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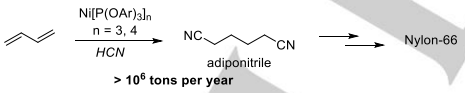
Asymmetric Hydrocyanation of Alkenes without HCN

Xiuxiu Li,[+a] Cai You,[+a] Jiaxin Yang,[b] Shuailong Li,[b] Dequan Zhang,[a] Hui Lv[b,c]* and Xumu Zhang[a,b]*

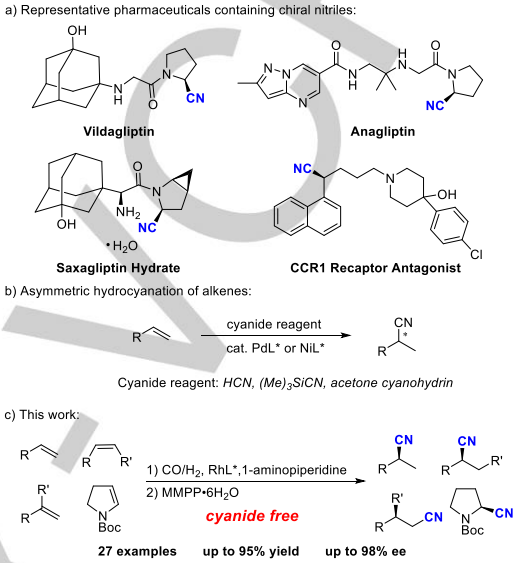
Abstract: A general and efficient rhodium-catalyzed asymmetric cyanide-free hydrocyanation of alkenes has been developed. Based on the asymmetric hydroformylation/condensation/aza-Cope elimination sequences, a broad scope of substrates including mono-substituted, 1,2- and 1,1-disubstituted alkenes (involving natural product *R*- and *S*-limonene) were employed, and a series of valuable chiral nitriles are prepared with high yields (up to 95%) and enantioselectivities (up to 98% ee). Notably, the critical factor to achieve high enantioseletivies is the addition of catalytic amount of benzoic acid. This novel methodology provides an efficient and concise synthetic route to the intermediate of vildagliptin and anagliptin.

The transition-metal-catalyzed hydrocyanation of olefins represents an efficient access to nitriles, which has been highlighted by the industrial production of adiponitrile from 1,3-butadiene (> 10^6 tons per year) with Ni-catalyzed hydrocyanation steps (Scheme 1).[1] Nitriles are one of the most versatile building blocks in organic chemistry and can be readily used as intermediates to other valuable functionalized compounds, such as carboxylic acid derivatives, amines, aldehydes, ketones, *N*-heterocycles.[2] In particular, chiral nitriles are important synthetic intermediates for many biologically active compounds and pharmaceuticals such as naproxen, ibuprofen and flurbiprofen.[3] In addition, there are some pharmaceutical molecules with the nitrile moiety as a key functional group, such as vildagliptin,[4] anagliptin,[5] saxagliptin hydrate[6] and the CCR1 recaptor antagonist (Scheme 2a).[7] Due to the significance of chiral nitriles, the development of efficient asymmetric synthetic methods for their preparation has attracted considerable attentions. To date, the synthesis of chiral nitriles are based on the asymmetric hydrocyanation of alkenes (Scheme 2b),[8] the Strecker reaction[9] and other cyanation reactions.[7,10] Owing to the high toxicity and volatile property of these cyanide reagents, the development of a cyanide-free method to synthesize chiral nitriles is highly desired. Herein, we report an asymmetric cyanide-free



Scheme 1. DuPont's production of adiponitrile *via* hydrocyanation.

hydrocyanation of mono-substituted, 1,2- and 1,1-disubstituted alkenes, and chiral nitriles are achieved with high yields (up to 95%) and enantioselectivities (up to 98% ee, Scheme 2c).



Scheme 2. Transition-metal-catalyzed hydrocyanation of alkenes.

Rhodium-catalyzed hydroformylation of alkenes represents a highly efficient route for the preparation of aldehydes.[11] Due to the various transformation of the aldehyde group, hydroformylation-initiated tandem reactions towards more complex molecules have been achieved, including hydroaminomethylation,[12] hydroformylation/Fischer indole synthesis,[13] hydroformylation/Wittig reaction[14] and other tandem processes.[15] By contrast, asymmetric hydroformylation-triggered cascade reactions have been rarely reported, although intensive research efforts and much progress have been made in asymmetric hydroformylation during the past decades.[16] The main reason may lie in the racemization of chiral branched aldehydes in the cascade process which usually led to the target products with very low enantioselectivity. In 2013, Landis reported one-pot AHF/Wittig olefination (AHF/WO) sequences with their bis-diazophos as the chiral ligand for the AHF step.[17] Recently, our group have developed the rhodium/YanPhos-catalyzed asymmetric interrupted intramolecular hydroaminomethylation of *trans*-1,2-disubstituted alkenes.[18] Inspired by these results, we envisioned that the chiral aldehyde, generated from alkenes by hydroformylation, can react with hydrazines to form relatively stable hydrazones that can further undergo aza-Cope elimination (accroding to the method reported by Lassaletta and co-workers in 1993[19]) to give chiral nitriles. In contrast to Landis' and our previous tandem reaction in which the reaction conditions are neutral, our reaction need to be carried out under alkaline conditions, which is difficult to keep high enantioselectivities. Therefore, to avoid racemization is the key factor in this asymmetric tandem transformation.

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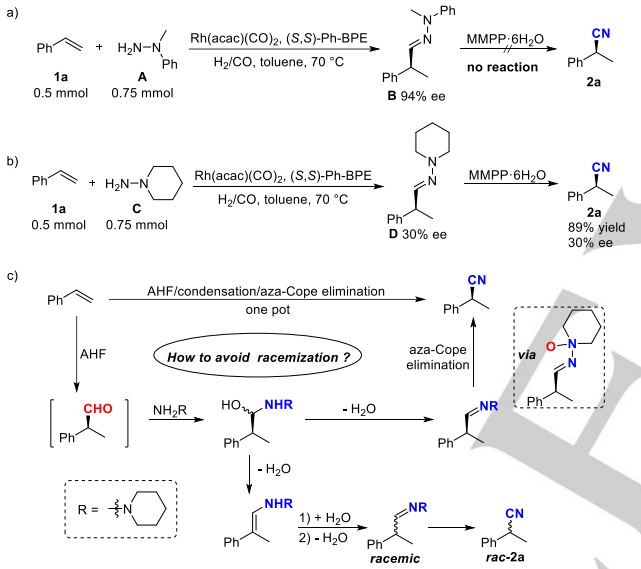
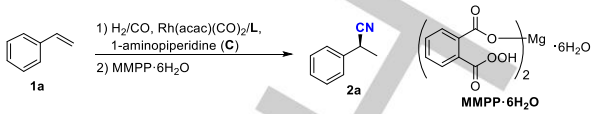
We started our investigation using styrene (**1a**) as a model substrate, 1-methylphenylhydrazine (**A**) as the *N*-source. Excellent ee values of the corresponding arylhydrazone **B** were achieved, but no desired **2a** was produced, because the aza-Cope elimination cannot realize for these arylhydrazones (Scheme 3a). Then, 1-aminopiperidine (**C**) was used as the *N*-source feedstock, the reaction underwent smoothly and the desired chiral nitrile **2a** was obtained in high yield, but the ee of **2a** was only 30% (Scheme 3b). We also found that the ee of **D** is as same as that of **2a**. These results disclosed that the condensation step is very important for keeping the ee values of the final chiral nitrile. As shown in Scheme 3c, when 1-methylphenylhydrazine **A** was employed, due to the strong conjugation of the arylhydrazone, dehydration condensation can undergo very fast, which is beneficial for the ee values. By contrast, when 1-aminopiperidine (**C**) was used, because of the weak conjugation of the corresponding hydrazone, dehydration condensation undergoes slowly, which is detrimental to the ee values of **2a**.



Scheme 3. General one-pot AHF/condensation/aza-Cope elimination sequence affording chiral nitriles.

To achieve higher ee values, we attempted to use some additives which possesses the following properties: (1) the additive can accelerate the dehydration condensation step to avoid racemization; (2) the additive cannot interfere the foregoing AHF step and the following aza-Cope elimination. As shown in Table 1, when molecular sieves were used, the ee values increased from 30% to 73%, which supports our hypothesis (Table 1, entry 2). Next, we tried a class of acids as the additive. When 10 mol% of benzoic acid was used, 85% ee was given (Table 1, entry 3). Besides benzoic acid, other acids were also investigated, which revealed benzoic acid to be superior to all others tested (see SI). The evaluation of solvents disclosed that THF should be the best solvent for this reaction (Table 1, entry 4). Different equivalents of 1-aminopiperidine (**C**) were also tested, and 3 equivalents give 90% ee (Table 1, entries 4-6). After investigating the concentration of **1a** and the reaction temperature, we obtained chiral nitrile **2a** with 92% yield and 92% ee (Table 1, entry 7).

Table 1. Investigation of reaction conditions.[a]



Entry	**C** (mmol)	Solvent	Additive	Yield [%][b]	*ee* [%][c]
1	0.75	toluene	none	89	30
2	0.75	toluene	3Å MS	90	73
3	0.75	toluene	PhCOOH (10 mol%)	93	85
4	0.75	THF	PhCOOH (10 mol%)	92	88
5	0.55	THF	PhCOOH (10 mol%)	91	85
6	1.5	THF	PhCOOH (10 mol%)	90	91
7[d]	**1.5**	**THF**	**PhCOOH (10 mol%)**	**92**	**92**

[a] Unless otherwise mentioned, all reactions were performed on a 0.5 mmol scale at 70 °C in 1.0 mL solvent with substrate/Rh = 100:1, (*S*,*S*)-Ph-BPE/Rh = 3:1, 20 bar CO/H_2 (1:1), a reaction time of 24 h, and MMPP·$6H_2O$ (1.0 mmol). [b] Isolated yield of **2a**. [c] Determined by HPLC analysis using a chiral stationary phase. The absolute configuration was assigned by comparing the sign of the optical rotation of (*S*)-**2a** with that reported in the literature.[20] [d] 60 °C, 2.5 mL THF.

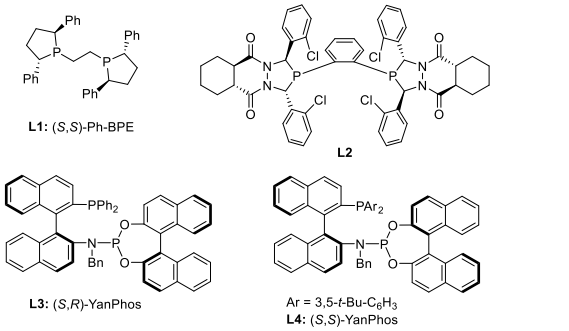


Figure 1. Structures of the phosphine ligands for asymmetric cyanide-free hydrocyanation.

To investigate the substrate scope and generality of this asymmetric tandem transformation, various alkenes were tested under the optimized conditions (Scheme 3). First, mono-substituted alkenes were employed. A series of functional groups, such as methyl (**2b**), methoxyl (**2c**), tertiary butyl (**2d**), isobutyl (**2e**) and halides (**2f-2h**), at the *para* position of the phenyl group are compatible with this transformation. Substrates with *meta*- and *ortho*- substitution on the phenyl group are also tolerated very well, and high yields with excellent ee values were achieved (**2i-2k**). Moreover, substrates containing other aromatic fragments, including naphthalenes, thiophenes, pyrroles and indoles (**2l-2o**), were also tolerated. Next, protected allylic alcohols and allylic amines were tested, and the corresponding chiral nitriles were produced with good yields and excellent ee values.

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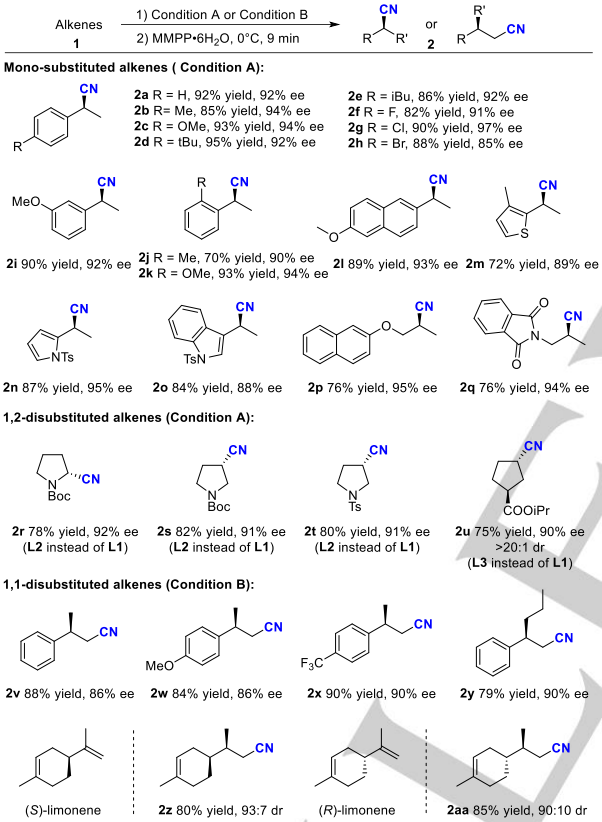
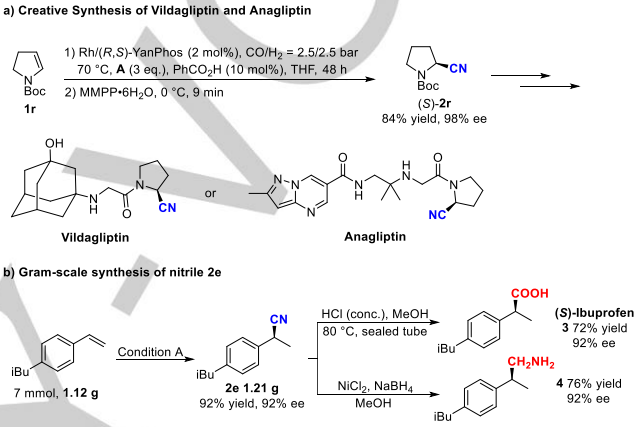
As exemplifed by **2r**, **2s** and **2t**, this tandem reaction was also effective for 1,2- disubstituted alkenes, and high yields with excellent ee values can be achieved. To our delight, the desymmetrizing strategy in current reaction is also efficient, and high diastereo- and enantioselectivities were obtained (**2u**, >20:1 dr, 90% ee).

We found that a variety of 1,1-disubstituted alkenes can be transformed to chiral nitriles in high ee's, which have never been reported before. When α-methylstyrene (**1v**) was employed, **2v** was produced in 88% yield with 86% ee. Substrates with methoxyl (**1w**) or trifluoromethyl (**1x**) on the phenyl group were also accommodated, and high ee values were obtained (**2w** and **2x**). Next, we introduced this tandem reaction to the modification of (*S*)-limonene and (*R*)-limonene, and the corresponding chiral nitriles were given with high diastereoselectivities (**2z** and **2aa**).



Scheme 4. Substrate scope. Condition A: **1** (0.5 mmol), 1-aminopiperidine (1.5 mmol), PhCOOH (0.05 mmol), $Rh(acac)(CO)_2$ (1.0 mol%), **L1** (3.0 mol%), CO (5 bar), H_2 (5 bar), THF (2.5 ml), 60 °C, 24 h. MMPP·$6H_2O$ (1.0 mmol). Condition B: **1** (0.5 mmol), 1-aminopiperidine (0.75 mmol), $Rh(acac)(CO)_2$ (2.0 mol%), **L4** (6.0 mol%), CO (2.5 bar), H_2 (2.5 bar), toluene (0.5 ml), 80 °C, 48 h. MMPP·$6H_2O$ (1.0 mmol). Isolated yields. Enantiomeric excesses (ee) were adetermined by HPLC analysis using a chiral stationary phase. The diastereoselectivities were determined by ^{1}H NMR or ^{13}C NMR analysis of the unpurified reaction mixture.

In order to further demonstrate the synthetic utility of the current tandem methodology, several transformations were conducted, as summarized in Scheme 5. A creative synthetic route to the key intermediate of vildagliptin and anagliptin was developed. Using (*R*,*S*)-YanPhos as the chiral ligand, **1r** underwent the one-pot tandem reaction very smoothly to give (*S*)-**2r** in 84% yield with 98% ee (Scheme 5a). Starting from (*S*)-**2r**, vildagliptin and anagliptin can be synthesized readily following literature procedures.[5,21] Furthermore, gram scale reaction of **1e** was achieved, affording the desired chiral nitrile **2e** with excellent yield and ee values (92% yield and 92% ee, Scheme 5b). Then, the non-steroidal anti-inflammatory drug (*S*)-Ibuprofen **3** was obtained in good yield with a high enantiomeric excess (92% ee) through the nitrile hydrolysis of **2e**. With $NiCl_2$/$NaBH_4$ in MeOH, **2e** can be also readily converted to the chiral primary amine **4** in good yield with no loss in ee.



Scheme 5. Synthetic transformations.

In conclusion, we have developed a general and efficient rhodium-catalyzed asymmetric cyanide-free formal hydrocyanation of alkenes. In current tandem transformation, the substrate scope, including mono-substituted, 1,2- and 1,1-disubstituted alkenes, is broad. It should be pointed that catalytic amount of benzoic acid is necessary to achieve high enantioseletivies in the asymmetric reaction of mono- and 1,2-disubstituted alkenes. Using the enantioselective one-pot AHF/condensation/aza-Cope elimination sequences, a series of valuable chiral nitriles are achieved with high yields (up to 95%) and enantioselectivities (up to 98%). This method provides a concise route to the synthesis of nitriles with α- or β-chirality, which are important intermediates in organic synthesis. Furthermore, a creative method for the synthesis of vildagliptin and anagliptin has been also disclosed. Further investigations on the asymmetric reactions in organic synthesis are in progress in our lab.

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Keywords: asymmetric synthesis • hydrocyanation • hydroformylation • nitriles • rhodium

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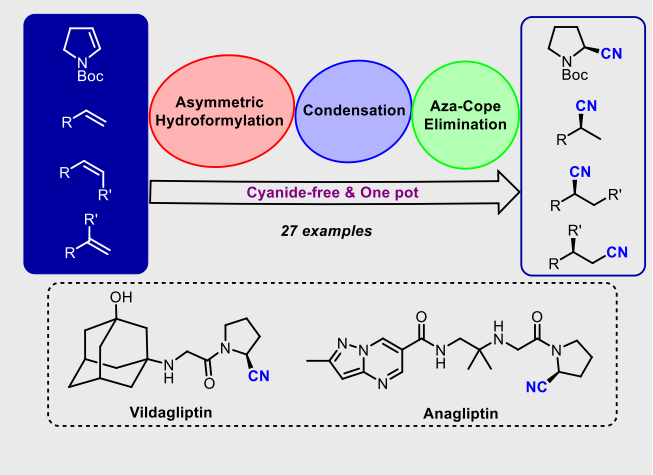

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