Synthetic Methods

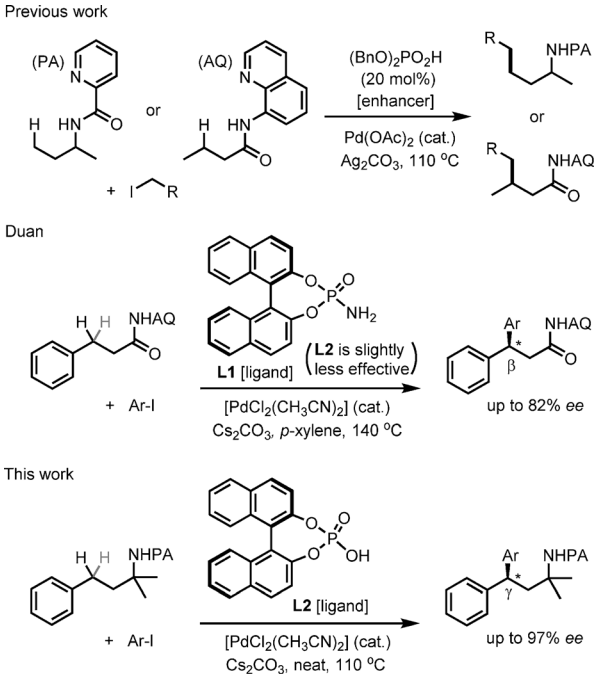
International Edition: DOI: 10.1002/anie.201609337
German Edition: DOI: 10.1002/ange.201609337

An Enantioselective Bidentate Auxiliary Directed Palladium-Catalyzed Benzylic C–H Arylation of Amines Using a BINOL Phosphate Ligand

Hao Wang, Hua-Rong Tong, Gang He, and Gong Chen**

Abstract: *A new enantioselective palladium(II)-catalyzed benzylic C–H arylation reaction of amines is enabled by the bidentate picolinamide (PA) directing group. This reaction provides the first example of enantioselective benzylic γ-C–H arylations of alkyl amines, and proceeds with up to 97% ee. The 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) phosphoric acid ligand, Cs_2CO_3, and solvent-free conditions are essential for high enantioselectivity. Mechanistic studies suggest that multiple BINOL ligands are involved in the stereodetermining C–H palladation step.*

Over the past decade, palladium-catalyzed auxiliary-directed C(sp^3)–H arylation reactions have been quickly developed.[1] However, few generally applicable asymmetric C(sp^3)–H arylation reactions have been reported, and the realization of this goal will likely require the development of new ligand-controlled chemistry.[2–8] Most notably, Yu and co-workers have shown that several palladium(II)-catalyzed monodentate auxiliary directed C(sp^3)–H arylation reactions can proceed with moderate to excellent enantioselectivity by the application of chiral amino acids or aminoethyl quinoline ligands.[3,4] In contrast, despite the diversity of palladium-catalyzed bidentate auxiliary directed C(sp^3)–H arylations,[9] they present a more challenging platform for enantioselective transformations because of the single available coordination site on the palladium catalyst during the stereodetermining C–H palladation step.[3d] Overall, ligands capable of modulating palladium-catalyzed bidentate auxiliary directed C-(sp^3)–H functionalization reactions are still very scarce, let alone chiral ligands. We have previously observed that $(BnO)_2PO_2H$ uniquely enhances palladium-catalyzed picolinamide (PA) and aminoquinoline (AQ) directed C(sp^3)–H alkylation reactions with alkyl halides (Scheme 1).[10,11] More recently, Duan and co-workers reported that the AQ-directed benzylic β-C–H arylation of 3-arylpropanamides with aryl iodides can be made enantioselective with a BINOL-based phosphoric amide (**L1**) and acid (**L2**) as ligands.[8] Herein, we report a complementary palladium(II)-catalyzed PA-directed enantioselective benzylic γ-C–H arylation of 3-arylpropylamines using the BINOL phosphoric acid **L2**.[4] The observation of a nonlinear ligand effect suggests that multiple BINOL phosphate ligands are involved in the stereodetermining C–H palladation step.



Scheme 1. Enantioselective palladium-catalyzed phosphate-mediated benzylic C–H arylation directed by N,N-bidentate auxiliary groups.

Although we originally suspected that $(BnO)_2PO_2H$ activates alkyl halides by acting as a phase-transfer catalyst for silver salts,[11a,b] subsequent studies have demonstrated that simple organic phosphates can influence other types of palladium-catalyzed bidentate auxiliary directed C–H functionalization reactions with or without silver.[11c–e,12–14] Duan's report showed that either BINOL phosphoric amide or acid can act as a chiral ligand, thus rendering the C–H palladation step enantioselective.[8] Encouraged by Duan's findings, we sought to study the effect of BINOL ligands on the PA-directed γ-C(sp^3)–H arylation of amines.[4] Initially, we observed poor yields from the γ-C–H arylation of unsubstituted 3-phenylpropylamine under various conditions. However, the PA-derivatized 1,1-dimethyl-3-phenylpropylamine

[*] H. Wang, H.-R. Tong, Prof. Dr. G. He, Prof. Dr. G. Chen
State Key Laboratory and Institute of Elemento-Organic Chemistry, Collaborative Innovation Center of Chemical Science and Engineering (Tianjin)
Nankai University, Tianjin 300071 (China)
E-mail: hegang@nankai.edu.cn
gongchen@nankai.edu.cn
Prof. Dr. G. Chen
Department of Chemistry
The Pennsylvania State University
University Park, Pennsylvania 16802 (USA)
E-mail: guc11@psu.edu
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201609337.

1, a more conformationally constrained substrate, provided **2a** in excellent yield, but with poor *ee* value under Duan's conditions (Table 1, entry 1). Use of **L2** gave a slightly higher *ee* value (entry 4), and the choice of solvent had a significant impact on yield and *ee* value (entries 3–5). Similar to Duan's system, modification of the BINOL scaffold resulted in decreased *ee* values (entries 6–9). Higher reaction concentration gave increased *ee* values (entry 4 versus 10). **2a** was obtained in 88% yield and 62% *ee* when the reaction was performed without solvent (entry 12). Lowering the reaction temperature to 110°C and adding an additional equivalent of Cs_2CO_3 further improved enantioselectivity (entries 13 and 14). Interestingly, a higher loading of the palladium catalyst (20 mol%) gave a noticeably decreased *ee* value (entry 17),[15] while a lower loading of palladium (5 mol%) gave a slightly improved *ee* value (entry 15). Finally, a 97% yield of isolated **2a** with 91% *ee* was obtained when 5 mol % $[PdCl_2(MeCN)_2]$, 2.5 equivalents of Cs_2CO_3, and 25 mol% of **L2** were used at 110°C without solvent. It is also worth noting that 1) use of Cs_2CO_3 is critical for obtaining high *ee* values (entries 20–22); 2) $Pd(OAc)_2$ provides a slightly lower *ee* value (entry 25); and 3) a decreased loading of palladium (2 mol%) gave a slightly lower yield but similar *ee* value (entry 19).

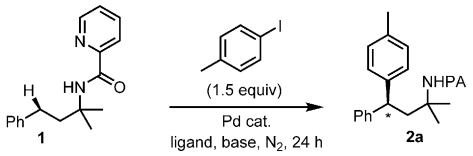
We then subjected **1** to a PA-directed C–H arylation with a variety of aryl iodides under these reaction conditions (Scheme 2). Aryl iodides bearing functional groups such as bromide (**2d**) and ester (**2f**) were well tolerated. The electronics of the aryl iodide influence the *ee* value of the reaction. Electron-rich aryl iodides gave relatively higher *ee* values (**2j** versus **2k**). The product **2e** from 4-iodoanisole was obtained with an excellent *ee* value of 97% (er: 98.4/1.6).[16] The steric characteristics of the aryl iodide also have a significant impact on the *ee* value of the reaction. In general, *meta*-substituted aryl iodides gave lower *ee* values than *para*-substituted aryl iodides (**2e** versus **2i**). The *ortho*-substituted aryl iodides, such as 2-iodoanisole, showed little reactivity (< 5% yield).

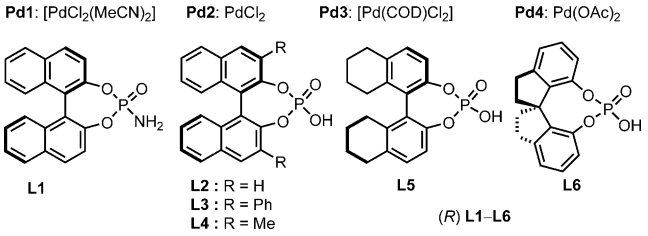
To evaluate the reaction with other amine substrates, we prepared a series of PA-derivatized 1,1-dimethyl-3-arylpropylamines (**4**) by palladium(II)-catalyzed γ-C(sp^3)–H arylation of 1,1-dimethylpropylamine (**3**) with various aryl iodides [Eq. (1); DMA = *N*,*N*′-dimethylacetamide]. The products **4** were obtained in good to excellent yields and excellent monoselectivity under the optimized reaction conditions [1.5 equiv of CuF_2, DMA solvent, 100°C; see the Supporting Information].

As shown in Scheme 3, **4**, bearing different 3-aryl substituents underwent PA-directed γ-C(sp^3)–H arylation reactions in moderate to excellent *ee* values under the standard reaction conditions. Sterically bulky aryl substituents on the amine substrate significantly diminish the *ee* value of the reaction (**5f** versus **2e**). The directing ability of various analogues of picolinic acid was also evaluated (Scheme 4). Interestingly, all modifications of the pyridine ring led to a decrease in enantioselectivity and/or yield. Notably, substitution at the C6 position of pyridine (**6e** and **6g**) caused dramatic loss in reactivity.

Palladium-catalyzed PA-directed C–H arylation reactions likely proceed through a catalytic cycle featuring C–H palladation, oxidative addition of ArI, and C–C bond-forming reductive elimination.[10b,17] Following the mechanistic model proposed for the BINOL phosphoric amide **L1** mediated β-C(sp^3)–H arylation of AQ-coupled alkyl carboxylic acid,[8] we initially thought that

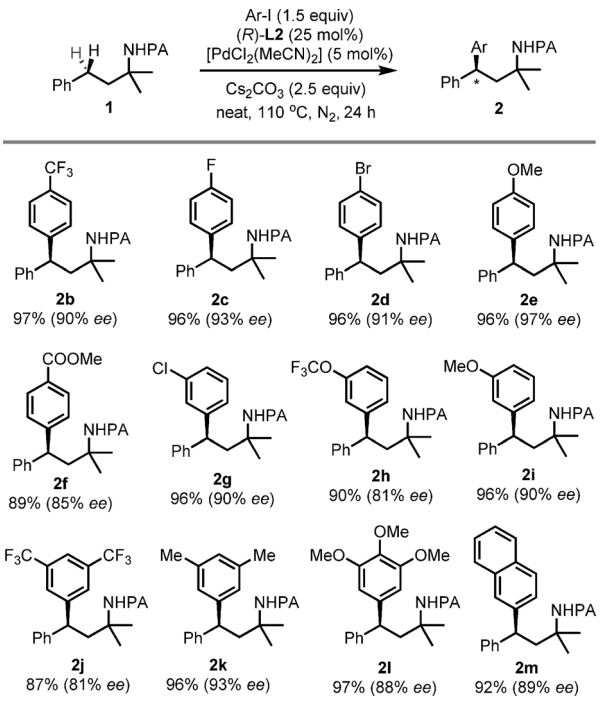
Table 1: Enantioselective γ-C(sp^3)–H arylation of **1** with 4-iodotoluene.



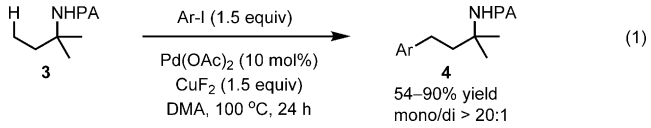


Entry	Pd, base (equiv), *T*	L (equiv)	Solvent	Yield [%][a]	*ee* [%][b]
1	**Pd1** (0.1), Cs_2CO_3 (1.5), 140°C	**L1** (0.2)	*p*-xylene	90	30
2	**Pd1** (0.1), Cs_2CO_3 (1.5), 140°C	**L1** (0.2)	*t*AmOH	98	32
3	**Pd1** (0.1), Cs_2CO_3 (1.5), 140°C	**L2** (0.2)	*p*-xylene	78	19
4	**Pd1** (0.1), Cs_2CO_3 (1.5), 140°C	**L2** (0.2)	*t*AmOH	87	42
5	**Pd1** (0.1), Cs_2CO_3 (1.5), 140°C	**L2** (0.2)	MeCN	66	35
6	**Pd1** (0.1), Cs_2CO_3 (1.5), 140°C	**L3** (0.2)	*t*AmOH	82	14
7	**Pd1** (0.1), Cs_2CO_3 (1.5), 140°C	**L4** (0.2)	*t*AmOH	74	16
8	**Pd1** (0.1), Cs_2CO_3 (1.5), 140°C	**L5** (0.2)	*t*AmOH	57	< 3
9	**Pd1** (0.1), Cs_2CO_3 (1.5), 140°C	**L6** (0.2)	*t*AmOH	52	< 3
10	**Pd1** (0.1), Cs_2CO_3 (1.5), 140°C	**L2** (0.2)	*t*AmOH[c]	90	50
11	**Pd1** (0.1), K_2CO_3 (1.5), 140°C	**L2** (0.2)	*t*AmOH	9	< 3
12	**Pd1** (0.1), Cs_2CO_3 (1.5), 140°C	**L2** (0.2)	neat	88	62
13	**Pd1** (0.1), Cs_2CO_3 (1.5), 110°C	**L2** (0.2)	neat	93	76
14	**Pd1** (0.1), Cs_2CO_3 (2.5), 110°C	**L2** (0.2)	neat	99	79
15	**Pd1** (0.05), Cs_2CO_3 (2.5), 110°C	**L2** (0.2)	neat	99	88
16	**Pd1** (0.05), Cs_2CO_3 (2.5), 110°C	**L2** (0.25)	neat	99 (97)[d]	91
17	**Pd1** (0.2), Cs_2CO_3 (2.5), 110°C	**L2** (0.2)	neat	99	62
18	**Pd1** (0.05), Cs_2CO_3 (2.5), 110°C	**L2** (0.05)	neat	99	79
19	**Pd1** (0.02), Cs_2CO_3 (2.5), 110°C	**L2** (0.25)	neat	87	91
20	**Pd1** (0.05), Rb_2CO_3 (2.5), 110°C	**L2** (0.25)	neat	90	81
21	**Pd1** (0.05), K_2CO_3 (2.5), 110°C	**L2** (0.25)	neat	47	35
22	**Pd1** (0.05), Na_2CO_3 (2.5), 110°C	**L2** (0.25)	neat	5	< 3
23	**Pd2** (0.05), Cs_2CO_3 (2.5), 110°C	**L2** (0.25)	neat	88	86
24	**Pd3** (0.05), Cs_2CO_3 (2.5), 110°C	**L2** (0.25)	neat	99	89
25	**Pd4** (0.05), Cs_2CO_3 (2.5), 110°C	**L2** (0.25)	neat	99	84
26	**Pd1** (0.05), Cs_2CO_3 (2.5), 110°C	**L1** (0.25)	neat	88	82

[a] Yields are based on HPLC analysis of reaction mixture on a 0.2 mmol scale. [b] Determined by HPLC using a chiral column. [c] Used 0.5 mL of solvent here compared to 1 mL of solvent used for other entries. [d] Yield of isolated products. See Supporting Information for additional screening conditions.

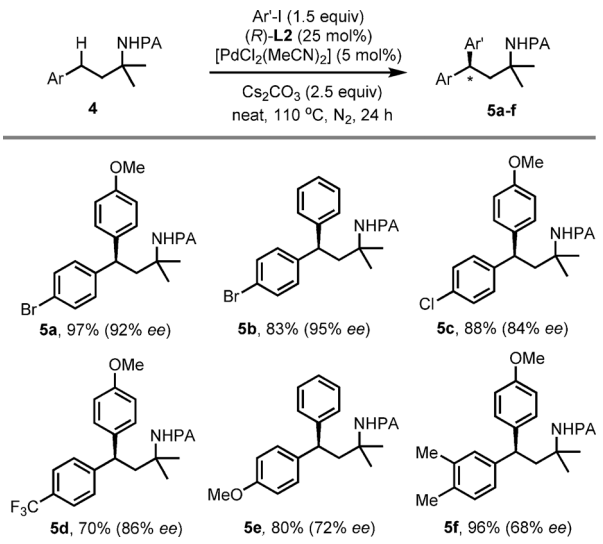


Scheme 2. Substrate for the γ-C(sp³)–H arylation of **1**. Yields are of products isolated from a 0.2 mmol scale reaction.

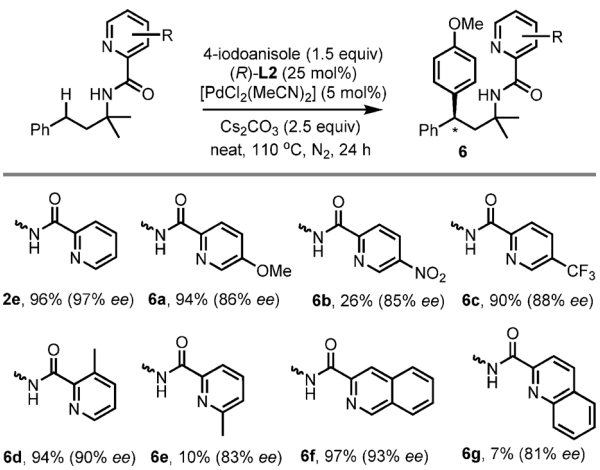


(1)

a single **L2** ligand was responsible for the enantioselective γ-C–H palladation of the PA-derivatized alkyl amines by a concerted metalation deprotonation (CMD)[18] mechanism (see model **A** in Scheme 5d).[19,20] However, when the enantiopurity of **L2** was varied in the reaction of **1** and 4-iodotoluene under otherwise standard reaction conditions, we did not observe a linear effect on the *ee* value of **2a** (Scheme 5a).[21] Furthermore, the yield of **2a** was influenced by the *ee* value of **L2**. These observations indicate that more than one **L2** molecule is involved in the enantioselective C–H palladation step. As shown in Scheme 5b, the identity of the alkali cation also strongly influences the yield and *ee* value of **2e**, thus suggesting the involvement of Cs^+ in the **L2**-mediated C–H palladation step. Because of its large size and high coordination number, Cs^+ tends to form high-valent coordination complexes, and even clusters.[22] We suspect that a monomeric 1:1 Cs(1)–**L2**(1) complex might dimerize to form cluster Cs(2)–**L2**(2), from which a Cs^+ can dissociate to give Cs(1)–**L2**(2)$^-$ (Scheme 5c).[23] To explain the nonlinear ligand effect and the critical role of Cs^+, we hypothesize that either Cs(1)–**L2**(2)$^-$ or Cs(2)–**L2**(2) may act as the ligand controlling the enantioselective C–H palladation step (see model **B**). Unlike the monomeric **L2** ligand in model **A**, one **L2** of the Cs complex binds to Pd^{II} while the other one serves as an internal base (Scheme 5d). However, the involvement of other forms of a Cs–**L2** cluster and/or carbonate species cannot be ruled out, and C–H palladation facilitated by monomeric-**L2** may still provide a competing pathway.

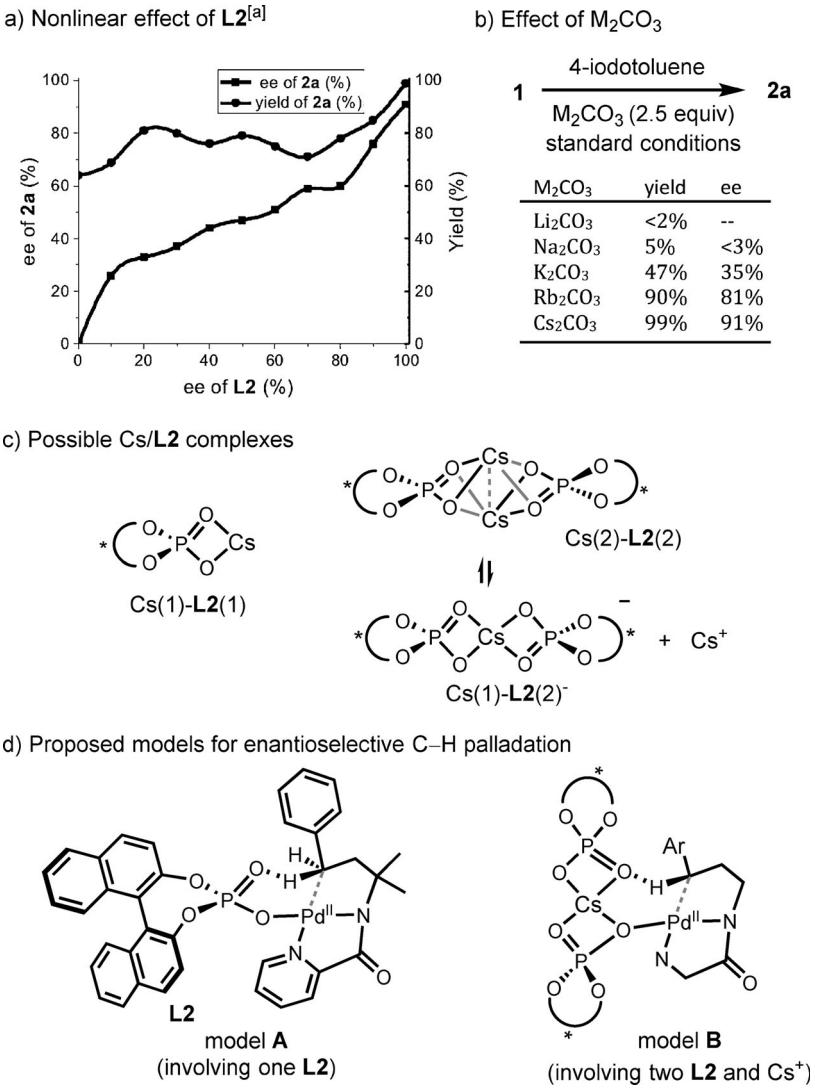


Scheme 3. γ-C(sp³)–H arylation of **4**. Yield is that of product isolated from a 0.2 mmol scale reaction run under the standard conditions.



Scheme 4. Evaluation of the directing ability of PA analogues.

In summary, we report an enantioselective palladium(II)-catalyzed bidentate auxiliary directed benzylic C–H arylation reaction of PA-derivatized alkyl amines with aryl iodides. Complementary to the previously reported BINOL phosphoric amide mediated enantioselective C–H arylation of aminoquinoline-derivatized alkyl carboxylic acid substrates, this reaction provides the first example of enantioselective γ-C–H arylation of PA-derivatized alkyl amines with up to 97% *ee*. The combination of a BINOL phosphate ligand and Cs_2CO_3 base under solvent-free conditions is essential to achieve high enantioselectivity. Mechanistic studies suggest that a cesium–phosphate complex might be involved in the stereodetermining C–H palladation step. Additional mechanistic investigations and the development of new chiral phosphate ligands are currently under investigation to broaden the scope of the enantioselective palladium-catalyzed bidentate auxiliary directed C–H functionalization.



Scheme 5. Mechanistic considerations of the palladium-catalyzed PA-directed **L2**-mediated benzylic C–H arylation of amines. [a] Average of four runs for the *ee* value and HPLC yield of **2a** (see the Supporting Information).

Acknowledgments

We thank the State Key Laboratory of Elemento-Organic Chemistry at Nankai University for financial support of this work.

Keywords: arylations · C–H activation · enantioselectivity · palladium · reaction mechanism

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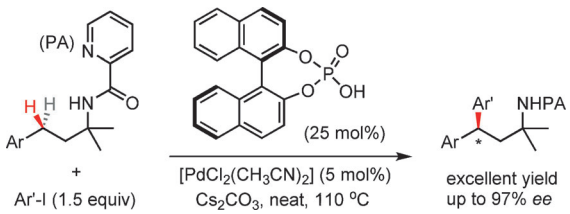
Received: September 23, 2016
Published online: ■■ ■■, ■■■■

Communications

Synthetic Methods

H. Wang, H.-R. Tong, G. He,*
G. Chen* ——————— ■■■■–■■■■

An Enantioselective Bidentate Auxiliary Directed Palladium-Catalyzed Benzylic C–H Arylation of Amines Using a BINOL Phosphate Ligand



Seeking direction: A new enantioselective palladium(II)-catalyzed benzylic C–H arylation of amines is enabled by the bidentate picolinamide (PA) directing group. The BINOL phosphoric acid ligand, Cs_2CO_3, and solvent-free conditions are essential for high enantioselectivity. Mechanistic studies indicate that multiple BINOL ligands are involved in the stereodetermining C–H palladation step.

