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Asymmetric Allylic C–H Alkylation via Palladium (II)/*cis*-ArSOX Catalysis

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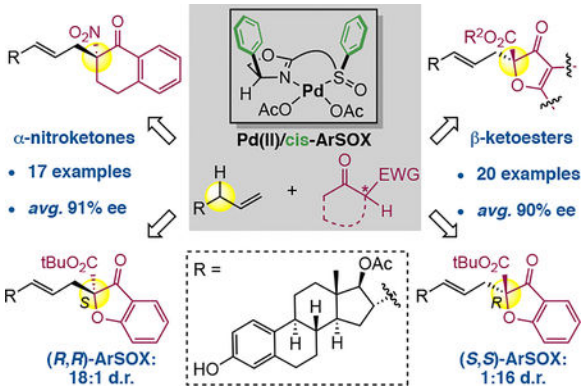
Abstract

We report the development of of Pd(II)/*cis*-aryl sulfoxide-oxazoline (*cis*-ArSOX) catalysts for asymmetric C–H alkylation of terminal olefins with a variety of synthetically versatile nucleophiles. The modular, tunable, and oxidatively stable ArSOX scaffold is key to the unprecedented broad scope and high enantioselectivity (37 examples, avg. >90% *ee*). Pd(II)/*cis*-ArSOX is unique in its ability to effect high reactivity and catalyst-controlled diastereoselectivity on the alkylation of aliphatic olefins. We anticipate that this new chiral ligand class will find use in other transition metal catalyzed processes that operate under oxidative conditions.

Graphical Abstract



The enantioselective transformation of C(sp^3)–H to C(sp^3)–C(sp^3) bond allows for the construction of a stereo-chemically enriched carbon framework via the union of two

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Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI. Experimental procedures, spectroscopic data for all new compounds and HPLC traces of racemic and enantiomerically enriched products (PDF);

X-ray crystallographic data for **3p** (CIF: CCDC 1856938);

X-ray crystallographic data for Pd(OAc)$_2$/**L9** complex (CIF: CCDC 1856936);

X-ray crystallographic data for **9e** (CIF: CCDC 1856939);

X-ray crystallographic data for **13b** (CIF: CCDC 1856937)

The University of Illinois has filed a patent application on Ar-SOX ligands for allylic C–H functionalizations.

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requisite fragments with minimal pre-activation.[1] Transition metal-catalyzed asymmetric C–C bond forming reactions under oxidative conditions are relatively rare.[2] For example, while Pd(0)-catalyzed allylic substitution has been established with broad scope to form chiral C(sp^3)–C(sp^3) bonds,[3] the direct asymmetric alkylation of allylic C–H bonds is underdeveloped.[4–6] Existing methods only demonstrate limited reactivity towards a focused set of olefins (e.g. electron deficient/neutral allylarenes[4] or 2 equiv. of olefins[5, 6]) with specialized nucleophiles (e.g. 1,3-diketone,[4] pyrazol-5-one,[5] 2-aryl propionaldehyde[6]) that are not readily amenable to diversification. One potential reason for such limitations is the paucity of chiral ligands designed for transition metal mediated processes proceeding under acidic, oxidative conditions. Herein, we report a novel and highly tunable (*S,S*)-aryl sulfoxide-oxazoline ligand class that enables the Pd(II)-catalyzed asymmetric C–H alkylation of a broad scope of allylarenes and aliphatic olefins (1 equiv.) with a variety of synthetically versatile nucleophiles leading to high levels of asymmetric induction (avg. >90% *ee*; avg. 10:1 d.r.).

Asymmetric allylic alkylation using prochiral nucleophiles requires a ligand framework that can establish a chiral environment opposite to the ligand/π-allylPd complex.[3] Previous C–H alkylation methods relied upon chiral phosphoramidite ligands that have demonstrated modest enantioselectivity alone (avg. 75% *ee*)[4] and must be combined with a BINOL-derived chiral phosphoric acid co-catalyst to afford high asymmetric induction[5]. Additionally, phosphoramidite ligands are sensitive to the oxidative reaction conditions, necessitating iterative addition of the catalyst[4] and/or rigorous exclusion of oxygen[5]. Oxidatively stable palladium(II)/bis-sulfoxide catalysis has demonstrated broad scope for allylic C–H alkylations; however due to fluxional binding of the sulfoxide ligand to the metal, it cannot be rendered asymmetric.[7] Pd(II)/aryl sulfoxide-oxazoline (Ar-SOX) catalysis[8] has been shown to display static ligand binding to Pd[8a] and to effect intramolecular asymmetric allylic C–H oxidation, where the Pd(II)/*trans*-(*S,R*)-ArSOX complex is able to impose high levels of π-allyl enantiofacial selection.[8b] Intermolecular allylic C–H alkylation generally proceeds with linear regioselectivity, dictating that the enantio-facial selectivity be achieved via a prochiral nucleophile, which occurs relatively remote from the ligand environment. Previous studies of phosphinoxazoline (PHOX) ligands in asymmetric allylic substitutions have shown that unsymmetrically substituted phosphines could significantly impact the remote chiral environment by placing large groups on the phosphine *cis* to substituents on the oxazoline.[3b] We envisioned the stereogenic sulfoxide moiety would allow us to access the Pd(II)/*cis*-(*S,S*)-ArSOX complex that may be able to extend its chiral environment to influence nucleophile enantiofacial selection. Moreover, the highly modular nature of ArSOX scaffold allows for extensive exploration of both steric and electronic parameters of the ligand, potentially leading to greater generality in nucleophile scope.

We commenced our study of asymmetric alkylation between 2-nitrotetralone (**1**) and allylbenzene (**2**). Using previously reported conditions for asymmetric allylic oxidation with (*S,R*)-ArSOX **L1**,[8b] the alkylated product was obtained in 65% yield and −20% *ee* (Table 1, entry 1). Consistent with our hypothesis, (*S,S*)-ArSOX **L2** furnished significant improvements in enantioselectivity (64% *ee*, entry 2). *Para*-tolyl sulfoxide (**L3**) performed

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comparably (entry 3), and was preferred for its relative ease of synthesis. Allylic C–H alkylation utilizing acidic pro-nucleophiles undergoes in situ deprotonation by the acetate anion of the Pd(II) catalyst. The nature of the cation/anionic nucleophile pairing has been shown to influence the facial bias and therefore significantly impact the stereoselectivity.[3a, 9] We wished to exploit the effect of ion pairing by introducing alternate sources of acetate with different cations. We surveyed seven acetate salts (see Table S2 in supporting information), known to form enolate complexes with nitroketones.[10a] $Zn(OAc)_2$[10, 11] was identified to be the optimal additive with benzene/dioxane as the solvent, increasing the selectivity to 79% *ee* (entry 4). Lowering the temperature to 5°C further improved the enantioselectivity (entry 5). We next turned to ligand modifications on the oxazoline: a trifluoromethyl group at the *para*-position of the aryl substituents was not beneficial (entry 6), whereas a bulky *tert*-butyl group (**L5**) or electron-rich methoxy group (**L6**) led to increases in selectivity (entry 7, 8). A cooperative effect between sterics and electronics was found using a *tert*-butoxy (**L7**) substituent, boosting the enantioselectivity to 92% *ee* (entry 9). The amount of $Zn(OAc)_2$ additive could be lowered to 25 mol% (entry 10, 11), with 50 mol% being the most broadly applicable (vide infra). With fragment coupling amounts of nucleophile (1 equiv.), a preparative yield was maintained (60%) without diminished enantioselectivity (91% *ee*, entry 12).

Using **L7** as the optimal ligand for 2-nitrotetralone, the scope for the terminal olefin partner was examined (Table 2). A wide range of *para*-substituted allylarenes were well tolerated: both electron neutral/donating (**3a, b**) and electron-withdrawing groups (**3c, d**) afforded preparative yields and enantioselectivities and provide useful handles for further manipulation. 4-Allylanisole **3b** afforded 90% *ee* using **L5**: previous asymmetric C–H alkylation methods have found this electron rich allylarene to be unreactive.[4] A substrate containing a primary, benzylic alcohol (**3e**) underwent smooth alkylation, with no alcohol oxidation observed. A variety of biologically relevant heteroaromatics were also successfully coupled with 2-nitrotetralone in good yield and high enantioselectivity, including coumarin (**3f**), chromene (**3g**), benzofuran (**3h**), benzothiophene (**3i**), 5’ and 3’-indoles (**3j, k**). Notably, benzothiophene (**3i**) housing a chelating and oxidizable sulfur moiety was alkylated with good yields and high enantioselectivity (92% *ee*). We next examined the substitution on the tetralone moiety. Commercially available O-substituted tetralone at 5’, 6’, 7’–positions (**31, n, p**) all served as competent nucleophiles, as well as a 6-bromo moiety useful for further derivatizations (**3m**). Incorporating an electron-donating O-benzyl group at 6’-position (**3o**) led to diminished reactivity and enantioselectivity (88% ee). The yield could be improved to 78% when running the reaction at room temperature. The absolute configuration was assigned to be (*R*) from the crystal structure of **3p**. Contrasting previous asymmetric allylic C–H alkylations that employ nucleophiles not easily diversifiable,[4, 5] α-nitroketones are versatile intermediates that can be transformed into a diverse array of common functionality. Chemoselective reduction of the nitro group revealed the medicinally relevant α-amino ketone motif **4** without erosion in enantioselectivity. Upon *N*-allylation of **4** with allyl bromide, ring-closing metathesis[12] furnished the spirocyclic tetralone-piperidine motif. Chemoselective olefin hydrogenation in the presence of benzylic ketone afforded **5**, a precursor to potassium-competitive acid blockers.[13] Importantly, the synthetic route based on asymmetric alkylation is highly efficient (43% overall yield and

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91% *ee*) when compared to a previous racemic synthesis[13] (6% overall yield). Additionally, the ketone moiety in **4** serves as a synthetic handle: both hydride reduction and Grignard addition of the ketone is achieved with high diastereoselectively to afford functionalized 1, 2-amino alcohol motifs as useful chiral building blocks.

β-ketoesters represent an important nucleophile class, furnishing versatile synthetic intermediates that can rapidly afford core skeletons of complex molecules.[14] We evaluated β-ketoesters **6** and 7 featuring the furan-3-one core, found in natural products with a broad range of medicinal properties.[15] With the previously optimal SOX ligands **L5** and **L7**, modest enantioselectivity (74% and 70%) was obtained with the benzofuranone nucleophile **6** (Table 3A). We hypothesized that taking advantage of the interactions between the *cis*-substituents on the oxazoline and sulfoxide may modulate the orientation of the steric elements towards the approaching trajectory of the compact 5-membered ring nucleophile. Given the benefits of electron-rich aromatics in promoting **π**–**π** interactions,[16] we examined the electron-donating 3,4,5-trimethoxyphenyl moiety on the oxazoline (**L8**), which led to a substantial increase in asymmetric induction to 89% *ee* (entry 3). Combined with a CF_3 group on the backbone (L9), a further increase in selectivity to 91% *ee* was achieved with excellent reactivity (entry 4). Crystallo-graphic analysis of $Pd(OAc)_2$/**L9** complex suggests a potential **π**–**π** interaction that orients the substituents on the trimethoxy aryl group outward, possibly accounting for the enhanced enantioselectivity. Switching to the smaller nucleophile 7, L9 resulted in 87% *ee* (entry 5). We made modifications to further extend the ligand out towards the plane of the **π**-allylPd: an expanded **π**-surface (9-anthracenyl, **L10**) on the sulfoxide lead to 90% *ee* (entry 6).

β-ketoesters **6** and 7 underwent alkylation with a broad scope (Table 3B). Using Pd(II)/**L9** catalyst, nucleophile **6** was found to be highly reactive even with lowered catalyst loading (5 mol%). Electronic variation on the nucleophile was well tolerated with 6-methoxy and 6-fluorine substitution both giving high yields and enantioselectivities in alkylated products **9b** and **9c**, respectively. For the terminal ole-fins, a wide range of sterically and electronically varied allylarenes were alkylated with excellent reactivity and high enantioselectivity. Important pharmacophores and heterocycles such as unprotected cyclopropyl amide (**9d**), sulfonamide (**9e**), safrole (**9f**), tetrahydroquinoline (**9g**), benzoxazinone (**9h**) are well tolerated. The absolute configuration was assigned to be (*R*) from the crystal structure of **9e**. Furthermore, whereas previous asymmetric allylic C–H alkylations have not been demonstrated with unactivated terminal olefins, the Pd(II)/ArSOX catalysis could be extended to this important olefin class (**9i**, **9j**), with good yields and promising enantioselectivity. For the furanone-based β-ketoester 7, the incorporation of thiophene (**10b**) and furan (**10c**) into the nucleophile was tolerated with high enantioselectivities. Importantly, **10c** establishes the requisite carbon skeleton that is found in a family of natural products such as cephalymysins with diverse biological activities.[17] The allylarene component could be rapidly varied to incorporate medicinally relevant phenylphosphate (**10d**), 3'-indole (**10e**) and safrole (**10f**), all in high enantioselectivi-ties. Challenging indanone-based β-ketoester nucleophiles furnishing all-carbon quaternary stereocenters (**11a**) were also evaluated. Analogous to previous observations in asymmetric allylic substitutions,[9, 18] this nucleophile proceeded with a moderate level of enantioselectivity

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(79% *ee*). Interestingly, 4-substitution at the indanone (**11b**) was found to be beneficial for enantioinduction, leading to >90% *ee* with a range of electronically varied allylarenes (**11c, d**).

While achiral olefins are limited in structural diversity, chiral aliphatic substrates offer the opportunity for sp^3-sp^3 cross-coupling of complex fragments. For transformations lacking substrate bias,[19] catalyst-controlled asymmetric induction is critical for forging such bonds selectively and may additionally enable synthesis of both stereoisomers. We questioned if the good levels of enantioselectivity observed for the achiral aliphatic substrates (**9i, 9j,** Table 3) would translate into synthetically useful levels of diastereoselectivity. We examined estrone derivative **12** and found that the inherent substrate bias for alkylation with racemic Pd(II)/**L11** catalyst was minimal (1.5:1 d.r.). Under Pd(II)/**L9** catalyzed asymmetric alkylation with nucleophile **6**, the reaction afforded product **13a** in excellent yield (89%) and diastereoselectivity (16:1). Moreover, when ligand enantiomer *ent*-**L9** was used, the sense of asymmetric induction was overturned to favor the other diastereomer (18:1) in 90% yield. The absolute stereochemistry of **13b** was confirmed via X-ray crystallography (see supporting information). We additionally observed good to excellent levels of catalyst-controlled diastereoselectivity in a wide range of aliphatic substrates having nitrogen, oxygen and carbon stereogenic centers in the homoallylic positions that allow for the access of either diastereomer in stereoenriched form: pyrrolidine (**12b**), Weinreb amide (**12c**), 1, 2-diol (**12d**) and androsterone derivative (**12e**). Collectively, these examples demonstrate the ability of Pd(II)/ArSOX to exert significant catalyst-controlled asymmetric induction with chiral substrates.

In conclusion, we have developed a new class of Pd(II)/*cis*-ArSOX catalysts for asymmetric allylic C–H alkylation. The continued study and development of SOX enabled catalysis will contribute novel ligands and reactivity platforms for organometallic reactions proceeding via oxidative pathways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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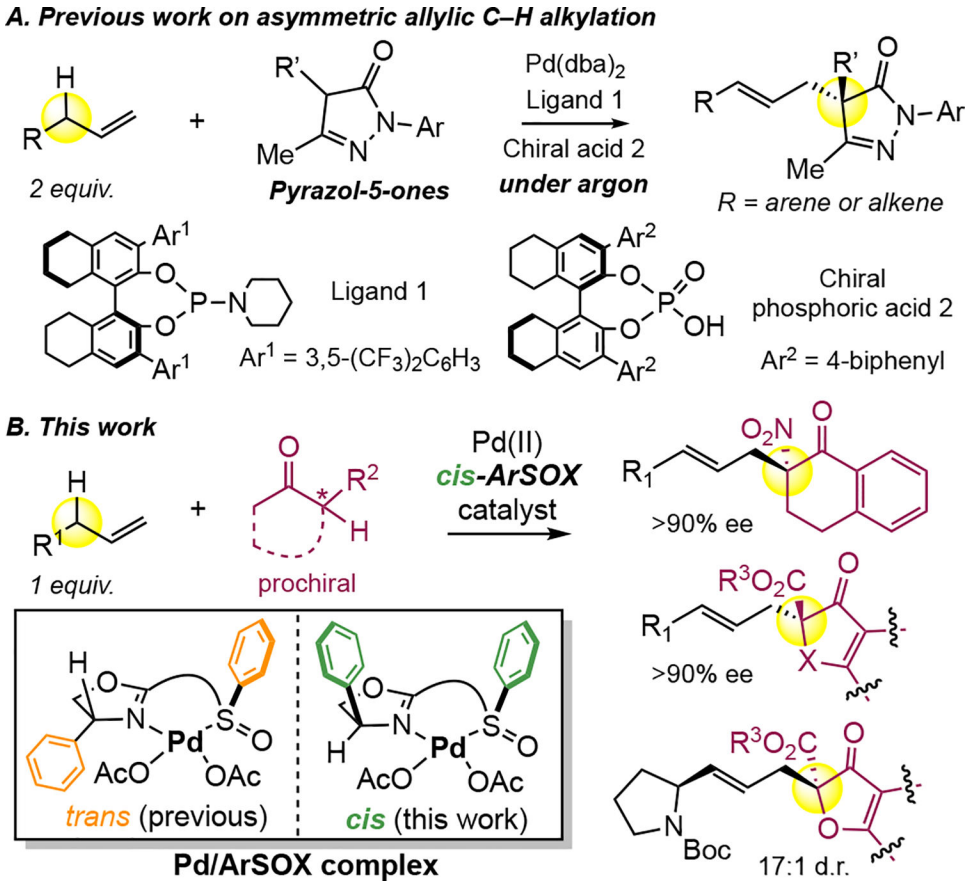
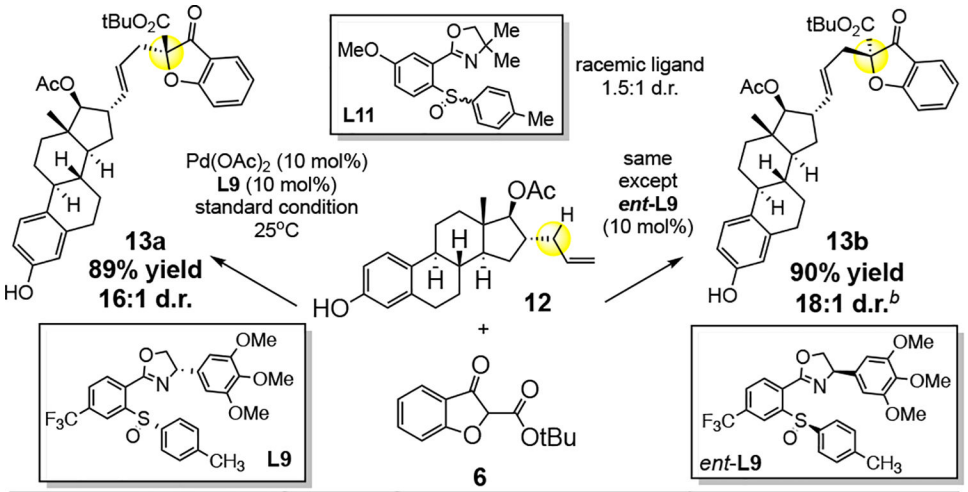
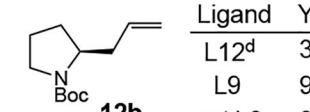


Scheme 1.

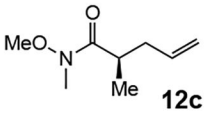
Asymmetric Allylic C–H Alkylation





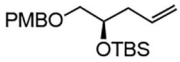
12b

Ligand	Yield	*d.r.*[c]
L12[d]	35%	1:1.3
L9	91%	8:1
ent-L9	84%	1:17



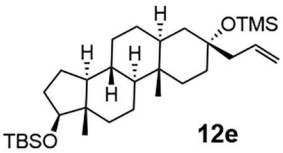
12c

Ligand	Yield	*d.r.*
L12[d]	21%	1:1
L9	93%	5:1
ent-L9	89%	1:4



12d

Ligand	Yield	*d.r.*
L12[d]	44%	1:1.2
L9	92%	3:1
ent-L9	90%	1:20



12e

Ligand	Yield	*d.r.*[c]
L11	31%	1:1
L9	90%	4:1
ent-L9	93%	1:5

Scheme 2. Diastereoselective Allylic C–H Alkylation[a]

[a] Reaction condition: Olefin **12** (0.2 mmol), Nuc **6** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), **Ligand** (0.02 mmol), $Zn(OAc)_2$ $2H_2O$ (0.1 mmol), 2,6-DMBQ (0.3 mmol), Benzene (1.2 ml) at 25°C for 72 h. Yields are isolated; *d.r.* are determined by ^{1}H NMR anaylsis. bAbsolute stereochemistry assigned by X-ray crystallography of **13b**, all other compounds assigned by analogy. [c]*d.r.* determined by chiral HPLC analysis. [d]L12: 1,2-Bis(phenylsulfinyl)ethane is used, when L11 gave no reaction.

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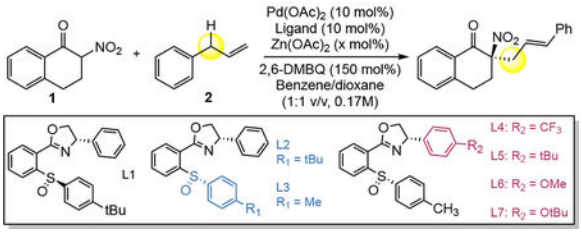
Table 1.

Reaction Development with Nitrotetralone[a]



Entry	Ligand	$Zn(OAc)_2$ $2H_2O$ (x mol%)	T (°C)	Yield (%)[b]	ee (%)[c]
1[d]	L1	0%	45	65	−20
2[d]	L2	0%	45	78	64
3[d]	L3	0%	45	80	66
4	L3	100%	45	82	79
5	L3	100%	5	70	88
6	L4	100%	5	78	87
7	L5	100%	5	77	90
8	L6	100%	5	74	89
9	L7	100%	5	81	92
10	L7	50%	5	83	92
11	L7	25%	5	79	92
12[e]	L7	25%	5	60	91

[a]Reaction conditions: Nuc 1 (0.2 mmol), Olefin 2 (0.1 mmol), Pd(OAc)2 (0.01 mmol), Ligand (0.01 mmol), 2,6-DMBQ (0.15 mmol) in benzene/dioxane (0.17 M) at 45°C for 24 h or at 5°C for 72 h.

[b]Isolated yields.

[c]Determined by chiral HPLC.

[d]in toluene.

[e]1 equiv. of Nuc 1

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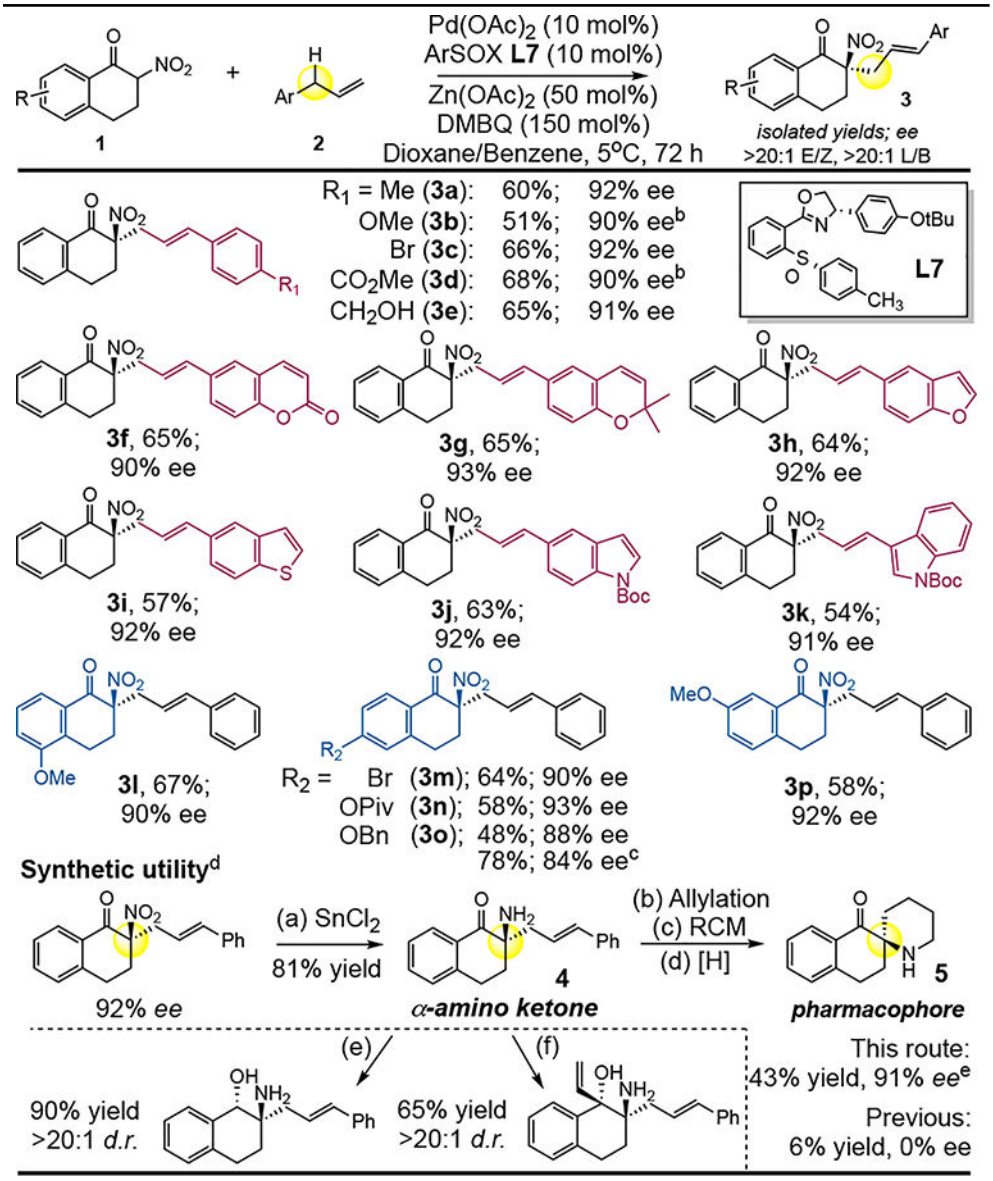
Table 2.

Asymmetric Alkylation with 2-Nitrotetralone[a]



[a]Reaction conditions: Nuc 1 (0.4 mmol), Olefin 2 (0.2 mmol), Pd(OAc)2 (0.02 mmol), Ligand (0.02 mmol), Zn(OAc)2 2H2O (0.1 mmol), 2,6-DMBQ (0.3 mmol), Dioxane/Benzene (1:1, 1.2 ml) at 5°C for 72 h; Yields are isolated; e.e. determined by chiral HPLC analysis; Absolute stereochemistry assigned based on X-ray crystallography of **3p**, all other compounds assigned by analogy.

[b]ArSOX **L5** was used.

[c]at 25°C.

[d](a)SnCl2 2H2O (10 equiv.), THF/H2O, 45°C, 24 h. 81% yield. (b)allyl bromide (1.1 equiv.), K2CO3 (1.1 equiv.), MeCN, 50°C, 18 h. 72% yield. (c)Grubbs II (10 mol%), TsOH (1 equiv.), DCM, reflux, 24 h. 94% yield. (d)Pd/C (20 wt.%), H2 (1 atm), MeOH, 2 h, quantitative. (e)NaBH (1.1 equiv.), MeOH, 0°4 C. (f)vinylmagnesium bromide (3 equiv.), THF, −78°C.

[e] **5** was acetylated before chiral HPLC anaylsis.

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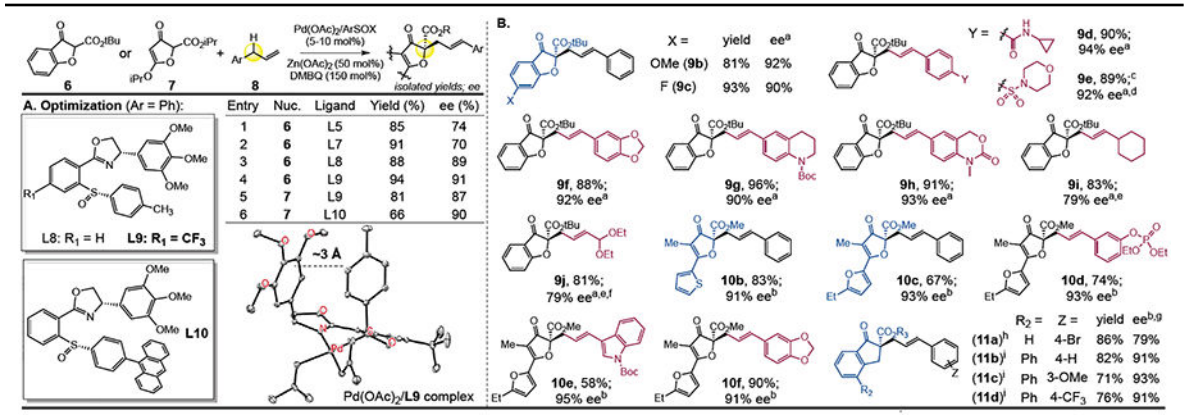
Table 3.

Asymmetric Allylic C–H Alkylation with β-ketoesters.



[a]**Condition A**: Nuc **6** (0.4 mmol), Olefin **8** (0.2 mmol), Pd(OAc)2 (0.01 mmol), **L9** (0.01 mmol), Zn(OAc)2 2H2O (0.1 mmol), 2,6-DMBQ (0.3 mmol), Benzene (1.2 ml) at 5°C for 72 h.

[b]**Condition B**: Nuc **7** (0.1 mmol), Olefin **8** (0.1 mmol), Pd(OAc)2 (0.01 mmol), **L10** (0.01 mmol), Zn(OAc)2 2H2O (0.05 mmol), 2,6-DMBQ (0.15 mmol), Dioxane at 5°C for 72 h.

[c]Pd(OAc)2/**L9** (2.5 mol%) gave 72% yield.

[d]Absolute stereochemistry assigned based on X-ray crystallography of **9e**, all other compounds assigned by analogy.

[e]25°C.

[f]ee determined by converting the acetal group to an aldehyde.

[g]2 equiv. of Nuc.

[h]R3 = methyl.

[i]R3 = benzyl.