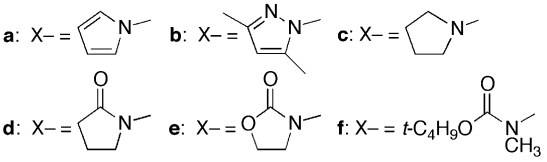
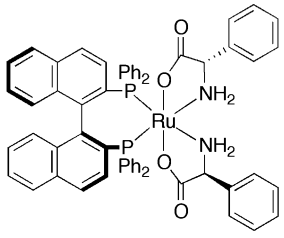
Table 1. Enantioselective Conjugate Cyanation of α,β-Unsaturated Carboxylic Acid Derivatives 1[a]







(SA,Sp)-3

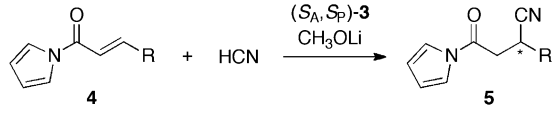
entry	1	S/C[b]	solvent[c]	temp, °C	time, h	% yield[d]	% ee[e]
1	**1a**	500	TBME	25	2	98	88 (*S*)
2	**1a**	500	CPME	25	2	98	82 (*S*)
3	**1a**	500	Et_2O	25	2	98	55 (*S*)
4	**1a**	500	toluene	25	2	<1	nd[f]
5	**1a**	500	TBME	0	12	97	91 (*S*)
6[g]	**1a**	500	TBME	0	12	88	91 (*S*)
7	**1a**	500	TBME	−20	25	96 (94)	96 (*S*)
8	**1b**	200	TBME	0	15	44 (43)	93
9	**1c**	200	TBME	0	12	<1	nd[f]
10	**1d**	200	TBME	0	24	>99 (92)	61
11	**1e**	200	TBME	0	24	99	81
12	**1e**	200	TBME	−20	48	98 (94)	92 (*S*)
13	**1f**	200	TBME	0	24	43	53

[a]Unless otherwise stated, the reactions were carried out using **1** (1.0 mmol) and HCN (1.5 mmol) in solvent (6 mL) with (S_A,S_P)-**3** and CH_3OLi (**3**/CH_3OLi = 1:1). HCN was prepared in situ from $(CH_3)_3SiCN$ and CH_3OH in a 1:1 ratio. [b]Substrate/catalyst (**3**) molar ratio. [c]TBME: *t*-$C_4H_9OCH_3$. CPME: *cyclo*-$C_5H_9OCH_3$. [d]Determined by GC or ^1H NMR analysis. The isolated yield is stated in parentheses. [e]Determined by chiral GC or HPLC analysis. The absolute configuration is given in parentheses. [f]Not determined. [g]Isolated HCN was used.

smoothly with better enantioselectivity (entry 11). The ee value of **2e** reached 92% in the reaction at −20 °C (entry 12). The linear analogue, *N*-acylcarbamate **1f**, showed moderate reactivity and enantioselectivity (entry 13).

Thus, we selected the α,β-unsaturated *N*-acylpyrroles **4** to examine the substrate scope for the asymmetric conjugate hydrocyanation catalyzed by the Ru[(*S*)-phgly]$_2$[(*S*)-binap][(S_A,S_P)-**3**]−CH_3OLi combined system in *t*-$C_4H_9OCH_3$. The results are summarized in Table 2. The hydrocyanation of the *N*-acylpyrrole derived from (*E*)-2-hexenoic acid **4a** (R = *n*-C_3H_7) with an S/C of 500 at −20 °C completed in 27 h to afford the β-cyano product (*S*)-**5a** in 97% ee (entry 1). The degree of enantioselectivity was comparable to that in the reaction of **1a** (R = CH_3; see Table 1, entry 7). The phenylethyl analogue **4b** reacted somewhat slowly, but it maintained the high enantioselectivity (entry 2). The cyanation of substrates with a secondary or tertiary alkyl group at the β-position, **4c** and **4d**, gave the products at around 90% ee (entries 3 and 4). The high reactivity of **4d** achieved complete conversion in this reaction with an S/C of 2000 at −20 °C in 72 h (entry 5). The ee value of **5d** reached >99% in the cyanation at −40 °C (entry 6). The β-aryl substrate **4e** reacted slowly with moderate enantioselectivity (entry 7).

Table 2. Enantioselective Conjugate Hydrocyanation of α,β-Unsaturated *N*-Acylpyrroles 4[a]



a: R = *n*-C_3H_7
b: R = $(CH_2)_2C_6H_5$
c: R = *cyclo*-C_6H_{11}
d: R = $C(CH_3)_3$
e: R = C_6H_4-4-Cl
f: R = $(CH_2)_2CO_2CH_3$
g: R = $CH_2N(CH_3)CO_2$-*t*-C_4H_9
h: R = $CH_2OCH_2C_6H_5$
i: R = $CH(OCH_3)_2$
j: R = CH_2Cl

entry	4	S/C[b]	temp, °C	time, h	% yield[c]	% ee[d]
1	**4a**	500	−20	27	>99 (91)	97 (*S*)
2	**4b**	500	−20	24	91 (88)	96 (*S*)
3	**4c**	500	−20	34	>99 (97)	88
4	**4d**	500	−20	22	>99 (99)	91
5	**4d**	2000	−20	72	>99 (95)	88
6	**4d**	500	−40	72	>99 (94)	>99
7	**4e**	50	25	48	61 (55)	41
8	**4f**	500	0	24	66 (40)	98
9	**4g**	250	0	13	>99 (86)	93
10	**4h**	500	−20	24	>99 (99)	92
11	**4i**	250	0	18	>99 (90)	88
12	**4j**	200	−20	16	94 (93)	88

[a]Unless otherwise stated, the reactions were carried out using substrates (0.5−1.0 mmol) and HCN (1.5 equiv) in *t*-$C_4H_9OCH_3$ with (S_A,S_P)-**3** and CH_3OLi (**3**/CH_3OLi = 1:1). HCN was prepared in situ from $(CH_3)_3SiCN$ and CH_3OH in a 1:1 ratio. [b]Substrate/catalyst (**3**) molar ratio. [c]Determined by GC or ^1H NMR analysis. The isolated yield is stated in parentheses. [d]Determined by chiral GC or HPLC analysis. The absolute configuration is given in parentheses.

The reactivity of the heterosubstituted unsaturated *N*-acylpyrroles seems to be highly dependent on the features of the functional groups. The *N*-acylpyrrole with an ester group **4f** exhibited excellent enantioselectivity of 98% at 0 °C with a modest reaction rate (Table 2, entry 8). The cyanation of **4g** bearing a carbamate functional group with an S/C of 250 at 0 °C completed in 13 h to afford the β-adduct in 93% ee (entry 9). The benzyl ether **4h** showed high reactivity and enantioselectivity comparable to those of the β-alkyl substrates (entry 10). The dimethoxy or chloro substituent led to a decrease in the reaction rate, but the desired products **5i** and **5j** were both obtained in ≥94% yield and in 88% ee under the appropriate conditions (entries 11 and 12).

We previously reported that the ruthenium complex **3** couples with a lithium alkoxide or lithium halide to form the Ru−Li combined species [Li{Ru(phgly)$_2$(binap)}]$^+$ ([Li(**3**)]$^+$) in the solution phase.[14,16] This species appears to act as a Lewis acidic catalyst for the hydrocyanation. A single-crystal X-ray analysis of [Li{(S_A,S_P)-**3**}]Br revealed that the lithium cation interacts with the carbonyl oxygen of PhGly, and the bromide locates between two nitrogens of PhGlys, probably due to hydrogen bonds with the amino protons of the coordinated amino groups (see the Supporting Information).[17]

A plausible reaction pathway incorporating these observations is shown in Scheme 1. CH_3OLi reacts with HCN to give

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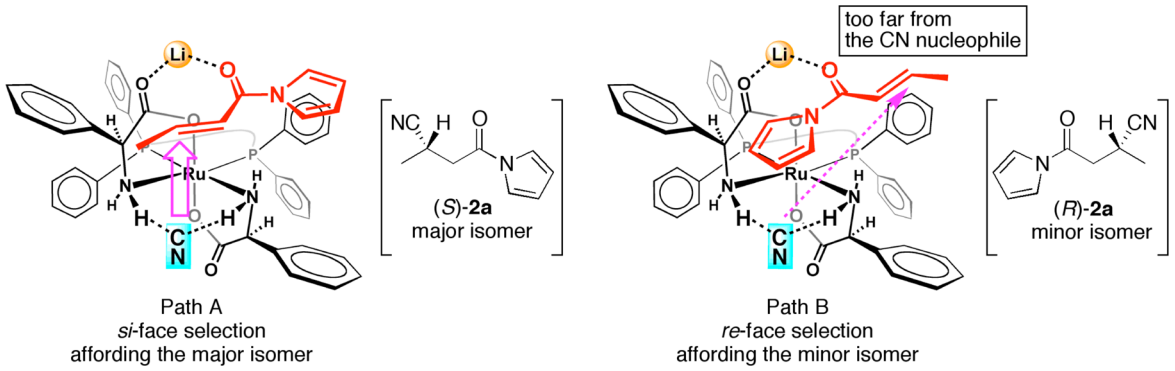
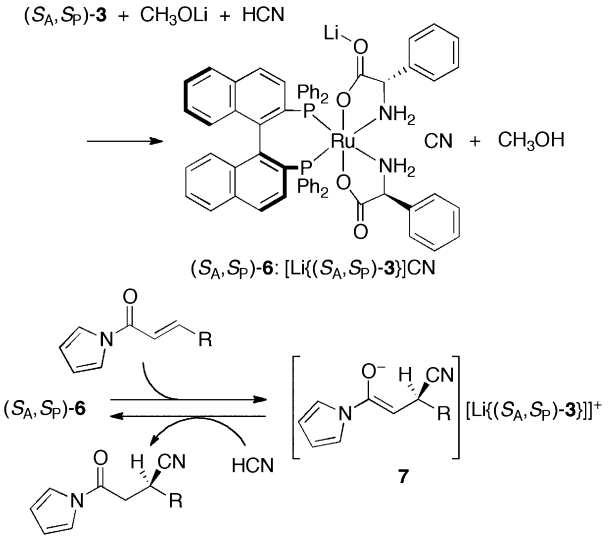


Figure 1. Molecular models for enantioselection in the conjugate cyanation of **1a** with the chiral Ru–Li combined catalyst (S_A,S_P)-**6**.

Scheme 1. Plausible Reaction Pathway of the Asymmetric Conjugate Hydrocyanation of *α,β*-Unsaturated *N*-Acylpyrroles



LiCN and CH_3OH. Complexation of (S_A,S_P)-**3** with LiCN forms the bimetallic cyanide species $[Li\{(S_A,S_P)\text{-}3\}]CN$ ((S_A,S_P)-**6**), which catalyzes the conjugate hydrocyanation. (S_A,S_P)-**6** reacts smoothly with the *α,β*-unsaturated *N*-acylpyrrole to afford the enolate of the *β*-cyano ketone with the bimetallic countercation **7**. Spontaneous protonation of **7** with HCN results in the desired *β*-adduct and regenerates the catalyst (S_A,S_P)-**6**.

We propose the mode of enantioselection in the cyanation of the *N*-acylpyrrole **1a** catalyzed by (S_A,S_P)-**6** resulting in (*S*)-**2a** as shown in Figure 1. The structure of **6** is drawn based on the X-ray-determined structure of $[Li\{(S_A,S_P)\text{-}3\}]Br$,[17] in which the Li cation interacts with the carbonyl oxygen of PhGly and the cyanide is located between two amino protons interacting with the hydrogen bonds. The unsaturated *N*-acylpyrrole **1a** is activated by the Lewis acidic lithium cation moiety of the catalyst **6**. Thus, addition of cyanide at the *β*-position of **1a** proceeds through Path A or Path B to afford enantiomers of **2a** in opposite configurations.[18] The reaction through path A proceeds smoothly because the cyanide and the *β*-position of **1a** are in close proximity. On the other hand, the *β*-position of **1a** is located too far from the cyanide to perform the smooth reaction through Path B. Therefore, (*S*)-**2a** is predominantly produced via the *si*-face selective Path A.

In summary, we have examined asymmetric conjugate hydrocyanation of *α,β*-unsaturated carboxylic acid derivatives catalyzed by the $Ru(phgly)_2(binap)$–CH_3OLi system. Among them, the *N*-acylpyrrole gave the best result in terms of reactivity and enantioselectivity. A series of substrates with alkyl or heterosubstituted alkyl groups at the *β*-position reacted with an S/C of 200–2000 to yield the *β*-cyano products in the range of 88%–>99% ee. The reaction pathway and the mode of enantioselection in this conjugate addition were also proposed.

■ ASSOCIATED CONTENT

Supporting Information

Procedures for asymmetric conjugate hydrocyanation of *α,β*-unsaturated carboxylic acid derivatives, NMR, GC, and HPLC behavior of products, together with $[\alpha]_D$ values (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) The coordinating solvents on the lithium cation may affect the conformation of the reaction models.

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