Asymmetric Cyanation of α-Ketimino Ester Derivatives with Chiral Ru–Li Combined Catalysts

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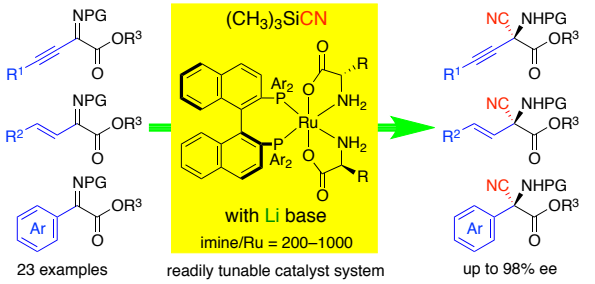
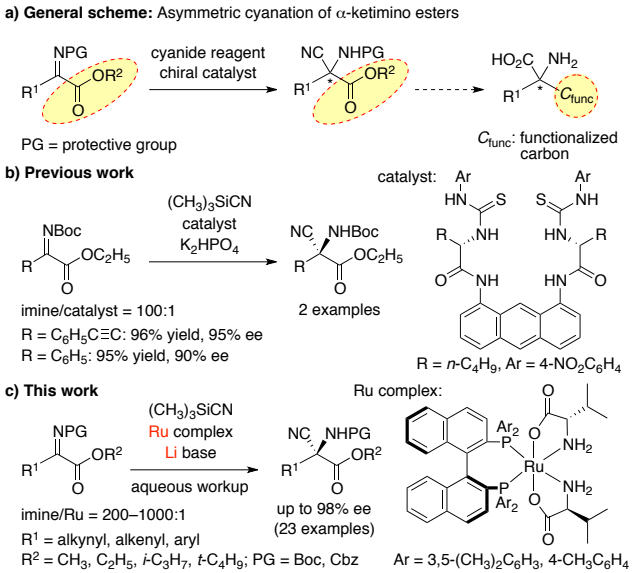


ABSTRACT: Asymmetric cyanation of α-ketimino esters catalyzed by the combined systems of amino acid/BINAP derivative/Ru(II) complexes and lithium compounds was examined. Use of an appropriate combination of amino acid and BINAP ligands achieved high enantioselectivity for a variety of α-alkynyl (Val/XylBINAP/Ru), α-alkenyl (Val/TolBINAP/Ru), and α-aryl imino esters (Val/XylBINAP/Ru) as well as an isatin-derived cyclic imino amide (*t*-Leu/BINAP/Ru) to afford the α-cyano-α-amino esters and the amide with an α-nitrogen-substituted quaternary chiral center in up to 98% ee.

Optically active α,α-disubstituted α-amino acids are key components found in various natural products and medicinally important compounds.[1] Introduction of these quaternary amino acids into peptides leads to an increase in their chemical and metabolic stability while also influencing their conformations and flexibility, and thus this approach has made a substantial contribution to research on peptidomimetics.[2] The development of asymmetric reactions to produce this class of compounds with nitrogen-substituted quaternary carbons is therefore a challenging and urgent synthetic topic. Enantioselective cyanation of ketimines affords chiral α,α-disubstituted α-aminonitriles, which are reliable precursors of the corresponding amino acids.[3] Several useful chiral catalysts have been reported for this reaction. Various unfunctionalized ketimines, such as alkyl aryl imines and alkyl alkenyl imines, are reacted in high enantioselectivity.[4] However, this transformation has rarely been applied to the synthesis of the optically active functionalized amino acids, including α-substituted serines, cysteines, and α,β-diamino acids.[5] Enantioselective cyanation of α-ketimino esters affording optically active α-cyano-α-amino esters is a promising method for this purpose (Scheme 1a). Recently, the cyanation of *N*-Boc-protected α-imino esters with a chiral bisthiourea-based catalyst was reported (Scheme 1b).[6] A high enantioselectivity (up to 95% ee) was obtained, but only two substrates were examined. Therefore, development of enantioselective cyanation of α-ketimino esters to realize a wider substrate scope would be highly desirable.

We have studied asymmetric cyanation of aldehydes, ketones, and aldimines, as well as conjugate cyanation of α,β-

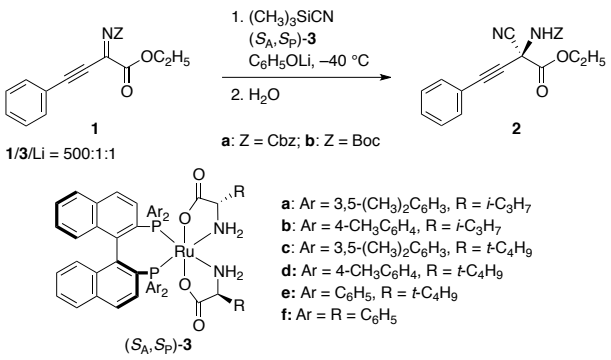
Scheme 1. Asymmetric cyanation of α-ketimino esters



unsaturated carbonyl compounds, using our original chiral Ru complex–Li compound combined catalyst systems.[7,8] The enantioselective cyanation occurs in the chiral template formed by the Ru complex coordinating to the Lewis acidic Li cation. The corresponding cyanated products were obtained in high ee. We herein report the enantioselective cyanation of α-ketimino esters catalyzed by the amino acid/BINAP derivative/Ru(II) complexes combined with a Li compound (Scheme 1c). A variety of the alkynyl-, alkenyl-, and aryl-substituted α-imino esters as well as an isatin-derived cyclic imino amide were converted to the α-cyano-α-amino ester derivatives in high ee.

We selected an α-alkynyl-α-imino ester **1a** as a standard substrate for screening of the catalyst structure and reaction conditions due to the versatility of alkynyl groups, which can be converted to a variety of functional groups through Pauson–Khand reaction, enyne cycloisomerization, heterocyclization, etc.[9] The chiral amino-acid motifs derived from **2** are expected to be readily bound onto the natural and artificial molecular architectures by means of the click azide–alkyne cycloadditions.[10] Ru[(*S*)-val]$_2$[(*S*)-xylbinap] ((S_A,S_P)-**3a**) was prepared according to the method for the related complexes described in our previous reports.[8,11] The reaction of imino ester **1a** and $(CH_3)_3SiCN$ with (S_A,S_P)-**3a** and C_6H_5OLi (THF solution, **1a**/**3a**/Li = 500:1:1) in *tert*-$C_4H_9OCH_3$ (TBME) at –40 °C was completed in 24 h to afford the α-alkynyl-α-cyano-α-amino ester **2a** in 95% ee quantitatively after a workup with water (Table 1, entry 1). The alkynyl moiety was left intact.

Table 1. Asymmetric cyanation of α-imino esters 1[a]



entry	1	3	time, h	% yield[b]	% ee[c]
1	**1a**	**3a**	24	99	95
2	**1a**	**3b**	4	97	89
3	**1a**	**3c**	24	69	88
4	**1a**	**3d**	24	96	95
5	**1a**	**3e**	4	82	91
6	**1a**	**3f**	4	94	60
7	**1b**	**3a**	24	96	96
8[d]	**1b**	**3a**	48	82	97
9[e,f]	**1b**	**3a**	24	98	92

[a] Unless otherwise stated, reactions were conducted at –40 °C using **1** (0.5 mmol) and $(CH_3)_3SiCN$ (2.0 mmol) in TBME (6 mL) with a solid (S_A,S_P)-**3** and C_6H_5OLi (20 mM in THF). The reaction was quenched with water. [b] Yield of isolated **2**. [c] Determined by HPLC on a chiral stationary phase. [d] Reaction conducted at –78 °C (**1**/**3**/Li = 200:1:1). [e] Reaction conducted at 0 °C (**1**/**3**/Li = 1000:1:1). [f] Reaction using 1.0 mmol of **1**.

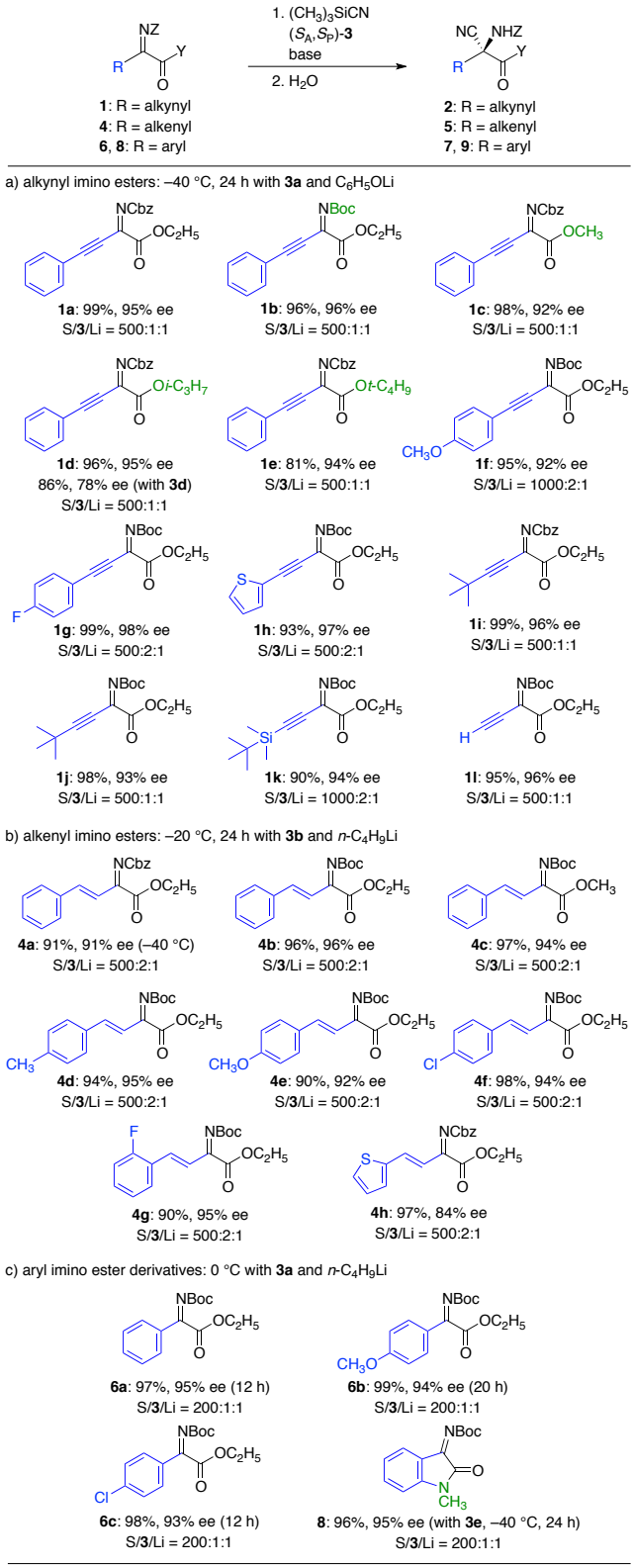
Appropriate combination of amino acid and diphosphine ligands in the Ru complexes **3** was important to achieve high catalyst performance (entries 2–6).[11,12] Thus, the (*S*)-Val/(*S*)-TolBINAP/Ru complex **3b** showed lower enantioselectivity (entry 2). Moderately stereo-demanding (*S*)-TolBINAP matched well with the bulky (*S*)-*t*-Leu ligand (Ru complex **3d**), resulting in high enantioselectivity (entry 4). To our surprise, the use of the (*S*)-PhGly/(*S*)-BINAP/Ru complex **3f**, which exhibits excellent performance in the asymmetric cyanation of aldehydes, ketones, and aldimines, resulted in a low product ee of 60% (entry 6).[7,8] Comparable enantioselectivity of 96% at –40 °C was obtained by using the ethyl 2-(*N*-Boc)imino ester **1b** with the **3a**/C_6H_5OLi system (entry 7). The ee value of **2b** was increased to 97% at –78 °C at the cost of the reaction rate (entry 8). The reaction with a **1b**/**3a**/C_6H_5OLi molar ratio of 1000:1:1 at 0 °C was completed in 24 h to afford **2b** in 92% ee (entry 9).

The catalytic cyanation was successfully applied to a variety of α-substituted α-ketimino esters by tuning the reaction conditions and the catalyst structure (Scheme 2). The substrate/Ru complex **3** molar ratio (S/**3**) was set at 200–500. The reaction of α-alkynyl imino esters **1** was catalyzed by the Ru complex **3a**/C_6H_5OLi system (substrate/**3a**/Li molar ratio (S/**3a**/Li) = 500–1000:1 or 2:1) at –40 °C for 24 h to afford the cyanated products **2** in 92%–98% ee without damage at the alkynyl moiety (Scheme 2a). The structure of the alkoxycarbonyl part was not highly influential (**1c**–**1e**). When the reaction of **1d** was conducted with the Ru complex **3d**, the ee value of the product was significantly lowered. In some cases, a 1:1 **3a**/C_6H_5OLi system gave products with less than 90% ee, probably due to the influence of achiral cyanation catalyzed by free C_6H_5OLi. Fortunately, the enantioselectivity was increased by setting the **3a**/C_6H_5OLi ratio at 2:1. Thus, α-phenylethynyl imines bearing 4-CH_3O (EDG) and 4-F (EWG) groups, **1f** and **1g**, were quantitatively cyanated with high enantioselectivity of 92% and 98%, respectively. Introduction of a thienyl ring to the substrate was permitted in this reaction (**1h**). Non-aromatic *t*-C_4H_9- (**1i**, **1j**) or *t*-$C_4H_9(CH_3)_2Si$- (**1k**) substituted compounds were also appropriate substrates affording the desired products in high ee. Notably, the terminal alkynyl imino ester **1l** was quantitatively converted to the cyanated product **2l** in 96% ee. No conjugate addition compound was observed.

For the reaction of α-(*E*)-(2-phenyl)ethenyl imino esters **4a**–**4c**, a catalyst system of (*S*)-Val/(*S*)-TolBINAP/Ru complex **3b** with *n*-C_4H_9Li (20 mM in hexane) (**4**/**3b**/Li = 500:2:1, –20 or –40 °C) achieved the highest enantioselectivity (Scheme 2b). The *N*-Boc imine with ethyl ester **4b** was quantitatively converted to the cyanated product **5b** in 96% ee. Use of C_6H_5OLi (20 mM in THF) instead of *n*-C_4H_9Li decreased the ee value, possibly due to contamination of THF. The reaction of 4-CH_3, 4-CH_3O, 4-Cl, or 2-F substituted phenylethenyl imino esters, **4d**–**4g**, successfully yielded the products in 92%–95% ee regardless of the electronic properties and positions of substituents. The *N*-Cbz imino ester with thienyl ring **4h** was converted in slightly lower enantioselectivity, although the yield was high. The corresponding *N*-Boc imine could not be prepared in pure form.

The α-aryl imino esters **6** were also appropriate substrates for this reaction (Scheme 2c). Ru complex **3a** provided the most enantioselective environment. The reactivity was lower

Scheme 2. Asymmetric cyanation of α-imino ester derivatives catalyzed by Ru–Li combined systems



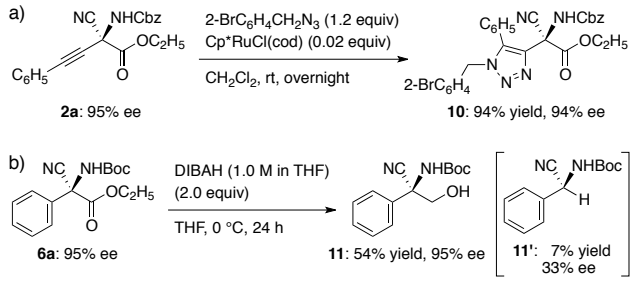
than that of the α-alkynyl and α-alkenyl imino esters, so that the reaction was carried out with a **6**/**3a**/*n*-C_4H_9Li ratio of 200:1:1 at 0 °C. The α-phenyl-substituted product **7a** was quantitatively obtained in 95% ee. Increasing the molar ratio of **3a**/*n*-C_4H_9Li did not significantly affect the selectivity in this case. The imino esters with 4-CH_3O and 4-Cl substituents on the phenyl rings, **6b** and **6c**, were also converted to **7b** and **7c** in high ees.

An isatin-derived cyclic imino amide **8** was quantitatively cyanated with the (*S*)-*t*-Leu/(*S*)-BINAP/Ru complex **3e** and *n*-C_4H_9Li catalyst system (**8**/**3e**/Li = 200:1:1) at –40 °C for 24 h to afford the product **9** in 95% ee.[6,13] The ee value was decreased to 85% by using C_6H_5OLi as a co-catalyst. The **3a**/C_6H_5OLi catalyst system was inappropriate for this reaction (69% ee). Optically active 3-substituted 3-amino-2-oxindols are an important class of structures found in many biologically active compounds.[14]

Cycloaddition of the α-alkynyl-substituted compound **2a** with 2-bromobenzyl azide was catalyzed by a Ru complex to afford selectively the 1,2,3-triazole **10** in high yield (Scheme 3a).[15] The regioisomer was not observed at all. The structure of racemic **10** was determined by a single crystal X-ray analysis.

The ethoxycarbonyl-selective reduction over the cyano group of the compound **6a** was done by using DIBAH in THF to give the alcoholic product **11** (Scheme 3b). Selection of the reducing agent and the solvent was crucial to obtain **11** selectively. Use of $LiAlH_4$, $NaAlH_2(OC_2H_4OCH_3)_2$, or $NaBH_4$ as a reagent mainly yielded the decarboxylated product **11'**. Unexpectedly, deprotection of the Boc group of **11** under usual acidic conditions was not accomplished, affording decomposed compounds.

Scheme 3. Transformations of the cyanated products



We previously reported that the Ru complex (S_A,S_P)-**3** and a lithium compound in the presence of $(CH_3)_3SiCN$ forms the Ru–Li combined species [Li{(S_A,S_P)-**3**}]CN ((S_A,S_P)-**12**) in which the lithium cation interacts with the carbonyl oxygen of the amino acid ligand, and the cyanide locates between the two amino groups of the ligands (Scheme 4).[7,8] The structure of [Li{(S_A,S_P)-**3f**}]Br was determined by a single-crystal X-ray analysis.[7,8b] The Ru–Li combined complex (S_A,S_P)-**12** is proposed as the catalyst of this reaction, as shown in Scheme 4. The cyanide is smoothly transferred from (S_A,S_P)-**12** to the imino ester forming the amino nitrile anion with the bimetallic counter cation $[Li\{(S_A,S_P)\text{-}\mathbf{3}\}]^+$. The anion reacts with $(CH_3)_3SiCN$ to afford the silylated amino nitrile with regeneration of (S_A,S_P)-**12**. The silylated compound is converted to the product by aqueous workup.

The mode of enantioselection in the cyanation of the alkynyl imino ester **1b** catalyzed by (S_A,S_P)-**12** is proposed as shown in Figure 1. The chiral structure of (S_A,S_P)-**12** is illustrated according to the X-ray analysis data of [Li{(S_A,S_P)-**3f**}]Br.[7,8b] The Boc oxygen interacts with the lithium cation of the catalyst, and the electrophilic imino carbon approaches the nucleophilic cyanide fixed by the hydrogen bonds with amino groups on the catalyst in a manner avoiding bulky isopropyl groups of (*S*)-Val ligands. Interestingly, calculation by

Scheme 4. Plausible reaction pathway

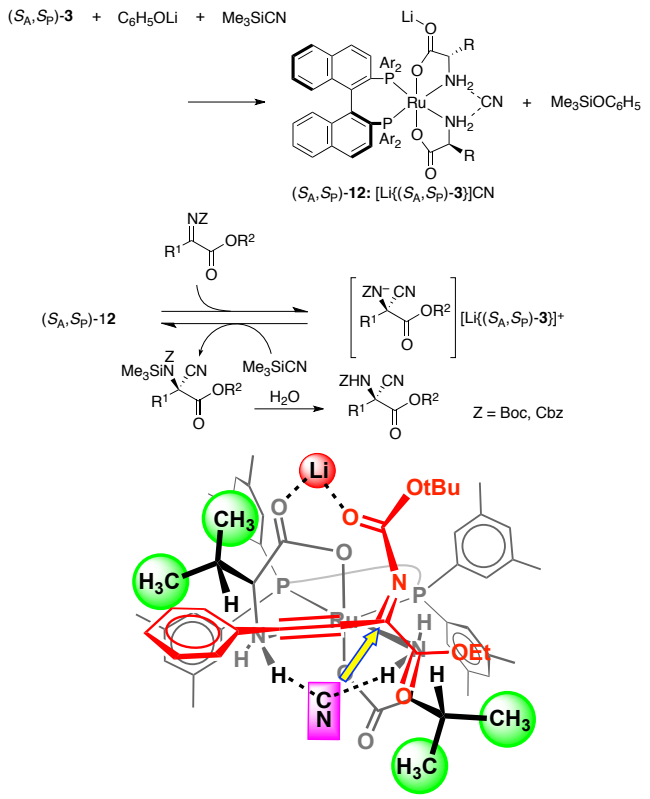


Figure 1. Molecular model for the enantioselection

B3LYP/6-31++G(d,p) suggested that **1b** has a twisted (not a planar) conformation, in which the dihedral angle around C=N–C=O(Boc) was estimated as 86.6° (see Supporting Information for detail). The calculation using the phenyl imino ester **6a** resulted in a similar angle (64.1°). Therefore, **1b** fits well with the chiral template of the catalyst to afford the product (*S*)-**2b** in high enantioselectivity. The major reason to provide the enantiomer (*R*)-**2b** could be the existence of the achiral cyanation catalyzed by free C_6H_5OLi.

In summary, we have reported the efficient asymmetric cyanation of α-ketimino ester derivatives with our original catalyst systems consisting of the amino acid/BINAP derivative/Ru(II) complex and a lithium compound. The reaction was carried out with an imine/Ru complex ratio of 200–500:1 (1000:1 in the best case) under the optimized conditions. The diverse modifiability of the catalyst structure achieved a wide substrate scope. Thus, a variety of α-alkynyl (Val/XylBINAP/Ru), α-alkenyl (Val/TolBINAP/Ru), and α-aryl imino esters (Val/XylBINAP/Ru) as well as an isatin-derived cyclic imino amide (*t*-Leu/BINAP/Ru) were transformed into the α-cyano-α-amino esters and the amide with an α-nitrogen-substituted quaternary chiral center in up to 98% ee by using the Ru–Li catalyst systems with an appropriate combination of amino acid and BINAP ligands.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information Statement

The Supporting Information is available free of charge on the ACS Publications website.
General information, experimental procedures, details of the experiment, spectral, and DFT calculation data (PDF and CIF)

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Notes

The authors declare no competing financial interest.

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