

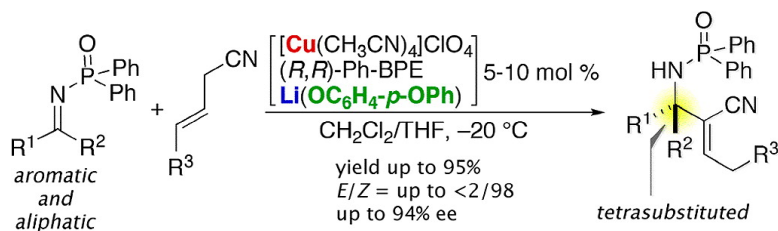
Communication

## Direct Catalytic Asymmetric Addition of Allylic Cyanides to Ketoimines

Ryo Yazaki, Tatsuya Nitabaru, Naoya Kumagai, and Masakatsu Shibasaki

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## Direct Catalytic Asymmetric Addition of Allylic Cyanides to Ketoimines

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Catalytic enantioselective construction of a chiral tetrasubstituted carbon center through an intermolecular C–C bond-forming reaction remains an intriguing challenge in modern organic synthesis.<sup>1</sup> Catalytic asymmetric additions to ketoimines<sup>1c</sup> using active organosilicon or organometallic nucleophiles, e.g., TMSCN,<sup>2</sup> allylboronates,<sup>3</sup> enol silyl ethers,<sup>4</sup> and dialkylzinc,<sup>5</sup> were recently developed as a new entry in this category. The formation of a C–C bond via proton transfer through catalytic generation of nucleophiles from otherwise inactive pronucleophiles, however, is an obviously more advantageous protocol<sup>6</sup> that has been rarely explored in this class of reactions except for HCN<sup>2a,7</sup> or highly active  $\alpha$ -alkoxycarbonyl-ketoimines.<sup>8</sup> Diastereoselective or racemic direct addition of nitroalkanes to ketoimines has been outlined via proton transfer conditions.<sup>9</sup> In this context, our particular interest was directed toward asymmetric addition of nitrile pronucleophiles to ketoimines because (1) nitriles are readily available and stable enough to allow easy handling; (2) their unique topology poses minimal steric bias, making them well suited to the highly congested transition state with ketoimines; and (3) they can be viewed as a masked carboxylic acid derivative or amine, which promises diverse transformation of the reaction product (Figure 1). Herein, we report a direct catalytic asymmetric addition of allylic cyanides to *N*-diphenylphosphinoyl (Dpp) ketoimines, affording  $\alpha,\beta$ -unsaturated nitriles with a stereogenic tetrasubstituted carbon. An exquisite combination of a soft Lewis acid and an alkali metal aryloxide enables the catalytic generation of an active nitrile nucleophile and the subsequent addition to *N*-Dpp ketoimines.

Despite the versatility of nitrile functionality from a synthetic standpoint,<sup>10</sup> its inertness toward deprotonation hampers the catalytic generation of nucleophiles from alkylnitriles.<sup>11</sup> We identified allylic cyanides as a viable pronucleophile bearing an  $\alpha$ -proton with reasonable acidity ( $pK_a = 21.1$  in DMSO)<sup>12</sup> that is suitable for achieving catalyst turnover via proton transfer.<sup>13</sup> In the reaction of *N*-Dpp ketoimine<sup>1c,14</sup> **1a** and allyl cyanide (**2a**),<sup>15</sup> initial attempts were performed with 10 mol % each of soft Lewis acidic metal and (*S,S*)-*i*-Pr-DuPHOS in combination with lithium *p*-methoxyphenoxide as the base (Table 1, entries 1–3). CuOAc promoted the  $\alpha$ -addition sluggishly at 0 °C in THF, and the  $\alpha$ -adduct rapidly isomerized to give  $\alpha,\beta$ -unsaturated nitrile **3aa** in 59% yield and 33% ee with almost exclusive geometric control.<sup>16</sup> The yield was diminished by the partial deamination reaction of the intermediary  $\alpha$ -adduct to give the undesired diene. Although the cationic Pd(II) and Ag(I) complex failed the reaction, the cationic Cu(I) complex exhibited an enhanced catalytic activity, allowing the reaction at –20 °C to reach 65% ee (entry 5). [Cu(CH<sub>3</sub>CN)<sub>4</sub>]ClO<sub>4</sub> was identified as the best Cu source and at –20 °C afforded **3aa** in 95% yield and 53% ee (entry 6). The use of Ph-BPE<sup>17</sup> and CH<sub>2</sub>Cl<sub>2</sub>/THF

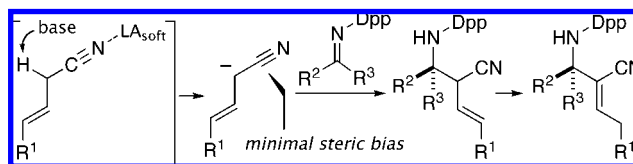
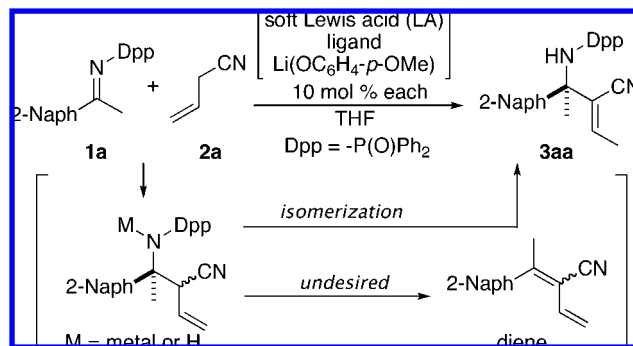
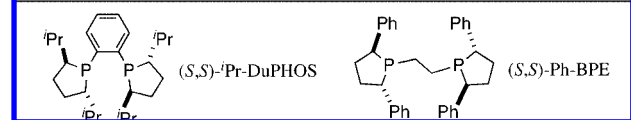


Figure 1. Exploitation of allylic cyanides as nucleophiles.

Table 1. Initial Screening<sup>a</sup>



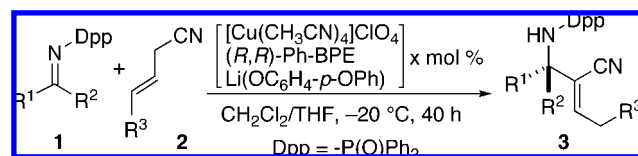
entry	LA	ligand	temp. (°C)	time (h)	yield <sup>b</sup> (%)	ee (%)
1	CuOAc	( <i>S,S</i> )- <i>i</i> -Pr-DuPHOS	0	16	59 <sup>c</sup>	33
2	[Cu(CH <sub>3</sub> CN) <sub>4</sub> ]PF <sub>6</sub>	( <i>S,S</i> )- <i>i</i> -Pr-DuPHOS	0	16	83 <sup>c</sup>	37
3	[Pd(CH <sub>3</sub> CN) <sub>4</sub> ](BF <sub>4</sub> ) <sub>2</sub>	( <i>S,S</i> )- <i>i</i> -Pr-DuPHOS	0-rt	24	<5	—
4	[Ag(CH <sub>3</sub> CN) <sub>4</sub> ]BF <sub>4</sub>	( <i>S,S</i> )- <i>i</i> -Pr-DuPHOS	0-rt	24	0	—
5	[Cu(CH <sub>3</sub> CN) <sub>4</sub> ]PF <sub>6</sub>	( <i>S,S</i> )- <i>i</i> -Pr-DuPHOS	–20	16	67	65
6 <sup>d</sup>	[Cu(CH <sub>3</sub> CN) <sub>4</sub> ]ClO <sub>4</sub>	( <i>S,S</i> )- <i>i</i> -Pr-DuPHOS	–20	16	95	53
7 <sup>d</sup>	[Cu(CH <sub>3</sub> CN) <sub>4</sub> ]ClO <sub>4</sub>	( <i>S,S</i> )-Ph-BPE	–20	16	95	86
8 <sup>d,e</sup>	[Cu(CH <sub>3</sub> CN) <sub>4</sub> ]ClO <sub>4</sub>	( <i>S,S</i> )-Ph-BPE	–20	12	50	73
9 <sup>d,f</sup>	[Cu(CH <sub>3</sub> CN) <sub>4</sub> ]ClO <sub>4</sub>	( <i>S,S</i> )-Ph-BPE	–20	12	<5	84



<sup>a</sup> **1a/2a** = 0.2 mmol/2.0 mmol. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis with Bn<sub>2</sub>O as an internal standard. <sup>c</sup> The formation of diene was observed. <sup>d</sup> Solvent was CH<sub>2</sub>Cl<sub>2</sub>/THF = 2/1. <sup>e</sup> Na(OC<sub>6</sub>H<sub>4</sub>-*p*-OMe) was used instead of Li(OC<sub>6</sub>H<sub>4</sub>-*p*-OMe). <sup>f</sup> K(OC<sub>6</sub>H<sub>4</sub>-*p*-OMe) was used instead of Li(OC<sub>6</sub>H<sub>4</sub>-*p*-OMe).

solvent further improved the enantioselectivity to 86% ee (entry 7). Despite the marginal difference in enantioselectivity, the use of Na or K aryloxide instead of Li(OC<sub>6</sub>H<sub>4</sub>-*p*-OMe) resulted in inferior conversion, likely due to variable stability of the bimetallic system (entries 8,9).

The substrate generality of the present protocol is summarized in Table 2. The use of Li(OC<sub>6</sub>H<sub>4</sub>-*p*-OPh) instead of Li(OC<sub>6</sub>H<sub>4</sub>-

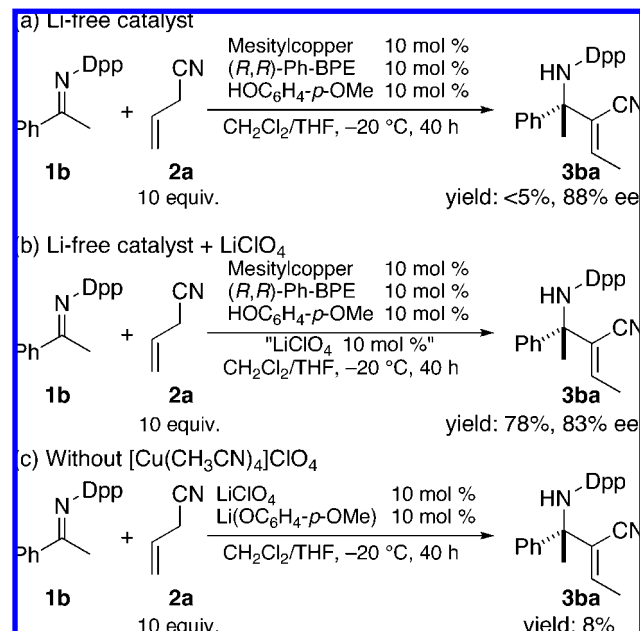
Table 2. Substrate Generality<sup>a</sup>

entry	ketoimine	allylic cyanide	x	product	yield <sup>b</sup> (%)	<i>E/Z</i> <sup>c</sup>	ee (%)
1 <sup>d</sup>			10	<b>3aa</b>	91	7/93	90 <sup>f</sup>
2			10	<b>3ba</b>	74	9/91	91
3			10	<b>3ca</b>	95	11/89	89
4			5	<b>3ca</b>	88	12/88	83
5 <sup>e</sup>			10	<b>3ca</b>	71	10/90	94
6 <sup>d</sup>			10	<b>3da</b>	84	5/95	77 <sup>f</sup>
7			10	<b>3ea</b>	78	6/94	90
8			10	<b>3fa</b>	83	3/97	88
9			10	<b>3ga</b>	63	8/92	71
10 <sup>f</sup>			10	<b>3ha</b>	76	<2/98	92
11 <sup>f</sup>			10	<b>3ia</b>	80	4/96	89
12 <sup>g</sup>			10	<b>3cb</b>	62 <sup>h</sup>	<2/98	90

<sup>a</sup> **1/2** = 0.2 mmol/2.0 mmol, CH<sub>2</sub>Cl<sub>2</sub>/THF = 2/1. <sup>b</sup> Isolated yield of *E* and *Z* geometrical isomers. <sup>c</sup> Determined by <sup>1</sup>H NMR analysis of the crude mixture. <sup>d</sup> (*S,S*)-Ph-BPE was used. <sup>e</sup> 3 equiv (0.6 mmol) of **2a** were used. <sup>f</sup> The reaction was conducted at 0.5 M in THF. Li(OC<sub>6</sub>H<sub>4</sub>-*p*-OMe) was used instead of Li(OC<sub>6</sub>H<sub>4</sub>-*p*-OPh). <sup>g</sup> Reaction time was 60 h. <sup>h</sup> Isolated yield after two steps ( $\alpha$ -addition/isomerization by DBU). <sup>i</sup> Opposite absolute configuration.

*p*-OMe) marginally impacted the asymmetric environment to improve the enantioselectivity, albeit with a slight detrimental effect on the reaction rate. The reaction of aryl methyl ketoimines (**1a–1d**) proceeded smoothly to give isomerized  $\alpha$ -adducts **3aa–3da** in high yield and enantioselectivity (entries 1–6). The catalyst loading could be reduced to 5 mol % without significant loss of ee (entry 4). The reaction could be conducted with 3

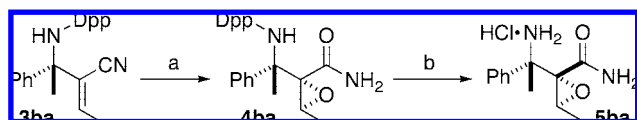
Scheme 1. Control Experiments



equiv of **2a**, affording the product **3ca** in acceptable yield with excellent ee (entry 5). Ketoimines with heteroaromatics were suitable substrates exhibiting high *E/Z* selectivity and ee (entries 7,8). Attenuated reactivity and ee were observed with ketoimines derived from ethyl ketone, due to the enhanced steric congestion and more severe enantiodifferentiation (entry 9). High *E/Z* and enantioselectivity were observed in the reaction with aliphatic ketoimines (entries 10, 11). Allylic cyanide with alkyl substituent **2b** required an extended reaction time to give diastereomeric  $\alpha$ -adducts, which isomerized to afford **3cb** with high *E* selectivity upon treatment with DBU at room temperature (entry 12).

Next we directed our focus toward the mechanistic aspects of the present catalysis. <sup>1</sup>H NMR and ESI-MS of a 1:1 Ph-BPE/[Cu(CH<sub>3</sub>CN)<sub>4</sub>]ClO<sub>4</sub> mixture indicated the formation of a Ph-BPE/Cu 1:1 complex,<sup>18</sup> which gave Ph-BPE/CuOAr and LiClO<sub>4</sub> upon addition of LiOAr.<sup>19</sup> **2a** would be activated through coordination to Cu and deprotonated by the neighboring aryloxide rather than the alkali metal aryloxide to afford a *C*-bound or *N*-bound active nitrile nucleophile.<sup>20</sup> The cooperative bimetallic catalysis of soft Lewis acid Cu and hard Lewis acid Li is intriguing. An attempted reaction using 10 mol % of Li-free Ph-BPE/Cu(OC<sub>6</sub>H<sub>4</sub>-*p*-OMe) catalyst prepared from mesitylcopper(I), Ph-BPE, and *p*-methoxyphenol provided trace amounts of **3ba** with 88% ee (Scheme 1a).<sup>21</sup> The Li-free catalyst regained catalytic activity upon the addition of 10 mol % of LiClO<sub>4</sub> to afford **3ba** in comparable yield to that obtained under the optimal conditions, suggesting that LiClO<sub>4</sub> generated in situ was essential to drive the reaction efficiently (Scheme 1b).<sup>22</sup> The reaction conditions lacking [Cu(CH<sub>3</sub>CN)<sub>4</sub>]ClO<sub>4</sub> provided only 8% of the product, verifying that soft Lewis acid Cu was required to promote the reaction (Scheme 1c).

The merit of the present protocol is a divergent transformation of product **3**. Here we demonstrated a preliminary transformation into a densely functionalized material (Scheme 2). **3ba** was treated with 30% aqueous hydrogen peroxide under basic conditions to provide epoxyamide **4ba** as a single diastereomer. Exposure of **4ba** to acidic media removed the Dpp group,

Scheme 2. Transformation of the Product<sup>a</sup>

<sup>a</sup> Reaction conditions: (a) 30% H<sub>2</sub>O<sub>2</sub> aq., K<sub>2</sub>CO<sub>3</sub>, DMSO, rt, 16 h, y. 76%; (b) 12N HCl aq., 70 °C, 2 h, y. quant.

affording an optically active  $\beta'$ -amino  $\alpha,\beta$ -epoxyamide **5ba** bearing two contiguous tetrasubstituted carbons.

In conclusion, we developed a direct catalytic asymmetric addition of allylic cyanides to ketoimines. CuOAr furnished with Ph-BPE worked cooperatively with LiClO<sub>4</sub> to render this otherwise less accessible transformation feasible, although a ketoimine derived from ethyl ketone exhibited limited reactivity. Facile and divergent conversion of the product streamlines the synthesis of chiral nitrogen synthons with tetrasubstituted carbon. More detailed mechanistic studies are ongoing.

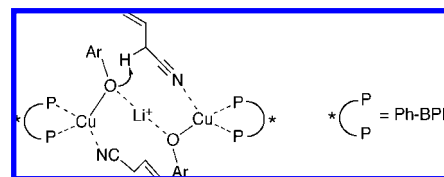
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**Supporting Information Available:** Experimental details and characterization of new compounds. This material is available free of charge via the Internet at <http://www.acs.org>.

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