

Ni-Catalyzed Asymmetric Allylation of Secondary Phosphine Oxides

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Supporting Information

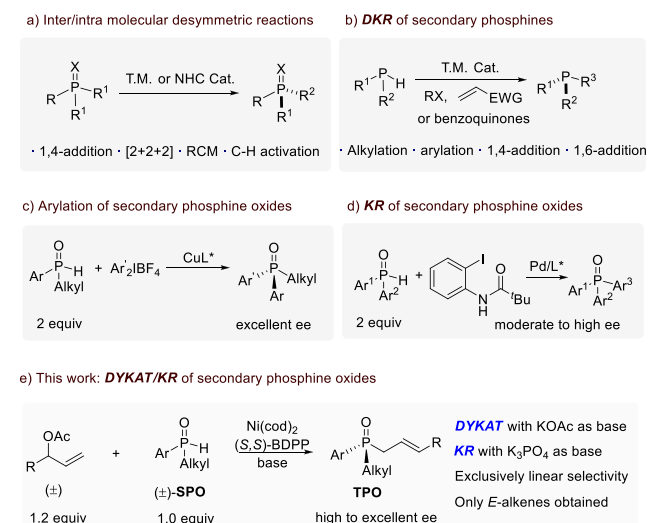
ABSTRACT: A nickel-catalyzed asymmetric allylation of secondary phosphine oxides (SPO) for the synthesis of tertiary phosphine oxides (TPO) was realized with high enantioselectivity. The dynamic kinetic asymmetric transformation of SPO was accomplished in the presence of nickel complex. By elucidating 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 organocatalysts.¹ However, they are less studied compared to their counterparts that have chiral carbon backbones, in part due to their less availability and synthetic challenges.² Traditional methods to synthesize *P*-stereogenic phosphines require the use of stoichiometric amounts of chiral reagents; such as methods include resolution,³ auxiliary-induced diastereoselective substitution,⁴ and enantioselective deprotonation/derivatization reactions.⁵ Ephedrine-based strategies are also considered as reliable and robust methods for the preparation of *P*-stereogenic phosphines.^{4d,e}

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 reactions¹⁰ have 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 and 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 asymmetric transformation (DYKAT),¹⁵ affording enantioenriched *P*-chiral compounds from racemates. However, the toxicity and liability of secondary phosphines have restricted their applications.¹⁶

In comparison, secondary phosphine 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

Scheme 1. Catalytic Asymmetric Synthesis of *P*-Stereogenic Phosphines



been published. In 2016, the Gaunt group reported the first catalytic asymmetric reaction of SPO, affording chiral TPO efficiently with excellent enantiomeric excess (ee) (Scheme 1c).¹⁷ Shortly after, the Cai group reported a Pd-catalyzed kinetic resolution arylation of SPO with moderate to high enantioselectivities (Scheme 1d).¹⁸ Despite their findings, however, 2 equiv of SPO is required either to offset the oxidative side reaction or to secure better enantioselectivities and yields. In addition, it is challenging to achieve the DYKAT reaction to a large extent due to the elusive racemization of SPO.^{19–21}

Transition-metal-catalyzed asymmetric allylic substitution reactions have led to tremendous achievements 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 DYKAT/*KR* allylation of SPO (Scheme 1e).²⁵

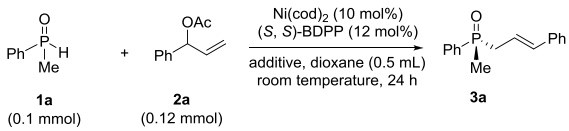
We commenced our study by conducting the reaction with phenylmethyl phosphine oxide (**1a**) and allylic acetate (**2a**) as model substrates with Ni(cod)₂ as catalyst. The initial screening of achiral ligands has enabled us to realize the

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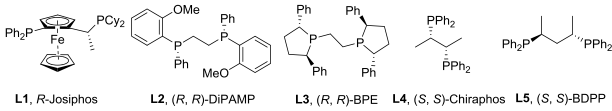
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reaction under mild conditions based on the preliminary results from the Lu group.²⁶ The asymmetric version of the reaction was then optimized (Table 1). At the outset of the

Table 1. Optimization of Reaction Conditions^a



Entry	Ligand	Additive	Yield(%) ^b	ee(%) ^c
1	L1	K ₃ PO ₄	15	<5%
2	L2	K ₃ PO ₄	18	17
3	L3	K ₃ PO ₄	18	30
4	L4	K ₃ PO ₄	30	53
5	L5	K ₃ PO ₄	>95	6
6 ^d	L5	K ₃ PO ₄	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



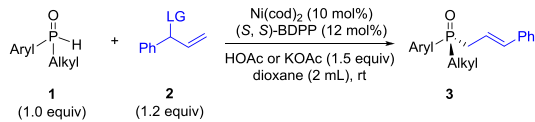
^aNi(cod)₂, (S, S)-BDPP in dioxane was stirred for 10 min, followed by the addition of **1a**, **2a**, and additive (1.5 equiv). ^bNMR yield with PO(OMe)₃ as internal standard; yield of remaining **1a** is shown in parentheses. ^cDetermined by chiral HPLC analysis; ee of remaining **1a** is shown in parentheses. ^d2 h. ^e2 mL dioxane. ^f48 h. ^g72 h. ^hIsolated yield.

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.

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 reactions with (R,R)-DiPAMP (**L2**), (R,R)-BPE (**L3**), and (S,S)-Chiraphos (**L4**) as ligands gave comparable yields but with better enantioselectivities of 17%, 30%, and 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 DYKAT of SPO. We are aware that the key factor to the success is to leverage the relative reaction rate of the enantio-determining step with the racemization of the remaining enantio-enriched SPO. In line with the notion, we screened a plethora of additives to accelerate the racemization of **1a** while decreasing the allylation reaction (entries 9–14, see SI). Compared to

K₃PO₄, organic bases like DBU and DABCO could give **3a** with significantly increased enantio-selectivities (45%, 57%) at >95% yield (entries 9 and 10). In the presence of a weaker base, KOAc, the ee of **3a** was increased to 71% ee (entry 11), and it was further improved to 82% ee in diluted solution (0.05 M, entry 12). The reaction could be conducted under acidic conditions, affording **3a** with better enantio-selectivity (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

Table 2. Scope of Phosphine Oxides



Entry	Yield (%)	ee (%)
3b	79% (96% ^a)	92% (94% ^a)
3c	95%	87%
3d	84%	81%
3e	61%	77%
3f	77%	74%
3g	53%	64%
3h	46%	66%
3i	91%	86%
3j	95%	91%
3k	95%	89%
3l	27%	75%
3m	35%	92%
3n	89%	90%
3o	76%	94%
3p	93%	86%

LG, Yield, ee of **3b**: OBz, 96% yield, 94% ee; OBoc, 22% yield, 94% ee; *p*-MeOBz, 95% yield, 94% ee.

^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. ^b40 °C.

instead, and **3b** was obtained with 94% ee and 96% isolated yield. The enantio-selectivity of the reaction is independent of the leaving group of the allylic ester: substrates bearing an Obz, OBoc, or *p*-methoxyl-Obz group all gave the desired product in 94% ee with 96%, 22%, or 95% yield, respectively. A π -allyl nickel intermediate was probably involved, and this hypotheses was further confirmed by the fact that linear allyl ester **2a'** could give results (95% yield and 94% ee) similar to those obtained with **2a**.

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

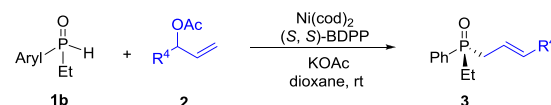
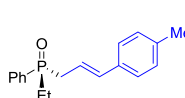
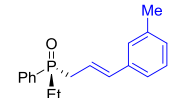
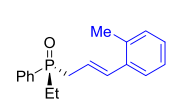
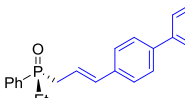
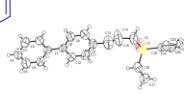
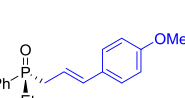
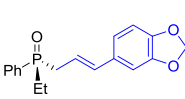
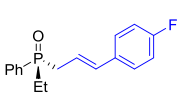
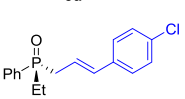
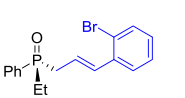
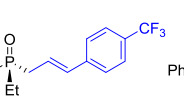
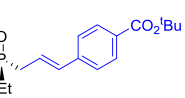
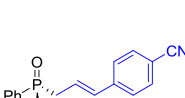
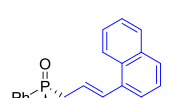
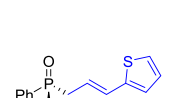
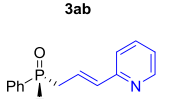
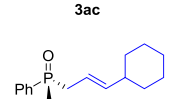
hindrance of the alkyl substituent has a significant impact on the reaction. Although these substrates (**1c–1h**) generally gave high enantio-selectivities, the less sterically hindered ones were more favorable in terms of both reactivity and enantio-selectivity (87% to 64% ee, **3c–3h**). Substrate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

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 enantio-selectivities (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 *o*-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 enantio-selectivities (90%–95% ee). However, a pyridyl group was detrimental to the reactivity, affording **3ae** in only 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/DYKAT, we monitored the reaction of **1b** with **2z** with KOAc and K₃PO₄ 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 was 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 K₃PO₄ was used, a kinetic resolution reaction was observed. Product **3z** was detected with high ee at conversion lower than 50% or low ee at high conversion (Figure 1). In contrast, the ee of **1b** was low at lower conversion but high at higher conversion. The selectivity factor was calculated to be 37 based on first-order kinetics. When KOAc was used, a DYKAT 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 the remaining **1b** was determined to be *R_p* as compared with known compound by HPLC retention time.

We also performed the racemization study of **1a** with each component of the reaction (please see SI). The results showed that the nickel(II) complex was probably responsible for the racemization in the presence of KOAc. However, the

Table 3. Scope of Allylic Esters

		
 77% yield, 94% ee 3q	 53% yield, 91% ee 3r	 91% yield, 87% ee 3s
 58% yield, 94% ee 3t	 ORTEP drawing of 3t	 90% yield, 92% ee 3u
 86% yield, 94% ee 3v	 88% yield, 92% ee 3w	 84% yield, 92% ee 3x
 98% yield, 88% ee 3y	 74% yield, 92% ee 3z	 88% yield, 93% ee 3aa
 83% yield, 83% ee 3ab	 85% yield, 90% ee 3ac	 73% yield, 93% ee 3ad
 37% yield, 95% ee 3ae	 ^b 78% yield, 93% ee 3af	

^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. ^b40 °C.

racemization could be inhibited by K₃PO₄. Based on the result above, a mechanism considering the origin of DYKAT was proposed (Scheme 2). Under the catalysis of a 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 the *P*-stereogenic center retained.

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–BH₃ 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).

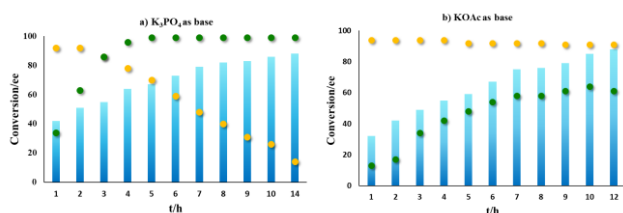
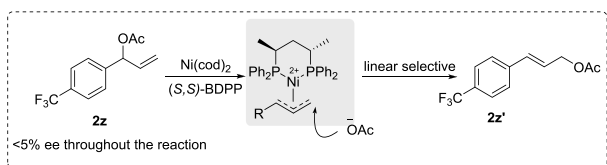
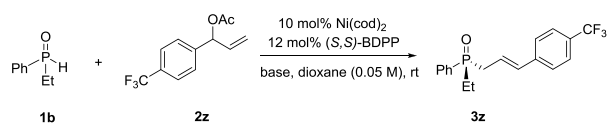
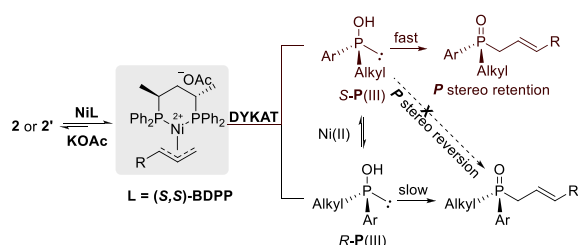
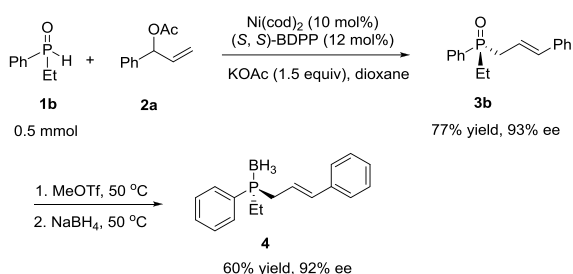


Figure 1. Mechanistic study. Green dots, ee of remaining **1b**; yellow dots, ee of **3z**; blue columns, conversion of **1b**.

Scheme 2. Proposed Reaction Mechanism in Terms of DYKAT



Scheme 3. Derivatization of the TPO Product



In summary, we have achieved the first example of nickel-catalyzed dynamic kinetic asymmetric transformation (DYKAT) 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 DYKAT 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 at DOI: 10.1021/jacs.9b08734.

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

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

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Notes

The authors declare no competing financial interest.

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