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Nickel-Catalyzed Asymmetric Hydrocyanation of Allenes

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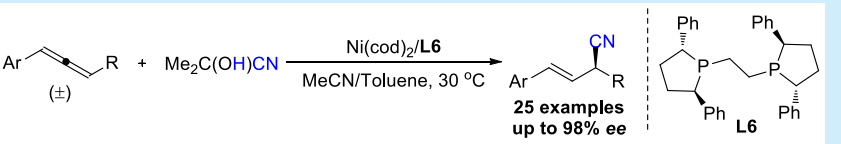

ABSTRACT: The first catalytic enantioselective hydrocyanation of allenes catalyzed by a (*R*,*R*)-Ph-BPE−Ni(0) complex catalyst has been accomplished. Numerous optically active allylic nitriles were obtained in good yield with excellent enantioselectivities (up to 98% *ee*).

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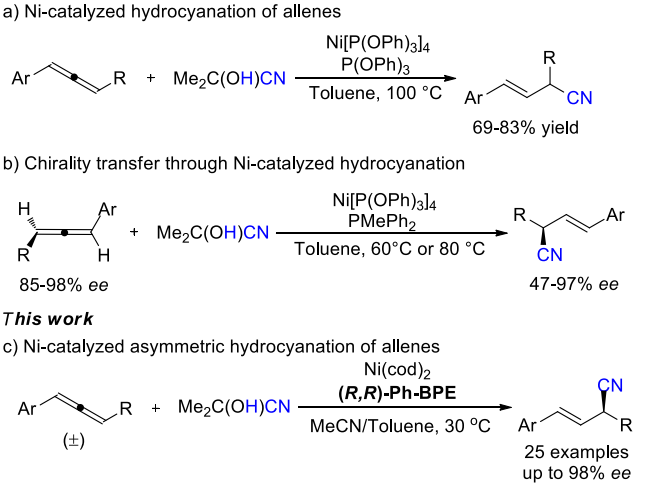
Enantioenriched organonitriles are crucial building blocks in organic synthesis and represent important moieties in diverse natural products and in molecules of medicinal and agrochemical interest.[1] The enantioselective transition-metal-catalyzed hydrocyanation of C−C double bonds is probably the most effective approach for their construction.[2−7] The hydrocyanation of multiple C−C bonds to prepare racemic organonitriles has been well studied.[8,9] The so-called DuPont adiponitrile process, hydrocyanation of 1,3-butadiene to adiponitrile, is a representative example of a successful commercial application in this area.[9] Nonetheless, the access routes to enantiomerically enriched organonitriles by the corresponding asymmetric catalysis have usually been restricted to norbornene, vinylarenes, and 1,3-dienes as prochiral substrates so far.[2]

The transition-metal-mediated asymmetric hydrocyanation of C−C double bonds has occasionally appeared in the literature[3−7] since the pioneering report[3a] from Elmes and Jackson in 1979. Since then, a wide range of novel chiral ligands have emerged and advanced the asymmetric hydrocyanation for the construction of various chiral nitriles.[2] Most notably, a Ni-catalyzed asymmetric hydrocyanation of 2-methoxy-6-vinyl-naphthalene in the presence of carbohydrate-derived diphosphonite ligands was developed by RajanBabu and Casalnuovo in 1992, affording the corresponding nitriles with excellent levels of enantiocontrol.[4a] This catalyst system was also examined in the hydrocyanation of 1-phenyl-1,3-butadiene, providing the desired product with 83% *ee*.[4d] The Vogt group reported the Ni-catalyzed asymmetric hydrocyanation of 1,3-cyclohexadiene in the presence of binaphthol-derived diphosphite ligand, which gives the corresponding product in 45% yield with 86% *ee*.[5b] Recently, Schmalz and coworkers succeeded in identifying a TADDOL-based phosphine−phosphite ligand for the Ni-catalyzed asymmetric hydrocyanation of styrenes with high enantioselectivities (up to 97% *ee*).[6a] Despite these contributions, good enantioselectivities of hydrocyanation have been limited to vinylarenes and 1,3-dienes. The development of new prochiral substrates for the asymmetric hydrocyanation remains desirable.[2]

Allenes are versatile intermediates in organic synthesis owing to the fact that numerous products could be formed through a single transformation from the functionalization of two different C−C double bonds.[10] It should be mentioned that the Arai group made outstanding contributions to the allene hydrocyanation reactions.[10f,11] In 2015, Arai and coworkers described a Ni-catalyzed regio- and stereoselective hydrocyanation of allenes (Scheme 1a).[11d] The key functionalities to

Scheme 1. Ni-Catalyzed Hydrocyanation of Allenes



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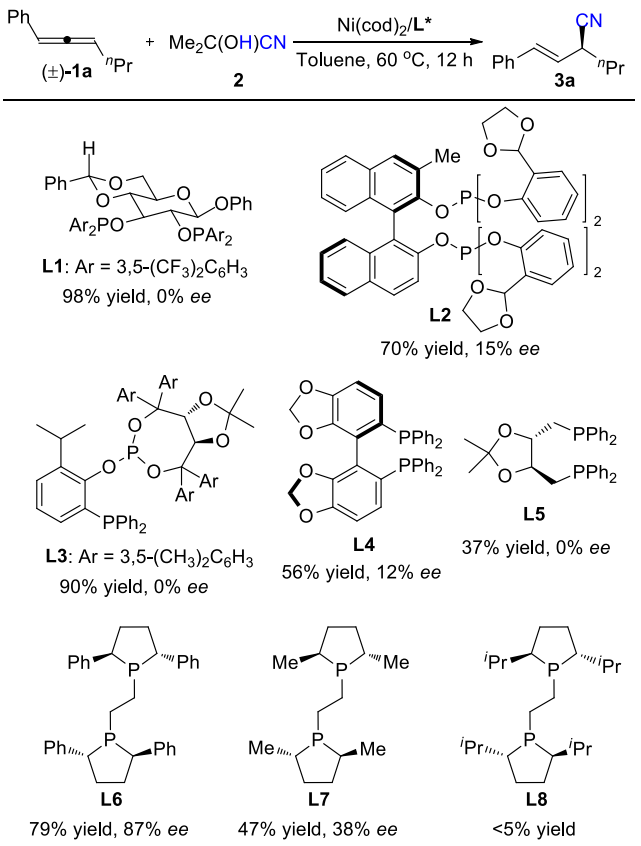
gain high regio- and stereocontrol rely on introducing aryl and cyclopropyl groups in the substrates. Recently, the Arai group managed to transfer the axial chirality of allenes through Ni-catalyzed hydrocyanation, which gives the corresponding chiral carbonitriles with up to 97% *ee* (Scheme 1b).[11f] However, for most substrates, a drastic loss of enantiomeric purity was detected in this transformation. Despite these contributions, the catalytic asymmetric hydrocyanation of allenes toward chiral carbonitrile preparation has not been documented. Therefore, we report herein the first Ni-catalyzed asymmetric hydrocyanation of allenes under mild reaction conditions, affording allyl nitriles with high optical purity (Scheme 1c).

Initially, we investigated the asymmetric hydrocyanation of (±)-**1a** with acetone cyanohydrin (**2**) as a model reaction in the presence of $Ni(cod)_2$ and different chiral phosphorus ligands **L1**–**L8** (Scheme 2). It is worth mentioning that no

Scheme 2. Influence of the Ligand on the Ni-Catalyzed Asymmetric Hydrocyanation of 1a[a]

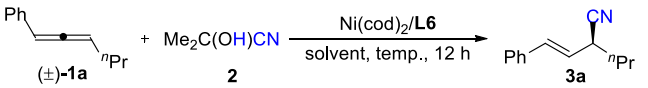


[a]Reactions were carried out at 60 °C for 12 h with (±)-**1a** (0.1 mmol), **2** (0.3 mmol, 3.0 equiv), and toluene (0.3 mL) in the presence of $Ni(cod)_2$ (10 mol %) and ligand (10 mol %). The yields were determined by gas chromatography (GC) analysis using *n*-dodecane as the internal standard. The *ee* values were determined by chiral high-performance liquid chromatography (HPLC) analysis.

conversion was observed in the absence of a ligand. Ligands **L1**–**L3**, which were previously proven to be effective in the asymmetric hydrocyanation reactions, were examined. Very low and even no enantioselectivities were observed, although the desired product **3a** was obtained in high yield. Moreover, commercially available bidentate ligands SEGPhos (**L4**) and DIOP (**L5**) exhibited moderate activity and nearly no enantioselectivities in the formation of **3a**. Next, 1,2-bis((2*R*,5*R*)-phospholano)ethane ligands **L6**–**L8** with different steric properties were tested. To our delight, (*R*,*R*)-Ph-BPE (**L6**) was identified as the most effective ligand, and the reaction led to the desired product **3a** in 79% yield with 87% *ee*.

To further improve the enantioselectivity, the influence of critical reaction parameters has been evaluated (e.g., temperature, solvent, catalyst loading) for the model reaction using **L6** as the ligand. As shown in Table 1, when the reaction

Table 1. Investigation of Reaction Conditions for the Ni-Catalyzed Asymmetric Hydrocyanation of 1a[a]



entry	solvent	temp (°C)	yield (%)[b]	*ee* (%)[c]
1	toluene	60	79	87
2	toluene	30	87	88
3	1,4-dioxane	30	51	46
4	THF	30	31	42
5	MTBE	30	89	83
6	MeCN	30	37	94
7	MeCN/toluene (1/1)[d]	30	82	82
8	MeCN/toluene (3/2)[d]	30	83 (78)[e]	96
9	MeCN/toluene (2/1)[d]	30	87	86
10[f]	MeCN/toluene (3/2)[d]	30	26	95

[a]Reaction conditions: (±)-**1a** (0.1 mmol), **2** (0.3 mmol, 3.0 equiv), and solvent (0.3 mL) in the presence of $Ni(cod)_2$ (10 mol %) and **L6** (10 mol %). [b]Yields were determined by GC analysis using *n*-dodecane as the internal standard. [c]*ee* values were determined by chiral HPLC analysis. [d]Solvent (v/v, 0.3 mL). [e]Isolated yield. [f]$Ni(cod)_2$ (5.0 mol %), **L6** (5.0 mol %).

temperature was lowered to 30 °C, the enantioselectivity of product **3a** remained at the same level, and the yield increased to 87% (Table 1, entry 2). Several other solvents were tested next (Table 1, entries 3–6), and 1,4-dioxane and tetrahydrofuran (THF) led to much lower yields and enantioselectivities than toluene and methyl *tert*-butyl ether (MTBE) (Table 1, entries 3–5). Acetonitrile (MeCN) was an effective solvent for high enantioselectivity, albeit in low yield (Table 1, entry 6). A solvent mixture of MeCN/toluene (3/2) was found to give both the highest reactivity and the highest enantioselectivity (Table 1, entry 8). Lowering the catalyst loading further caused a significant decrease in yield (Table 1, entry 10). As a result, the optimal reaction conditions were established as 30 °C $Ni(cod)_2$/**L6**/MeCN/toluene (3/2). It is worth mentioning that the regioisomer **3a′** was isolated in 13% yield under standard conditions. (For details, see the Supporting Information (SI).)

After the preliminary optimization (Table 1, entry 8), we examined the scope and generality of this asymmetric transformation (Scheme 3). Besides propyl substitution at the R position, a variety of alkyl-substituted allenes were all suitable for the reaction, and the corresponding allyl nitrile products (**3b**–**f**) were obtained in 46–75% yield with 83–96% *ee*. A 1 mmol scale reaction with (±)-**1b** was achieved, affording the desired chiral nitrile **3b** in good yield and with high enantioselectivity (60% yield and 92% *ee*). Notably, −Cl and −OH functional groups were well tolerated (**3e**, **3f**). According to Arai's report, substrates having aryl group are conducive to achieving high regio- and stereocontrol.[11d] Thus

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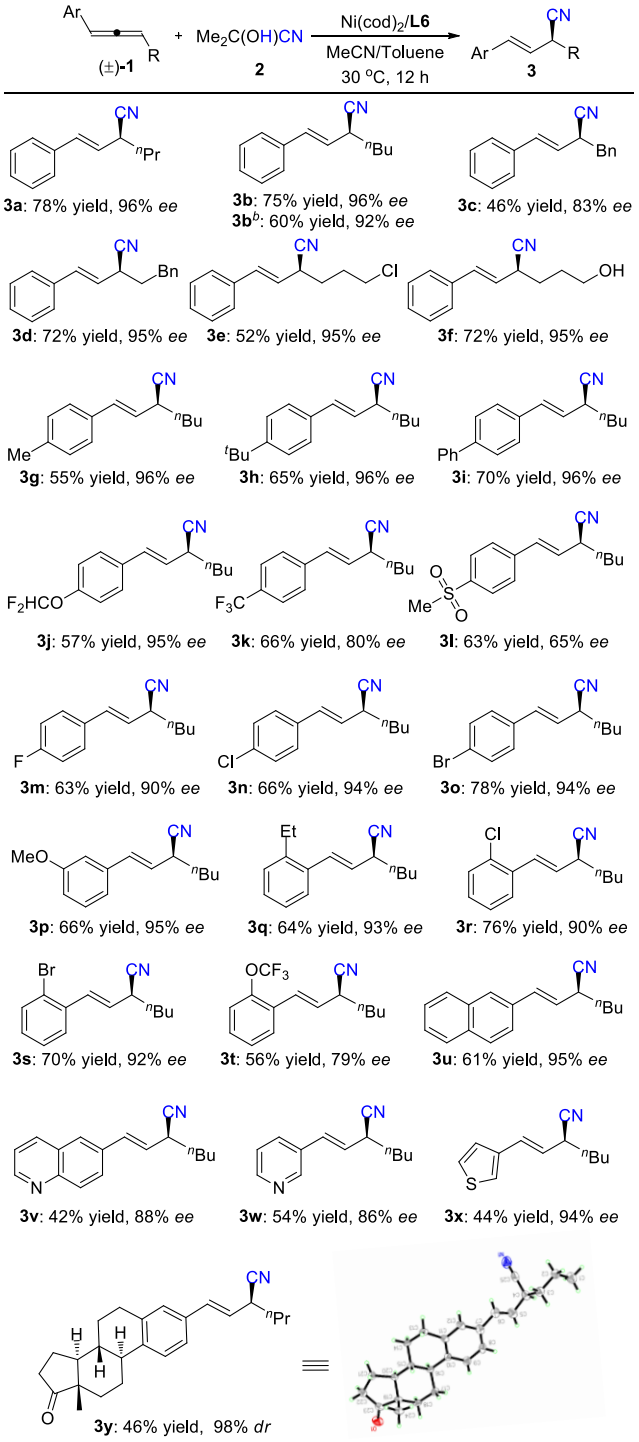
Scheme 3. Reaction Scope[a]

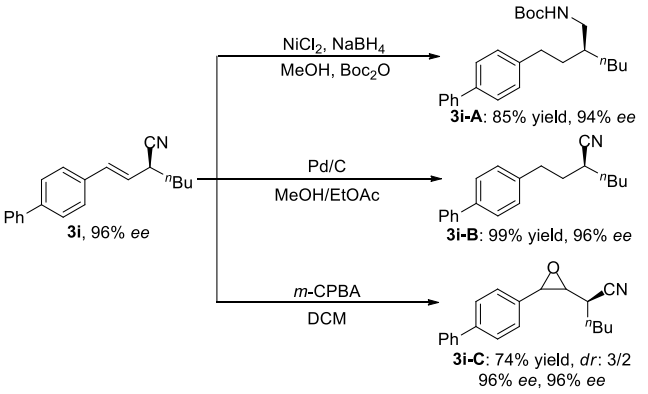


[a]Reaction conditions: (±)-**1** (0.1 mmol), **2** (0.3 mmol, 3.0 equiv), and MeCN/toluene (3/2, 0.3 mL) in the presence of $Ni(cod)_2$ (10 mol %) and **L6** (10 mol %) at 30 °C for 12 h. Yields of isolated products after flash column chromatography. The *ee* values were determined by chiral HPLC. [b]1 mmol scale reaction.

various aryl-substituted allenes with electron-neutral/deficient/rich substituents underwent efficient and regioselective hydrocyanation to form the corresponding allyl nitriles in moderate to good yield with good to excellent enantioselectivities (**3g**–**y**). It should be pointed out that the reaction of allenes with electron-deficient substituents (**1k**, **1l**, **1t**) proceeded smoothly but gave products with lower *ee* when compared with the result obtained with allenes with electron-neutral and electron-rich substituents. Substrates bearing versatile flexible functional groups including halogens (**1m**, **1n**, **1o**, **1r**, **1s**), ethers (**1j**, **1p**, **1t**), trifluoromethyl (**1k**), and methanesulfonyl (**1l**) were also well accommodated. In addition, substrates with heterocyclic substituents (such as quinolyl, pyridyl, and thiophenyl groups) were established to be efficient coupling partners to generate the corresponding products in acceptable yield with high enantioselectivities (**3v**–**x**). Moreover, the substrate employing the structurally complex estrone was also successfully converted into the desired product **3y** in moderate yield with excellent enantioselectivity. The absolute configuration of product **3y** was confirmed to be *S* by X-ray diffraction analysis, and the stereochemical assignments of the other products were tentatively made on this basis.

To illustrate the preparative utility of the current enantioselective hydrocyanation reaction, several transformations were conducted, as shown in Scheme 4. Because the

Scheme 4. Synthetic Transformations of Product 3i



product **3i** contains a cyano and an alkene, two unsaturated functional groups, the selective reductions can be readily performed. For example, with $NiCl_2/NaBH_4$ in MeOH, **3i** can be fully reduced and converted into the aliphatic chiral amine **3i-A** in good yield. Additionally, the alkene can be selectively reduced in the presence of the cyano group to give aliphatic chiral nitrile **3i-B** in excellent yield. Furthermore, epoxide **3i-C** can be efficiently synthesized following alkene epoxidation. Importantly, almost no loss of enantiomeric purity was observed in these manipulations.

Then, fully deuterium-labeled acetone cyanohydrin (**D-2**, 97% D) was subjected to the model reaction under standard conditions (eq 1). In this experiment, we observed deuterium incorporation (60% D) only at the C2 position of **D-3a**. This observation is consistent with a previously reported result from Arai.[11f] The erosion of deuterium content is due to the deuterocyanation of 1,5-cyclooctadiene, and the corresponding deuterated adducts were detected by GC–MS analysis. Finally, (*S*)-**1b** and (*R*)-**1b** were successively prepared and subjected to the hydrocyanation reaction under standard conditions (eq 2). The same configuration of product (*S*)-**3b** was isolated in similar yield with the same *ee* value when compared with the racemic **1b**. These results indicate that the reaction rate does not depend on any of the enantiomers of the substrate.

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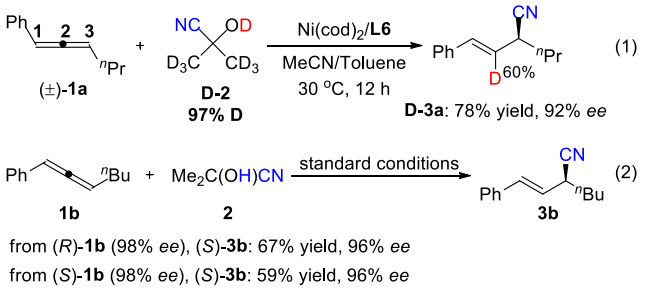

In summary, we developed the first example of the Ni/diphosphine complex-catalyzed asymmetric hydrocyanation of allenes. The protocol provides a regio- and stereoselective approach to various enantiomerically enriched allylic nitriles. The products are densely functionalized and ready for further transformations, as demonstrated here by selective reductions and epoxidation to saturated amine, nitrile, and epoxide. A further expansion of the scope of aliphatic terminal allenes is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03938.

Experimental procedures and full characterization data for all new compounds (PDF)

Accession Codes

CCDC 1957685 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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