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A new class of readily available and conformationally rigid phosphino-oxazoline ligands for asymmetric catalysis

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Abstract—A new class of conformationally rigid phosphino-oxazoline ligands **3** were synthesized via an efficient *ortho*-substitution of phenyl glycinol as the key step. Divergent synthetic routes for easy ligand modulation, as well as a procedure suitable for scale-up synthesis, were established. The catalytic potential of ligands **3** has been demonstrated in the highly enantioselective Ir-catalyzed hydrogenation of alkenes and Pd-catalyzed allylic substitution and intermolecular Heck reactions.

1. Introduction

Discovering metal-catalyzed asymmetric transformations is among the most attractive frontiers in modern organic chemistry.[1] Since, chiral ligand has a significant influence on the metal catalyst reactivity and enantioselectivity, searching ligands with appropriate steric and electronic natures is one of the major tasks in asymmetric catalysis. Hetero-bidentate ligands, especially those bearing a phosphorus and a nitrogen as the donor atoms (called P,N-ligands), have become a particularly interesting ligand family because of the good π-acceptor character of phosphorus atom and the good σ-donor ability of nitrogen atom, the combination of which can help to stabilize the intermediate oxidation states during the catalytic cycle.[2] In addition, independent structural alternation on each of the P and N donor site makes it convenient to build a ligand set for optimization of a given reaction (Fig. 1).

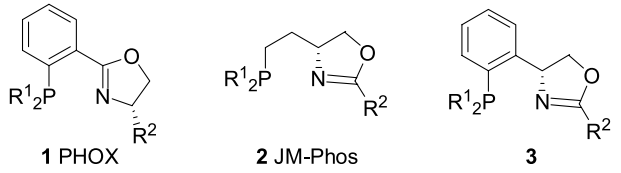

Figure 1.

Numerous chiral P,N-ligands have been reported for asymmetric catalysis by a number of groups during the past decades.[3] However, for most of these ligands, the application scope is limited regarding both the reaction type and enantioselectivity. Discovering readily available new P,N-ligands with high catalytic efficiency in various type of transformations is still needed. Ligand **1** (PHOX), invented by Pfaltz/Helmchen/Williams, has proven to be a superior ligand in a number of transition metal catalyzed reactions.[4] Burgess also obtained very good enantioselectivities in Pd-catalyzed allylic alkylation reactions and Ir-catalyzed hydrogenation of several unfunctionalized olefins with ligand **2** (JM-Phos),[5] although this ligand is fairly conformationally flexible with an ethylene linker. Recently, we have designed many conformationally rigid chiral bisphosphine ligands for achieving high enantioselectivities in asymmetric hydrogenation.[6] Bidentate ligand with a more rigid linker reduces the number of conformations in the transition state of the stereo-determining step and consequently enhances the enantioface differentiation.[7] On the basis of this consideration, we envisioned that ligands **3** might be superior to JM-Phos due to their more rigid 1,2-phenyl linker. Furthermore, ligands **3** are structurally highly resemble the PHOX, it would be of interest for a comparison with PHOX in their catalytic behavior. We have previously communicated the divergent syntheses of a series of ligands **3a–e** and their utilities in Ir-catalyzed highly enantioselective hydrogenation of unfunctionalized alkenes and α,β-unsaturated esters.[8] In this article, we want to give full details of the ligand synthesis including a new procedure suitable for scale-up ligand preparation. In addition to previously reported Ir-catalyzed hydrogenation reactions, evaluations of this new class of P,N-ligands in Pd-catalyzed asymmetric allylic substitution and intermolecular Heck reactions are also discussed.

Keywords: Ligand; Catalysis; Enantioselectivity.
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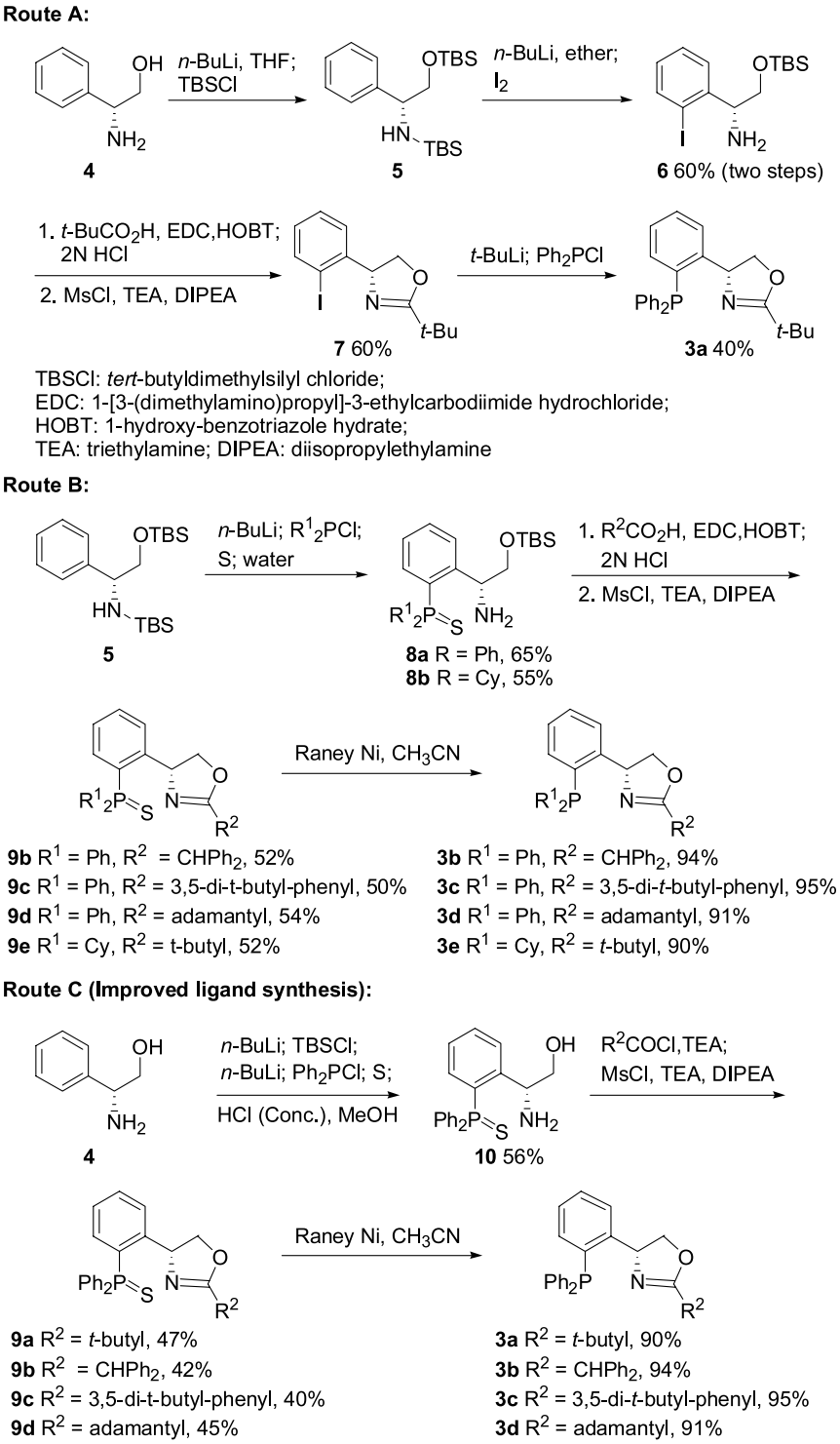
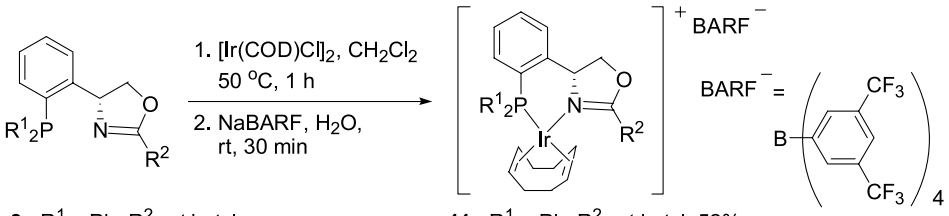


Scheme 1. Divergent synthesis of ligands **3a–e**.

2. Results and disccussion

2.1. Synthesis of phosphino-oxazoline ligands

The inexpensive enantiopure phenyl glycinol is widely used as a building block for the preparation of chiral ligands and auxilaries.[4,9] However, *ortho*-substituted phenyl glycinol derivatives are rarely used due to the lack of efficient synthesis.[10] One of the most direct ways to make ligands **3** would be based on *ortho*-substitution of phenyl glycinol. Thus, developing an efficient method of *ortho*-substitution of phenyl glycinol was desirable. Although the α-*N*,*N*-dimethyl amino group is commonly used as an *ortho*-directing group for metallation of aromatic rings,[11] direct use of primary amines for such a purpose was much less explored and was not used to construct chiral ligands.[12] Polniaszek et al. prepared (2-chloro or 2,6-dichlorophenyl) ethylamine from phenylethylamine via *ortho*-lithiation



3a R^1 = Ph, R^2 = *t*-butyl
3b R^1 = Ph, R^2 = $CHPh_2$
3c R^1 = Ph, R^2 = 3,5-di-*t*-butyl-phenyl
3d R^1 = Ph, R^2 = Adamantyl
3e R^1 = Cy, R^2 = *t*-butyl

11a R^1 = Ph, R^2 = *t*-butyl, 52%
11b R^1 = Ph, R^2 = $CHPh_2$, 50%
11c R^1 = Ph, R^2 = 3,5-di-*t*-butyl-phenyl, 63%
11d R^1 = Ph, R^2 = Adamantyl, 57%
11e R^1 = Cy, R^2 = *t*-butyl, 58%

Scheme 2. Preparation of Ir-complexes with P,N-ligands **3a–e**.

directed by the in situ generated *N*-lithiosilylamine.[13] After modification of their method, we successfully carried out, for the first time, an *ortho*-lithiation of silyl-protected phenyl glycinol. Subsequent reaction with I_2 or different phosphine chlorides efficiently gave rise to (2-iodo or 2-phosphino) phenyl glycinol derivatives, which are novel and highly modular chiral synthons for ligand synthesis. On the basis of this method, two different routes were developed for making ligands **3** (Scheme 1). In route A, (*R*)-phenyl glycinol (**4**) was protected with TBSCl to give an intermediate **5**, which was directly subjected to *ortho*-lithiation with 3 equiv of *n*-BuLi. Subsequent iodination followed by aqueous workup afforded aryl iodide **6**. Oxazoline formation using literature methods[4] gave the key intermediate **7**. Lithium–halogen exchange of **7** with *t*-BuLi followed by reaction with Ph_2PCl afforded the desired ligand **3a**. Presumably, variation of the phosphine chloride in the last step would allow a facile tuning of the phosphine site. In route B, a phosphine chloride, instead of I_2, was used as the electrophile after the *ortho*-lithiation step. Subsequent protection of the phosphine with sulfur followed by aqueous workup generated a phosphine sulfide **8**, which could be converted into a series of oxazolines **9** with various R^2 substituents by reaction with essentially unlimited carboxylic acids. Reduction of **9** with Raney-Ni[14] afforded ligands **3b–e**. The combination of both routes provides convenient ways of tuning either the phosphine site or the oxazoline site from intermediates **7** or **8**. This is useful for building a ligand set to optimize a particular reaction.

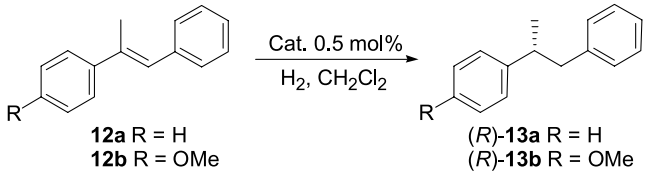
It is noteworthy that relatively expensive reagents EDC and HOBT were used in the preparation of oxazoline derivatives **7** and **9**. This renders a negative cost effect to scale-up ligand synthesis. In addition, both **6** and **8**, which are fairly polar intermediates, need to be purified by column chromatography before transformations to **7** and **9**, respectively. This adds another problem to the practicability of ligand synthesis. Solving these problems is critical for potential application of ligands **3** in catalysis. Route C in Scheme 1 outlines a slightly revised procedure for the synthesis of several ligands of **3**. After *ortho*-substitution of **4** with a diphenylphosphino group and subsequent sulfur protection, the crude product was treated with HCl (conc.) in MeOH to afford amino alcohol **10**, which can be purified by conventional washing and extraction procedures under different pH conditions. Therefore, **10** (90% pure by NMR) was obtained in 56% yield, which could be directly used for the next step. In instead of using EDC and HOBT, we attempted applying readily available and inexpensive carboxylic acid chlorides for the amide intermediates formation. We were pleased to find that this method provided comparable yields of the oxazolines **9a–c** and **9e** (42–47%) after subsequent one-pot mesylation and substitution reactions, considering that the starting material **10** of only 90% purity was used. **9a–d** were then reduced with Raney-Ni to afford **3a–d** in high yields, respectively. Thus, an overall three step synthesis of ligands **3** was established. Ligand **3a** was then prepared in 3.7 g scale through route C and this indicates that the new procedure is scalable.

2.2. Ir-Catalyzed asymmetric hydrogenations

Various P,N-ligands have exhibited superior reactivities and selectivities in Ir-catalyzed asymmetric hydrogenation of unfunctionalized alkenes.[15] To evaluate the catalytic properties of ligands **3** in asymmetric hydrogenation, their Ir-complexes **11** were prepared according to a literature procedure,[16] in which a weakly coordinating group BARF (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) was used as the counter ion. These complexes are air-stable and can be stored in air for months without losing their catalytic properties (Scheme 2).

Methylstilbene (**12a**), a typical substrate for Ir-catalyzed asymmetric hydrogenation of unfunctionallized olefins, was initially tested with complexes **11a–e** under 50 bar of H_2 pressure at rt in CH_2Cl_2. As shown in Table 1, all the catalysts gave excellent enantioselectivity (97–99% ee), except for **11b** (83% ee). Although the conversions were not satisfactory with **11a**, **11b**, and **11c**, high conversions were obtained with **11d** and **11e** (entries 7 and 8). Pressure and temperature effects were examined with **11a** on the same substrate (entries 1–4). Increasing the H_2 pressure dramatically improved the conversion, while the enantioselectivity did not change significantly. Performing the reaction at an elevated temperature also resulted in a great increase in conversion. Pfaltz et al. reported that the formation of inactive hydride-bridged Ir-trimers during the catalytic cycle might be one of the major reasons for the deactivation of catalyst and isolated a trimeric Ir(PHOX)-hydride complex after treating the corresponding Ir-complex with H_2 (Fig. 2).[15a] On the basis of this hypothesis and our observations, we suppose that: (1) a relatively larger R^2 substituent on the oxazoline ring might be beneficial not only for the enantioselectivity, but also for the reactivity; (2) more electron-donating ligands might form more reactive

Table 1. Asymmetric hydrogenation of methylstilbene derivatives with **11**[a]



Entry	Substrate	Catalyst	H_2 pressure (bar)	Temperature	Conversion (%)[b]	ee (%)[c]
1	**12a**	**11a**	10	rt	31	98
2	**12a**	**11a**	50	rt	64	98
3	**12a**	**11a**	90	rt	94	97
4	**12a**	**11a**	50	50 °C	98	98
5	**12a**	**11b**	50	rt	77	83
6	**12a**	**11c**	50	rt	68	97
7	**12a**	**11d**	50	rt	98	97
8	**12a**	**11e**	50	rt	>99	99
9	**12a**	**11e**	100	rt	>99	98
10	**12b**	**11a**	100	rt	>99	97
11	**12b**	**11d**	100	rt	>99	97
12	**12b**	**11e**	100	rt	>99	90

[a] For a general procedure, see Section 4.
[b] The conversions were determined by GC.
[c] The enantiomeric excesses were determined by chiral HPLC (Chiralcel OJ-H) or chiral GC (Chiralselect 1000). The absolute configuration was assigned by comparison of the retention times of two enantiomers with reported data.[15g]

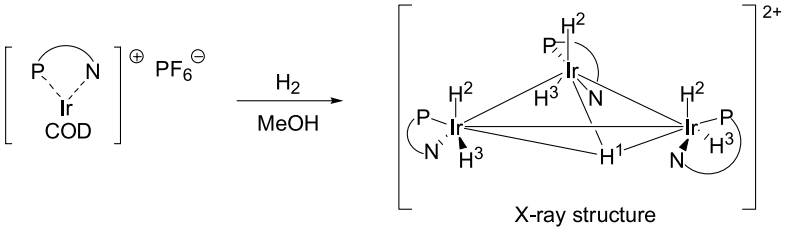
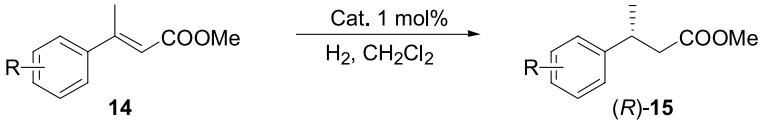


Figure 2. Formation of a hydride-bridged Ir-trimer.

catalyst or more stable catalytic species by preventing the formation of the hydride-bridged Ir-trimer, presumably through a *trans*-effect; (3) increasing the H_2 pressure might accelerate the desired catalytic cycle relative to the formation of the Ir-trimer; (4) a higher reaction temperature might either accelerate the desired catalytic cycle or possibly decelerate the formation of the Ir-trimer. These hypotheses can give us some guidance for further ligand modification and optimization of reaction conditions for a particular substrate. Another methylstilbene derivative **12b**

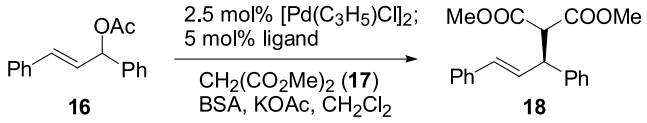
Table 2. Asymmetric hydrogenation of β-methylcinnamic esters with **11**[a]



Entry	Substrate	Catalyst	H_2 pressure (bar)	Temperature	Conversion (%)[b]	ee (%)[c]
1	**14a** R=H	**11a**	100	rt	>99	98
2	**14a** R=H	**11d**	100	rt	>99	99
3	**14a** R=H	**11e**	100	rt	>99	91
4	**14b** R=*p*-F	**11a**	100	rt	32	89
5	**14b** R=*p*-F	**11d**	100	rt	58	91
6	**14b** R=*p*-F	**11e**	100	rt	94	85
7	**14b** R=*p*-F	**11d**	100	50 °C	90	96
8	**14a** R=H	**11d**	100	50 °C	>99	99
9	**14c** R=*p*-Cl	**11d**	100	50 °C	87	98
10	**14d** R=*p*-CH_3	**11d**	100	50 °C	>99	98
11	**14e** R=*m*-CH_3	**11d**	100	50 °C	>99	99
12	**14f** R=*p*-OCH_3	**11d**	100	50 °C	96	94
13	**14g** R=*p*-OCF_3	**11d**	100	50 °C	84	95

[a] For a general procedure, see Section 4.
[b] The conversions were determined by GC.
[c] The enantiomeric excesses were determined by chiral HPLC (Chiralcel OJ-H) or chiral GC (Chiralselect 1000). The absolute configuration was assigned by comparison of the retention times of two enantiomers with reported data.[15g]

Table 3. Pd-Catalyzed asymmetric allylic alkylation of **16**



Entry	Ligand	Temperature	Time (h)	Yield (%)	ee (%)[a]
1	**3a**	rt	12	97	93(*S*)
2	**3b**	rt	12	93	2(*S*)
3	**3c**	rt	12	86	93(*S*)
4	**3d**	rt	12	91	97(*S*)
5	**3a**	0 °C	12	85	88(*S*)
6	**3a**	40 °C	4	97	98(*S*)
7	**3d**	40 °C	4	90	97(*S*)
8[b]	**3a**	40 °C	12	73	98(*S*)

[a] The ee values were determined by chiral HPLC (Chiral AD column) and the absolute configuration was assigned by comparison of the sign of the optical rotation with reported data.[4c]
[b] 0.1 mol% of $[Pd(C_3H_5)Cl]_2$ and 0.2 mol% of **3a** were used.

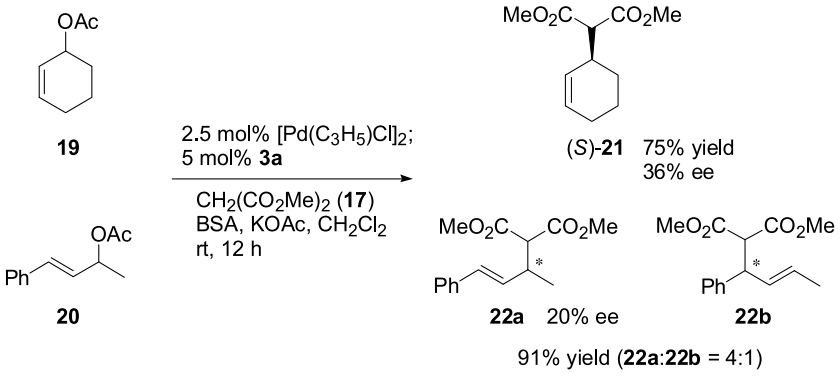
was then examined as the substrate with a few of the best catalysts (**11a**, **11d**, and **11e**). Complete conversions and very high enantioselectivities were obtained with **11a** and **11d** (entries 10 and 11), while **11e**, the most reactive catalyst, gave a little lower selectivity (entry 12). Thus, the overall results for asymmetric hydrogenation of biaryl alkenes with ligands **3** compare favorably with those obtained with JM-Phos **2** (95% ee for **12a** and 93% ee for **12b**).[15i]

Asymmetric hydrogenation of β-methyl cinnamic esters, followed by reduction of the ester function, can efficiently form chiral 3-arylbutanols, which are important intermediates for the synthesis of aromatic sesquiterpenes of the bisabolane family.[17] Few systems have been reported to be highly selective for this type of substrates.[15a,g] We were certainly interested in examining these important hydrogenation substrates with the air-stable catalysts **11**. Methyl-(*E*)-β-methyl cinnamate (**14a**) was initially selected as the substrate to screen ligands and reaction conditions. Complete conversions and extremely high enantioselectivities were observed with complexes **11a** and **11d** under 100 bar at rt (entries 1–3). The ee values are significantly higher than that with PHOX as a ligand (84% ee). However, when substrate **14b** having a *para*-fluoro substituent on the phenyl ring was subjected to hydrogenation, the conversion was not complete even at elevated temperature. The best result (96% ee and 90% conversion) for **14b** were obtained with **11d** at 50 °C under 100 bar (entry 7). We therefore used **11d** as catalyst and these optimized conditions for hydrogenation of several other aryl-(*E*)-β-methylcinnamic esters **14c–g**. Excellent ee values (94–99%) were obtained regardless of the substitution pattern on the phenyl ring, which were comparable to the best reported to date.[15a,g] The reactivities seemed quite substrate dependent. However, no obvious trend could be observed.

2.3. Pd-Catalyzed asymmetric C–C bond formations

2.3.1. Asymmetric allylic substitutions. Our next exploration of ligands **3** in asymmetric catalysis was focused on Pd-catalyzed allylic substitutions, a extensively studied reaction due to its synthetic potential.[18] A typical substrate 1,3-diphenylpropenyl acetate (**16**) in conjunction with the anion of dimethyl malonate (**17**) as a nucleophile was first tested with ligands **3a–d**. Under standard reaction conditions with $[Pd(\pi\text{-}C_3H_5)Cl]_2$ as a catalyst precursor, BSA as a base and KOAc as an additive in CH_2Cl_2 at rt, all the catalysts derived from **3a–d** provided product **18** in very good yields (86–97%) and high enantiomeric excesses (93–97%) (Table 3, entries 1–4), except that the catalyst derived from ligand **3b** showed essentially no enantioselectivity for this transformation. Lowering the reaction temperature has proven to be effective to improve the enantioselectivities in some allylic substitutions.[19] Thus, we carried out the same reaction with ligand **3a** at 0 °C instead of rt. Surprisingly, not only the yield was diminished as expected, but also the enantioselectivity dropped from 93–88% (entry 1 vs entry 5). On the opposite, when we increased the reaction temperature from rt to 40 °C, product **18** was obtained in the same yield but a higher ee value of 98% (entry 6). While for ligand **3d**, little difference was observed regarding both yields and ee values of **18** at a higher temperature (entry 7). In general, higher temperature increases the catalyst reactivity. Thus, this relatively uncommon property of ligand **3a** (higher ee at higher temperature) prompted us to test the possibility of lowering the catalyst loading for this reaction, which is generally used in 1–10 mol%, while maintaining high enantioselectivity. As shown in entry 8, when the reaction was carried out with only 0.2 mol% of Pd catalyst at 40 °C for 12 h, product **18** was obtained in 73% yield without any diminishment of enantioselectivity (98% ee). Such a low catalyst loading ($S/C = 500$) is rarely reported for Pd-catalyzed allylic substitution reactions with P,N-ligands, showing the superior reactivity of the catalyst of ligand **3a**. However, further decreasing the catalyst loading to 0.1 mol% was not satisfactory with only 38% yield of **18**.

To test the substrate scope and limitations of our new catalysts in allylation reactions of dimethyl malonate, a couple of more demanding substrates **19** and **20** were tested with ligand **3a**. Under standard reaction conditions, products **21** and **22** were obtained in good yields but disappointing ee values (Scheme 3). For the reaction of a cyclic substrate **19**,[20] only 36% ee was observed. For the reaction of an unsymmetric substrate **20**,[21] the product was obtained as a mixture of two regio-isomers in 4:1 ratio with 20% ee for



Scheme 3.

the major isomer 2-(1-methyl-3-phenylallyl) malonic acid dimethyl ester (**22a**). These results indicate this transformation is highly substrate dependent.

2.3.2. Asymmetric intermolecular Heck reaction. To further demonstrate the utility of ligand **3**, Pd-catalyzed asymmetric intermolecular Heck reaction[22] of 2,3-dihydrofuran (**23**) and phenyl triflate (**24**) was also investigated. Under typical conditions with $Pd_2(dba)_3 \cdot dba$ as the catalyst precursor and *N*,*N*-diisopropylethylamine as a base in benzene, ligands **3a** and **3d** provided product **25** in good yield and high ee value (entries 1 and 4). While much poorer yield and ee value of **25** were observed with **3b** and **3c** (entries 2 and 3), implying that a bulky substituent R^2 on the oxazoline ring of the ligand is beneficial for both higher reactivity and enantioselectivity in this reaction. Another regioisomer **26**, generated via C–C double bond migration in this reaction, was not observed under these conditions. Changing the catalyst precursor from $Pd_2(dba)_3 \cdot dba$ to $Pd_2(dba)_3 \cdot CHCl_3$ resulted in a mixture of **25** and **26** (93:7), though the overall yield and the ee value of the major product **25** were not affected significantly (entry 1 vs entry 5). Using THF in place of benzene as a solvent improved both yield and ee value of **25** (entry 1 vs entry 6 and entry 5 vs entry 7). Therefore, **25** was obtained almost quantitatively in 94% ee (entry 6), which is comparable to the best obtained with other P,N-ligands. Somewhat surprisingly, proton sponge, another commonly used base in this transformation, did not promote the reaction at all (entry 8) (Table 4).

3. Conclusion

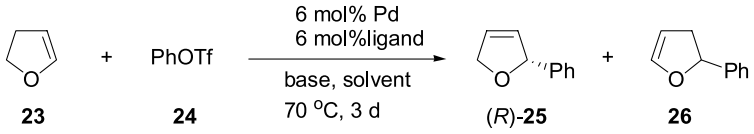
In summary, we have established a novel and efficient method of *ortho*-substitution of phenyl glycinol. Using this strategy as the key step, a new class of conformationally rigid phosphino-oxazoline ligands **3** were synthesized via divergent synthetic routes. A procedure that is suitable for scale-up ligand preparation was also developed, making this new class of ligands readily available from inexpensive phenyl glycinol. Their catalytic potential has been demonstrated in the highly enantioselective Ir-catalyzed hydrogenation of alkenes and Pd-catalyzed allylic substitution and intermolecular Heck reactions.

4. Experimental

4.1. General methods

All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. THF, ether, and benzene

Table 4. Pd-Catalyzed intermolecular Heck reaction[a]



Entry	Ligand	Pd complex	Base	Solvent	Yield(%)(**25**:**26**)[b]	ee(%)[c]
1	**3a**	$Pd_2(dba)_3 \cdot dba$	$^iPr_2EtN$	Benzene	87(>99:1)	91
2	**3b**	$Pd_2(dba)_3 \cdot dba$	$^iPr_2EtN$	Benzene	32(>99:1)	88
3	**3c**	$Pd_2(dba)_3 \cdot dba$	$^iPr_2EtN$	Benzene	45(>99:1)	78
4	**3d**	$Pd_2(dba)_3 \cdot dba$	$^iPr_2EtN$	Benzene	91(>99:1)	90
5	**3a**	$Pd_2(dba)_3 \cdot CHCl_3$	$^iPr_2EtN$	Benzene	90 (93:7)	90 (86)
6	**3a**	$Pd_2(dba)_3 \cdot dba$	$^iPr_2EtN$	THF	99(>99:1)	94
7	**3a**	$Pd_2(dba)_3 \cdot CHCl_3$	$^iPr_2EtN$	THF	93 (93:7)	93 (91)
8	**3a**	$Pd_2(dba)_3 \cdot dba$	Proton sponge	Benzene	No reaction	n/a

[a] For a typical reaction precedure, see Section 4.
[b] The total isolated yield of **25** and **26**. The ratio of **25**:**26** was determined by GC.
[c] The enantiomeric excesses of major isomer **25**. The data in parentheses were enantiomeric excesses of the minor isomer **26**, if detectable. They were all determined by chiral GC (β-DEX 120 column). The absolution configuration of **25** was assigned by comparison of the sign of the optical rotation with reported data.[23]

were dried and distilled from sodium-benzophenone ketyl under nitrogen. Methylene chloride was dried over CaH_2 under nitrogen. Column chromatography was performed using sorbent silica gel 60 Å (230×450 mesh). ^1H, ^{13}C, and ^{31}P were recorded on Bruker AM-300, AMX-360, and APX-400 spectrometers. Chemical shifts were reported in ppm up field to tetramethylsilane with the solvent resonance as the internal standard. MS spectra were recorded on a KRATOS mass spectrometer MS 9/50 for LR-ESI and HR-ESI or LR-APCI and HR-APCI. GC analysis was carried on Helwett–Packard 6890 gas chromatography using chiral capillary columns. HPLC analysis was carried on WatersTM 600 chromatography.

4.1.1. 2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-(2-iodophenyl)-ethylamine (6). To a suspention of (*R*)-α-methylbenzylamine **4** (1.37 g, 10.0 mmol) in 40 mL of THF at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 8 mL) dropwise. The resulting purple solution was stirred at −78 °C for 30 min before a solution of TBSCl (*tert*-butyldimethylsilyl chloride) (3.17 g, 21.0 mmol) in 20 mL of THF was added at the same temperature. The reaction mixture was allowed to warm to rt naturally and was stirred overnight. After removing the THF solvent under reduced pressure, the residue was redissolved in 50 mL of ether. To this solution at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 12 mL) dropwise. The reaction mixture was allowed to slowly warm to rt during 3 h and stirred at rt for 1 h. I_2 (5.08 g, 20.0 mmol) was added at −78 °C and the reaction mixture was allowed to warm to rt and stirred at rt for 1 h. 10% $Na_2S_2O_3$ solution (20 mL) was added and the resulting mixture was stirred vigorously for 10 min. After usual work up, the product **7** was isolated by flash column chromatography (hexane/EtOAc=80:20) as a brown oil (2.27 g, 60%). $[\alpha]_D^{20}$ −49.4 (*c* 0.82, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.79 (dd, J=1.1, 7.9 Hz, 1H), 7.57 (dd, J=1.6, 7.8 Hz, 1H), 7.32 (dt, J=1.0, 7.8 Hz, 1H), 6.93 (dt, J=1.7, 7.7 Hz, 1H), 4.33 (dd, J=3.6, 7.9 Hz, 1H), 3.80 (dd, J=3.6, 9.9 Hz, 1H), 3.42 (dd, J=7.9, 9.9 Hz, 1H), 1.82 (s, 2H), 0.91 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 144.5, 139.5, 129.1, 128.3, 99.9, 67.6, 60.9, 26.1, 18.4, −5.1, −5.2; HRMS (M^++1) *m*/*z* calcd for $C_{14}H_{25}NOSiI$ 378.07447, found 378.07638.

4.1.2. 2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-[2-(diphenyl-phosphinothioyl)-phenyl]-ethylamine (8a). To a suspention of (*R*)-α-methylbenzylamine **4** (1.37 g, 10.0 mmol, 1 equiv) in 40 mL THF at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 8 mL) dropwise. The resulting purple solution was stirred at −78 °C for 30 min before a solution of TBSCl (3.17 g, 21.0 mmol) in 20 mL THF was added at the same temperature. The reaction mixture was allowed to warm to rt naturally and stirred overnight. After removing the THF solvent under reduced pressure, the residue was redissolved in 50 mL ether. To this solution at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 12 mL) dropwise. The reaction mixture was allowed to slowly warm to rt during 3 h and stirred at rt for 1 h. Diphenylchlorophosphine (4.42 g, 20.0 mmol) was slowly added at −78 °C and the resulting solution was allowed to warm to rt and stirred overnight. Sulfur (0.960 g, 30.0 mmol) was added at rt and the mixture was stirred for 1 h before water was added. After usual work up, the product **9a** was isolated by flash column chromatography (hexane/EtOAc=90:10) as a white solid (3.03 g, 65%). $[\alpha]_D^{20}$ −66.6 (*c* 1.6, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 7.85–7.74 (m, 5H), 7.56–7.46 (m, 7H), 7.14 (m, 1H), 6.87 (dd, J=7.8, 14.7 Hz, 1H), 4.80 (dd, J=3.6, 8.0 Hz, 1H), 3.60–3.47 (m, 2H), 1.73 (s, 2H), 0.83 (s, 9H), −0.04 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2 (d, J=9.0 Hz), 133.5–131.6 (m), 130.2 (d, J=10.2 Hz), 128.6 (d, J=1.2 Hz), 128.4 (d, J=1.6 Hz), 126.8 (d, J=12.7 Hz), 66.9, 53.6 (d, J=7.0 Hz), 25.8, 18.2, −5.3, −5.5; ^{31}P NMR (145 MHz, $CDCl_3$) δ 42.11; HRMS (M^++1) *m*/*z* calcd for $C_{26}H_{35}NOSiPS$ 468.19408, found 468.19092.

4.1.3. 2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-[2-(dicyclohexyl-phosphinothioyl)-phenyl]-ethylamine (8b). To a suspention of (*R*)-α-methylbenzylamine **4** (0.343 g, 2.50 mmol, 1 equiv) in 10 mL THF at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 2 mL) dropwise. The resulting purple solution was stirred at −78 °C for 30 min before a solution of TBSCl (0.791 g, 5.25 mmol) in 5 mL THF was added at the same temperature. The reaction mixture was allowed to warm to rt naturally and was stirred overnight. After removing the THF solvent under reduced pressure, the residue was redissolved in 15 mL ether. To this solution at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 3 mL) dropwise. The reaction mixture was allowed to slowly warm to rt during 3 h and was stirred at rt for 1 h. Dicyclohexylchlorophosphine (0.873 g, 3.75 mmol) was slowly added at −78 °C and the resulting solution was allowed to warm to rt and was stirred overnight. Sulfur (0.240 g, 7.50 mmol) was added at rt and the mixture was stirred for 1 h before water was added. After usual work up, the product **9b** was isolated by flash column chromatography (hexane/EtOAc=90:10) as a yellow oil (0.660 g, 55%). $[\alpha]_D^{20}$ −48.6 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz) δ 8.00 (br s, 1H), 7.72–7.69 (m, 1H), 7.52–7.47 (m, 1H), 7.38–7.34 (m, 1H), 5.18 (br s, 1H), 3.82–3.70 (m, 2H), 2.41–2.35 (m, 2H), 2.11–2.08 (m, 2H), 1.87–1.19 (m, 20H), 0.95 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 147.1, 133.5 (m), 130.9, 128.5 (m), 127.0, 126.6, 126.5, 126.3, 68.2, 53.1, 39.8 (d, J=44.6 Hz), 39.3 (d, J=48.9 Hz), 27.0, 26.8, 26.4–26.1 (m), 25.7, 25.5, 18.0, −5.4, −5.5; ^{31}P NMR ($CDCl_3$, 145 MHz) δ 61.43 (br s); HRMS (M^++1) *m*/*z* calcd for $C_{26}H_{46}NOSiPS$ 480.28798, found 480.28543.

4.2. General procedure for preparation of oxazolines 7 and 9b–e

A mixture of **8a** (437 mg, 0.934 mmol), EDC·HCl (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) (357 mg, 1.87 mmol), HOBT·H_2O (1-hydroxy-benzotriazole hydrate) (126 mg, 0.934 mmol), 1-adamantanecarboxylic acid (168 mg, 0.934 mmol), and TEA (triethylamine) (0.53 mL, 3.7 mmol) in 10 mL DMF was stirred at 70 °C overnight. To the cooled mixture was added 10 mL 2 N HCl solution followed by 20 mL EtOAc. The resulting mixture was stirred at rt for 30 min and then the two layers were separated. The aqueous layer was extracted with EtOAc (10 mL×2). The combined organic layer was washed with water and brine, dried with Na_2SO_4. After removal of the solvent, the resulting residue was purified by column flash chromatography (hexane/EtOAc/

CH_2Cl_2=70:20:10) to give condensation product as a white solid (336 mg). To a mixture of the above condensation product (316 mg, 0.613 mmol), DIPEA (*N*,*N*-diisopropylethylamine) (0.73 mL, 2.5 mmol) and TEA (0.51 mL, 6.1 mmol) in 10 mL CH_2Cl_2, was added methanesulfonyl chloride (95 μL, 1.2 mmol) at 0 °C. The resulting mixture was allowed to warm to rt and stirred overnight. After removal of the solvent and the excessive DIPEA and TEA under reduced pressure, **9d** was isolated by column flash chromatography (hexane/EtOAc=85:15) as a white solid (235 mg, 54% two steps).

4.2.1. 2-*tert*-Butyl-(4*R*)-(2-iodo-phenyl)-4,5-dihydro-oxazole (7). This compound was produced from **6** and dimethyl acetic acid following the general procedure as a colorless oil (60%). $[\alpha]_D^{20}-87.5$ (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.79 (dd, *J*=1.2, 7.9 Hz, 1H), 7.32 (dt, *J*=1.2, 7.7 Hz, 1H), 7.20 (dd, *J*=1.7, 7.8 Hz, 1H), 6.94 (dt, *J*=1.8, 7.6 Hz, 1H), 5.37 (dd, *J*=7.8, 10.3 Hz, 1H), 4.76 (dd, *J*=8.5, 10.3 Hz, 1H), 3.85 (t, *J*=8.1 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 176.3, 146.0, 139.2, 129.1 (d, *J*=22.0 Hz), 128.6, 127.4, 98.3, 74.3, 72.8, 33.6, 28.1; HRMS (M^++1) *m*/*z* calcd for $C_{13}H_{17}NOI$ 330.03494, found 330.03633.

4.2.2. 2-Benzhydryl-(4*R*)-[2-(diphenyl-phosphinothioyl)-phenyl]-4,5-dihydro-oxazole (9b). This compound was produced from **8a** and diphenyl acetic acid following the general procedure as a white solid (52%). $[\alpha]_D^{20}+35.4$ (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.83–7.71 (m, 4H), 7.56–7.45 (m, 7H), 7.41–7.24 (m, 11H), 7.16 (m, 1H), 6.87 (dd, *J*=7.7, 14.8 Hz, 1H), 5.91 (t, *J*=9.1 Hz, 1H), 5.26 (s, 1H), 4.72 (t, *J*=9.6 Hz, 1H), 3.96 (t, *J*=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 146.8 (d, *J*=8.5 Hz), 139.2 (d, *J*=8.7 Hz), 133.1–130.1 (m), 129.0–128.5 (m), 127.2 (d, *J*=4.2 Hz), 127.0 (d, *J*=12.5 Hz), 76.3, 66.8 (d, *J*=7.2 Hz), 51.2; ^{31}P NMR ($CDCl_3$, 145 MHz) δ 42.38; HRMS (M^++1) *m*/*z* calcd for $C_{34}H_{29}NOPS$ 530.17020, found 530.17347.

4.2.3. 2-(3,5-Di-*tert*-butyl-phenyl)-(4*R*)-[2-(diphenyl-phosphinothioyl)-phenyl]-4,5-dihydro-oxazole (9c). This compound was produced from **8a** and 3,5-di-*tert*-butylbenzoic acid following the general procedure as a white solid (50%). $[\alpha]_D^{20}+34.0$ (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.92–7.76 (m, 6H), 7.57–7.49 (m, 9H), 7.19 (t, *J*=7.4 Hz, 1H), 6.95 (dd, *J*=7.7, 14.8 Hz, 1H), 6.03 (t, *J*=8.9 Hz, 1H), 4.72 (t, *J*=9.7 Hz, 1H), 4.07 (t, *J*=8.5 Hz, 1H), 1.35 (s, 18H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 166.6, 151.1, 147.5 (d, *J*=8.5 Hz), 133.4–131.6 (m), 130.7, 129.6–129.0 (m), 127.1, 125.9, 123.0, 75.9, 68.0, 35.2, 31.6; ^{31}P NMR ($CDCl_3$, 145 MHz) δ 42.30; HRMS (M^++1) *m*/*z* calcd for $C_{35}H_{39}NOPS$ 552.24845, found 552.24701.

4.2.4. 2-Adamantan-1-yl-(4*R*)-[2-(diphenyl-phosphinothioyl)-phenyl]-4,5-dihydro-oxazole (9d). $[\alpha]_D^{20}+9.35$ (*c* 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.83–7.66 (m, 4H), 7.52–7.40 (m, 7H), 7.32 (dd, *J*=4.8, 6.8 Hz, 1H), 7.12 (m, 1H), 6.85 (ddd, *J*=0.7, 7.8, 14.8 Hz, 1H), 5.74 (t, *J*=9.0 Hz, 1H), 4.49 (dd, *J*=9.0, 9.9 Hz, 1H), 3.78 (t, *J*=8.4 Hz, 1H), 1.98 (s, 3H), 1.91 (s, 6H), 1.69 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.5, 147.4 (d, *J*=8.5 Hz), 133.0 (d, *J*=5.5 Hz), 132.7–132.3 (m), 131.9–131.7 (m), 131.6 (d, *J*=2.9 Hz), 130.5 (d, *J*=83.4 Hz), 128.8–128.4 (m), 126.7 (d, *J*=12.5 Hz), 75.3, 66.6 (d, *J*=7.0 Hz), 39.6, 36.5, 35.3, 27.8; ^{31}P NMR ($CDCl_3$, 145 MHz) δ 42.30; HRMS (M^++1) *m*/*z* calcd for $C_{31}H_{33}NOPS$ 498.20150, found 498.19902.

4.2.5. 2-*tert*-Butyl-(4*R*)-[2-(dicyclohexyl-phosphinothioyl)-phenyl]-4,5-dihydro-oxazole (9e). This compound was produced from **8b** and dimethyl acetic acid following the general procedure as a colorless oil (52%). $[\alpha]_D^{20}-78.0$ (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54–7.49 (m, 2H), 7.37–7.31 (m, 2H), 6.53 (m, 1H), 4.94 (t, *J*=9.5 Hz, 1H), 3.92 (t, *J*=8.0 Hz, 1H), 2.54 (m, 1H), 2.31 (m, 1H), 2.09 (m, 1H), 1.91–1.13 (m, 19H), 1.34 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.7, 149.2, 131.7 (d, *J*=2.6 Hz), 131.3, 128.6 (d, *J*=9.0 Hz), 126.3 (d, *J*=10.5 Hz), 125.0 (d, *J*=63.8 Hz), 76.2, 66.5 (d, *J*=3.7 Hz), 41.2 (d, *J*=48.2 Hz), 36.5 (d, *J*=51.2 Hz), 33.3, 27.9, 26.6–25.2 (m); ^{31}P NMR ($CDCl_3$, 145 MHz) δ 57.27 (br); HRMS (M^++1) *m*/*z* calcd for $C_{25}H_{39}NOPS$ 432.24845, found 432.24619.

4.2.6. 2-*tert*-Butyl-(4*R*)-(2-diphenylphosphanyl-phenyl)-4,5-dihydro-oxazole (3a). To a solution of **7** (94 mg, 0.286 mmol) in 4 mL ether was added *t*-BuLi (1.7 M solution, 0.34 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min before diphenylchlorophosphine (2.43 g, 11.0 mmol) was added slowly. The solution was allowed to warm to rt and was stirred overnight. Water was added. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to give **3a** as a white solid (40%). $[\alpha]_D^{20}-50.9$ (*c* 2.0, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.40–7.26 (m, 12H), 7.19 (dt, *J*=1.5, 7.5 Hz, 1H), 6.93–6.89 (m, 1H), 5.82–5.75 (m, 1H), 4.24 (dd, *J*=8.4, 10.2 Hz, 1H), 3.64 (dt, *J*=0.5, 8.4 Hz, 1H), 1.28 (s, 9H); ^{13}C NMR (CD_2Cl_2, 90 MHz) δ 175.8, 148.4 (d, *J*=24.0 Hz), 136.9 (d, *J*=10.2 Hz), 135.4–134.2 (m), 130.0–129.3 (m), 127.9 (br s), 126.8 (br s), 75.4 (d, *J*=4.4 Hz), 67.5 (m), 33.9, 28.3; ^{31}P NMR (CD_2Cl_2, 145 MHz) δ −14.97; HRMS (M^++1) *m*/*z* calcd for $C_{25}H_{27}NOP$ 388.18248, found 388.17930.

4.3. General procedure for preparation of ligands 3b–e

To a N_2-flushed Schlenk flask was loaded about 1 g of Raney-Ni 2800 slurry. The Raney-Ni was washed sequentially with methanol (3 mL×3), ether (3 mL×3), and dried degassed CH_3CN (3 mL×3). To this flask was then transferred a solution of **9d** (190 mg, 0.382 mmol) in 6 mL CH_3CN. The resulting mixture was stirred under N_2 at rt for 1 d. The mixture was filtered under N_2. The Raney-Ni solid was washed with CH_3CN (3 mL×3). The combined filtrate was concentrated under reduced pressure and the residue was passed through a short silica gel plug under N_2 to give pure product **3d** as a white solid (91%).

4.3.1. 2-Benzhydryl-(4*R*)-(2-diphenylphosphanyl-phenyl)-4,5-dihydro-oxazole (3b). This compound was produced from **9b** following the general procedure as a white solid (94%). $[\alpha]_D^{20}-67.9$ (*c* 0.66, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.44–7.21 (m, 23H), 6.98–6.95 (m, 1H), 5.97 (dt, *J*=5.6, 9.4 Hz, 1H), 5.24 (s, 1H), 4.38 (dd,

J=8.6, 10.3 Hz), 3.74 (t, J=8.6 Hz); ^{13}C NMR (CD_2Cl_2, 90 MHz) δ 169.3, 147.9 (d, J=24.4 Hz), 140.4 (d, J=3.6 Hz), 136.7 (d, J=10.3 Hz), 135.5–134.0 (m), 130.1–126.9 (m), 75.6 (d, J=5.3 Hz), 68.0, 51.7; ^{31}P NMR (CD_2Cl_2, 145 MHz) δ −15.10; HRMS (M^++1) *m/z* calcd for $C_{34}H_{29}NOP$ 498.19813, found 498.19772.

4.3.2. 2-(3,5-Di-*tert*-butyl-phenyl)-(4*R*)-(2-diphenylphosphanyl-phenyl)-4,5-dihydro-oxazole (3c). This compound was produced from **9c** following the general procedure as a white solid (95%). $[\alpha]_D^{20}$ −48.3 (*c* 0.87, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.95 (d, J=1.8 Hz, 2H), 7.67 (t, J=1.8 Hz, 1H), 7.50–7.47 (m, 1H), 7.43–7.34 (m, 1H), 7.24 (dt, J=1.3, 7.5 Hz, 1H), 7.01 (ddd, J=1.1, 4.4, 7.6 Hz, 1H), 6.11 (ddd, J=5.9, 8.7, 14.5 Hz, 1H), 4.48 (dd, J=8.4, 10.2 Hz, 1H), 3.90 (t, J=8.5 Hz, 1H), 1.42 (s, 18H); ^{13}C NMR (CD_2Cl_2, 90 MHz) δ 166.1, 151.7, 148.2 (d, J=23.9 Hz), 137.0 (m), 135.6–133.9 (m), 130.2–126.3 (m), 123.3, 75.4 (d, J=4.2 Hz), 68.6, 35.5, 31.9; ^{31}P NMR (CD_2Cl_2, 145 MHz) δ −14.83; HRMS (M^++1) *m/z* calcd for $C_{35}H_{39}NOP$ 520.27638, found 520.27501.

4.3.3. 2-Adamantan-1-yl-(4*R*)-(2-diphenylphosphanyl-phenyl)-4,5-dihydro-oxazole (3d). $[\alpha]_D^{20}$ −66.1 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.05 (m, 12H), 6.79 (ddd, J=0.9, 4.4, 7.8 Hz, 1H), 5.74 (ddd, J=5.1, 8.3, 13.4 Hz, 1H), 4.15 (dd, J=8.5, 10.3 Hz, 1H), 3.53 (t, J=8.3 Hz, 1H), 1.96 (s, 3H), 1.90 (s, 6H), 1.66 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.2, 147.8 (d, J=24.3 Hz), 136.4–136.1 (m), 134.7, 134.4, 134.0, 133.7, 133.5, 129.7, 129.2, 128.9, 128.8, 128.7, 127.6, 126.1 (d, J=5.7 Hz), 74.6 (d, J=5.0 Hz), 66.8 (d, J=24.2 Hz), 39.9, 36.8, 35.6, 28.2; ^{31}P NMR ($CDCl_3$, 145 MHz) δ −15.14; HRMS (M^++1) *m/z* calcd for $C_{31}H_{33}NOP$ 466.22943, found 466.22620.

4.3.4. 2-*tert*-Butyl-(4*R*)-(2-dicyclohexylphosphanyl-phenyl)-4,5-dihydro-oxazole (3e). This compound was produced from **9e** following the general procedure as a colorless oil (90%). $[\alpha]_D^{20}$ −70.9 (*c* 0.53, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.49–7.47 (m, 1H), 7.37–7.24 (m, 3H), 6.02 (ddd, J=5.7, 8.4, 14.1 Hz, 1H), 4.76 (dd, J=8.3, 10.3 Hz, 1H), 3.79 (t, J=8.3 Hz, 1H), 2.00–0.85 (m, 31H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 175.2, 151.0 (d, J=25.3 Hz), 133.2 (d, J=20.8 Hz), 133.1 (d, J=3.4 Hz), 129.5, 126.7, 126.2 (d, J=6.3 Hz), 75.9 (d, J=7.2 Hz), 67.9 (d, J=25.9 Hz), 35.2 (d, J=12.9 Hz), 34.0 (d, J=11.7 Hz), 33.7, 31.3–30.9 (m), 30.0 (d, J=10.2 Hz), 29.2 (d, J=6.2 Hz), 28.1, 27.7–27.3 (m), 26.8 (d, J=3.9 Hz); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ −14.46; HRMS (M^++1) *m/z* calcd for $C_{25}H_{39}NOP$ 400.27638, found 400.27262.

4.4. Multigram scale synthesis of ligand 3a via route C

4.4.1. 2-Hydroxyl-(1*R*)-[2-(diphenyl-phosphinothioyl)-phenyl]-ethylamine (10). To a suspention of (*R*)-α-methylbenzylamine **4** (5.46 g, 0.04 mol) in 150 mL of THF at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 32 mL) dropwise. The resulting purple solution was stirred at −78 °C for 30 min before a solution of TBSCl (12.7 g, 0.084 mol) in 80 mL of THF was added at the same temperature. The reaction mixture was allowed to warm to rt naturally and stirred overnight. After removing the THF solvent under reduced pressure, the residue was redissolved in 200 mL of ether. To this solution at −78 °C was added *n*-BuLi (2.5 M solution in hexane, 48 mL) dropwise. The reaction mixture was allowed to slowly warm to rt during 3 h and stirred at rt for 1 h. Diphenylchlorophosphine (17.7 g, 0.08 mol) was slowly added at −78 °C and the resulting solution was allowed to warm to rt and stirred overnight. Sulfur (3.84 g, 0.12 mol) was added at rt and the mixture was stirred for 1 h. The solvent was removed and the residue was dissolved in 100 mL of methanol followed by addition of 20 mL of conc. HCl. The mixture was heated at 50 °C for 4 h. After removal of methanol the yellow solid residue was redissolved in 150 mL of water and washed with ether (80 mL×3). The aqueous layer was then basicified by adding 60 mL of 4 N NaOH solution. The precipitate was dissolved in CH_2Cl_2 and extracted from the aqueous layer. After removal of the solvent, the crude product **10** was obtained as an offwhite solid (7.88 g, 56%, about 90% purity shown by NMR); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.68–7.72 (m, 4H), 7.41–7.49 (m, 8H), 7.10 (m, 1H), 6.81 (m, 1H), 4.69 (dd, J=1.3, 6.6 Hz, 1H), 3.48 (d, J=6.9 Hz, 2H), 1.88 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.3–132.9 (m), 129.0–129.3 (m), 127.4 (d, J=13.1 Hz), 67.1, 53.9; ^{31}P NMR (145 MHz, $CDCl_3$) δ 42.4.

4.4.2. 2-*tert*-Butyl-(4*R*)-[2-(diphenyl-phosphinothioyl)-phenyl]-4,5-dihydro-oxazole (9a). A mixture of **10** (7.88 g, 22.3 mmol), trimethyl acetyl chloride (3.0 mL, 24.5 mmol), and TEA (13.0 mL, 89.2 mmol) in 200 mL of CH_2Cl_2 was stirred at 0 °C for 2 h. 10 equiv of TEA (32.5 mL, 0.223 mol), 4 equiv of DIPEA (15.6 mL, 89.2 mmol) and 2 equiv of methanesulfonyl chloride (3.45 mL, 44.6 mmol) was added sequentially at the same temperature. The resulting mixture was allowed to warm to rt during 2 h and stirred for another 24 h. TLC showed the completion of the reaction. After removal of the solvent and the excessive TEA and DIPEA under reduced pressure, **9a** was isolated by column flash chromatography (hexane/EtOAc=85:15) as a white solid (4.4 g, 47% yield).

4.4.3. 2-*tert*-Butyl-(4*R*)-(2-diphenylphosphanyl-phenyl)-4,5-dihydro-oxazole (3a). To a N_2-flushed Schlenk flask was loaded about 20 g of Raney-Ni 2800 slurry. The Raney-Ni was washed sequentially with methanol (30 mL×3), ether (30 mL×3), and dried degassed CH_3CN (30 mL×3). To this flask was then transferred a solution of **9a** (4.4 g, 10.5 mmol) in CH_3CN (100 mL). The resulting mixture was stirred under N_2 at rt for 1 d. The reaction mixture was filtered under N_2 and washed with CH_3CN (50 mL×3). The combined filtrate was concentrated under reduced pressure and the residue was passed through a short silica gel plug under N_2 to give **3a** as a white solid (3.66 g, 90% yield).

4.5. General procedure for preparation of complex 11a–e

To a Schlenk tube was added **3d** (76 mg, 0.163 mmol), $[Ir(COD)Cl]_2$ (54.8 mg, 0.0816 mmol) and dried CH_2Cl_2 (3 mL). The resulting red solution was heated under N_2 at 50 °C for 1 h. TLC indicated that **3d** was consumed completely. After the solution was cooled to rt, Na[BARF] (217 mg, 0.245 mmol) was added followed by H_2O (3 mL). The resulting mixture was stirred vigorously for 30 min. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 mL×2). The combined organic

layer was dried with Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (hexanes/CH_2Cl_2=1:1) to give **11d** as an orange solid (57%).

4.5.1. Compound 11a. This compound was produced from **2a** following the general procedure as a yellow solid (52%); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.74 (s, 8H), 7.60–6.54 (m, 8H), 7.46–7.31 (m, 6H), 7.25–7.17 (m, 3H), 7.05 (ddd, J=1.2, 7.9, 10.9 Hz, 1H), 5.81 (dd, J=3.7, 9.7 Hz, 1H), 4.96 (m, 1H), 4.94 (dd, J=4.2, 9.4 Hz, 1H), 4.81 (t, J=9.7 Hz, 1H), 4.26 (m, 1H), 4.16 (m, 1H), 3.22 (m, 1H), 2.50–2.33 (m, 2H), 2.24 (m, 1H), 2.13–2.00 (m, 2H), 1.71 (m, 1H), 1.55 (m, 1H), 0.93 (s, 9H); ^{31}P NMR ($CDCl_3$, 145 MHz) δ 15.55; HRMS (cation) m/z calcd for $C_{33}H_{38}NOPIr$ 688.23150, found 688.22827; HRMS (anion) m/z calcd for $C_{32}H_{12}BF_{24}$ 863.06434, found 863.06754.

4.5.2. Compound 11b. This compound was produced from **2b** following the general procedure as a red solid (50%); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.77–6.78 (m, 34H), 5.93 (d, J=7.2 Hz, 2H), 5.76 (dd, J=5.6, 9.7 Hz, 1H), 5.20–5.11 (m, 2H), 4.90–4.80 (m, 2H), 3.95 (m, 1H), 3.80 (m, 1H), 3.00 (m, 1H), 2.53–2.45 (m, 2H), 2.35–2.19 (m, 2H), 1.90 (m, 1H), 1.75 (m, 1H), 1.52–1.34 (m, 2H); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 16.33; HRMS (cation) m/z calcd for $C_{42}H_{40}NOPIr$ 798.24715, found 798.24948; HRMS (anion) m/z calcd for $C_{32}H_{12}BF_{24}$ 863.06434, found 863.07128.

4.5.3. Compound 11c. This compound was produced from **2c** following the general procedure as an orange solid (63%); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.79 (m, 2H), 7.73 (s, 9H), 7.62 (m, 1H), 7.56 (br s, 4H), 7.50–7.36 (m, 12H), 7.22 (m, 1H), 6.04 (dd, J=4.2, 9.1 Hz, 1H), 5.21 (dd, J=4.4, 9.5 Hz, 1H), 5.07 (t, J=9.4 Hz, 1H), 5.04 (m, 1H), 4.08 (m, 1H), 3.87 (m, 1H), 3.52 (m, 1H), 2.54–2.39 (m, 2H), 2.30 (m, 1H), 2.22–2.14 (m, 2H), 1.90 (m, 1H), 1.70–1.64 (m, 2H), 1.31 (s, 18H); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 12.47; HRMS (cation) m/z calcd for $C_{43}H_{50}NOPIr$ 820.32540, found 820.32552; HRMS (anion) m/z calcd for $C_{32}H_{12}BF_{24}$ 863.06434, found 863.06159.

4.5.4. Compound 11d. ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.75 (s, 8H), 7.66–7.58 (m, 8H), 7.43–7.38 (m, 5H), 7.35–7.26 (m, 4H), 7.05 (m, 1H), 5.84 (dd, J=3.5, 9.8 Hz, 1H), 5.05 (m, 1H), 5.01 (dd, J=4.0, 9.4 Hz, 1H), 4.84 (t, J=9.6 Hz, 1H), 4.35 (m, 1H), 4.28 (m, 1H), 3.23 (m, 1H), 2.52–2.36 (m, 3H), 2.25 (m, 1H), 2.16–2.01 (m, 2H), 1.84–1.74 (m, 7H), 1.64–1.52 (m, 4H), 1.41–1.36 (m, 6H); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 15.89; HRMS (cation) m/z calcd for $C_{39}H_{44}NOPIr$ 766.27845, found 766.27163; HRMS (anion) m/z calcd for $C_{32}H_{12}BF_{24}$ 863.06434, found 863.07188.

4.5.5. Compound 11e. This compound was produced from **2e** following the general procedure as an orange solid (58%); ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.74 (m, 8H), 7.65–7.51 (m, 7H), 7.39 (m, 1H), 5.67 (d, J=7.2 Hz, 1H), 5.28 (dd, J=1.2, 10.2 Hz, 1H), 5.06 (m, 1H), 4.92 (m, 1H), 4.43 (dd, J=7.5, 10.2 Hz, 1H), 3.76 (m, 1H), 3.56 (m, 1H), 2.97 (m, 1H), 2.60–2.51 (m, 2H), 2.39–2.10 (m, 5H), 1.94–1.63 (m, 12H), 1.52–1.32 (m, 19H); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 9.00; HRMS (cation) m/z calcd for $C_{33}H_{50}NOPIr$ 700.32540, found 700.32349; HRMS (anion) m/z calcd for $C_{32}H_{12}BF_{24}$ 863.06434, found 863.07146.

4.6. General procedure for enantioselective hydrogenations

α-Methylstilbene (25.9 mg, 0.133 mmol) and Ir-complex **11d** (1 mg, 0.614 μmol) was dissolved in CH_2CH_2 (2 mL). This solution was then transferred into an autoclave. The hydrogenation was performed at rt under 50 bar of H_2 (or under reaction conditions described in Tables 1 and 2) for 12 h. After carefully releasing the hydrogen, the reaction mixture was directly passed through a short silica gel plug and flashed with ether. After evaporation, the residue was directly used for chiral HPLC analysis to measure the enantiomeric excess and for GC to measure the conversion.

4.7. General procedure for enantioselective allylic substitutions

In a schlenk tube, allylpalladium chloride dimer (4.57 mg, 0.0125 mmol), ligand **3a** (9.68 mg, 0.025 mmol) and solid potassium acetate (4.9 mg, 0.05 mmol) were dissolved in 2 mL of CH_2Cl_2. The solution was stirred at rt for 15 min. Dimethyl malonate (0.172 mL, 1.5 mmol) and *N*,*O*-bis(trimethylsilyl) acetamide (0.37 mL, 1.5 mmol) and a solution of *rac*-(*E*)-1-acetoxy-1,3-diphenyl-2-propene (**17**) (126 mg, 0.5 mmol) in 1 mL of CH_2Cl_2 were added subsequently. The reaction mixture was stirred at rt for 12 h. The solvent was removed under vacuum and the residue was passed through a short silica gel column (EtOAc/hexanes=1:9) to give product **18**.

4.7.1. 2-(1,3-Diphenyl-allyl) malonic acid dimethyl ester (18). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.15–7.29 (m, 10H), 6.45 (d, J=15.8 Hz, 1H), 6.31 (dd, J=15.7, 8.5 Hz, 1H), 4.24 (dd, J=10.3, 8.8 Hz, 1H), 3.93 (d, J=10.9 Hz, 1H), 3.70 (s, 3H), 3.65 (s, 3H). The ee of product was analyzed via chiral HPLC (AD column; eluting with 90:10 hexanes/2-propanol).

4.7.2. 2-Cyclohex-2-enylmalonic acid dimethyl ester (21). ^{1}H NMR (360 MHz) δ 5.68–5.71 (m, 1H), 5.43–5.46 (m, 1H), 3.66 (s, 6H), 3.21 (d, J=9.5 Hz, 1H), 2.82–2.84 (m, 3H), 1.27–1.92 (m, 6H). The ee of product was analyzed via chiral GC (Supelco Chiral Select 1000 column).

4.7.3. Compounds 22a and 22b. ^{1}H NMR showed an inseparable mixture of **22a** and **22b** (80:20) was obtained. 2-(1-Methyl-3-phenylallyl) malonic acid dimethyl ester (**22a**); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.11–7.21 (m, 5H), 6.31 (d, J=15.8 Hz, 1H), 5.98 (dd, J=15.8, 8.5 Hz, 1H), 3.60 (s, 3H), 3.53 (s, 3H), 3.25 (d, J=8.9 Hz, 1H), 2.97–3.00 (m, 1H), 1.05 (d, J=6.8 Hz, 3H); ^{1}H NMR for 2-(1-phenyl-but-2-enyl) malonic acid dimethyl ester (**22b**) can be found in literature.[21a] The ee of **22a** was analyzed via chiral HPLC (OJ-H column; eluting with 95:5 hexanes/2-propanol).

4.8. General procedure for enantioselective Heck reactions

2-Phenyl-2,5-dihydrofuran (**25**). In a schlenk tube, $[Pd_2(dba)_3 \cdot dba]$ (8.61 mg, 0.015 mmol), ligand **3a** (11.61 mg, 0.03 mmol) were dissolved in 3 mL of THF. The solution was stirred at 70 °C for 15 min. Phenyl triflate (**24**) (80.7 μL, 0.5 mmol), 2,3-dihydrofuran (**23**) (0.19 mL, 2.5 mmol) and *N*,*N*-diisopropylethylamine (0.26 mL, 1.5 mmol) were added subsequently. The reaction mixture was stirred at 70 °C for 3 d. The solvent was removed under reduced pressure and the residue was purified by a silica gel column (EtOAc/hexanes = 1:9) to afford **25**; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.20–7.25 (m, 5H), 5.92 (m, 1H), 5.79 (m, 1H), 5.70 (m, 1H), 4.76 (m, 1H), 4.69 (m, 1H). The product was analyzed via chiral GC (Supelco β-DEX 120 column).

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