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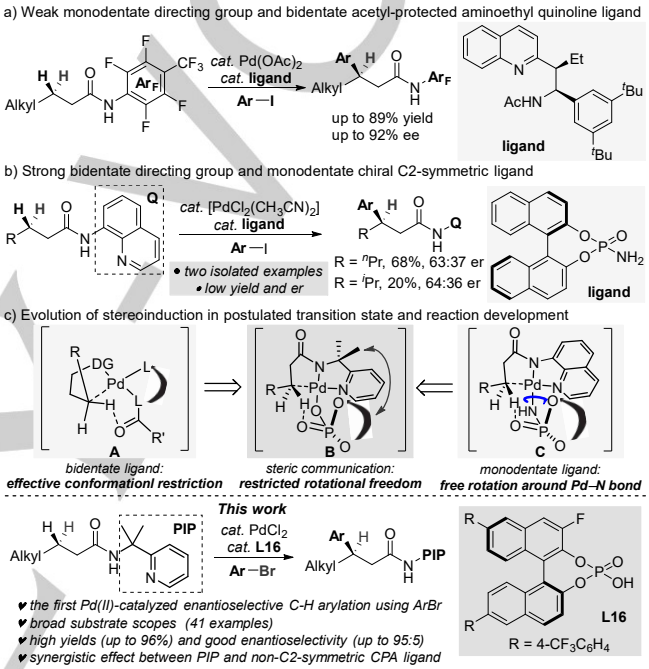
Pd(II)-Catalyzed Enantioselective Arylation of Unbiased Methylene C(sp^3)–H Bonds Enabled by 2-Pyridinylisopropyl Auxiliary and Chiral Phosphoric Acids

Sheng-Yi Yan,[†] Ye-Qiang Han,[†] Qi-Jun Yao, Xing-Liang Nie, Lei-Liu and Bing-Feng Shi*

Abstract: Enantioselective functionalization of unbiased methylene C(sp^3)-H bonds of linear systems via metal insertion is intrinsically challenging and remains a largely unsolved problem. Herein, we report a Pd(II)-catalyzed enantioselective arylation of unbiased methylene β-C(sp^3)-H bonds enabled by the combination of strongly coordinating bidentate PIP auxiliary and monodentate chiral phosphoric acids (CPAs). A synergistic effect between PIP auxiliary and a non-C2-asymmetric CPA (**L16**) is crucial for the effective stereocontrol. A broad range of aliphatic carboxylic acids and aryl bromides can be used, providing β-arylated aliphatic carboxylic acid derivatives in high yields (up to 96%) with good enantioselectivity (up to 95:5 er). Notably, this also represents the first Pd(II)-catalyzed enantioselective C-H activation using less reactive and cost-effective aryl bromides as arylating reagents. Mechanistic studies suggest that a single CPA is responsible for the stereodetermining C-H palladation step.

The creation of chiral centers via enantioselective C-H functionalization can potentially change the strategy of organic synthesis and streamline the access of complex molecules from simple and abundant sources of hydrocarbons.[1] Enantioselective metallocarbene and metallonitrene insertion into aliphatic C-H bonds has been well investigated in the stereoselective formation of C-C and C-N bonds.[2] On the other hand, enantioselective metal insertion into C(sp^3)-H bonds could be considered as a more appealing strategy, especially when considering that the newly formed chiral organometallic intermediate could be diversely functionalized to C-C and C-hetereoatom bonds other than C-N bond.[1,3] Recent efforts have led to significant achievements in Pd-catalyzed enantioselective C(sp^3)-H functionalization through desymmetrization of prochiral methyl groups.[4-9] For example, Kagan, Kündig, Baudoin, and Cramer have realized the highly enantioselective Pd(0)-catalyzed intramolecular cyclization using chiral N-heterocyclic carbene or phosphine ligands.[4-7] By the combination of monodentate directing groups with bidentate chiral ligands, Yu and co-workers have achieved the Pd-catalyzed enantioselective desymmetrization of prochiral methyl groups via C(sp^3)-H activation.[8] Gaunt reported the Pd(II)-catalyzed desymmetric amination of methyl C(sp^3)-H bonds using a CPA ligand.[9] Additionally, Pd-catalyzed enantioselective functionalization of methylene C(sp^3)-H bonds at positions activated via hyperconjugation, such as benzylic C-H bonds,[10,11] or those adjacent to heteroatom,[12] or on conformationally rigid cyclic systems,[13,14] have also been widely investigated. To date, enantioselective functionalization of unbiased methylene C(sp^3)-H bonds of linear systems via metal insertion is intrinsically challenging.[10a,15]



Scheme 1. State-of-the-art and strategies for Pd(II)-catalyzed enantioselective arylation of unbiased methylene C(sp^3)-H bonds.

The major breakthrough was made by the Yu group in 2016. They revealed that the combination of a weak monodentate directing group and a bidentate acetyl-protected aminoethyl quinoline ligand could dramatically enhance the reactivity and high enantioselectivity (Scheme 1b, up to 89% yield, up to 92% ee).[15] In a seminal report by Duan and coworkers, they achieved the first Pd(II)-catalyzed arylation of benzylic C(sp^3)-H bonds in moderate enantiomeric ratios (er, 74:26 to 91:9) by the use of a strong bidentate 8-aminoquinoline (AQ) directing group and a monodentate chiral C_2-symmetric phosphoric amide ligand. However, both of yields and enantioselectivities dropped drastically when this protocol was adopted to electronically unbiased methylene C-H bonds (Scheme 1a, R = ^{n}Pr, 68%, 63:37 er; R = ^{i}Pr, 20%, 64:36 er).[10a] There are two major hurdles for the poor selectivity: First, the strongly coordinating bidentate auxiliary AQ could promote the cleavage of C-H bonds in the absence of a chiral ligand as exemplified by Daugulis,[16] thus leading to the erosion of enantioselectivity. Second, due to the lack of vacant coordination sites in the bidentate system, only monodentate chiral ligand can be used. In the pretransition state intermediate **C**, the chiral phosphoric amide is realtively free to rotate (Scheme 1c), which could result in different chiral

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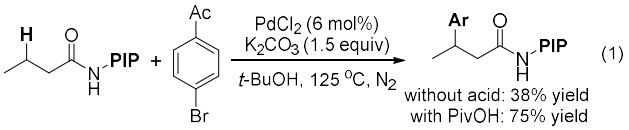
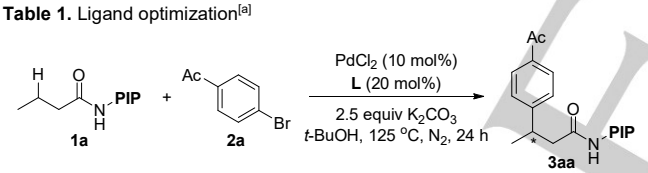
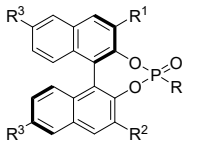
environments with opposite stereoinduction and erode the enantioselectivity. Considering a rich wealth of aliphatic C-H functionalization reactions that enabled by bidentate directing groups,[3g-j] the realization of suitable chiral ligands to enable stereocontrol of unbiased aliphatic C-H bonds with bidentate auxiliaries would be highly desirable.



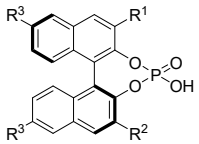
To achieve high enantioselectivity, the chiral ligands should be capable of creating a steric environment to induce stereocontrol and accelerating or enabling the cleavage of C-H bonds.[17] We have disclosed a Pd-catalyzed arylation of secondary C(sp^3)-H bonds with aryl bromides assisted by our newly developed 2-pyridinylisopropyl (PIP) auxiliary.[18,19] The use of PivOH as ligand could significantly improve the reactivity (eq 1); thus, we imagined that this reaction may provide an opportunity for outcompeting the background reaction. We also hypothesized that the steric communication between *gem*-dimethyl group in PIP auxliliary and backbone of CPA ligand could limit the free rotation to create a rigid and stronger chiral environment around the substrate (Scheme 1c, **B**). Herein we report a Pd(II)-catalyzed enantioselective arylation of unbiased methylene C(sp^3)–H bonds with aryl bromides enabled by cooperative effects between PIP auxiliary and CPA ligands.[20] It is worth noting that this reaction represents the first Pd(II)-catalyzed enantioselective C-H arylation using less reactive and cost-effective aryl bromides as arylating reagents while previous reports could only use aryl iodides.[10,11,12a,15]

Table 1. Ligand optimization[a]





(R)-**L2**, $R^1 = R^2 = R^3$ = H, 55%, 30:70 er[b]
(R)-**L2**, $R^1 = R^2 = R^3$ = H, 63%, 16:84 er
L3, $R^1 = R^2$ = Me, R^3 = H, 66%, 26:74 er
L4, $R^1 = R^2 = CF_3$, R^3 = H, 41%, 21:79 er
L5, $R^1 = R^3$ = H, R^2 = Ph, 56%, 49:51 er
L6, $R^1 = R^2$ = F, R^3 = H, 66%, 11:89 er
L8, $R^1 = R^2$ = H, R^3 = 1-naphthyl, 36%, 25:75 er
L9, $R^1 = R^2$ = H, R^3 = 3,5-$(CF_3)_2C_6H_3$, 86%, 9:91 er
L10, $R^1 = R^2$ = H, R^3 = 4-$CF_3C_6H_4$, 85%, 10.5:90.5 er



(S)-**L2**, $R^1 = R^2 = R^3$ = H, 63%, 85:15 er
L12, $R^1 = R^2$ = H, R^3 = F, 66%, 90:10 er
L13, $R^1 = R^2$ = H, R^3 = 3,4,5-$F_3C_6H_2$, 73%, 85:15 er
L14, R^1 = H, R^2 = F, R^3 = 3,5-$(CF_3)_2C_6H_3$, 70%, 92:8 er
L15, $R^1 = R^2$ = F, R^3 = 3,5-$(CF_3)_2C_6H_3$, 79%, 90.5:9.5 er
L16, R^1 = H, R^2 = F, R^3 = 4-$CF_3C_6H_4$, 74%, 92:8 er
L17, $R^1 = R^2$ = F, R^3 = 4-$CF_3C_6H_4$, 77%, 90.5:9.5 er
L18, R^1 = H, $R^2 = R^3$ = F, 75%, 91:9 er
L19, R^1 = F, $R^2 = R^3$ = H, 54%, 80:20 er
L20, R^1 = H, R^2 = F, $R^3 = CF_3$, 72%, 91.5:8.5 er
L21, R^1 = H, R^2 = F, R^3 = 4-MeC_6H_4, 62%, 85:15 er

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.3 mmol), $PdCl_2$ (10 mol%), **L** (20 mol%), K_2CO_3 (2.5 equiv) in *t*-BuOH (1.5 mL) at 125 °C under N_2 for 24 h. Yields were determined by ^1H NMR using CH_2Br_2 as internal standard, the er value was determined by chiral HPLC. [b] $Pd(OAc)_2$ (10 mol%), 120 °C.

To test this hypothesis, we commenced our investigations by replacing PivOH with **L2** under otherwise identical conditions we reported previously (Table 1).[18] Thus, using butyric amide **1a** and *p*-acetyl bromobenzene **2a** as the model system, the desired β-arylation product **3aa** was afforded in 55% yield and 30:70 er. Considering that the acetate anion would compete with ligands to inhibit the formation of the chiral Pd-complex and erode enantioselectivity. We then evaluated a range of Pd(II) salts with different counter anions and were delighted to find that the use of $PdCl_2$ with ligand **L2** could increase the er to 15:85 (see the supporting infromation for details). Improving the reaction temperature to 125 °C slightly increased the yield without erossion of enantioselectivity (Table 1, 63%, 16:84 er).

A comprehensive evaluation of CPA ligands was then performed (Table 1). We first investigated substitutions on the 3,3'-positions. The use of 3,3'-bismethyl and 3,3'-bistrifluoromethyl substituted CPAs (**L3** and **L4)** resulted in significant erosion in enantioselectivity. Sterically more demanding 3-phenyl substituted CPA (**L5**) almost gave a racemic mixture of products (49:51 er). To our delight, **L6** bearing fluorine atom at 3,3'-position increased the er to 11:89. Next, the effects of substitutions on 6,6'-position of CPAs were examined (**L8-L10**). Notably, 6,6'-bis[3,5-bis(trifluoromethyl)phenyl] CPA (**L9**) and 6,6'-bis(4-trifluoromethylphenyl) CPA (**L10**) gave improved er (9:91 and 10.5:89.5, respectively). When (*S*)-**L2** was used, the opposite isomer of the product could be afforded with similar enantioselectivity (85:15 er).

We then thoroughly investigated the substituents on both 3,3'- and 6,6'-positions (**L12-L19**). Interestingly, non-C2-symmetric CPAs (**L14** and **L16**) with only one fluorine atom at 3-position gave best results with 92:8 er. Preliminary structure-enantioselectivity relationships of ligand are rationalized based on the results in Tables 1 and S5: *1) in contrast to the importance of steric bulk at the 3,3'-positions in other asymmetric reactions, bulky substituents led to reduced ers in this C-H arylation protocol; 2) a unique effect of fluoro-containing substituents has been observed (fluoro at the 3,3'-positions:* ***L2*** *vs* ***L6****; (bis)trifluoromethyl-substituted phenyl at 6,6'-positions:* ***L2*** *vs* ***L9*** *and* ***L10****,* ***L16*** *vs* ***L20****; trifluoro at the 3,6,6'-positions:* ***L18****); 3) 3-fluoro-substituted non-C2-symmetric CPAs gave higher ee than their 3,3'-difluoro analoges (****L14*** *vs* ***L15****;* ***L16*** *vs* ***L17****;* ***L20*** *vs* ***L21****).* Further experimental and theoretical studies are needed to elucidate the underlying factors that could influence the enantioselectivity.

We futher optimized the conditions using **L16** as the ligand and discovered that the desired product **3aa** could be produced in 72% yield with 93.5:6.5 er under the following optimized conditions (standard conditions): 6 mol% $PdCl_2$, 6 mol% **L16** and 1.5 equiv K_2CO_3 in 1 mL *t*-BuOH at 125 °C under N_2 for 24 h (see supporting information for details).

At the very beginning of the design of PIP auxiliary,[19] we have envisioned that its sterically and electronically tuneable structure could significant affect the reactivity. Thus, we subsequently undertook a study to investigate the influence of the modified directing groups in greater details (Table 2). As expected, the modification of PIP auxiliary displayed a very pronounced influenece on both the reactivity and enantioselectivity. For example, the replacement of *gem*-dimethyl group with sterically more demanding longer chains or cyclic structures resulted in less reactivity and eroded enantioselectivity (**5a-5f**). All substitutions on the pyridyl ring led to a decrease in enantioselectivity and/or yield (**5g-5m**). Not surprisingly, substitution at the C6 position of pyridine led to loss in reactivity (**5m**). The enantioselective C-H arylation directed by AQ auxiliary was also investigated. The reaction of **4a** under the standard reaction conditions gave **5a** in low yield (31%) with

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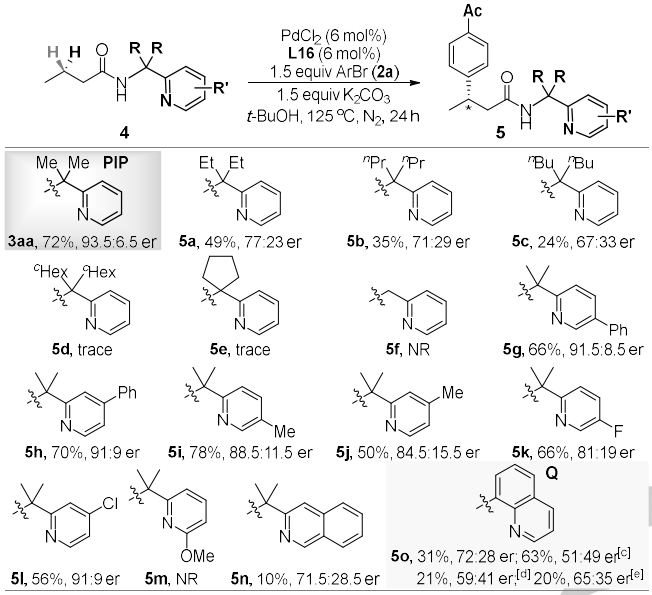
poor er (72:28). The use of (*S*)-**L2** under Duan's conditions using aryl iodide as arylation reagents gave an improved yield (63%) but led to erosion of the er (51:49).[10a] Previously, Pd(II)-catalyzed arylation of methylene C(sp^3)-H bonds with aryl bromide has also been reported.[21] The use of (*S*-**L2** under such conditions again gave poor reactivity and er (21%, 59:41 er). However, the use of **L16** as chiral ligand under identical conditions gave better er than (*S*)-**L2** (65:35). These results indicated that the newly designed fluoro-containing non-C2-symmetric CPA possesses unique effects on enantiocontrol and might find further applications in C-H activation.

Table 2. Evaluation of the directing ability of PIP-NH_2 analogues.[a,b]

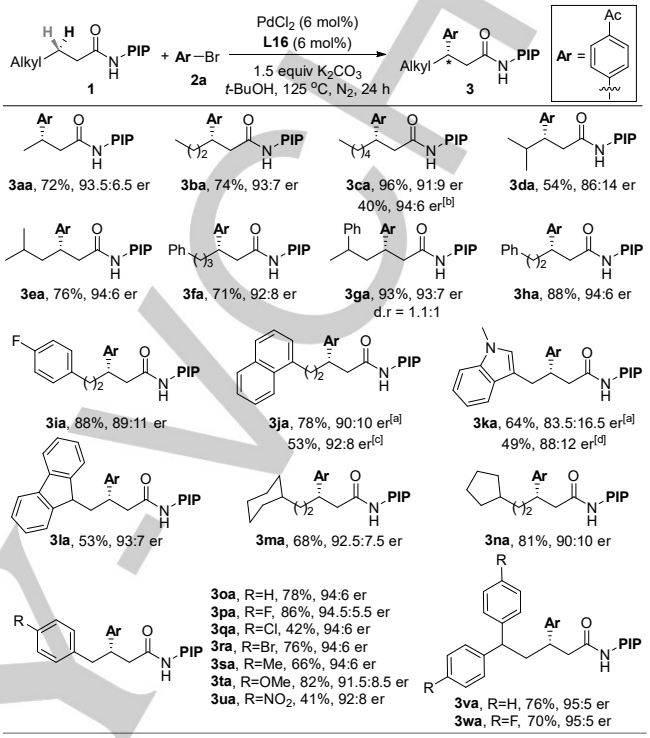


[a] Standard conditions. [b] Isolated yield and the er value was determined by chiral HPLC. [c] Conditions reported in Ref. [10a] using (*S*)-**L2** as chiral ligand. [d] Conditions reported in Ref. [21] using (*S*)-**L2** as chiral ligand. [e] Conditions reported in Ref. [21] using **L16** as chiral ligand.

With the optimized reaction conditions in hand, the scope of aliphatic amides was examined (Table 3). Aliphatic amides bearing various linear chains gave comparable yields and selectivities (**3aa-3ca**). Although aliphatic amide bearing sterically demanding isopropyl group at β-position led to reduced yield and er (**3da**, 54%, 86:14 er), this result is still promising compared the lower reactivity and selectivity using AQ auxiliary (Scheme 1b, 20%, 64:36 er). The presence of sterically demanding groups at γ- or distal positions didn't significantly affect the enantioselectiviy (**3ea**-**3wa**). Various substituents, such as halides, methyl, methoxyl and nitro, at γ-phenyl ring, also gave good ers (**3oa**-**3ua**, 91.5:8.5 to 94.5:5.5).

Next, the scope of aryl bromides was explored (Table 4). In general, a broad range of electron-donating and electron-withdrawing substituents on the aryl bromides were well tolerated. Aryl bromides with strong electron-withdrawing groups, such as methoxycarbonyl (**2h**), cyano (**2k**), nitro (**2l**) and acetyl (**2o**), were also compatible. Notably, halides, such as fluoro (**2i**) and chloro (**2j**), at the para position of aryl bromides performed well. We have found that fluoro-containing substituents at the 3,3'- or 6,6'-positions could improve the enantioselectivity. Therefore, improved enantioslectivity could be achieved by judicious choice of CPA ligands with suitable fluoro-containing substituents (**L14**, **3ca** and **3hh**; **L18**, **3hc** and **3hr**; **L19**, **3hd**). In certain cases, the enantioselectivity could also be improved by reducing the loading of $PdCl_2$ to 3 mol% (**3ja**, **3ka**, **3hb**, **3he**, **3hi**, **3hj**, **3hm**, **3hn**, **3ho** and **3hq**), presumably because of the suppression of background reaction. Other electrophiles, such as aryl chlorides, aryl triflates and vinyl bromides, didn't give any desired product. The absolute configuration of the products was confirmed by X-ray crystallographic analysis of **3hf**.[22]

Table 3. The scope of aliphatic amides.[a]



[a] Standard conditions. [b] $PdCl_2$ (3 mol%), **L14** (3 mol%), *t*-BuOH (1.0 mL), 0.3 mmol scale. [c] $PdCl_2$ (3 mol%), **L16** (3 mol%), *t*-BuOH (1.0 mL), 0.3 mmol scale. [d] $PdCl_2$ (3 mol%), **L16** (3 mol%), *t*-BuOH (0.5 mL), 0.3 mmol scale.

In order to gain some insights into the mechanism of this reaction, a series of experiments have been performed. First, the kinetic isotope effect was investigated using β-deuterium-labeled substrate [D_2]-**1f** and k_H/k_D = 2.1 was observed (see supporting information for details). This indicates that the C−H bond cleavage might be the rate-limiting step in this reaction. To find out how CPAs effect the enantioselective of this Pd(II)-catalyzed arylation reaction, the linear relationship between the ee value of ligand and the ee value of product was conducted using **1a** and **L2** (Figure S1). The result reveals a clear linear effect, suggesting that a single CPA ligand is responsible for the stereodetermining C-H palladation step.[23] This is in sharp contrast to Pd(II)-catalyzed enantioselective arylation of benzylic methylene C(sp^3)-H bonds directed by picolamide, in which a nonlinear effect was observed.[10b]

In conclusion, we have described a Pd-catalyzed enantioselective arylation of unbiased methylene C(sp^3)-H bonds in aliphatic amides assisted by PIP auxiliary. This protocol respresents the first universal method to generate enantioriched β-arylated carboxylic acid derivatives using less reactive and cost effective aryl bromides as the arylating reagents. A non-C2-symmetric CPA ligand has been identified to have prominent effects on the control of enantioselectivity and a single CPA ligand is responsible for the stereodetermining C-H palladation step. Considering the wealth of aliphatic C-H functionalization reactions enabled by bidentate directing groups, we expect this approach might open intriguing opportunities for other types of C-H functionalization reactions in the future.

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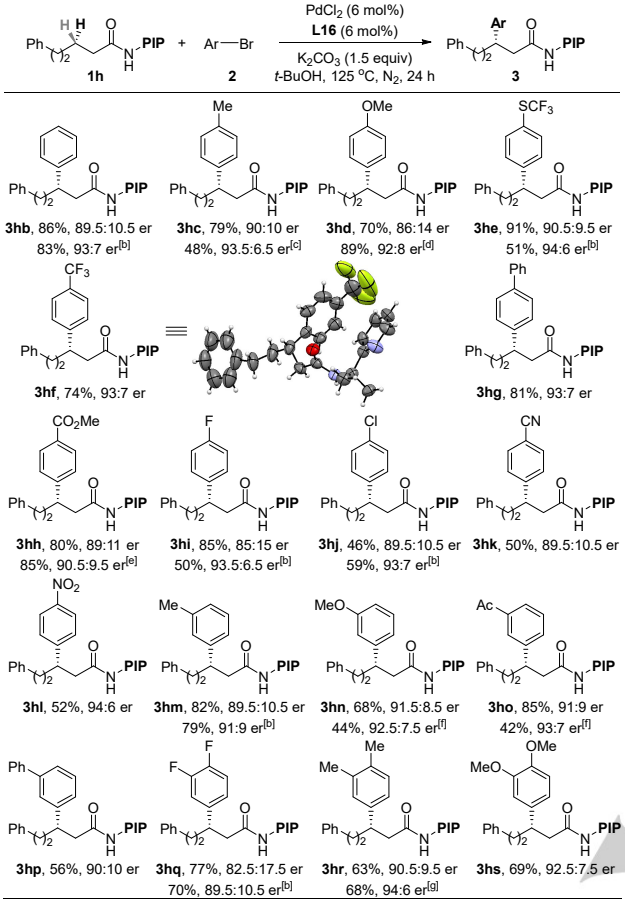
Table 4. The scope of aryl bromides.[a]



[a] Standard conditions. [b] $PdCl_2$ (3 mol%), **L16** (3 mol%), *t*-BuOH (0.5 mL), 0.3 mmol scale. [c] $PdCl_2$ (3 mol%), **L18** (3 mol%), *t*-BuOH (1.0 mL), 0.3 mmol scale. [d] $PdCl_2$ (3 mol%), **L19** (3 mol%), *t*-BuOH (0.5 mL), 0.3 mmol scale. [e] $PdCl_2$ (3 mol%), **L14** (3 mol%), *t*-BuOH (1.0 mL), 0.3 mmol scale. [f] $PdCl_2$ (3 mol%), **L16** (3 mol%), *t*-BuOH (1.0 mL), 0.3 mmol scale. [g] $PdCl_2$ (3 mol%), **L18** (3 mol%), *t*-BuOH (0.5 mL), 0.3 mmol scale.

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Keywords: enantioselectivity • C-H activation • cooperative effects • palladium• bidentate auxiliary

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[22] CCDC 1835310 (**3hf**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[23] Consistent with this result, the use of a well-defined Pd(**L16**)$_2$(CH_3CN)$_2$ complex as catalyst resulted in a slightly lower ee than the optimized conditions using 6 mol% $PdCl_2$ and 6 mol% CPA **L16** (Table S6, entries 13 and 9).

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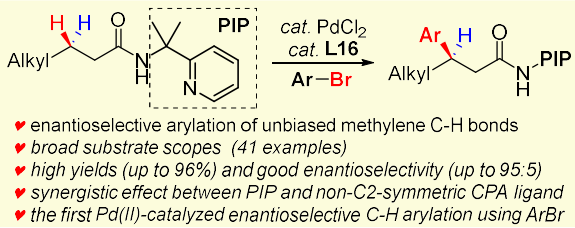

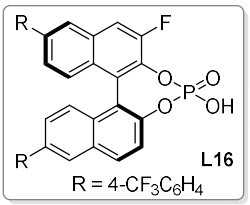

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Pd(II)-Catalyzed Enantioselective Arylation of Unbiased Methylene C(sp³)–H Bonds Enabled by 2-Pyridinylisopropyl Auxiliary and Chiral Phosphoric Acids

Enantioselective C-H arylation of unbiased methylene C-H bonds: A Pd(II)-catalyzed enantioselective arylation of unbiased methylene β-C(sp³)-H bonds enabled by the combination of strongly coordinating bidentate PIP auxiliary and monodentate chiral phosphoric acids (CPAs) has been reported. A synergistic effect between PIP auxiliary and a non-C2-asymmetric CPA is crucial for the effective stereocontrol. Notably, this also represents the first Pd(II)-catalyzed enantioselective C-H activation using less reactive and cost-effective aryl bromides as arylating reagents.