OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

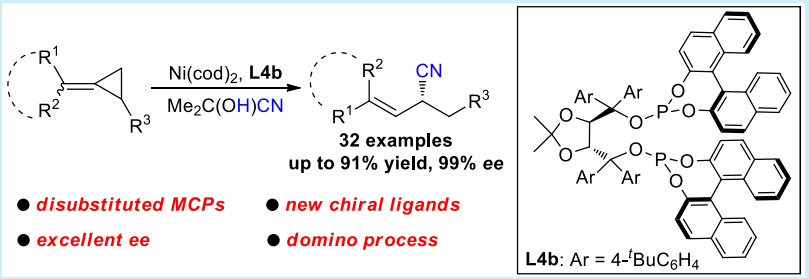
pubs.acs.org/OrgLett

# Highly Enantioselective Nickel-Catalyzed Hydrocyanation of Disubstituted Methylenecyclopropanes Enabled by TADDOL-based Diphosphite Ligands

Rongrong Yu and Xianjie Fang*

Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, People's Republic of China

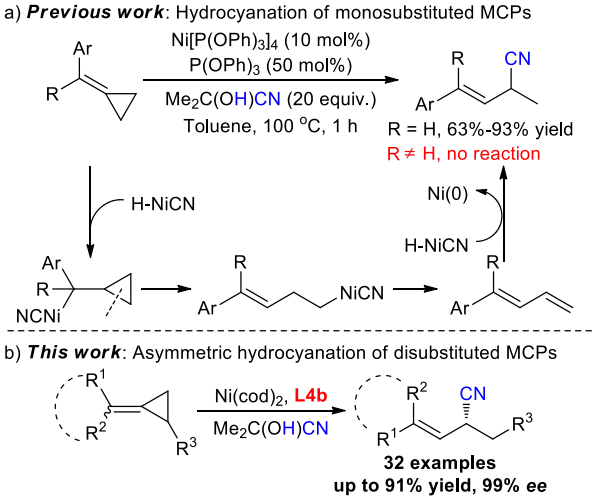
Supporting Information




**ABSTRACT:** A vast range of novel TADDOL-based diphosphite ligands were first synthesized and applied in the nickel-catalyzed asymmetric hydrocyanation of disubstituted methylenecyclopropanes. By employing these new catalysts, the conversion of diverse methylenecyclopropanes into their corresponding allylic nitriles was first enabled, in good yield with excellent enantioselectivities.

The transition-metal-catalyzed asymmetric hydrocyanation of alkenes is probably the most atom-economical strategy for enantiomerically enriched nitrile preparation.[1] During the past several decades, the emergence of a wide range of chiral ligands has allowed for the construction of various chiral nitriles through asymmetric hydrocyanation.[2] Nonetheless, these asymmetric catalysts are usually restricted to prochiral substrates, namely, norbornene,[3] vinylarenes,[4] and 1,3-dienes.[5]

**Scheme 1. Hydrocyanation of MCPs**




Thus the development of new chiral ligands and new prochiral substrates for the highly enantioselective hydrocyanations remains highly desirable.

Methylenecyclopropanes (MCPs) are highly strained but easily accessible adequately reactive synthetic intermediates that are well-established and useful building blocks in organic synthesis.[6,7] Owing to the unique chemical reactivity and electronic properties, the chemistry of MCPs was thoroughly explored during the last few decades, in particular, in the presence of transition-metal catalysts.[8] Notably, Arai and coworkers described in 2017 a nickel-catalyzed hydrocyanation of MCPs (Scheme 1a) and suggested that the reactions may proceed through a cyclopropane cleavage/conjugated diene hydrocyanation sequence.[9] However, this reaction is restricted to monosubstituted MCPs as substrates, and to the best of our knowledge, the asymmetric variation of this reaction has not yet been reported.

Since the pioneering report from Seebach in 1987,[10] TADDOL-based derivatives have now been established as an important source of chirality in organic synthesis.[11] To the best of our knowledge, although complexes of transition metals with TADDOL-based phosphorus ligands have shown excellent performance in various enantioselective reactions (Scheme 2a),[12−14,4g,h] the TADDOL-based diphosphite ligands have no literature precedent.[15] Herein we report the synthesis of novel TADDOL-based diphosphite ligands, which allow for the

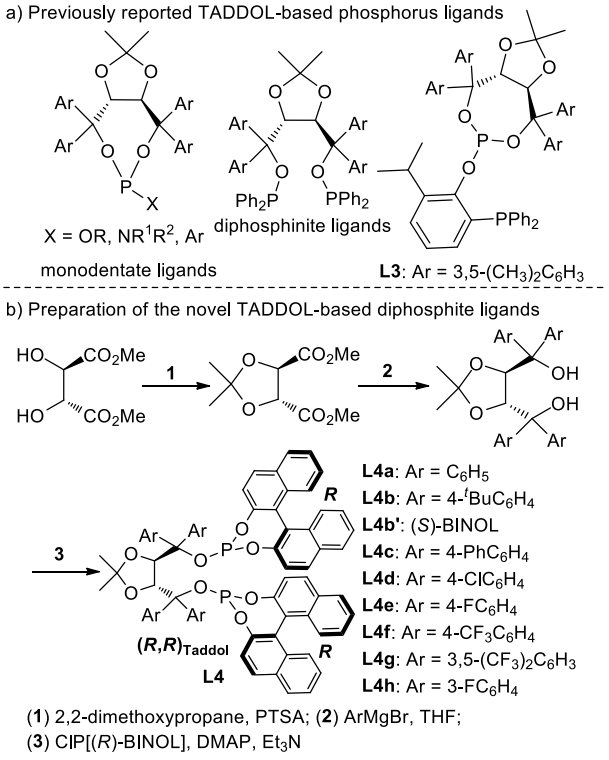
Received: December 6, 2019






DOI: 10.1021/acs.orglett.9b04374
Org. Lett. XXXX, XXX, XXX−XXX

**Scheme 2. TADDOL-based Phosphorus Ligands**

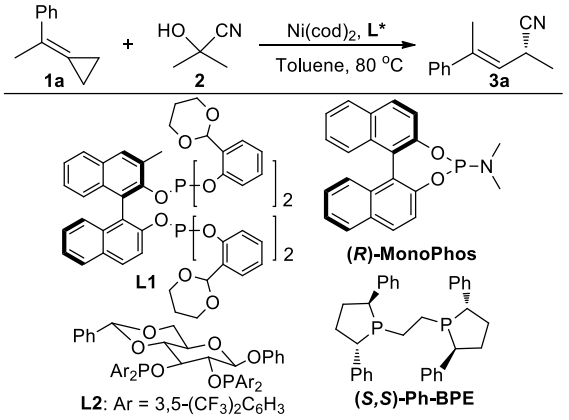



nickel-catalyzed asymmetric hydrocyanation of disubstituted MCPs with excellent enantioselectivities (Scheme 1b).

We successfully prepared a series of novel TADDOL-derived diphosphite ligands following the general method described in Scheme 2b. (See the SI for details.) These ligands are accessible from the commercially available tartaric acid dimethyl ester in only three steps. Their modular nature allows a facile structural fine-tuning to obtain both high conversion and high enantioselectivity. In this Letter, we focus on TADDOL-based diphosphite ligands with sterically and electronically different aryl substituents.

With these new ligands in hand, we began our studies by testing the asymmetric hydrocyanation of MCP **1a** with acetone cyanohydrin (**2**) as the HCN source under nickel catalysis with a variety of chiral ligands and examined the yield and the *ee* value of the corresponding product **3a** (Table 1). When the ligands **L1**−**L3** were used, which proved to be effective in the asymmetric hydrocyanation of alkenes,[4a,b,g,h,5] no conversion or just trace amounts of the desired product were observed (Table 1, entries 1−3). Commercially available chiral ligands showed no reactivity in the formation of the desired product **3a** (Table 1, entries 4−7). DIOP exhibited moderate reactivity and nearly no enantioselectivity in the formation of **3a** (Table 1, entry 8). These studies failed to reveal a system that could provide good yield and good enantioselectivity. Hence, our TADDOL-based diphosphite ligands with different steric properties were tested (Table 1, entries 9−16). To our delight, these ligands were effective in this asymmetric transformation. The substituents on the aryl group have a significant influence on both the yield and *ee* value of the reaction. It was remarkable that the *para-tert*-butyl -substituted **L4b** gave the product **3a** in 85% isolated yield with 96% *ee* (Table 1, entry 10). In a contrast, for the ligand **L4b′**, with mismatched chiralities, no conversion was observed (Table 1, entry 11). The optimization of other

**Table 1. Optimization of Reaction Conditions**[a]




| entry | L* | 3a yield (%)[b] | 3a *ee* (%)[c] |
|---|---|---|---|
| 1 | **L1** | 0 | |
| 2 | **L2** | trace | |
| 3 | **L3** | 0 | |
| 4 | (*R*)-**SEGPhos** | 0 | |
| 5 | (*R*)-**MonoPhos** | 0 | |
| 6 | (*R*)-**BINAP** | 0 | |
| 7 | (*S,S*)-**Ph-BPE** | 0 | |
| 8 | (*R,R*)-**DIOP** | 56 | 3 |
| 9 | **L4a** | 34 | 94 |
| 10 | **L4b** | 87 (85)[d] | 96 |
| 11 | **L4b′** | 0 | |
| 12 | **L4c** | 76 | 94 |
| 13 | **L4d** | 78 | 94 |
| 14 | **L4e** | 58 | 95 |
| 15 | **L4f** | 52 | 94 |
| 16 | **L4g** | 18 | |
| 17 | **L4h** | 28 | 81 |
| 18[e] | **L4b** | 0 | |
| 19[f] | **L4b** | 0 | |
| 20[g] | **L4b** | 46 | 67 |
| 21[h] | **L4b** | 24 | 87 |

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), $Ni(cod)_2$ (5 mol %), ligand (5 mol %), toluene (0.3 mL), 80 °C, 12 h. [b]Determined by GC analysis using *n*-dodecane as the internal standard. [c]Determined by chiral HPLC. [d]Isolated yield. [e]$Ni(acac)_2$. [f]$NiCl_2$. [g]1,4-Dioxane. [h]DMSO.

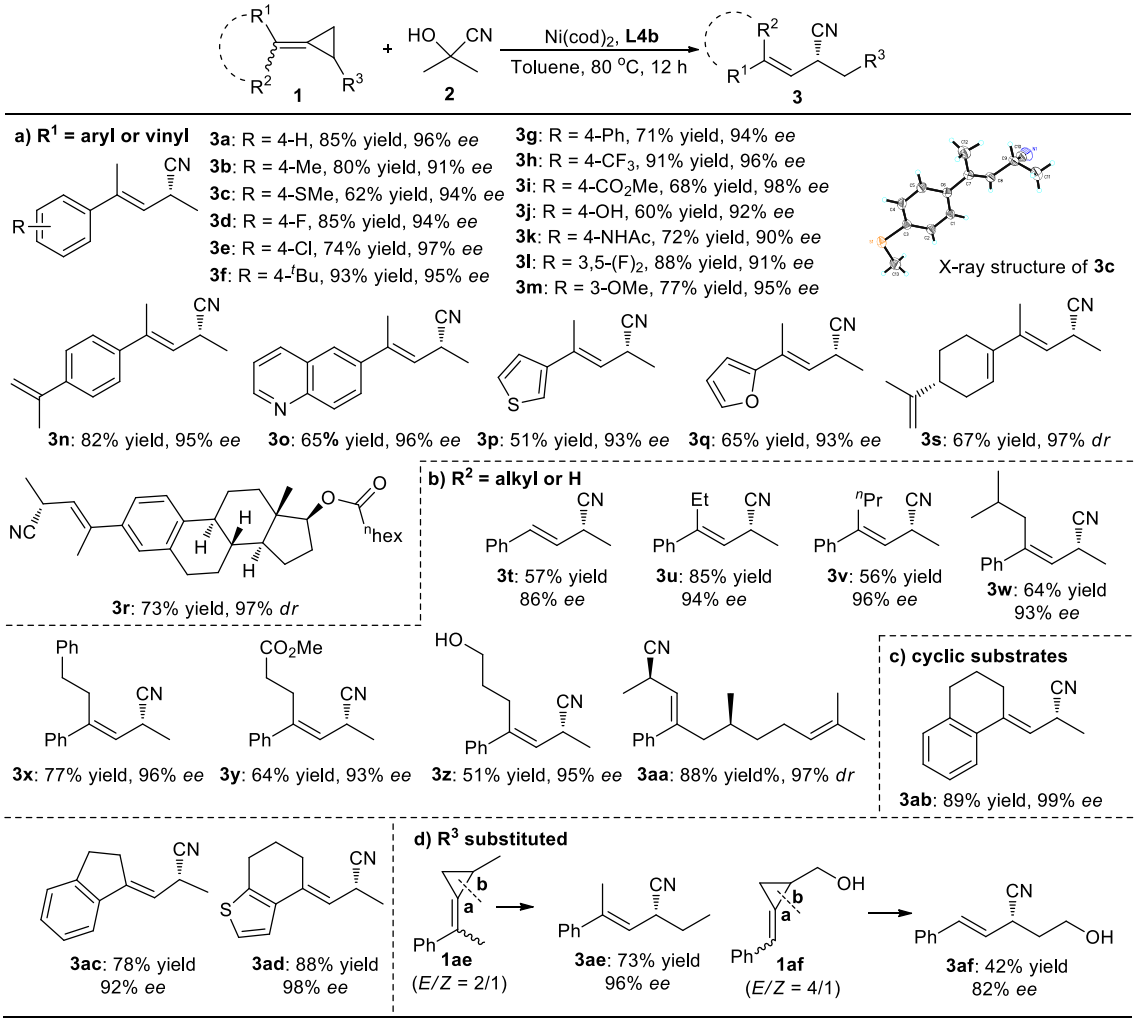
reaction parameters was then performed with optimal ligand **L4b**. Ni(II) precatalysts such as $Ni(acac)_2$ and $NiCl_2$ led to the recovery of the starting materials under the reaction conditions (Table 1, entries 18 and 19). Polar solvents such as 1,4-dioxane and DMSO led to much lower yields and enantioselectivities than toluene (Table 1, entries 20 and 21).

Next, we examined the general scope of our asymmetrical synthetic protocol. As shown in Scheme 3, various 1-methyl-1-aryl disubstituted MCPs with electron-neutral, electron-deficient, and electron-rich substituents underwent efficient hydrocyanation to afford the corresponding allyl nitriles in good yield with excellent enantioselectivities (**3a**−**n**). The absolute configuration of product **3c** was confirmed as *R* by X-ray diffraction analysis, and stereochemical assignments of the other products were tentatively made on this basis. Substrates having different functional groups (i.e., $-CO_2Me$, −OH, −NHAc, and —C═C) were well tolerated (**3i**, **3j**, **3k**, **3n**). Substrates with heterocyclic substituents (such as quinolyl, thiophenyl, and furyl groups) were established to be efficient coupling partners to



DOI: 10.1021/acs.orglett.9b04374
*Org. Lett.* XXXX, XXX, XXX−XXX

**Scheme 3. Substrate Scope**[a]




[a]All reactions were performed on a 0.2 mmol scale under the standard reaction conditions (see Table 1, entry 10). Yields of isolated products after flash column chromatography. The *ee* and *dr* values were determined by chiral HPLC.

produce corresponding products in acceptable yield with excellent enantioselectivities (**3o**–**q**). Moreover, 1-methyl-1-vinyl-disubstituted MCPs were well tolerated and afforded the hydrocyanated products in good yield with high *ee* values (**3s**). The efficient use of the method in the late-stage asymmetric hydrocyanation of a perillal (**3s**), estradiol (**3r**), and citronellal (**3aa**) showcases its feasibility for relatively more complicated molecular scaffolds. Besides the methyl substituent at the $R^2$ position, a variety of alkyl-substituted MCPs were all suitable for the reaction, and the corresponding allylic nitrile products (**3u**–**aa**) were obtained in 51–88% yield with 93–97% *ee*. Notably, cyclic MCPs were tolerated to provide products (**3ab**–**ad**) in good yield with excellent *ee* values. To our delight, with our current catalytic system being regiospecific, the substrates with substituents on the cyclopropane ring underwent the cleavage of the $C_a$–$C_b$ bond of cyclopropane, giving the desired products (**3ae** and **3af**) in acceptable to good yield with high levels of enantioselectivity.

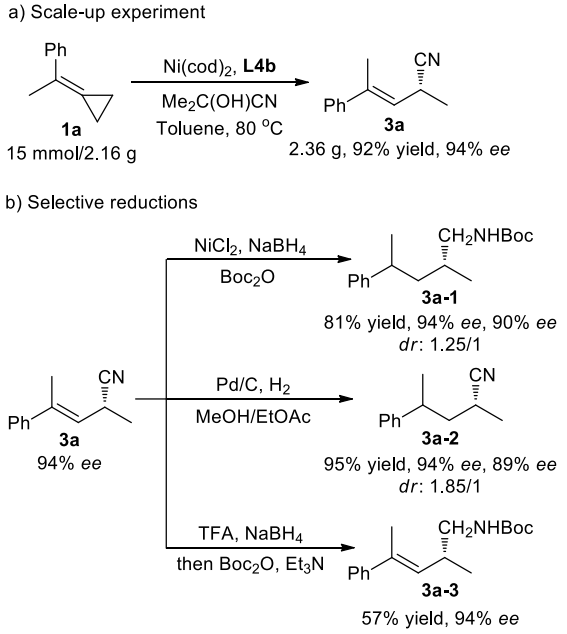
Finally, to verify the synthetic utility of the current enantioselective hydrocyanation reaction, several transformations were conducted, as shown in Scheme 4. A gram-scale reaction of **1a** was achieved, producing the desired chiral nitrile **3a** in excellent yield and with excellent *ee* values (92% yield and 94% *ee*, Scheme 4a). Considering that the product **3a** contains a cyano and an alkene, two unsaturated functional groups, the selective reductions can be readily performed. With $NiCl_2$/$NaBH_4$ in MeOH, **3a** can be fully reduced and converted into the aliphatic chiral amine **3a-1** in good yield. Additionally, even in the presence of cyano group, the alkene could be selectively reduced to give aliphatic chiral nitrile **3a-2** in excellent yield. Alternatively, the nitrile can be selectively reduced in the presence of the alkene group to give chiral homoallylic amine **3a-3** in acceptable yield. Importantly, the enentiomeric purity was intact in these manipulations (Scheme 4b).

In summary, we have developed a new class of TADDOL-based diphosphite ligands, which enable, for the first time, the nickel-catalyzed asymmetric hydrocyanation of disubstituted MCPs. Our protocol provides versatile optically active allylic nitriles with excellent enantioselectivities. We also demonstrated that the hydrocyanated products can be used as diverse precursors in the preparation of chiral aliphatic amine and nitrile as well as chiral homoallylic amine.



DOI: 10.1021/acs.orglett.9b04374
*Org. Lett.* XXXX, XXX, XXX–XXX

**Scheme 4. Gram-Scale Reaction and Further Product Transformations**




## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04374.

Experimental details and characterization data (PDF)

### Accession Codes

CCDC 1949402 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.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: fangxj@sjtu.edu.cn.

### ORCID

Xianjie Fang: 0000-0002-3471-8171


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was financially supported by the Recruitment Program of Global Experts and the start-up funding from Shanghai Jiao Tong University. We thank Prof. Bill Morandi (ETH, Zürich) and Dr. Bastien Cacherat (SIOC, Shanghai) for the critical proofreading of this manuscript.

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(15) TADDOLs herein refers to containing two adjacent diarylhydroxymethyl groups on a 1,3-dioxolane ring, which is in line with the definition of TADDOLs in ref 11a.



DOI: 10.1021/acs.orglett.9b04374
*Org. Lett.* XXXX, XXX, XXX−XXX