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One stone three birds: Ni-catalyzed asymmetric allenylic substitution of allenic ethers, hydroalkylation of 1,3-enynes and double alkylation of enynyl ethers

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ABSTRACT

The development of low-cost, earth-abundant and environmentally benign transition metal catalysts, which can catalyze multiple different types of asymmetric reactions, is an important objective in modern asymmetric catalysis. Herein we demonstrate that a chiral Ni/P-Phos catalyst achieves three types of asymmetric reactions: allenylic substitution of racemic allenic ethers, 1,4-hydroalkylation of prochiral 1,3-enynes and double alkylation of newly designed enynyl ether reagents. Three methods complement each other and produce various axially chiral allene derivatives bearing a pyrazolidine-3,5–dione unit, which is widely present in drugs and biologically active molecules with versatile pharmacological activities.

The development of low-cost, earth-abundant and environmentally benign transition metal catalysts, which can catalyze multiple different types of asymmetric reactions, is an important objective in asymmetric catalysis. Transition-metal (TM)-catalyzed asymmetric allenylic substitution of racemic allenylic electrophiles of the type **I**, which involves alkylene-π-allyl-metal intermediates, provides a platform to synthesize axially chiral allenes (Fig. 1a) [1–8]. However, TM-catalyzed asymmetric allenylic substitution reactions are still limited to the use of precious-metal-based catalysts, such as palladium complexes [9,10]. To our knowledge, non-precious and earth-abundant metal catalysts, such as nickel complexes, have not been used in the asymmetric allenylic substitution reactions. Meanwhile, allenylic substrates bearing good leaving groups, such as carboxylates (acetates), carbonates, and phosphates, have been successfully utilized to form alkylene-π-allyl-metal complexes. However, the direct use of allenic ethers **II** in TM-catalyzed asymmetric allenylic substitution remains an elusive challenge, because of the high stability of the C–O bond of allenic ethers. To expand catalytic systems as well as the type and scope of substrates that are applicable to asymmetric allenylic substitution reactions, we became interested in developing chiral nickel complexes as the catalysts and accessible allenic ethers as the substrates for the asymmetric allenylic substitution reactions.

On the other hand, TM-catalyzed asymmetric 1,4-hydrofunctionzation of prochiral 1,3-enynes has emerged as an attractive complementary strategy to synthesize axially chiral allenes (Fig. 1b) [11–13]. In this regard, Malcolmson recently disclosed a Pd-catalyzed 1,4-hydroamination to deliver chiral allenes with pendant allylic amines [14]. Tsukamoto reported an elegant palladium(0)–lithium iodide cocatalyzed asymmetric hydroalkylation of 1,3-enynes [15]. He and Lin described a protocol for the synthesis of tertiary fluoride-tethered allenes bearing a stereogenic center and stereogenic axis *via* Pd/Cu synergistic catalysis [16]. In 2023, Luo and Mi developed an asymmetric α-allylic allenylation of β-ketocarbonyls and aldehydes with 1,3-enynes by synergistic Pd/chiral primary amine catalysis [17]. Despite these impressive advances, the application of chiral nickel catalysts in the asymmetric 1,4-hydrofunctionalization of 1,3-enynes with nucleophiles to synthesize axially chiral allenes remains elusive, although it can enable the development of unprecedented trans-

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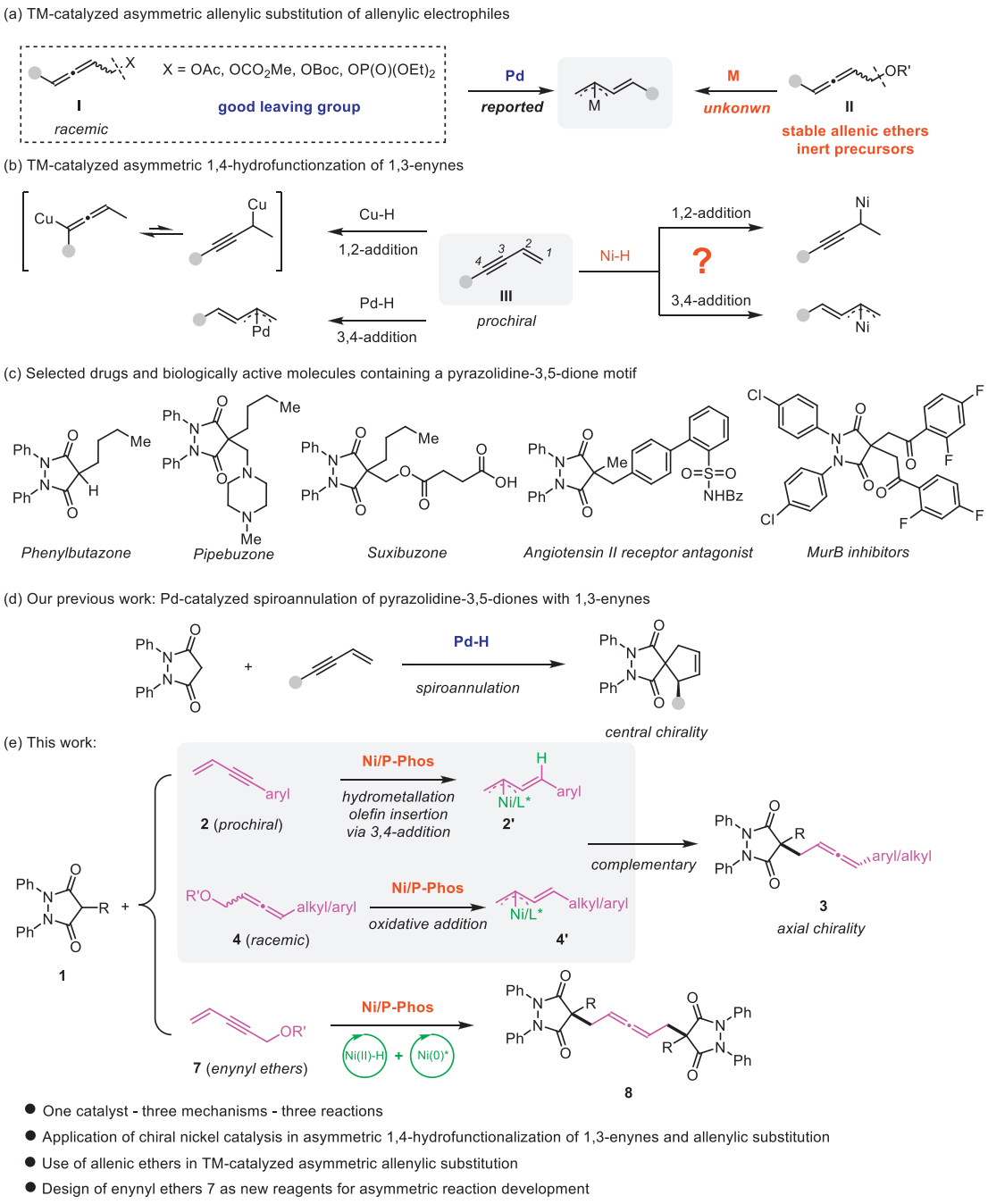


Fig. 1. Backgrounds and this work.

formations that is not possible by use of precious-metal-based catalysts, and can potentially enable the assembly of structurally diverse axially chiral allene products that are not readily accessible otherwise. Several questions remained with regard to the reactivity, regio- and enantio-selectivity for the Ni-catalyzed process. (1) Could a nickel catalyst activate 1,3-enynes and enable the 1,4-hydrofunctionzation of 1,3-enynes? (2) How does a nickel catalyst control the regioselectivity (olefin insertion *versus* alkyne insertion)? It is noted that Buchwald group recently disclosed a copper hydride catalyzed asymmetric reaction of 1,3-enynes with electrophiles [18]. In this protocol, Cu–H insertion occurs at the olefin rather than at the alkyne, and 1,2-hydrofunctionzation products were obtained. Although Ni–H insertion could occur at the olefin, this cannot generate a stable alkylene-π-allyl-complex for nucleophilic addition. (3) Would a nickel catalyst, which is active and can control regio-selectivity, also provide a high level of enantioselectivity control?

As particularly attractive pro-nucleophiles we selected pyrazolidine-3,5-diones. Pyrazolidine-3,5-diones are a class of important nitrogen heterocyclic scaffolds, which are widely present in drugs and biologically active molecules such as antiphlogistics, antirheumatics, diuretics, analgesics, insecticides, acaricides, herbicides, and acetyl-CoA carboxylase inhibitors (Fig. 1c) [19–23]. Thus, the development of methods to prepare diverse pyrazolidine-3,5–dione derivatives is of great interest due to their versatile pharmacological activities. Although a variety of non-asymmetric reactions have been developed, general, catalytic and asymmetric variants to allow for the synthesis of chiral pyrazolidine-3,5-diones derivatives have been less developed [24,25]. Kang and co-workers reported a Rh-catalyzed enantioselective Michael addition reaction

of pyrazolidine-3,5-diones with α,β-unsaturated 2-acyl imidazoles [24]. We recently reported a Pd-catalyzed asymmetric spirocyclization of pyrazolidine-3,5-diones with 1,3-enynes (Fig. 1d) [25]. Both reports target chiral pyrazolidine-3,5-diones with a central chirality. To our knowledge, chiral pyrazolidine-3,5-diones with a different type of chiral element such as axial chirality have not been synthesized, and their applications remain unknown. Chiral allenes represent an important type of axially chiral structural motif in natural products and bioactive molecules, and also are a versatile functional group in chemical transformations [26–29]. The development of efficient methods for catalytic asymmetric synthesis of allene-containing compounds have attracted much attention [30–34]. We envisioned that the enantioselective 2,3-allenylation of pyrazolidine-3,5-diones would not only be an attractive combination for medicinal chemistry due to the unique biological and chemical properties of the axially chiral allene unit and pyrazolone motif but also dramatically increase the diversity of pyrazolidine-3,5-diones derivatives.

As part of our interest in the TM-catalyzed asymmetric 1,4-hydrofunctionzation of 1,3-enynes [12,25] and allenylic substitution reactions [7,8], we herein demonstrate that a chiral Ni/P-Phos catalyst to achieve both asymmetric 1,4-hydroalkylation of prochiral 1,3-enynes and asymmetric allenylic substitution of racemic allenic ethers with pyrazolidine-3,5-diones (Fig. 1e). Two methods do not require any additives, complement each other, and produce various axially chiral allene derivatives bearing a pyrazolidine-3,5–dione unit with high levels of regioselectivity and enantioselectivity. Moreover, we have designed a new class of multifunctional reagents, enynyl ethers, and developed an unprecedented Ni-catalyzed asymmetric double alkylation, providing a platform for the reaction development and the allene synthesis.

On the basis of our previous work [25], we initially examined chiral palladium catalysts for the asymmetric 1,4-hydroalkylation of 1,3-enyne **1a** with pyrazolidine-3,5–dione **2a** in the presence of $[Pd(allyl)Cl]_2$ and chiral ligands (Table 1). The use of Wing-Phos **L4** [35,36], which was effective in the Pd-catalyzed asymmetric spirocyclizations of pyrazolidine-3,5-diones with 1,3-enynes [25], led to the 1,4-hydroalkylation product **3a** in 54% yield but with 28% enantioselectivity. Other several chiral ligands also furnished the 1,4-hydroalkylation product **3a**, with (*S*)-P-Phos **L6** offering the highest yield (90%) (entry 6). Unfortunately, no enantioselectivity can be obtained in all chiral ligands examined. Interestingly, when $Ni(PPh_3)_2Cl_2$ was used in combination of (*S*)-P-Phos **L6**, the desired axially allene **3a** was obtained in 91% *ee* and 77% yield (entry 7). Screening other nickel salts (entries 8–17) and chiral ligands (see Supporting information for details), no better results were obtained. It is worth mentioning that despite P-Phos as a family of versatile and effective atropisomeric dipyridylphosphine ligands in asymmetric catalysis [37], this class of chiral ligands has not been successfully applied in the catalytic asymmetric 1,4-hydrofunctionzation reaction of 1,3-enynes.

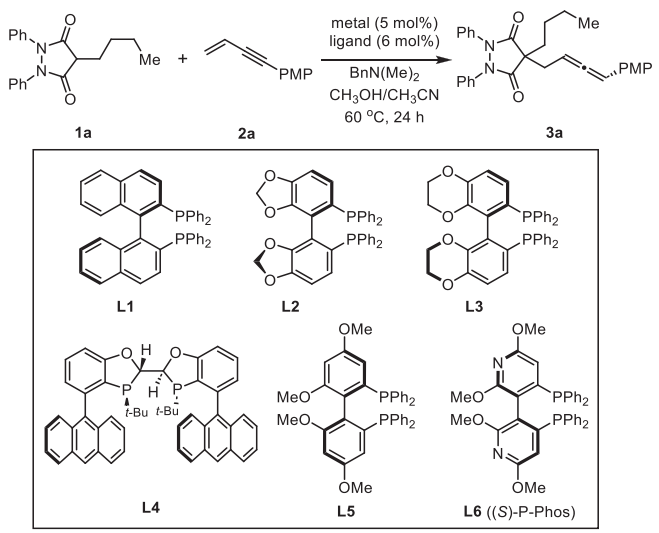
With the optimized catalytic system in hand, we explored the substrate scope of nickel-catalyzed 1,4-hydroalkylation of 1,3-enynes (Scheme 1). A variety of 1,3-enynes bearing electron neutral, donating, and withdrawing groups on the (hetero)aryl group substituents reacted smoothly with various pyrazolidine-3,5-diones to furnish the products **3b**-**3q** in good yields with high levels of regio- and enantioselectivity. The absolute configuration of the product **3r** was determined by X-ray analysis.

It is worth noting that in the above asymmetric 1,4-hydroalkylation of 1,3-enynes, although alkyl-substituted enynes have good reactivity, the enantioselectivity of the corresponding products is low (**3s** and **3t**). Fortunately, we found that when allenic ethers **4a** and **4b** were used as alternative allenylation reagents, the target products **3s** (87% yield, 89% *ee*) and **3t** (80% yield, 90% *ee*) could be obtained in good yield and good enantioselectivity in the presence of Ni/P-Phos catalytic system (Scheme 2). Other alkyl-substituted allenic ether substrates were also suitable (**3u**-**3z**) for the asymmetric allenylic substitution. Moreover, aryl-substituted allenic ethers also provided the corresponding product **3a** in 88% yield with 90% *ee* (Eq. 1) and **3ab** in 76% yield with 92% *ee* (Eq. 2). It is important to synthesize allenylic substituted product **3a** on a gram-scale with 74% yield and 92% *ee* (Eq. 1). Other heterocyclic 1,3-dicarbonyl compounds such as barbituric acid **5** can also be compatible with Ni/P-Phos catalyst, providing the product **6** in 80% yield with 89% *ee* (Eq. 3). In addition, we also investigated the leaving groups of allelic ethers, and found that (4-bromobenzyl)oxy was a good leaving group rather than phenoxy and benzyloxy (see Supporting information for details).

In order to further test the generality of Ni/P-Phos catalytic system and develop new chemistry, we designed a new class of bifunctional reagents, enynyl ethers **7**, and investigated the Ni/P-Phos catalyzed asymmetric reaction of such substrates with pyrazolidine-3,5-diones (Scheme 3). To our delight, the double alkylation products **8** with novel structures were obtained in good yields and good enantioselectivity.

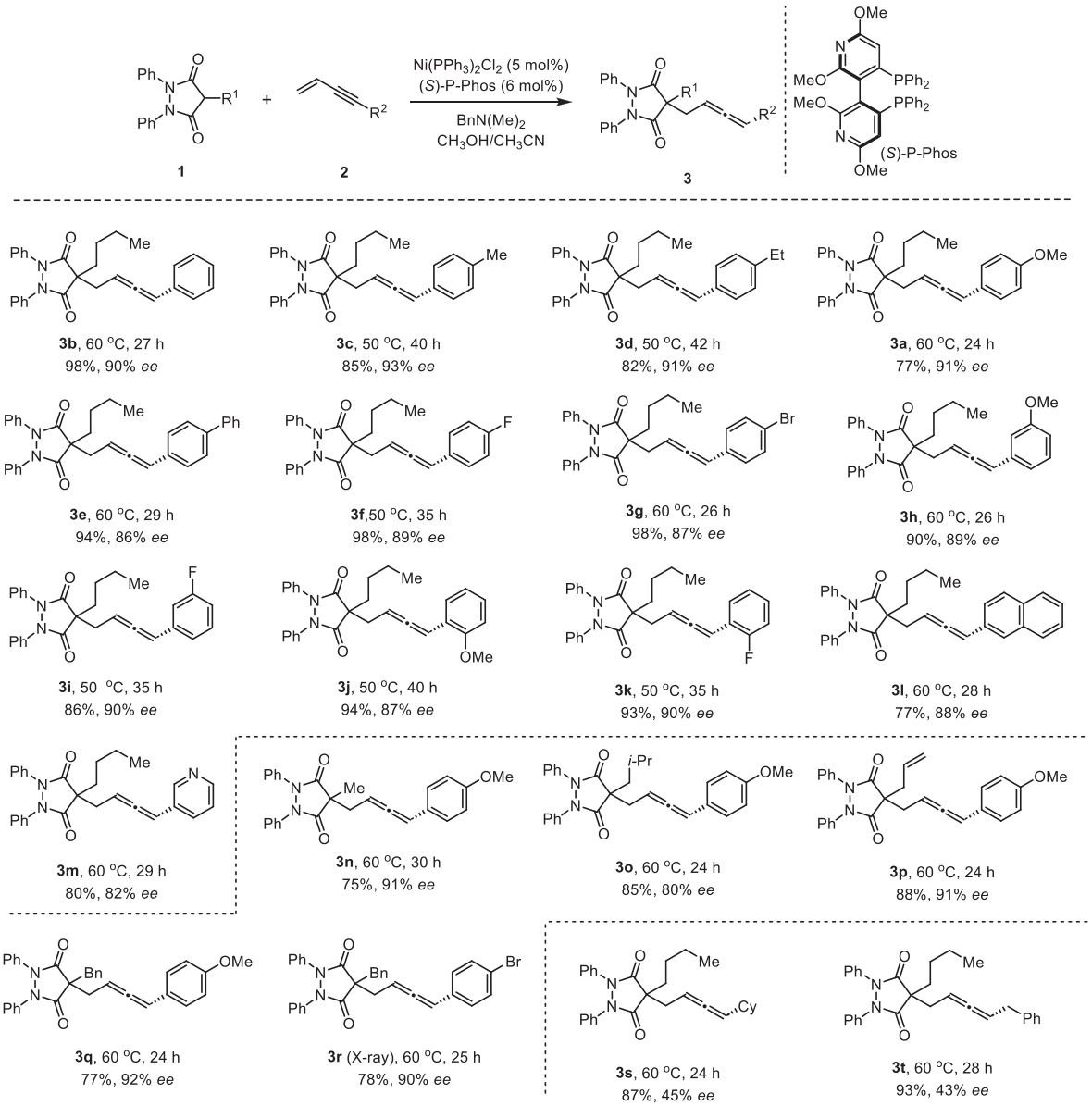
To understand the mechanism of Ni-catalyzed symmetric reaction of enynyl ethers **7**, we attempted to synthesize a possible intermediate **4aa** (Eq. 4). When **4aa** reacted with pyrazolidine-3,5–

Table 1
Reaction optimization.[a]



Entry	Metal	Ligand	Yield (%)[b]	*ee* (%)[c]
1	$[Pd(allyl)Cl]_2$	**L1**	30	0
2	$[Pd(allyl)Cl]_2$	**L2**	35	10
3	$[Pd(allyl)Cl]_2$	**L3**	32	0
4	$[Pd(allyl)Cl]_2$	**L4**	54	28
5	$[Pd(allyl)Cl]_2$	**L5**	45	10
6	$[Pd(allyl)Cl]_2$	**L6**	90	0
7	$Ni(PPh_3)_2Cl_2$	**L6**	77	91
8	$NiCl_2$·DME	**L6**	37	74
9	$NiBr_2$·DME	**L6**	31	90
10	NiI_2	**L6**	30	90
11	$NiCl_2·6H_2O$	**L6**	trace	–
12	$NiI_2·6H_2O$	**L6**	70	88
13	$Ni(P(Cy)_3)_2Cl_2$	**L6**	30	90
14	$Ni(BF_4)_2·6H_2O$	**L6**	35	90
15	$Ni(OAc)_2·4H_2O$	**L6**	trace	–
16	$Ni(OTf)_2$	**L6**	32	90
17	$Ni(COD)_2$	**L6**	95	81

[a] Reactions were performed with **1a** (0.1 mmol), **2a** (0.12 mmol), metal (5 mol%), ligand (6 mol%) and $BnN(Me)_2$ (8 equiv.) in 0.5 mL of solvent ($CH_3OH/CH_3CN = 3:2$) at 60 °C for 24 h.
[b] Yield of isolated product.
[c] *ee* was determined by chiral HPLC. PMP = 4-MeO–C_6H_4.

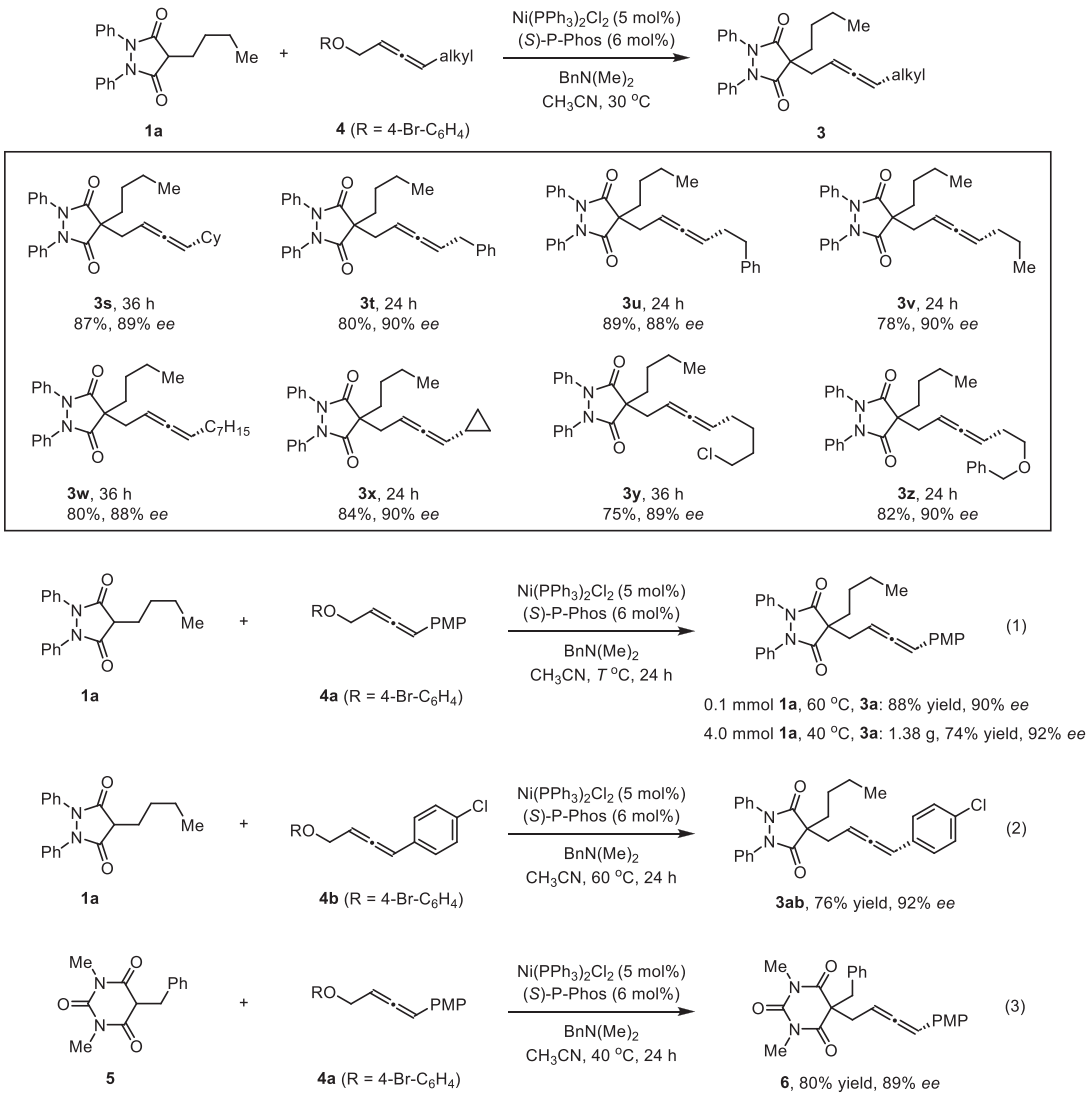


Scheme 1. Ni-catalyzed asymmetric 1,4-hydroalkylation of 1,3-enynes 1 with pyrazolidine-3,5-diones. Reactions were performed with **1** (0.1 mmol), **2** (0.12 mmol), $Ni(PPh_3)_2Cl_2$ (5 mol%), (*S*)-P-Phos (6 mol%) and $BnN(Me)_2$ (8 equiv.) in 0.5 mL of solvent ($CH_3OH/CH_3CN = 3:2$).

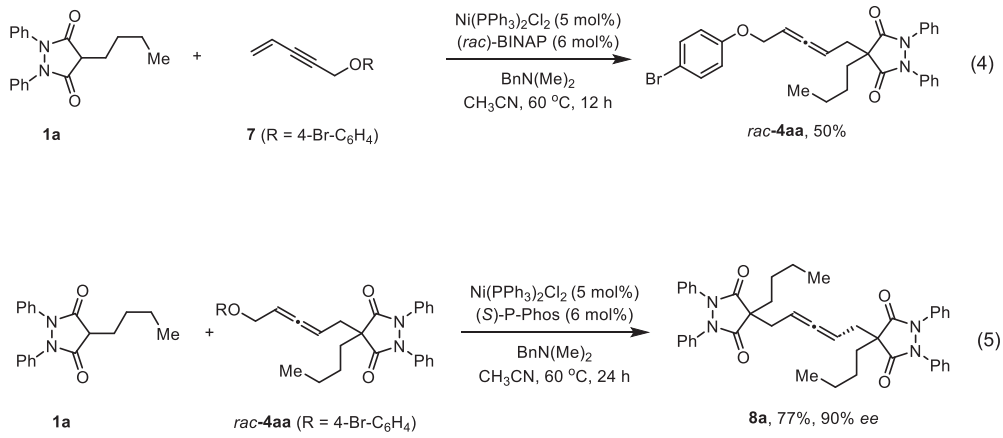
dione **1a** in the Ni/P-Phos catalytic system, the product **8a** was obtained with 77% yield and 90% *ee* (Eq. 5). The results indicate that Ni/P-Phos catalyzed asymmetric reaction of enynyl ethers proceeds through a new one-pot sequence involving intermolecular 1,4-hydroalkylation and intermolecular allenylic alkylation where intermolecular allenylic alkylation was the enantio-determining step.

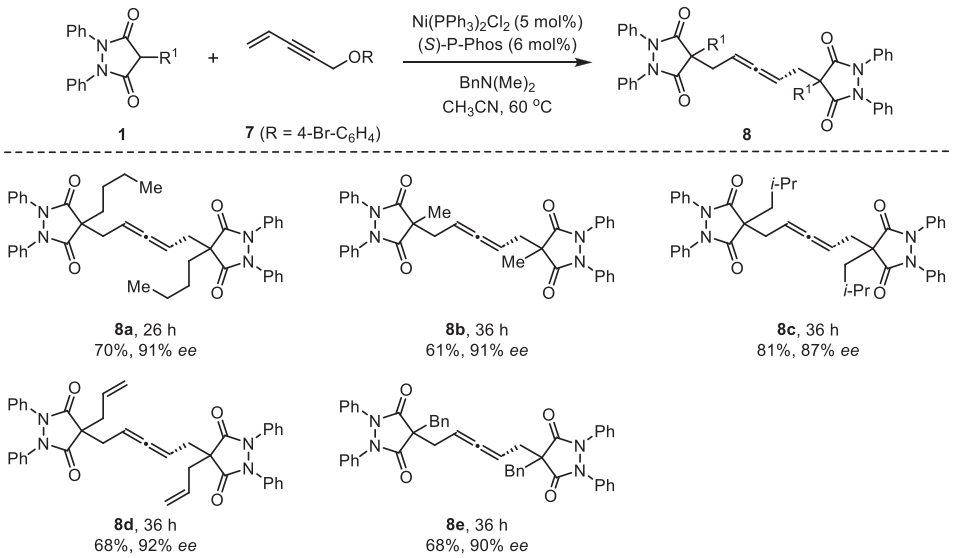
A possible mechanism for the Ni-catalyzed asymmetric reaction of enynyl ethers **7** was proposed in Fig. 2. The intermediate **A** was formed by regioselective Ni–H insertion occurs at the olefin group in enynyl ethers **7**. **A** was captured by **1a**, forming the intermediate **4aa**. Next, **4aa** underwent a nickel(0)-catalyzed oxidation addition to form the intermediate **B**. Then the intermediate **B** reacted with **1a** to provide the double alkylation product **8a** and regenerate nickel(0).

In conclusion, we have developed chiral Ni-catalyzed asymmetric 1,4-hydroalkylation of prochiral 1,3-enynes and asymmetric allenylic substitution of racemic allenic ethers with pyrazolidine-3,5-diones, and synthesized a class of important nitrogen heterocyclic compounds which are key motifs widely present in drugs and biologically active molecules. Two methods do not require any additives, complement each other and furnish a variety of axially chiral allene derivatives bearing a pyrazolidine-3,5–dione unit with high levels of regio- and enantioselectivity. These studies provide not only an elusive example of asymmetric 1,4-hydrofunctionalization of 1,3-enynes using low-cost chiral nickel catalyst, enriching the catalytic systems and providing a new opportunity for the activation of 1,3-enynes for reaction development, but also offer an elusive asymmetric allenylic substitution using a chiral nickel catalyst, expanding the substrate type/scope and enabling stable allenic ethers bearing a challenging leaving group as the substrates in TM-asymmetric allenylic substitution reaction that has not previously been reported. Moreover, we have designed a new class of multifunctional reagents, enynyl ethers, and developed an unprecedented Ni-catalyzed asymmetric double alkylation, providing a platform for the reaction development and the allene synthesis.



Scheme 2. Ni-catalyzed asymmetric allenylic substitution of allenic ethers with pyrazolidine-3,5-diones. Reactions were performed with **1a** (0.1 mmol) or **5** (0.1 mmol), **4** (0.12 mmol), $Ni(PPh_3)_2Cl_2$ (5 mol%), (*S*)-P-Phos (6 mol%) and $BnN(Me)_2$ (12 equiv.) in 0.5 mL of CH_3CN at 30 °C.





Scheme 3. Ni-catalyzed asymmetric double alkylation of enynyl ethers with pyrazolidine-3,5-diones. Reactions were performed with **1** (0.12 mmol), **7** (0.1 mmol), $Ni(PPh_3)_2Cl_2$ (5 mol%), (*S*)-P-Phos (6 mol%) and $BnN(Me)_2$ (12 equiv.) in 0.5 mL of CH_3CN at 60 °C.

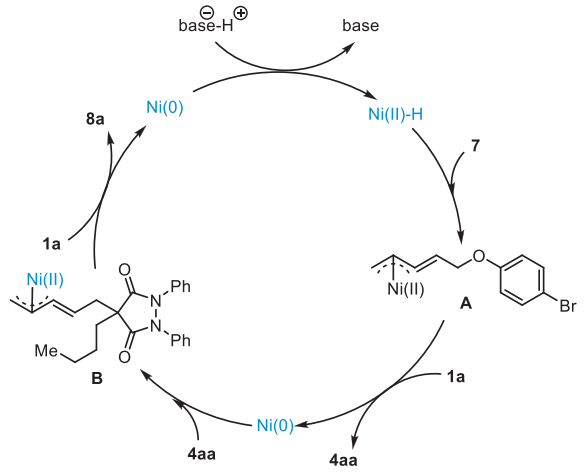


Fig. 2. Proposed mechanism for Ni-catalyzed asymmetric reaction of enynyl ethers.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109518.

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