Communication

Ni-Catalyzed Asymmetric Allylation of Secondary Phosphine Oxides

Xu-Teng Liu, Ya-Qian Zhang, Xue-Yu Han, Shi-Ping Sun, and Qing-wei Zhang

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Xu-Teng Liu, Ya-Qian Zhang, Xue-Yu Han, Shi-Ping Sun, Qing-Wei Zhang*

Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

Supporting Information Placeholder

ABSTRACT: A nickel catalyzed asymmetric allylation of secondary phosphine oxides (SPO) for the synthesis of tertiary phosphine oxides (TPO) was realized with high enantioselectivity. By elucidating the absolute configurations of the reacted SPO starting material and the TPO product, we confirmed that the allylation reaction proceeded through a *P*-stereo retention process. The protocol represents the first example of synthesizing *P*-stereogenic phosphine oxides by allylation reaction.

Enantioenriched *P*-stereogenic phosphines have served as important chiral ligands for transition metals as well as organocatalyts.[1] However, they are less studied compared to their counterparts that have chiral carbon backbones, in part due to the less availability and synthetic challenges.[2] Traditional methods to synthesize *P*-stereogenic phosphines require the use of stoichiometric amount of chiral reagents, such as resolution,[3] auxiliary induced diastereoselective substitution[4] and enantioselective deprotonation/derivatization reactions.[5] Nevertheless, the ephedrine based strategies were still considered as a reliable and robust preparation of *P*-stereogenic phosphines.[4d,4e]

As a more efficient alternative, catalytic asymmetric synthesis of *P*-stereogenic phosphines has attracted broad attention. During the past decade, a series of inter- or intramolecular desymmetrization reactions of prochiral phosphine derivatives have been developed. Transition metal catalyzed 1,4-addition,[6] [2+2+2],[7] ring-closing metathesis[8], C-H bond activation reactions,[9] and N-heterocyclic carbene catalyzed allylic alkylation and acylation reactions,[10] enabled the synthesis of a wide range of *P*-chiral compounds (Scheme 1a). The direct coupling of secondary phosphines with various electrophiles provided a more straightforward way to access *P*-chiral compounds with diverse functional groups, *e.g.*, transition metal catalyzed alkylation,[11] arylation,[12] 1,4- and 1,6-addition reactions[13,14] (Scheme 1b). The facile interconversion of both enantiomers of secondary phosphines under mild conditions was one key factors to allow these reactions to proceed through dynamic kinetic resolutions (DKR),[15] affording enantioenriched *P*-chiral compounds from racemates. However, the toxicity and liability of secondary phosphines have restricted their applications.[16]

In comparison, secondary phosphines oxides (SPO), which are bench stable, less toxic and odorless, could serve as promising alternatives. However, only two catalytic asymmetric reactions of SPO for the synthesis of *P*-chiral compounds have been published. In 2016, Gaunt group reported the first catalytic asymmetric reaction of SPO, affording chiral TPO efficiently with excellent *ee* (Scheme 1c).[17] Shortly after, Cai group reported a Pd-catalyzed kinetic resolution arylation of SPO with moderate to high enantioselectivities (Scheme 1d).[18] Despite of both findings, however, two equivalents of SPO are required either to offset the oxidative side

reaction or to secure better enantioselectivities and yields. In addition, it is challenging to achieve the DKR reaction to a large extend due to the elusive racemization of SPO.[19-21]

Scheme 1. Catalytic Asymmetric Synthesis of *P*-stereogenic Phosphines
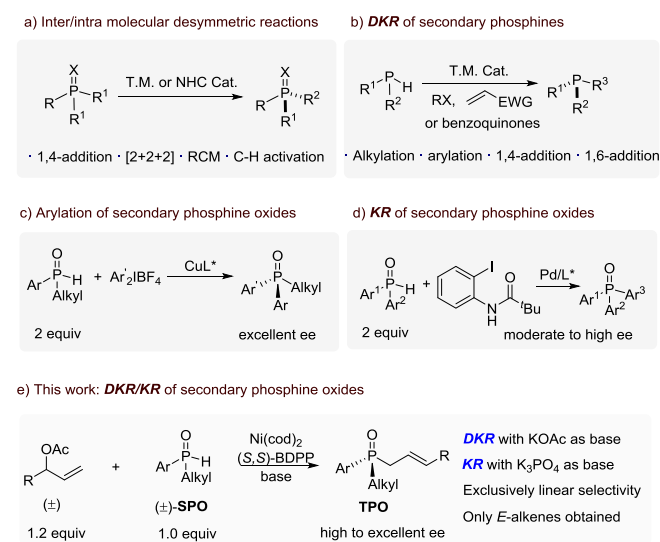
Transition metal catalyzed asymmetric allylic substitution reaction has made tremendous achievement in synthetic organic chemistry, serving as a powerful strategy to construct C-C and C-X bonds with chiral carbon centers.[22] Among them, only a few examples have been reported with nickel complexes as catalysts.[23] One drawback associated with nickel catalysis is that only hard nucleophiles which suffer from poor functional group tolerance could deliver the products with satisfactory enantioselectivities.[24] Herein, we report our finding on Ni-catalyzed DKR/KR allylation of SPO (scheme 1e).[25]

We commenced our study by conducting the reaction with phenylmethyl phosphine oxide (**1a**) and allylic acetate (**2a**) as model substrates with Ni(cod)$_2$ as catalyst. The initial screening of achiral ligands has enabled us to realize the reaction under mild conditions based on the preliminary results from the Lu group.[26] The asymmetric version of the reaction was then optimized (Table 1). At the outset of the screening, we were aware that the racemization of **1a** might be problematic and full conversion of **1a** might result in decreased enantioselectivity. Therefore, the ee of the product **3a** was detected at <50% conversion.

Table 1. Optimization of reaction conditions[a]

Table 1 scheme (1a + 2a → 3a)
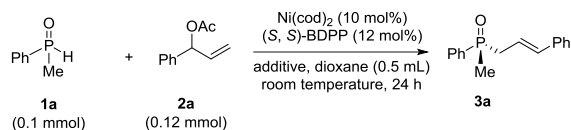
Entry	Ligand	Additive	Yield(%)[b]	ee(%)[c]
1	L1	K₃PO₄	15	<5%
2	L2	K₃PO₄	18	17
3	L3	K₃PO₄	18	30
4	L4	K₃PO₄	30	53
5	L5	K₃PO₄	>95	6
6[d]	L5	K₃PO₄	51 (42)	87 (80)
9	L5	DBU	>95	45
10	L5	DABCO	>95	57
11	L5	KOAc	>95	71
12[e,f]	L5	KOAc	>95	82
13[e,g]	L5	HOAc	>95, 96[h]	89

L1, *R*-Josiphos   L2, (*R, R*)-DiPAMP   L3, (*R, R*)-BPE   L4, (*S, S*)-Chiraphos   L5, (*S, S*)-BDPP

[a] Ni(cod)₂, (*S, S*)-BDPP were dissolved in dioxane and stirred for 10 min followed by the addition of **1a**, **2a** and additive (1.5 equiv). [b]NMR yield with P(OMe)₃ as internal standard, yield of remaining **1a** was shown in parentheses. [c]Determined by chiral HPLC analysis, ee of remaining **1a** was shown in parentheses. [d]2 hours. [e]In 2 mL dioxane. [f]48 h. [g]72 h. [h]Isolated yield.

A series of chiral bisphosphine ligands were initially screened (entries 1-4), among which (*R*)-Josiphos (**L1**) gave **3a** in only 15% yield with marginal ee (<5%, entry 1). The reaction with (*R, R*)-DiPAMP (**L2**), (*R, R*)-BPE (**L3**) and (*S, S*)-Chiraphos (**L4**) as ligands gave comparable yields while with better enantioselectivities of 17%, 30%, 53% ee respectively (entries 2-4). Surprisingly, (*S, S*)-BDPP (**L5**), a close analogue of chiraphos, exhibited superior reactivity, affording **3a** with >95% yield albeit with low ee (6%, entry 5). The reaction was then quenched at around 50% yield, to our delight, both **3a** and the remaining **1a** were obtained with high enantioselectivities (87% and 80% ee). This phenomenon revealed that the reaction proceeded through a kinetic resolution process. Encouraged by the result, we tried to further achieve more promising DKR of SPO. We are aware that the key factor to the success is to leverage the relative reaction rate of the enantiodetermining step with the racemization of the remaining enantioenriched SPO. In line with the notion, we screened a plethora of additives to accelerate the racemization of **1a** while decrease the allylation reaction (entries 9-14, see SI). Compared to K₃PO₄, organic bases like DBU, DABCO could give **3a** with significant increased enantioselectivities (45%, 57%) at >95% yield (entries 9-10). In the presence of a weaker base KOAc, the ee of **3a** was increased to 71% ee (entry 11), and further improved to 82% ee in diluted solution (0.05 M, entry 12). The reaction could be conducted under acidic condition, affording **3a** with better enantioselectivity (89% ee) and 96% isolated yield (entry 13). However, substrate **1b** reacted slowly with HOAc as additive, affording **3b** in 79% yield and 92% ee (table 2). Thereafter KOAc was used instead, **3b** was obtained with 94% ee and 96% isolated yield. The enantioselectivity of the reaction is independent to the leaving group of the allylic ester, substrates bearing a Obz, OBoc or *para*-methoxyl Obz group all gave the desired product in 94% ee with 96%, 22% and 95% yield respectively. A
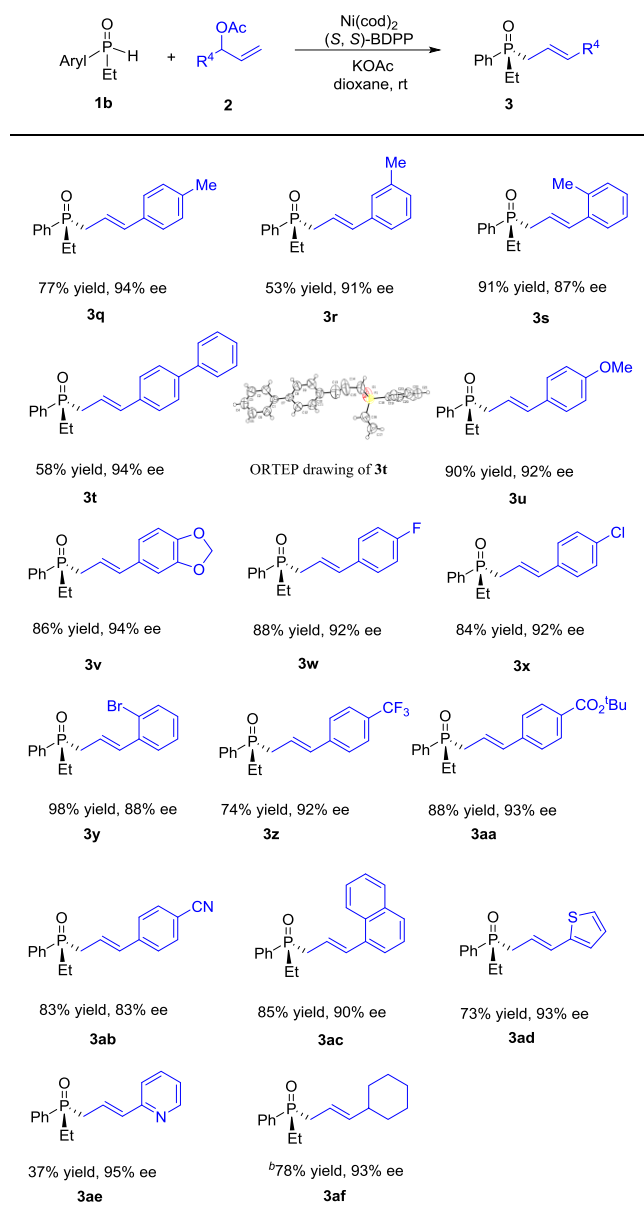
π-allyl nickel intermediate was probably involved and the hypotheses was further confirmed by the fact that linear allyl ester **2a'** could give (95% yield and 94% ee) similar results as **2a** did.

Table 2. Scope of phosphine oxides

[a] **1** (0.1 mmol), **2** (0.12 mmol), Ni(cod)₂ (10 mol%), (*S, S*)-BDPP (12 mol%), KOAc (1.5 equiv), 2.0 mL Dioxane, rt. LG = OAc unless noted. [b]40 °C.

The substrate scope was investigated under standard conditions (table 2). A series of SPO with different alkyl (**1c-1i**) or aryl (**1j-1p**) groups were initially tested. The steric hindrance of alkyl substituent has a significant impact on the reaction. Although these substrates (**1c-1h**) generally gave high enantioselectivities, the less sterically hindered ones were more favorable in terms of both reactivity and enantioselectivity (87% to 64% ee, **3c-3h**). Substrate **1i** with an allyl substituent was also compatible with the reaction, producing **3i** in 91% yield and 86% ee. A number of secondary arylethyl phosphine oxides were then tested. Substrates with a *meta*- or *para*-methyl phenyl group (**1j**, **1k**) reacted smoothly, affording products **3j** and **3k** in 95% yields with 91%, 89% ee respectively. However, substrate **1l** bearing an *ortho*-methylphenyl groups exhibit poor reactivity (27% yield at 40 °C) and gave diminished enantioselectivity (75% ee). The electron donating *para*-methoxyl group in substrate **1m** was also detrimental to the reactivity affording **3m** in 35% yield, but the enantioselectivity was not influenced (92% ee). **1n** with an electron withdrawing *para*-F substituent was compatible with the condition, affording **3n** in 89% yield and 90% ee. Substrates **1o** and **1p** with 2-naphthyl, 2-thienyl groups also reacted smoothly, delivering **3o** and **3p** in high yields (76%, 93%) and ee values (94%, 86%).

Table 3. Scope of allylic esters

3q
77% yield, 94% ee

3r
53% yield, 91% ee

3s
91% yield, 87% ee

3t
58% yield, 94% ee

ORTEP drawing of **3t**

3u
90% yield, 92% ee

3v
86% yield, 94% ee

3w
88% yield, 92% ee

3x
84% yield, 92% ee

3y
98% yield, 88% ee

3z
74% yield, 92% ee

3aa
88% yield, 93% ee

3ab
83% yield, 83% ee

3ac
85% yield, 90% ee

3ad
73% yield, 93% ee

3ae
37% yield, 95% ee

3af
[b]78% yield, 93% ee

[a] **1b** (0.1 mmol), **2** (0.12 mmol), Ni(cod)$_2$ (10 mol%), (S, S)-BDPP (12 mol%), KOAc (1.5 equiv), 2.0 mL Dioxane, rt. [b]40 °C.

We then investigated the scope of allylic esters with **1b** as the reaction partner (Table 3). A series of aromatic substituents bearing electron donating or electron withdrawing groups were all well tolerated, furnishing desired products (**3q**-**3ab**) in moderate to high yields (53%-98%) with high enantioselectivities (83%-94% ee). Among them, the absolute configuration of product **3t** was unambiguously determined to be *R* by single crystal XRD analysis.[27] Substrate **1y** with an *ortho*-Br group could survive the nickel catalysis condition, affording **3y** in 98% yield and 88% ee. The reaction was applicable to other aryl/heteroaryl substituents including 1-naphthyl, 2-thienyl and 2-pyridyl groups, producing **3ac**, **3ad** and **3ae** with high enantioselectivities (90%-95% ee). However, pyridyl group was detrimental to the reactivity, affording **3ae** in a modest yield (37%). Allylic ester with an alkyl group (cyclohexyl) could also deliver the product in 78% yield and 93% ee at elevated temperature (40 °C). It should be noted that all products were obtained with exclusively linear selectivity and *E* configuration.

To investigate the origin of KR/DKR, we monitored the reaction of **1b** with **2z** with KOAc and K$_3$PO$_4$ as the additive separately (Figure 1). In both cases, the *ee* of unreacted **2z** remained <5% throughout the reaction, and the linear regioisomer **2z'** which probably generated from the nickel catalyzed linear selective allylic substitution reaction was also detected (please see SI). In contrast, the variation of ee of **1b** and **3z** was closely associated with the additive. When K$_3$PO$_4$ was used, a kinetic resolution reaction was observed. Product **3z** was detected with high ee at conversion lower than 50% while low *ee* at high conversion (figure 1). On the contrary, the ee of **1b** was low at lower conversion while high at higher conversion. The selectivity factor was calculated to be 37 based on first order kinetics. When KOAc was used, a dynamic kinetic resolution reaction was observed. Although only partial racemization of the remaining **1b** was achieved, the ee of product **3z** was substantially maintained. In both cases, the absolute configuration of remained **1b** was determined to be R_p as compared with known compound by HPLC retention time.

Figure 1. Mechanistic study
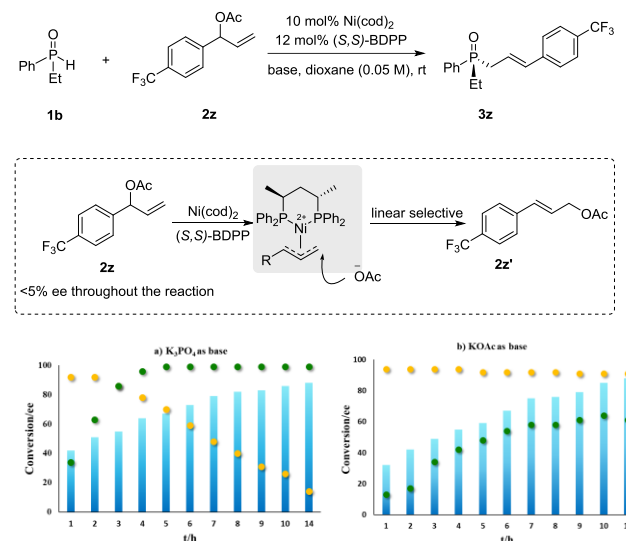
Green dots, ee of remaining **1b**; yellow dots, ee of **3z**; blue columns, conversion of **1b**.

We also performed the racemization study of **1a** with each component of the reaction (please see SI). The results showed that nickel (II) complex was probably responsible for the racemization in the presence of KOAc. However, the racemization could be inhibited by K$_3$PO$_4$. Based on the result above, a mechanism considering the origin of dynamic kinetic resolution was proposed (scheme 2). Under the catalysis of nickel complex, allylic ester **2** or **2'** could form a nickel π-allyl intermediate followed by enantioselective nucleophilic addition of the secondary phosphine oxide which could be racemized by Ni(II) complex when KOAc was used as an additive. During the reaction the absolute configuration of *P*-stereogenic center retained.

Scheme 2. Proposed reaction mechanism in terms of DKR
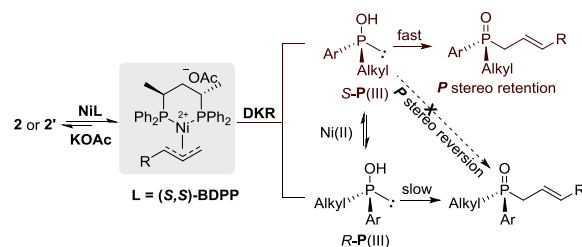
We also carried out the reaction on 0.5 mmol scale (Scheme 3), and product **3b** was obtained in 77% yield while maintaining the enantioselectivity (93% ee). The efficient transformation to *P*-chiral phosphine-BH_3 adduct was also realized without affecting the double bond geometry following a reported procedure,[28] producing the desired product **4** in one pot in 60% yield with 92% ee (Scheme 3).

Scheme 3. Derivatization of the TPO product
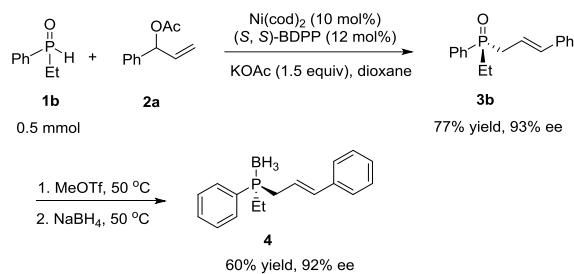
In summary, we have achieved the first example of nickel catalyzed dynamic kinetic resolution (DKR) allylation of SPO. A series of *P*-stereogenic tertiary phosphine oxides were synthesized from both racemic allylic esters and secondary phosphine oxides (SPO). The kinetic and racemization study revealed the origin of the DKR reaction which relies on the Ni(II) catalyzed racemization of the SPO when KOAc was used as an additive. The finding of this research will expand the applications of SPO in the synthesis of *P*-stereogenic phosphines.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data, copies of ^{1}H, ^{13}C, ^{31}P, ^{19}F NMR spectra and HPLC chromatograms (PDF)

Crystallographic data for **3t** (CIF)

AUTHOR INFORMATION

Corresponding Author

qingweiz@ustc.edu.cn

Notes

The authors declare no competing financial interests.

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