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Directed, Palladium(II)-Catalyzed Enantioselective anti-Carboboration of Alkenyl Carbonyl Compounds

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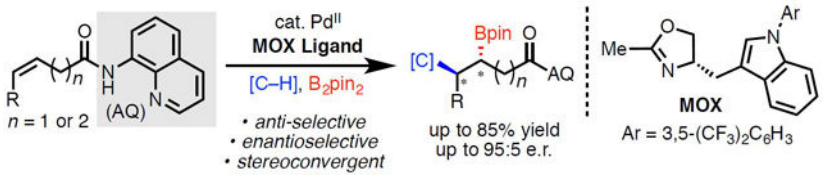
Abstract

A substrate-directed enantioselective anti-carboboration reaction of alkenes has been developed, wherein a carbon-based nucleophile and a boron moiety are installed across the C=C bond through a 5-membered palladacycle intermediate. A preliminary result also shows it is possible to extend this reaction to alkenes that are more distal from the directing group and react via a 6-membered palladacycle. The reaction is promoted by a palladium(II) catalyst and a monodentate oxazoline ligand. A range of enantioenriched secondary alkylboronate products were obtained with moderate to high enantioselectivity that could be further upgraded by recrystallization. This work represents an efficient method to synthesize versatile and valuable alkylboronate building blocks. Building on an earlier mechanistic proposal by Peng, He, and Chen, a revised model is proposed to account for the stereoconvergent nature of this transformation.

Graphical Abstract



Keywords

palladium; directing group; carboboration; enantioselective catalysis; MOX ligand

Substrate-directed nucleopalladation offers a powerful platform for generating multiple consecutive stereocenters (Scheme 1A). The key feature of these transformations is the formation of a stabilized 5- or 6-membered metallacycle intermediate, which enables trapping with an additional reaction partner, such as a proton, an electrophile, or a nucleophile, under various redox manifolds. Recently, our group[1] and others[2] have

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Supporting Information

Experiment details, spectra data, copies of ^1H and ^{13}C NMR spectra, and X-ray crystallographic data. These materials are available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

developed numerous alkene hydrofunctionalization and 1,2-difunctionalization reactions by exploiting this approach. A frontier in this area of research is controlling the absolute stereochemistry of the products by developing enantioselective variants of these transformations. In 2016, we reported a non-stereoselective γ-selective hydrocarbofunctionalization,[1b] which was subsequently rendered enantioselective in 2018 by He, Peng, and Chen through the elegant design and development of a monodentate oxazoline (MOX) ligand.[2c] In a complementary line of inquiry using prochiral carbon nucleophiles, our laboratory[1f] and the group of Zhang and Gong[2e] have achieved enantioselective transformations with a chiral phosphoric acid (CPA) ligand and a chiral amine catalyst respectively. Although these strategies have been successful in enantioselective hydrocarbofunctionalization, enantioselective alkene 1,2-difunctionalization within this family of reactions has not been reported to date. Herein, we describe the first asymmetric alkene *anti*-carboboration reaction via directed nucleopalladation.[3] As in our previously reported racemic version,[4] the reaction proceeds smoothly via either 5- or 6-membered palladacycle intermediates. The resulting enantioenriched organoboron compounds are highly valuable in organic synthesis[5,6] and naturally map onto various bioactive compounds, such as β-homotryptophan. [7]

To begin our study, we selected *N*-methylindole (**2a**) as the nucleophile, B_2pin_2 (**3a**) as boron coupling partner, and 8-aminoquinoline (AQ)-masked[8] (*Z*)-3-hexenoic acid (**1d**) as our pilot alkene substrate. In order to render this reaction enantioselective, we carried out extensive screening of base, solvent, and reaction temperature, while at the same time examining a variety of chiral ligands (Table 1). During optimization of the solvent, we found that HFIP provided high yield but low *ee*, while THF delivered moderate *ee* but lower yield. Interestingly, using a mixture of HFIP and THF (1:1) as solvent improved both the yield and *ee* (see the Supporting Information (SI) for optimization details). Adding DMF as a third solvent component further improved the *ee*. Commonly used bi- and tridentate oxazoline-based ligands as well as Yu's APAO[9] and MPAAM[10] ligands (**L2–L10**) only induced low to moderate enantioselectivity with attenuated reactivity. Initial screening of monodentate ligands such as CPA (**L1**) and electron-deficient olefins (**L11–L13**) also failed to exert any chiral induction. To our delight, screening of monodentate imidazoline (MIM)(**L15–L17**) and MOX ligands (**L18–L39**) gave us reasonable levels of enantioselectivity, showing that these ligand scaffolds are privileged in this reaction. We decided to choose the MOX scaffold for further optimization based on synthetic accessibility considerations. The effect of different MOX ligands on the alkene carboboration reaction is similar to the trends in He, Peng, and Chen's report.[2c] Tryptophan-derived ligands showed higher levels of chiral induction than other amino acid derivatives in terms of chiral induction. Systematically varying the *N*-aryl group revealed that the steric and electronic nature of the substituents impacts both yield and *er* (albeit to a minor extent), with electron-withdrawing groups proved to be advantageous. Ultimately, our optimization efforts converged with earlier findings from the aforementioned study[2c] in identifying **L34,** which bears a 3,5-bis-CF3-phenyl substituent on the indole nitrogen, as the optimal ligand, providing up to 94:6 *er* and 71% yield. Interestingly, 3,5-bis-nitro-phenyl substituted ligand **L36** also offered the same enantioselectivity, albeit with slightly lower yield. Additionally, several oxazolines bearing a phenyl or methyl group at C-5 (**L37–L39**) were prepared based on the idea that increased

steric hindrance could further improve the enantioselectivity. Unfortunately, none of these ligands performed better than **L34.**

After identifying the optimal ligand and reaction conditions, we next investigated the scope of this palladium(II)-catalyzed asymmetric alkene *anti*-1,2-carboboration reaction (Table 2). A variety of AQ-masked alkenyl carbonyl compounds (**1a–1h**) were competent substrates in this transformation, providing the desired products in moderate to good yields with satisfactory *er*. The absolute configurations of products **4f** and **4g** were assigned as (*R*, *R*) by X-ray crystallography analysis, and other products were assigned by analogy.[11] Increasing the size of R group on the alkene substrate improved the *er* while slightly lowering the yield. For example, terminal alkene **1a** (R = H) showed only a moderate *er* of 86:14, while switching the R group to methyl (**4d** and **4e**) and ethyl (**4f**), led to higher enantiomeric ratios of 91:9 and 94:6, respectively. More sterically bulky groups on the alkene, however, shut down the reaction. For instance, in the case of **4q,** only trace amount of product was formed under the standard reaction conditions. Generally, *Z*-alkene substrates are more reactive than *E*-alkenes. Under the standard conditions, *E*-alkene **1b** was carboborylated in less than 50% conversion. Nevertheless, with more forcing conditions, **4d** could be generated from **1b** in high yield and good enantioselectivity. In all the cases where internal alkene substrates were used, >20:1 *dr* was observed,[12] demonstrating the excellent stereocontrol of this carboboration reaction. To our surprise, both *E*- and *Z*-alkene substrates (**1b** and **1c**) resulted in the same major diastereomer after carboboration (**4d** and **4e**), which is inconsistent with the stereoinduction and -convergence model proposed by He, Peng, and Chen.[2c] We instead believe the *E*-alkene is first isomerized to *Z*-configuration upon Pd(II) coordination, followed by *anti*-nucleopalladation to give a common alkylpalladium intermediate in both cases (*vide infra*). Gratifyingly, AQ-masked 4-pentenoic acid substrate **1i** underwent this transformation smoothly through a putative 6-membered palladacycle delivering **4p** in high yield and moderate *er*. However, internal alkene **1k** was incompatible with this difunctionalization reaction.

We have also studied the scope of indole nucleophiles under the standard reaction conditions. Various indole derivatives bearing substituents at different positions on the indole ring were well tolerated in this transformation (**4m–4o**). Indoles with electron-withdrawing substituents were incompatible coupling partners (**2i–2k**), potentially due to diminished nucleophilicity (**4r–4t**). Different groups on indole nitrogen also have a significant effect on reaction outcomes. With larger substituents (**4k** and **4l**), the enantioselectivity of the reaction was improved, albeit with diminished yields. We have also attempted nucleophiles that were demonstrated to be compatible in our previously published hydrocarbofunctionalization method,[1b] such as 1,3-cyclopentadione and 3-(dimethylamino)phenol. However, these nucleophiles were ineffective in 1,2-carboboration, even under non-stereoselective conditions (See SI). To our delight, 1,3-dicarbonyl compound **2c** was found to be a suitable nucleophile and provided the corresponding product (**4c**) in low yield and moderate *er*.

Subsequently, this Pd(II)-catalyzed asymmetric alkene carboboration method was performed on gram-scale to demonstrate its operational simplicity and practicality (Scheme 2). Compound **4f** was prepared from *Z*-alkene **1d**, *N*-methylindole (**2a**), and B_2pin_2 (**3a**) on

gram scale, with the yield and *er* consistent with the smaller scale experiment. Furthermore, recrystallization of the final product from Et_2O or EtOH could provide nearly enantiopure secondary boronate **4f** in satisfying overall yield.

A series of derivatizations were next conducted to further illustrate the synthetic utility of the carboborylated products (Scheme 3). Treatment of compound **4f** with aqueous KHF_2 generated trifluoroborate salt **5** in high conversion. Initial attempts of boronate oxidation with strong oxidants, such as H_2O_2 solution, proved to be unsuccessful, presumably because of undesired oxidation of the electron-rich indole ring. Finally, using a mild oxidant $NaBO_3$•$4H_2O$,[13] boronate **4f** was efficiently converted into chiral alcohol **6** with almost complete stereoretention. $Ni(tmhd)_2$-mediated methanolysis[14,15] and a two-step transamidation deprotection[16] of the AQ protecting group were also performed to deliver the corresponding methyl ester **7** and amide **8** with retention of the C–B bond, which could potentially be carried forward into further transformations.

Both in He, Peng, and Chen's asymmetric hydrocarbonation reaction[2c] and this work, stereoconvergence was observed, with *Z*- and *E*-alkene substrates giving the same absolute and relative stereochemistry (Scheme 4A). In the previously proposed stereoinduction model (Scheme 4B),[2c] with an *E*-alkene, **Int-E-I-down** was computed to be more stable than **Int-*E*-II-up**, and with a *Z*-alkene, **Int-*Z*-II-up** was computed to be more stable than **Int-*Z*-I-down**. These trends also hold in the corresponding transition state energies, where nucleopalladation from **Int-*E*-I-down** (to give **Int-*E*-III**) and from **Int-*Z*-II-up** (to give **Int-*Z*-III**) is favored for *E* and *Z* alkenes, respectively. This model predicts that the $C(sp^3)$–Pd stereocenter at C2 would have opposite configuration with *E* and *Z* alkenes, which is not in agreement with our results.[17] This discrepancy prompted us to consider an alternative explanation (Scheme 4C). Specifically, we envisioned a different scenario in which alkene isomerization to interconvert **Int-*E*-I-down** and **Int-*Z*-II-up** takes place under the reaction conditions, followed by nucleopalladation, which occurs preferentially through the lower-energy pathway involving **Int-*Z*-II-up**. Although the precise mechanism of alkene isomerization remains unclear at this stage,[18] evidence suggests that it occurs in the present system only after alkene complexation with palladium(II). To test the viability of this alternative mechanism, several mechanistic experiments were performed (Scheme 4D). At room temperature, treatment of *Z*-alkene **1d** with stoichiometric $Pd(OAc)_2$ both with and without **L34** led to formation of the corresponding palladium(II) complex **Pd-I** with the retention of alkene geometry. In contrast, *E*-alkene **1l** underwent *E/Z* isomerization in the presence and absence of MOX ligand. Interestingly, **L34** seems to promote *E*-to-*Z* isomerization, possibly by creating a more sterically hindered environment around the palladium(II) center (See SI for additional mechanistic experiments).[19] These results are consistent with the model depicted in Scheme 4C, where isomerization of **Int-*E*-I-down** to **Int-*Z*-II-up** takes place before the nucleopalladation step for the *E*-alkene substrates. which accounts for the observed stereoconvergence in the described 1,2-difunctionalization.

In conclusion, we have developed an enantioselective carboboration reaction of unactivated alkenyl carbonyl compounds using a chiral monodentate oxazoline (MOX) ligand. This reaction proceeded smoothly through 5- and 6-membered palladacycle intermediates to install a secondary boron group to the β or γ positions relative to the carbonyl group. A

variety of carbon nucleophiles and alkene substrates were demonstrated to be compatible, with moderate to good yields and enantioselectivity. Recrystallization of the final product was shown to greatly improve the product *er*. The reaction was scalable, and cleavage of the 8-aminoquinoline (AQ) directing group was demonstrated. To explain the stereoconvergence of *Z*- and *E*-alkenes, a revised mechanism based on Chen's original stereoinduction model was proposed. Future work will focus on the development of new chiral ligands and expanding the scope of substrated-directed palladium(II)-catalyzed 1,2-difunctionalization to other types of reactions and substrates. These results will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(11). The absolute stereochemistry of compound **4a** was determined by ^{1}H NMR analysis of its Mosher ester (see SI).

(12). The *dr* values in these cases are notably higher than those observed under non-stereoselective conditions (Ref. 4), which merits brief comment. Based on the experimental data in Scheme 4, we surmise that E-alkenes will isomerize to the corresponding *Z*-alkenes under the reaction conditions, both with and without the MOX ligand, and furthermore that *Z*-alkenes react much faster in carbopalladation than *E*-alkenes. Under the enantioselective conditions, the MOX ligand appears to facilitate rapid *E*-to-*Z* isomerization, which results in good diastereocontrol (see examples **4d** and **4e**). However, under the non-stereoselective conditions (Ref. 4), where the

reaction temperature is higher and there is no ancillary ligand to promote alkene isomerization, *E*-alkenes can react via carboboration at a rate that is competitive with that of the *Z*-isomers (and that is similar to the rate of *E*-to-*Z* isomerization), which results in low levels of diastereocontrol.

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(17). In hydrocarbofunctionalization (Ref. 2c) this C(sp^3)–Pd stereocenter is ablated in the next elementary step (protodepalladation), but in the present transformation with B_2Pin_2, the C(sp^3)–Pd is transferred to the C(sp^3)–B stereocenter in the product.

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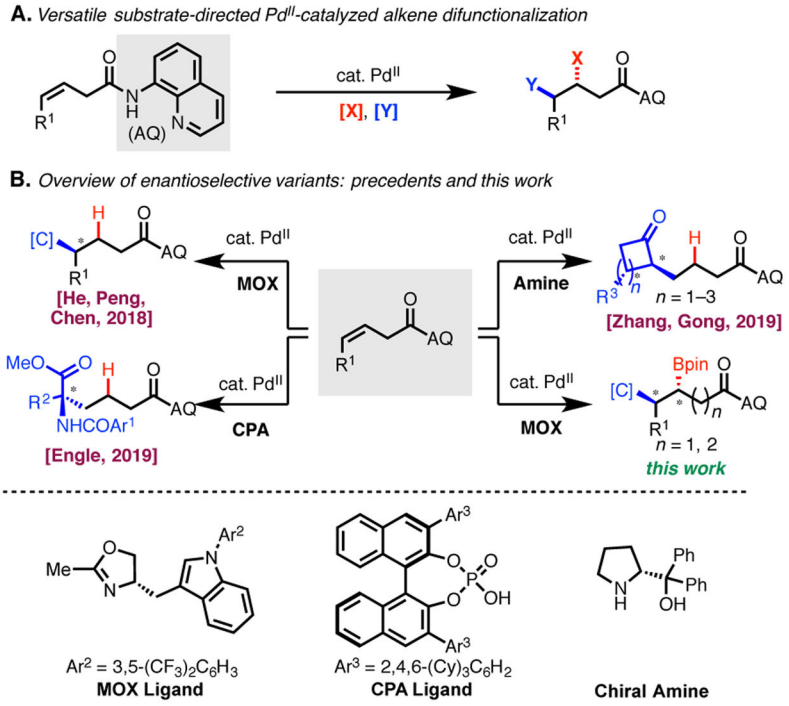
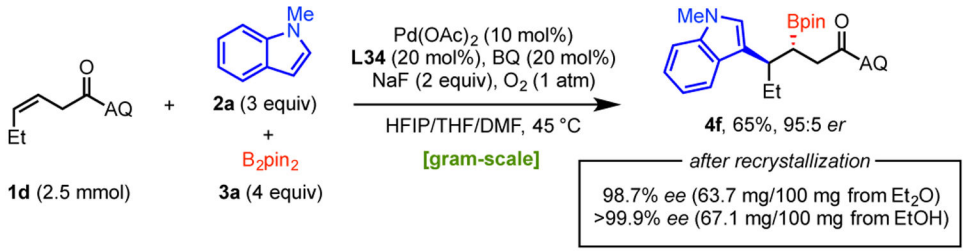
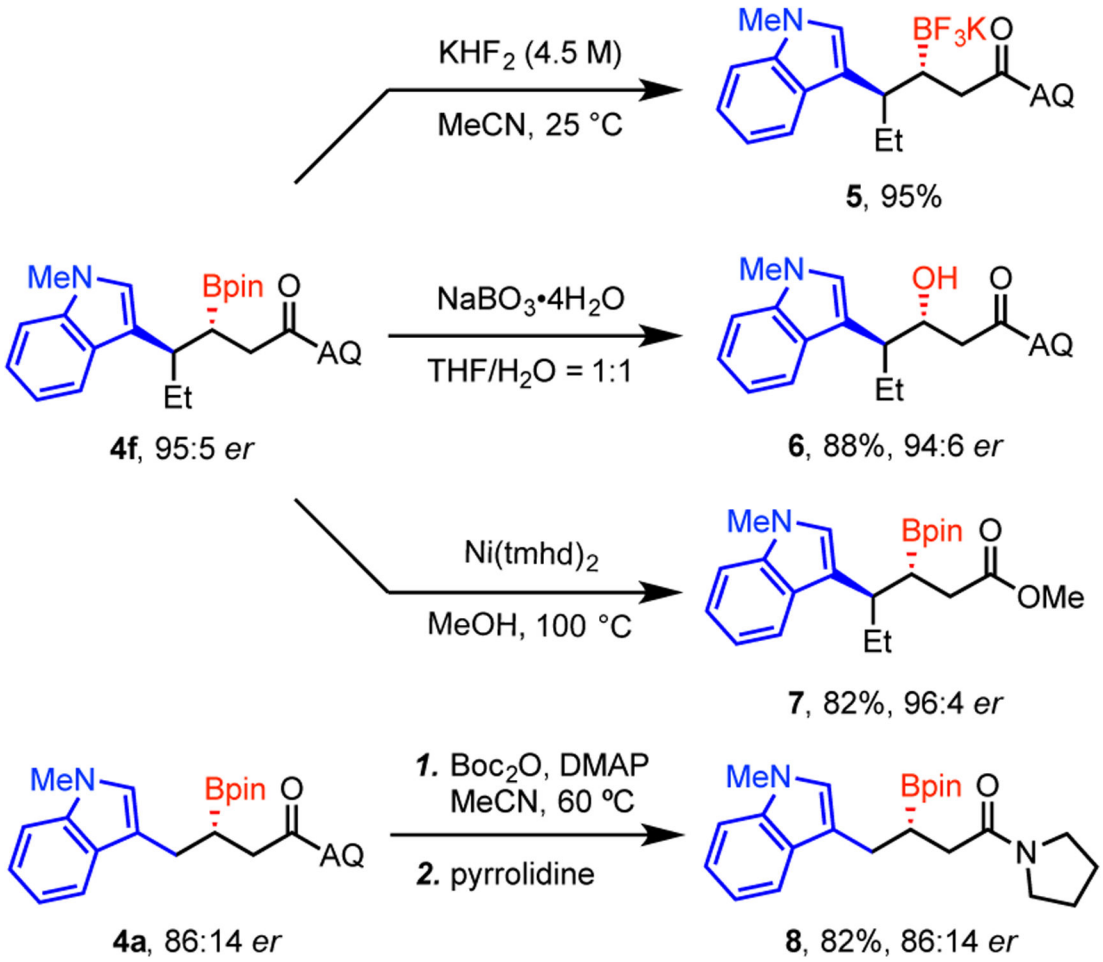
(19). In Ref. 2c the authors note that isomerized alkene was not observed in solution during the course of the reaction, but the authors did not examine the *E/Z*-configuration of the corresponding complex. Stoichiometric experiments in MeOH (the solvent used in Ref. 2c) suggest that *E*-to-*Z* isomerization of the complex is rapid at room temperature (see SI).



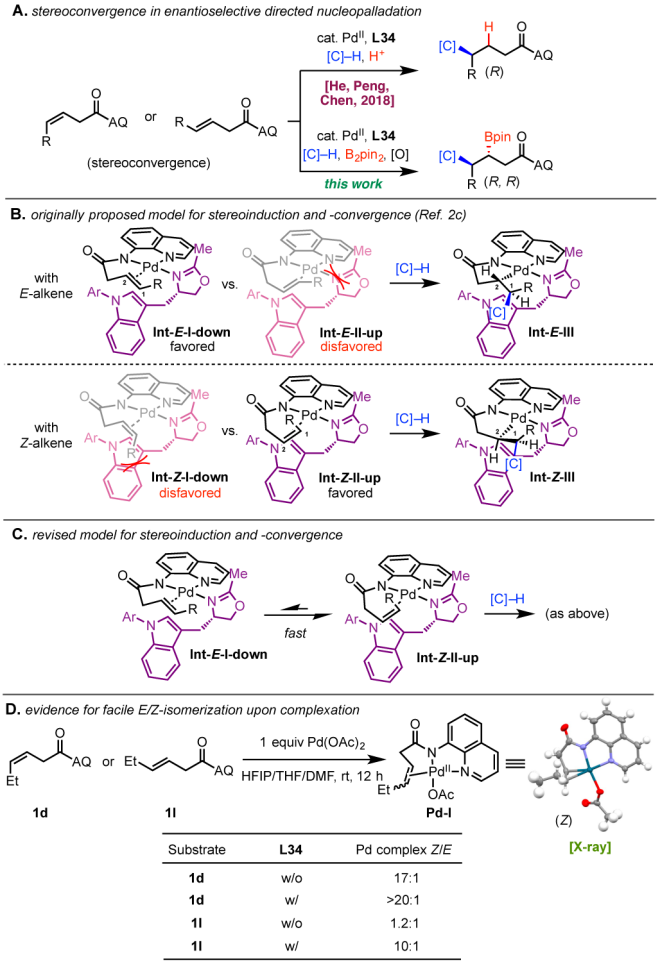
Scheme 1.
Background and Project Synopsis



Scheme 2.
Gram-Scale Synthesis and Recrystallization



Scheme 3.
Product Diversification

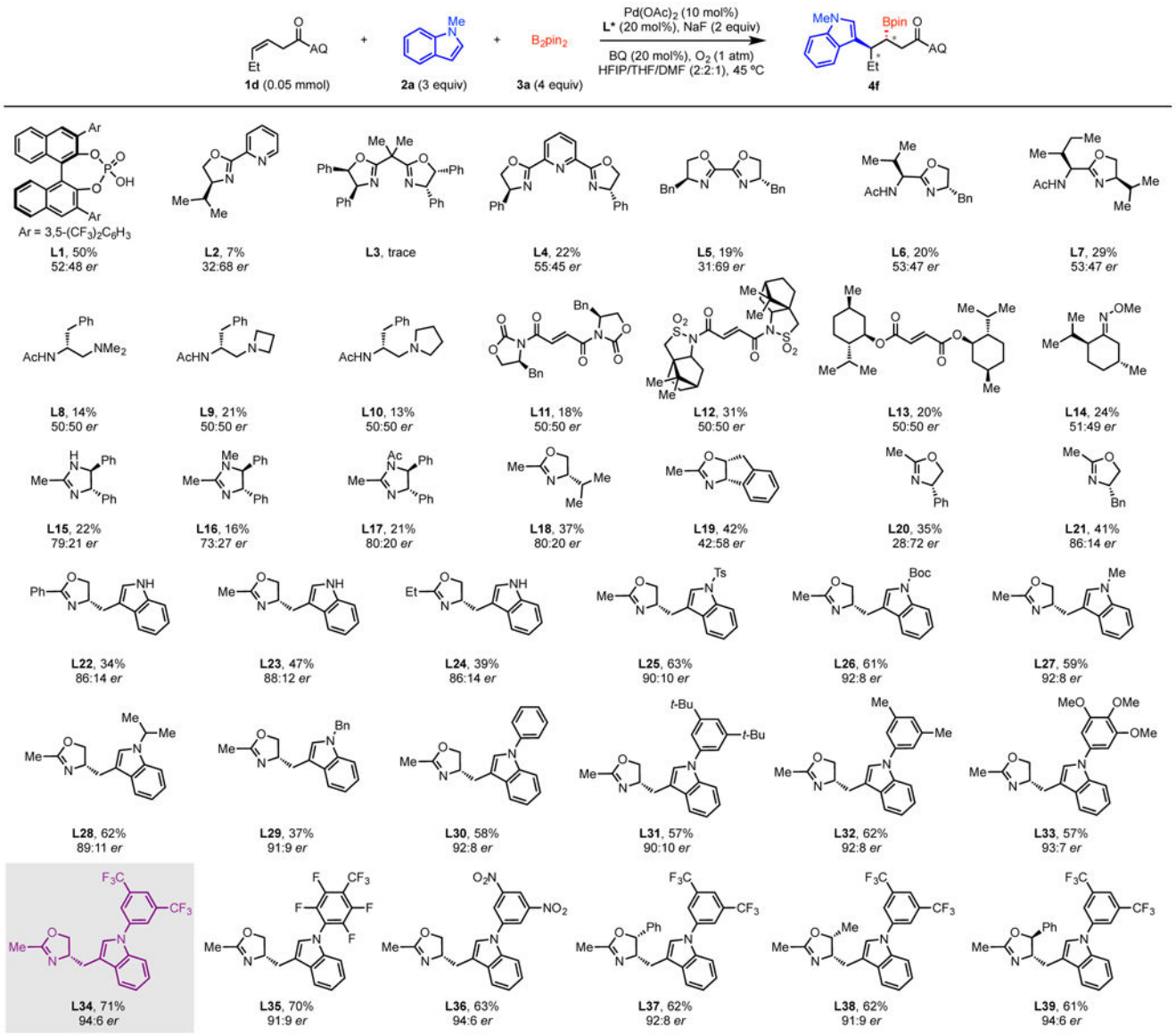


Substrate	L34	Pd complex *Z*/*E*
1d	w/o	17:1
1d	w/	>20:1
1l	w/o	1.2:1
1l	w/	10:1

Scheme 4.
Investigation of Stereoconvergent Nucleopalladation

Table 1.

Screening of Chiral Ligands[a]



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[a]Reaction conditions: **1d** (0.05 mmol), **2a** (3 equiv), **3a** (4 equiv), $Pd(OAc)_2$ (10 mol%), chiral ligand (20 mol%), BQ (20 mol%), NaF (2 equiv), HFIP/THF/DMF (2:2:1, 0.1 mL), 45 °C, O_2 (1 atm), 5 d.

Percentages refer to ^1H NMR yields with CH_2Br_2 as internal standard. The enantioselectivity was determined by SFC analysis.

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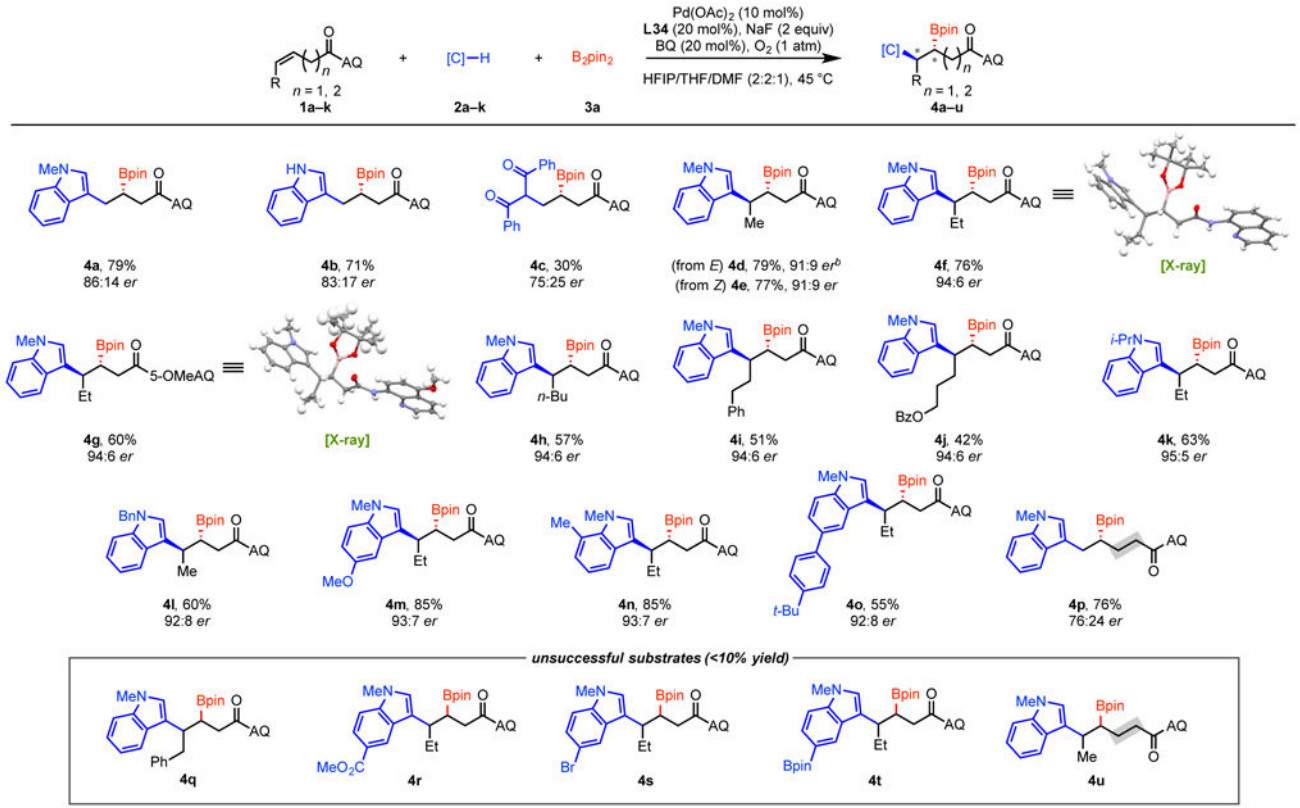
Table 2.

Enantioselective Alkene Carboboration Scope[a]



[a]Reaction conditions: **1a–k** (0.1 mmol), **2a–k** (3 equiv), **3a** (4 equiv), $Pd(OAc)_2$ (10 mol%), **L34** (20 mol%), BQ (20 mol%), NaF (2 equiv), HFIP/THF/DMF (2:2:1, 0.2 mL), 45 °C, O_2, 5 d. Percentages refer to isolated yields. Diastereomeric ratios (*dr*) are >20:1 in all cases. The enantioselectivity was determined by SFC analysis. [b]KF (2 equiv), HFIP/THF (1:1, 0.2 mL), 60 °C, 2 d.