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Access to 1,3-Dinitriles by Enantioselective Auto-Tandem Catalysis: Merging Allylic Cyanation with Asymmetric Hydrocyanation

Jinguo Long, Rongrong Yu, Jihui Gao, and Xianjie Fang*

Abstract: *Enantioselective auto-tandem catalysis represents a challenging yet highlight attractive topic in the field of asymmetric catalysis. In this context, we describe a dual catalytic cycle merging allylic cyanation and asymmetric hydrocyanation. The one pot conversion of a broad array of allylic alcohols into their corresponding 1,3-dinitriles has been obtained in good yield with high enantioselectivities. The products are densely functionalized and can be easily transformed to chiral diamine, dinitrile, diester and piperidines. Mechanistic studies clearly support a novel sequential cyanation/hydrocyanation pathway.*

The development of new catalytic transformations with maximized atom and step economy is the everlasting pursuit in modern organic synthesis.[1] Tandem catalysis has, in this regard, attracted considerable attention, owing to implement one pot, multi-step procedures without isolation, purification and workup of intermediates, thereby saving time and cutting wastes.[2] In particular, auto-tandem catalysis (ATC) is strikingly fascinating since a sole catalyst can efficiently promote tandem reactions, where two or more mechanisms are involved in a reactor (Figure 1).[3] Although this field significantly progressed,[3,4] examples of enantioselective ATC to construct enantiomerically enriched molecules remain particularly limited.

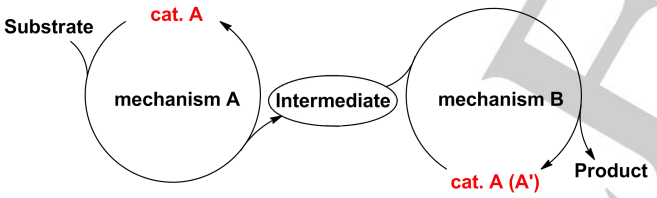
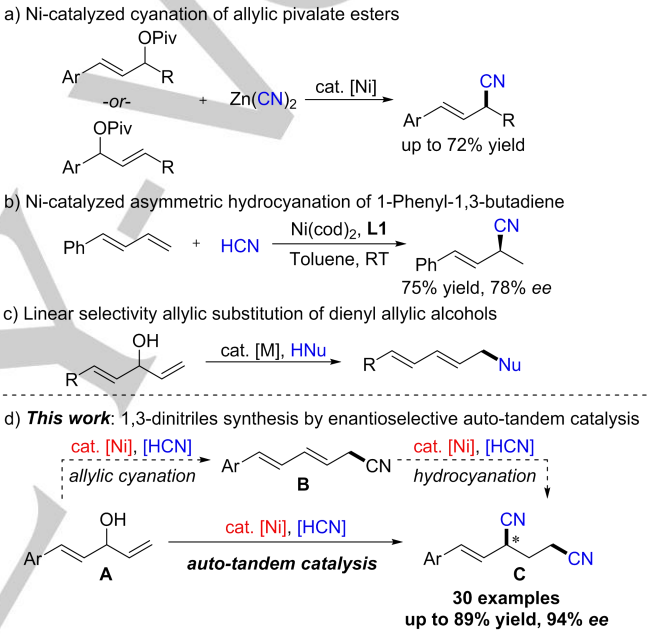


Figure 1. Schematic illustration of auto-tandem catalysis.

The transition-metal-catalyzed allylic substitution reaction is a highly robust method for the formation of C–C and C–X (X = N, O, S etc.) bonds,[5] which has significant influence in the field of synthetic chemistry. In recent years, both low-cost catalysts and unprotected allylic alcohols as electrophiles continuously developed in this field.[5k,6,7] In this context, low cost and highly abundant nickel appears as the ideal catalyst for these transformations.[7-11] Nickel-catalyzed Negishi cross-couplings[8b] Suzuki cross-couplings,[8c] allylic aminations,[9] and alkylations[10] with unprotected allylic alcohols have been demonstrated. A nickel-catalyzed cyanation reaction was reported by Rousseaux and coworkers using allylic pivalate esters as electrophiles to access allylic nitriles (Scheme 1a).[11] Apart from this elegant transformation, nickel-catalyzed C−CN bond forming cyanation reactions with unprotected alcohol electrophiles have, to the best of our knowledge, not been reported to date.



Scheme 1. Merging allylic cyanation with asymmetric hydrocyanation.

Owing to a perfect atom economy, the transition-metal-catalyzed hydrocyanation of multiple C–C bonds represents one of the most straightforward strategies for the preparation of nitriles.[12] Since 1979, the various synthetic protocols for chiral nitriles via asymmetric hydrocyanation could be achieved due to the emergence/utilization of wide variety of chiral ligands.[12] However, It should be worth mentioning that such strategies were restricted to strained alkenes,[13] vinylarenes,[14] 1,3-dienes[15a,b] and allenes[15c] as prochiral substrates. In 1992, RajanBabu developed a Ni-catalyzed asymmetric hydrocyanation protocol of 2-methoxy-6-vinyl-naphthalene with sugar-derived diphosphonite ligand **L1**, that led to corresponding nitriles with excellent levels of enantiocontrol.[14a] The same protocol was also utilized for the hydrocyanation of 1-Phenyl-1,3-butadiene, providing the desired allylic nitrile with 78% *ee* (Scheme 1b).[15a] Nevertheless, no example of asymmetric hydrocyanation using acyclic 1,4-disubstituted 1,3-dienes were reported to date. These dienes can be easily prepared via transition-metal-catalyzed allylic substitution of dienyl allylic alcohols (Scheme 1c).[16]

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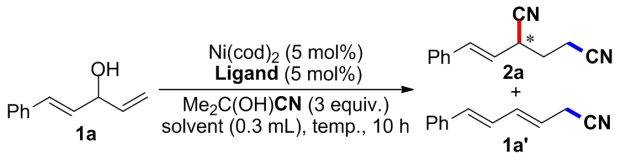
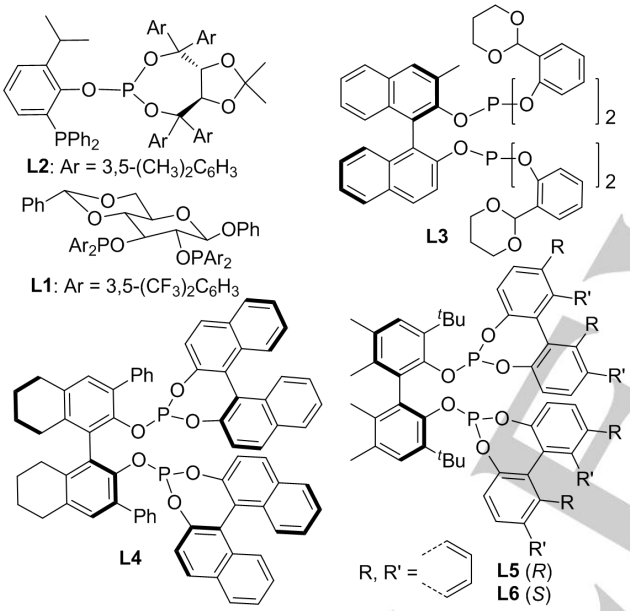
Table 1: Investigation of reaction conditions.[a]



entry	ligand	solvent	temp./^{o} C	yield **1a'**/%[b]	yield **2a**/%[b]	*ee* **2a**/%[c]
1	**L1**	toluene	80	52	0	–
2	**L2**	toluene	80	56	6	60
3	**L3**	toluene	80	trace	trace	–
4	**L4**	toluene	80	trace	66	69
5	**L5**	toluene	80	3	60	94
6	**L6**	toluene	80	10	29	-23
7	**L5**	Cyh[e]	80	–	73	92
8	**L5**	*n*-hexane	80	–	86	88
9	**L5**	*n*-hexane	70	–	86	88
10	**L5**	*n*-hexane/Cyh[f]	70	–	86 (83)[d]	92



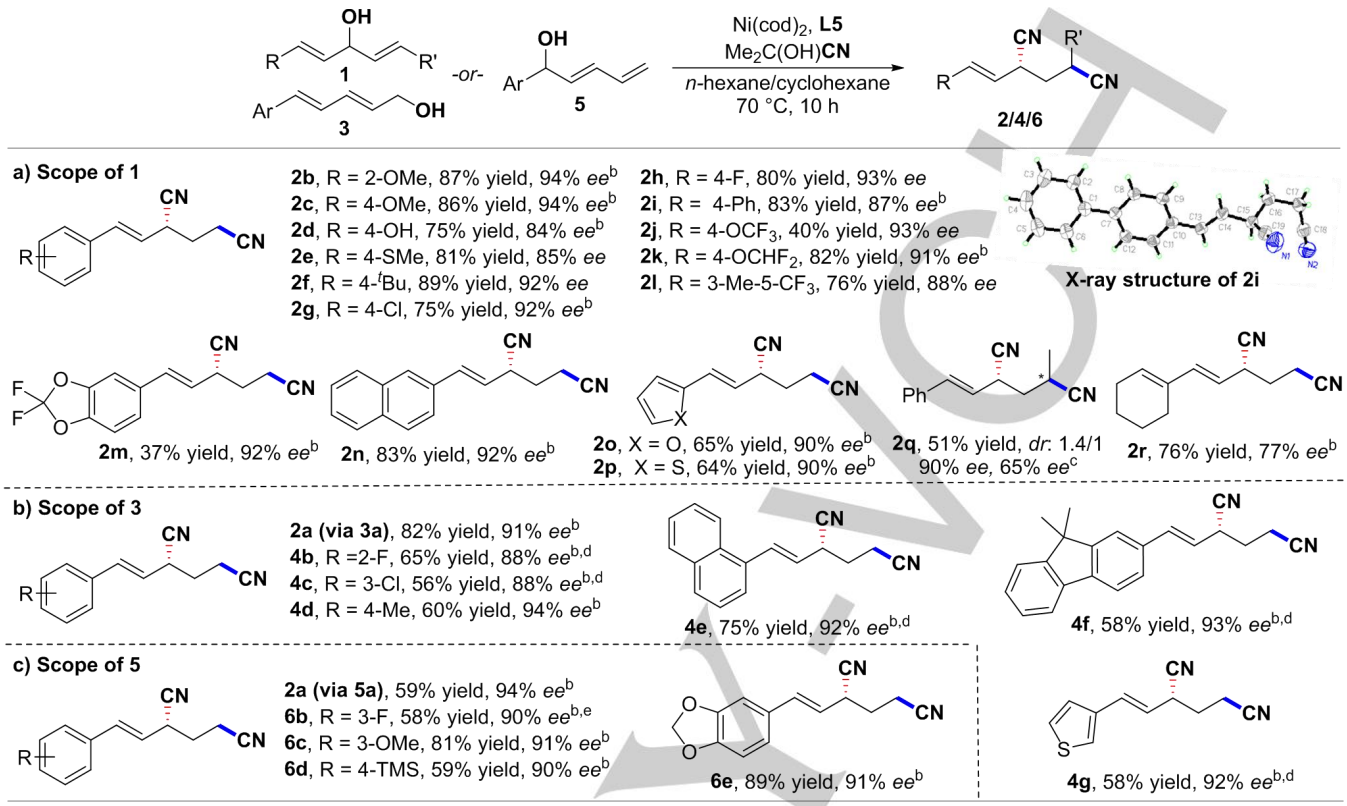
[a] Reactions conducted on 0.1 mmol scale under a N_2 atmosphere, solvent (0.3 mL). [b] Determined by ^{1}H-NMR (Mesitylene as the internal standard). [c] Determined by HPLC over chiral stationary phase. [d] Isolated yield. [e] Cyh = Cyclohexane. [f] *n*-hexane/Cyh (3/2, v/v).

We reasoned that an auto-tandem catalytic reaction could be developed to directly access chiral dinitriles starting from easily accessible dienyl allylic alcohols if we can develop a suitable chiral nickel system. This system would catalyze both the allylic cyanation and the asymmetric hydrocyanation reaction (Scheme 1d, direct **A** to **C**). With two C−C double bonds, the product of allylation (Scheme 1d, **B**) has the potential to undergo hydrocyanation (Scheme 1d, **B** to **C**). One of the most noticeable challenge lies in the cyanide reagent that will be playing both the cyanide and the hydrogen cyanide source in the reaction. Moreover, a catalyst system that meets both broad reaction activity and selectivity criterias is another key challenge, especially when the optimum condition for multiple transformations differs from one another. Herein, we report the successful development of a novel and highly enantioselective synthesis of 1,3-dinitriles through an ATC strategy (Scheme 1d).

We started our investigations using secondary dienyl allylic alcohol **1a** as model substrate, $Me_2C(OH)CN$ (acetone cyanohydrin) as cyanide reagent (Table 1). First and foremost, it is worth noticing that no conversion of **1a** to **2a** was detected in the absence of ligand. Thus, we began by undertaking different chiral phosphorus ligands for the model reaction. Ligands **L1**−**L3**, which was previously utilized for the asymmetric hydrocyanation of alkenes in an efficient manner,[14a-c,14f-h,15a,b] were examined (entries 1−3). These studies failed to reveal a system that could provide high yield as well as high enantioselectivity. Then, **L4** was tested and the reaction led to the formation of the desired product **2a** in 60% yield with 69% *ee* (entry 4). BiPhePhos-like ligand **L5**, which was first reported by Bower in a C−H bond functionalization reaction,[17] afforded **2a** in 60% yield with 94% *ee* (entry 5). When changing the ligand configuration (**L6**), we noted both a lower yield and *ee* in the desired product **2a** with opposite configuration compared to **L5** (entry 6). To increase the yield further, the influence of critical reaction parameters (i.e., solvent, temperature etc.) using **L5** as ligand were evaluated too (for details, see SI). Several solvents were first investigated (entries 7−10). With a slight decrease in enantioselectivities but significant increase in yield, *n*-hexane appeared as the most effective solvent (entry 8). When changing the temperature, we found that lowering the reaction temperature to 70 °C had no impact on the enantioselectivity and the yield (entry 9). A solvent mixture of cyclohexane/*n*-hexane (2/3) led to both the highest reactivity and enantioselectivity (entry 10). As a result, the optimal reaction conditions were established as 70 °C, $Ni(cod)_2$/**L5**/*n*-hexane/cyclohexane (3/2).

With the optimized reaction conditions established, we started to evaluate the substrate scope of this asymmetric transformation (Table 2). Various substrates **1** with electron-neutral, electron-deficient, and electron-rich substituents undergo an efficient and regioselective transformation to afford the corresponding dinitriles in moderate to high yields with high enantioselectivities (**2b**−**2n**). The −OH functional group was notably well tolerated (**2d**). The reaction of dienyl allylic alcohols with electron-deficient substituents (**1j**, **1m**) proceeded in moderate yields, but gave products with high *ee*. X-ray analysis was performed to confirm the absolute configuration of **2i** as *R*, and stereochemical assignments of the products were tentatively made on this basis. Substrates with heterocyclic substituents such as furanyl and thienyl groups found to be effective coupling partners to produce the corresponding products in acceptable yields with high enantioselectivities (**2o**−**2p**). R' substituted substrate **1q** was also compatible with the reaction using **L4** as ligand, and led to the desired product **2q** in moderate yield, albeit with low diastereoselectivity. Vinyl substituted substrate **1r** was tolerated in this reaction, although the enantioselectivity was lower than with the aryl substituted substrate. It is worth mentioning that alkyl-substituted starting materials are not compatible in these reactions due to lack of chemoselectivity (1,2-addition and 1,4-addition product mixture). In addition, various substrates **3** proceeded smoothly (Table 2b).

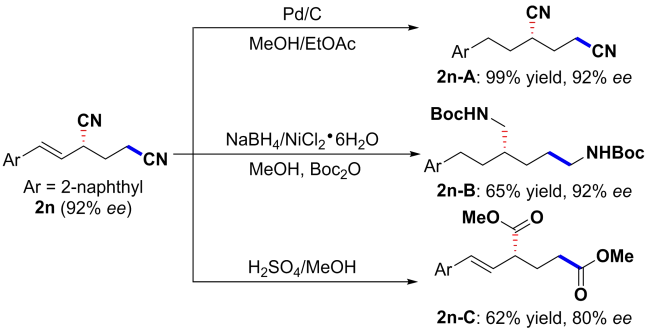
Table 2: Substrate scope.[a]



[a] Reaction conditions: A mixture of **1**/**3**/**5** (0.1 mmol), acetone cyanohydrin (0.3 mmol), [Ni(cod)$_2$] (5 mol%), **L5** (5 mol%), and *n*-hexane/cyclohexane (3/2, v/v, 0.3 mL) was stirred at 70 °C for 10 h. Yield of isolated product. The *ee* values were determined by HPLC over chiral stationary phase. [b] Using *n*-hexane/toluene (4/1, 0.3 mL) as solvent. [c] Using **L4** as ligand. [d] Reaction conducted at 65 °C. [e] Reaction conducted at 80 °C.

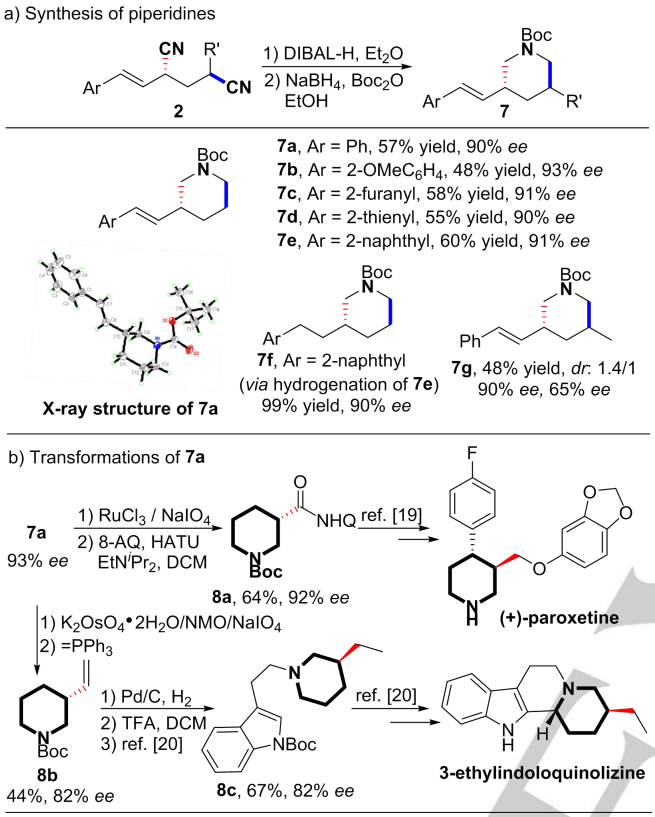
Substrates having different functional groups (i.e. −F, −Cl) were well tolerated (**4b** and **4c**). Substrates with naphthalene **3e** and fluorene **3f** led the corresponding products in good yield with high *ee*. Furthermore, our method was successfully implemented in the reaction employing substrates **5**. The permutations of substitution on the phenyl ring (**5a** − **5e**) were rightly tolerated and gave the desired products in good yield with high *ee* values (Table 2c).

To highlight the synthetic utility of the current enantioselective ATC, several transformations have been performed, as shown in Scheme 2 and Scheme 3a. The selective reduction of product **2n** can be readily performed thanks to the presence of both a −CN and an –C=C group, two unsaturated functional groups. The alkene was selectively reduced to give aliphatic chiral nitrile **2n-A** in excellent yield in the presence of the −CN group. **2n** can be fully reduced and transformed into the aliphatic chiral amine **2n-B** in good yield when treated with $NiCl_2/NaBH_4$ in MeOH. Importantly, no loss of enantiomeric purity has been detected in these manipulations. The chiral diester **2n-C** can be efficiently synthesized through alcoholysis. Interestingly, reduction of dinitriles by DIBAL-H and $NaBH_4$ affords chiral piperidines **7** in a one pot manner (Scheme 3a). For instance, substrates with heterocyclic substituents such as furanyl and thienyl groups were rightly tolerated (**7c**, **7d**). The piperidine **7e** can be hydrogenated to give alkyl substituted chiral piperidine **7f** in excellent yield. Furthermore, 3,5-disubstituted piperidine **7g** can also be synthesized through this transformation. Thence, this methodology provides a novel synthetic route to chiral piperidines, which are the most prevalent heterocycles found in medicines.[18] To demonstrate the applicability of the chiral piperidines, further transformations of **7a** were conducted (Scheme 3b). As examples, **7a** was treated by oxidation and condensation reaction conditions to deliver **8a** in 64% yield with 92% *ee*, which is the key intermediate in the synthesis of the antidepressant blockbuster drug (+)-paroxetine.[19]

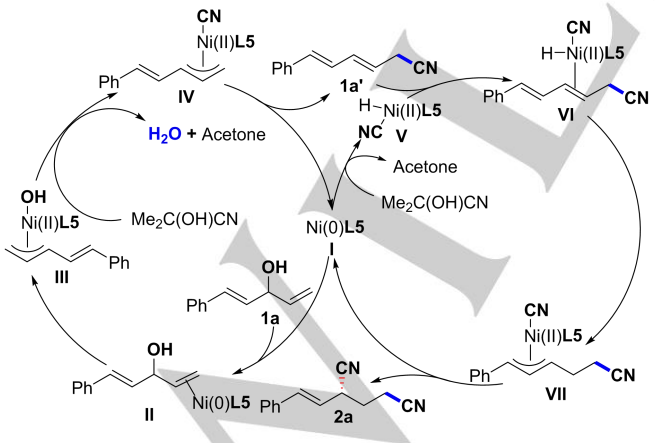


Scheme 2. Synthetic transformations of product **2n**.

Additionally, when subjected to oxidation and Wittig reaction conditions, **7a** was easily transformed into **8b** in 44% yield but with partial racemization. Starting from **8b**, the key skeleton for the synthesis of 3-ethylindoloquinolizine[20] **8c** can be obtained through subsequent hydrogenation, removal of the Boc group and S_N2 substitution reaction procedure.[20]



Scheme 3. Synthesis and applications of piperidines.



Scheme 4. Proposed catalytic cycle.

In order to gain insight about this catalytic transformation, several control experiments were conducted (for details, see SI). These results indicate that the reaction proceed through a sequential cyanation/hydrocyanation pathway, and that the hydrocyanation reaction is the rate-determining step in this sequence. The proposed mechanism is illustrated in Scheme 4 based on literature reports[5,7-10,12] as well as our own observations. The Ni(0) precatalyst undergoes ligand substitution with ligand **L5** to form the active Ni(0) species **I**. The coordination of allyl alcohol to species **I** lead to the formation of species **II**, and subsequent oxidative addition to allyl alcohol to forms species **III**. Then, species **IV** was formed via reaction with acetone cyanohydrin,[5,7-10] and could lead to the formation of intermediate **1a'** after reductive elimination. At this point, complexation of **1a'** with species **V**, which was generated through oxidative addition of acetone cyanohydrin onto **I**, leads to the formation of species **VI**. Subsequently, the migratory insertion of C−C double bond into H−Ni bond should afford the key π−allyl−Ni intermediate **VII**. Finally, reductive elimination of species **VII** furnishes the desired product **2a** and regenerates the Ni(0) complex **I**.

In summary, we report on an enantioselective auto-tandem catalysis strategy for the one pot conversion of allylic alcohols into 1,3-dinitriles. This new transformation merges allylic cyanation with asymmetric hydrocyanation and proceeds in high yields and enantioselectivities over a broad range of substrates. The products can be easily transformed to chiral diamine, dinitrile and diester as well as the most prevalent drug heterocycles chiral piperidines. Mechanistic experiments clearly support that this reaction proceeds through a novel sequential cyanation/hydrocyanation pathway.

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Keywords: auto-tandem catalysis • allylic alcohols • cyanation • asymmetric hydrocyanation • chiral dinitriles

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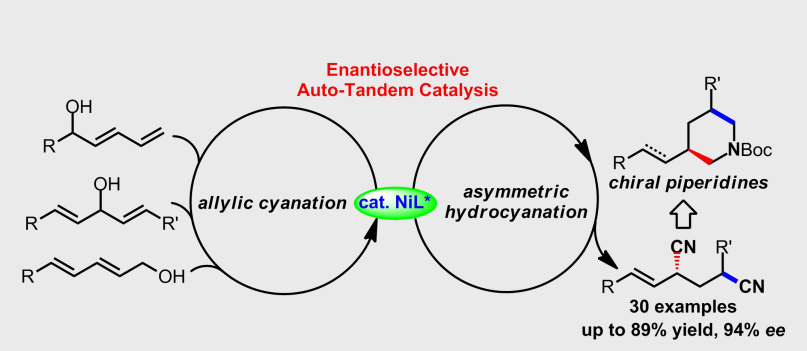

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Access to 1,3-Dinitriles by Enantioselective Auto-Tandem Catalysis: Merging Allylic Cyanation with Asymmetric Hydrocyanation

The one pot conversion of allylic alcohols to 1,3-dinitriles by enantioselective auto-tandem catalysis has been developed. This novel asymmetric transformation, which consists in an allylic cyanation with concomitant hydrocyanation, proceeds in high yield and enantioselectivities for a broad range of substrates.