Asymmetric Synthesis of β-Lactam via Palladium-Catalyzed Enantioselective Intramolecular C(sp^3)–H Amidation

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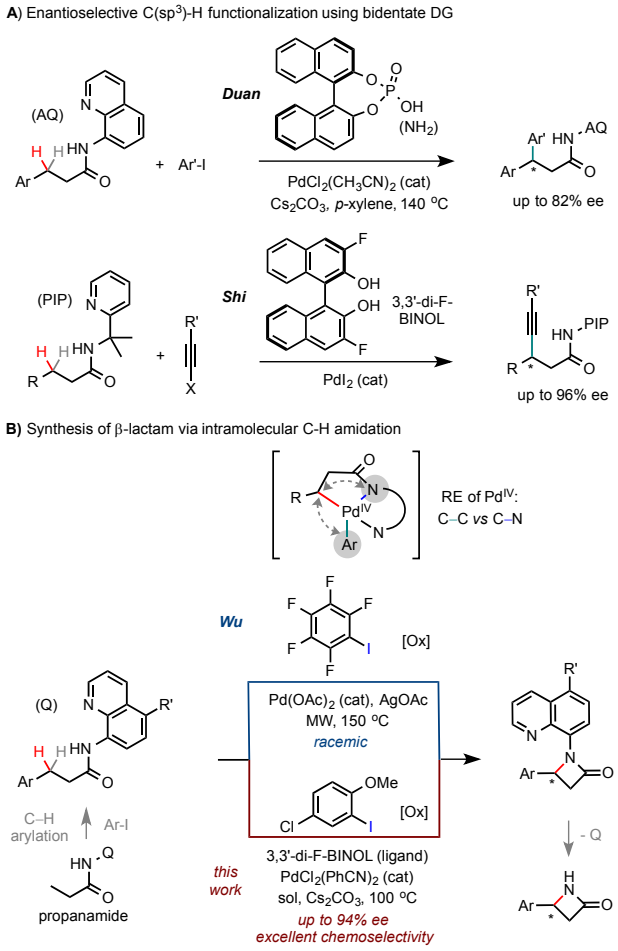
ABSTRACT: β-Lactams are important scaffolds in drug design and frequently used as reactive intermediates in organic synthesis. Catalytic reactions featuring intramolecular C–H amidation of alkyl carboxamide substrates could provide a straightforward disconnection strategy for β-lactams synthesis. Herein, we report a streamlined method for asymmetric synthesis of β-aryl β-lactams from propanoic acid and aryl iodides via Pd-catalyzed sequential C(sp^3)-H functionalization. The lactam-forming reaction provides an example of Pd^{II}-catalyzed enantioselective intramolecular C(sp^3)–H amidation reaction, and proceeds in up to 94% ee. The use of a 2-methoxy-5-chlorophenyl iodide oxidant is critical to control the competing reductive elimination pathways of Pd^{IV} intermediate to achieve the desired chemoselectivity. Mechanistic studies suggest that both steric and electronic effects of the unconventional aryl iodide oxidant are responsible for controlling the competing C-N vs C-C reductive elimination pathways of Pd^{IV} intermediate. **Key words:** Pd, C−H amidation, enantioselective, β-lactams, bidentate auxiliary

INTRODUCTION

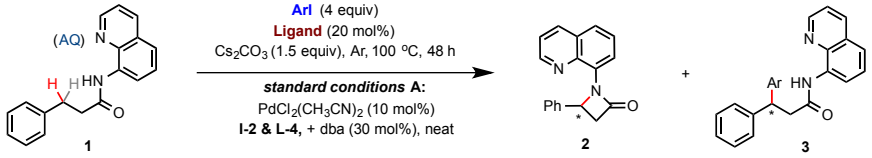
Palladium-catalyzed directed C(sp^3)–H functionalization has emerged as a powerful strategy to construct various aliphatic frameworks.[1] Among the directing groups, amide-linked bidentate auxiliaries have shown unique advantage of high reactivity and versatility in forming new bonds.[2-4] However, the complexation mode of these bidentate auxiliaries also caused inherent obstacles for enantiocontrol due to the lack of suitable coordination sites on metal center. Despite the challenge, recent endeavors showed such enantio-induction is possible (Scheme 1A).[5-8] Notably, Duan reported that Pd^{II}-catalyzed aminoquinoline (AQ)-directed benzylic β-C–H arylation of 3-arylpropanamides with aryl iodides can proceed in moderate to good enantioselectivity using BINOL-based chiral phosphoric acid or amide ligands.[5a] Shi reported Pd^{II}-catalyzed pyridinylisopropylamine (PIP)-directed enantioselective β-C(sp^3)-H alkynylation of 3-alkyllpropanamides with alkynyl bromide can proceed in good to excellent ee using a fluoro-substituted 3,3′-di-F-BINOL ligand.[6b] To further expand the synthetic utility of bidentate auxiliary-mediated C(sp^3)–H functionalization chemistry, new enantioselective reaction modes needs to be developed.

Recently, Wu demonstrated the reaction pathway of Pd^{II}-catalyzed AQ-directed β-C–H functionalization of 3-alkyl and 3-aryl propanamide can be modulated to give β-lactam products in high yield and chemoselectivity when excess amount of pentafluorophenyl iodide was used as oxidant (Scheme 1B).[9] It was believed that the strong electron-withdrawing property of C_6F_5 group is responsible for suppressing the C-C reductive elimination (RE) of Pd^{IV} intermediate, promoting the intramolecular C-N RE.[10] Herein, we report a streamlined method for asymmetric synthesis of β-aryl

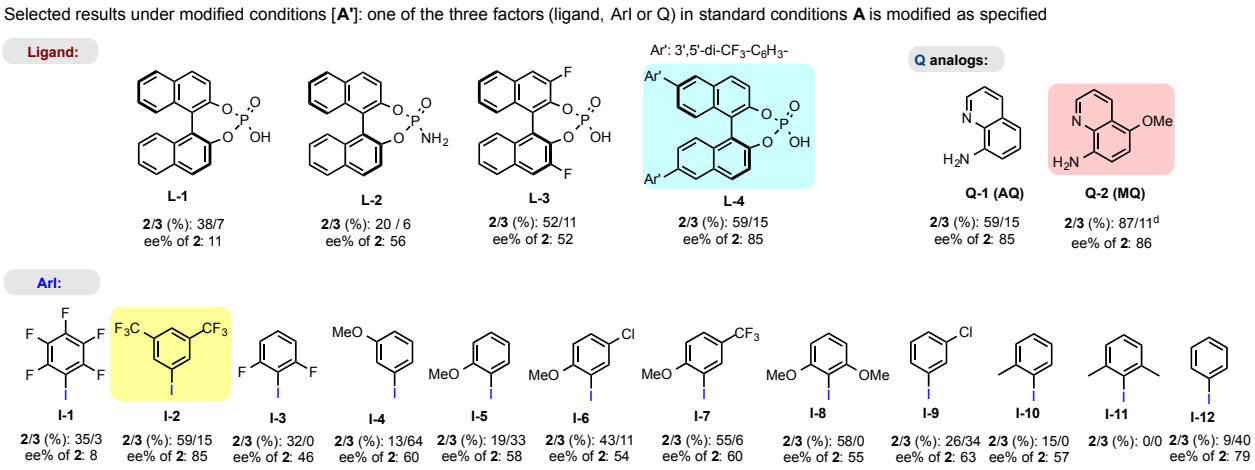


Scheme 1. Pd-catalyzed enantioselective C(sp³)–H functionalization directed by *N,N*-bidentate auxiliary groups.

Table 1. Pd-catalyzed quinoline-directed enantioselective intramolecular C(sp³)-H amidation of **1** using chiral phosphate ligand.



Entry	Change from the standard conditions [A] (equiv)	Yield of 2 /3 (%)[a,b]	recovered 1 (%)	ee of 2 (%)
1	Conditions [**A**]: **I-2** & **L-4**	59 (54[c]) / 15	25	85
2	[**A'**]: Cs_2CO_3 → Ag_2CO_3	54 / 17	20	0
3	[**A'**]: Cs_2CO_3 → K_2CO_3	44 / 8	47	4
4	[**A'**]: $PdCl_2(CH_3CN)_2$ → $Pd(OAc)_2$	46 / 18	28	69
5	[**A'**]: Neat → m-xylene	54 / 18	22	72
6	[**A'**]: Neat → 1,3-di-CF_3Ph	77 / 16	5	82
7	[**A'**]: No dba	59 / 18	21	73
8	[**A'**]: **I-2** (4 → 2 equiv)	31 / 8	54	60
9	[**A'**]: AQ **(Q-1)** → **Q-2**	87[d] / 11[d]	0[d]	86



(a) Yields are based on ^{1}H-NMR analysis of reaction mixture on a 0.1 mmol scale. (b) ee was determined by HPLC using a chiral column. (c) Isolated yield. (d) Product bearing the corresponding modified Q group. See SI for additional screening conditions and ArI oxidants.

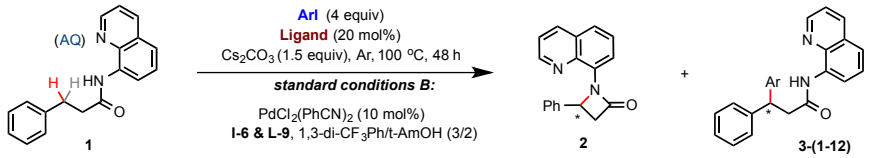
β-lactams via Pd^{II}-catalyzed quinoline-directed enantioselective intramolecular C(sp^3)-H amidation of 3-arylpropylamines using 3,3'-di-F-BINOL chiral ligand[6b,11,12] and 2-methoxy-5-chlorophenyl iodide as oxidant.

RESULTS AND DISCUSSION

β-Lactams are important scaffolds in drug design and frequently used as reactive intermediates in organic synthesis.[13,14] C-H functionalization strategy via metal-catalyzed intramolecular C-H carbene insertion has long been employed for synthesis of β-lactams.[15] In recent years, Pd-catalyzed intramolecular C(sp^3)-H functionalization reactions including C-H alkylation,[16] carbonylative amination[17], carbamoylation[18] process via Pd$^{0/II}$ or Pd$^{II/0}$ catalytic cycles have offered new ways to construct β-lactams. Among these reactions, enantioselective transformations based on C-H alkylation[16] and carbamoylation[18] have also been demonstrated using chiral phosphonite and phosphoramidites ligand respectively. In comparison, catalytic reactions featuring C-H amidation of alkyl carboxamide substrates could provide a more straightforward disconnection strategy. Racemic versions of this type of transformation have been achieved via promoting C-N RE from high valent metal intermediates under oxidative conditions.[19, 20] To make this transformation enantioselective, a proper combination of chiral ligand and oxidant need to be exploited.

During our recent re-investigation of Pd^{II}-catalyzed AQ-directed enantioselective C(sp^3)-H arylation of 3-phenylpropanamide **1** with aryl iodides, we noticed that β-lactam **2** was formed as a side product in varied yield and enantioselectivity using chiral phosphate ligands (Table 1).[5c] While pentafluoro phenyl iodide **I-1** oxidant gave the best reactivity and chemo-selectivity (lactam vs C-H arylation) in Wu's racemic system (Pd(OAc)$_2$ as catalyst and AgOAc as I$^-$ scavenger at 150 °C),[9a] it gave poor reactivity under the conditions of PdCl$_2$(CH$_3$CN)$_2$ catalyst, Cs$_2$CO$_3$ base and chiral phosphate ligand at lower temperature (100 °C), which are critical to achieve high enantioselectivity in this AQ-directed system.[5] In comparison, 3,5-di-CF$_3$-phenyl iodide (**I-2**) stood out among the electron-deficient ArI oxidants tested, offering the best balance of chemo- and enantioselectivity. A 59% yield of **2** with 85% ee along with 15% yield of C-H arylation product **3** were obtained using 4 equiv of **I-2,** 20 mol% of 3,3'-di-aryl (3,5-di-CF$_3$-C$_6$H$_3$) substituted BINOL-derived phosphate ligand **L4**[6a] and 30 mol% of dibenzylideneacetone (dba) additive at 100 °C without any solvent

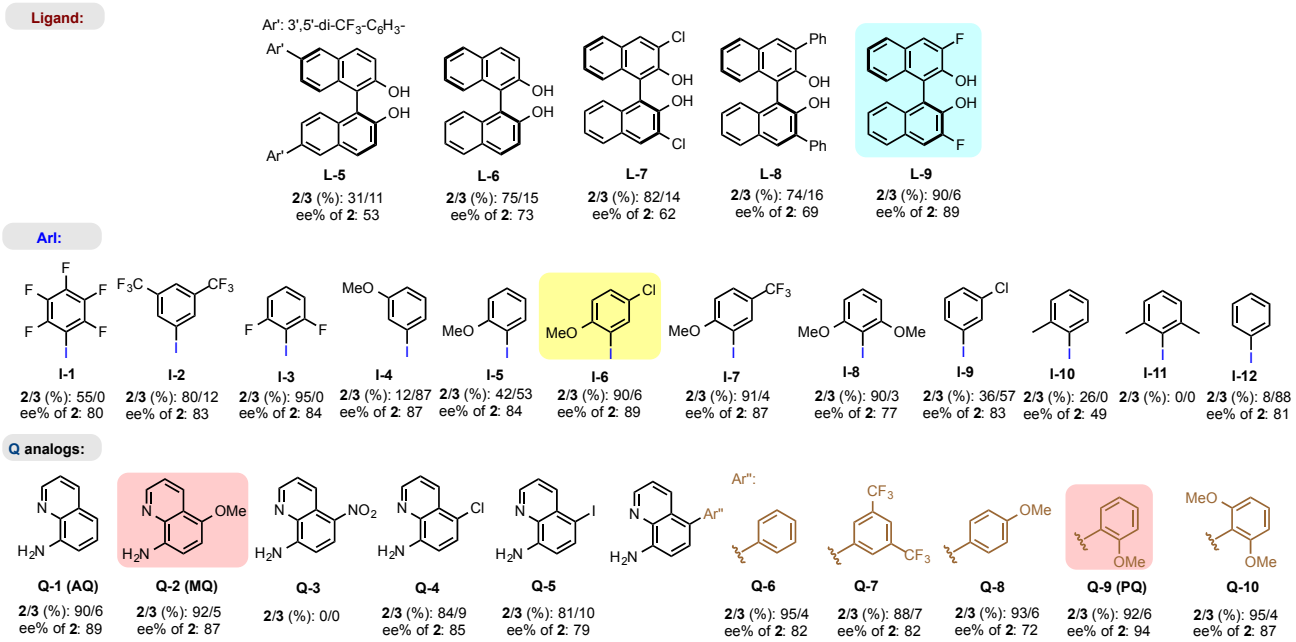
Table 2. Pd-catalyzed quinoline-directed enantioselective intramolecular C(sp^3)-H amidation of **1** using chiral BINOL ligand.



Entry	Change from the standard conditions [B]	Yield of 2 {ee%}/3 [a,b]	recovered 1	ee of 2

	(equiv)		(%)	(%)
1	Conditions [**B**]: **I-6** & **L-9**	90 (84[c]) / 6	~1	89
2	[**B'**]: Cs_2CO_3 → Ag_2CO_3	13 / 2	76	55
3	[**B'**]: $PdCl_2(PhCN)_2$ → $Pd(OAc)_2$	59 / 13	23	74
4	[**B'**]: $PdCl_2(PhCN)_2$ → $PdCl_2(CH_3CN)_2$	88 / 5	~1	82
5	[**B'**]: 1,3-di-CF_3Ph/tAmOH → m-xylene	65 / 20	10	46
6	[**B'**]: **I-6** (4 → 2 equiv)	72 / 14	12	81
7	[**B'**]: AQ **(Q-1)**→ **Q-2**	92 (88[c]) / 5[d]	0	87
8	[**B'**]: AQ **(Q-1)**→ **Q-9**	92 (89[c]) / 6[d]	0	94

Selected results under conditions [**B'**]: one of the three factors (ligand, ArI, or Q) in conditions **B** is modified as specified



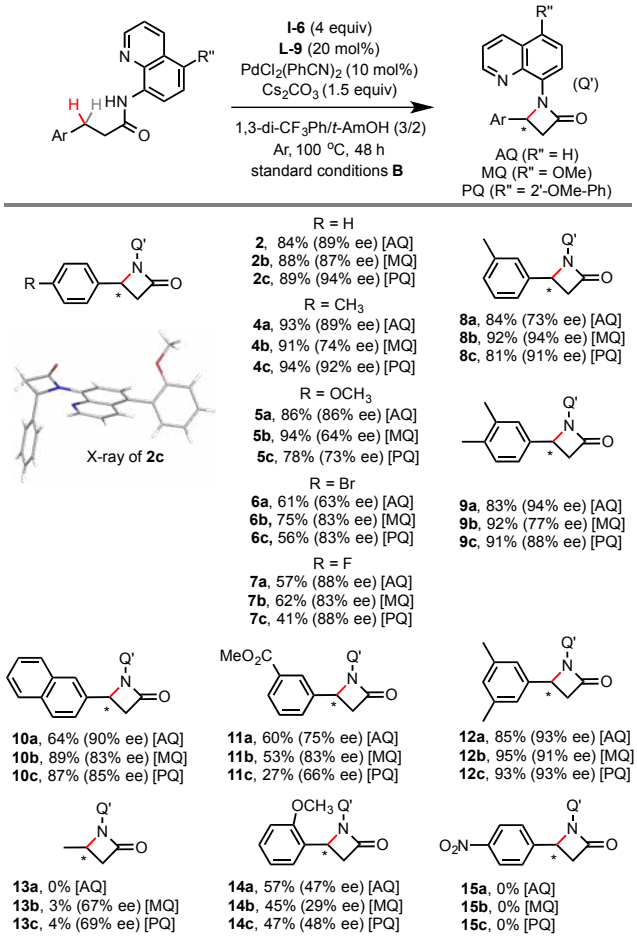
(a) Yields are based on ^{1}H-NMR analysis of reaction mixture on a 0.1 mmol scale. (b) ee was determined by HPLC using a chiral column. (c) Isolated yield . (d) Product bearing the corresponding modified Q group. See Supporting Information for additional screening conditions and ArI oxidants.

(entry 1, standard conditions **A**). The structure of quinoline auxiliary also had an impact on reactivity and ee. **Q-2** (MQ)[21], a C5-methoxy analog of AQ, gave lactam product in significantly improved yield and ee (entry 9). Beside electron-deficient ArIs, we found electron-rich ArIs bearing various *ortho* substituents can also promote the formation of **2** to varied extent. For example, **I-10** bearing an *ortho*-methyl group exclusively gave cyclization product but low reactivity. **I-8** bearing two *ortho*-MeO groups gave **2** in 58% yield and with moderate ee.

As outlined in Table 2, we were pleased to find that use of chiral BINOL ligands also gave moderate to good enantioselectivity with both electron rich and poor ArI oxidants.[6b, 11, 12] **I-5** bearing an *ortho*-MeO group gave more **2** than **I-4** bearing a *meta*-MeO and **I-12** (PhI). As seen in **I-6** and **I-7**, installation of electron-withdrawing group on C5 position of **I-5** further improved the chemo-selectivity. Due to the low cost, **I-6** was chosen for further reaction optimization.[22] The combination of di-F-BINOL ligand **L-9** and **L-6** gave the best results. Reaction of **1** with 4 equiv of **I-6**, 10 mol% of $PdCl_2(PhCN)_2$ catalyst, 20 mol% of **L-9** in the mixed solvent of 1,3-di-CF_3-Ph and *t*AmOH at 100 °C gave **2** in 90% yield with 89% ee along with 6% of arylation byproduct (entry 1, standard conditions **B**). The use of MQ gave comparable results to AQ under conditions **B'** (entry 1 vs 7). **Q-9** (PQ) with an *ortho*-methoxyphenyl group on the C5 of AQ gave lactam product with the highest ee of 94% (entry 8). It is also worth noting that 1) Use of Cs_2CO_3 is critical for obtaining high ee. [23] 2) Addition of Ag additives e.g. Ag_2CO_3 gave significantly decreased ee (entry 2). 3) Use of $Pd(OAc)_2$ catalyst gave lower ee (entry 3). 4) 4 equiv of ArI is needed to achieve high yield (entry 6).

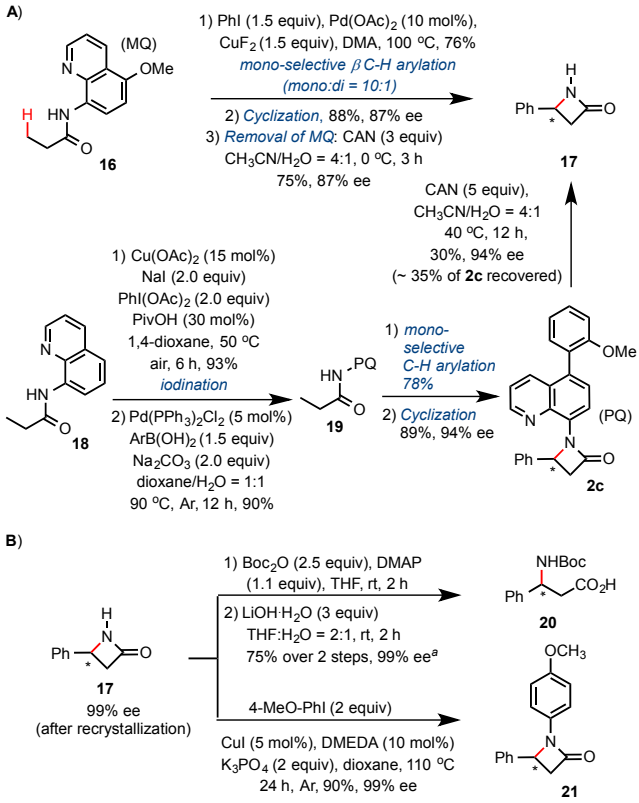
Substrate scope. The reaction scope using AQ, MQ and PQ auxiliary groups under the optimized reaction conditions **B** were summarized in Scheme 2. The 3-arylpropanamide starting materials can be readily prepared via Pd-catalyzed mono-selective β C–H arylation of the corresponding auxiliary-coupled propanamide precursors with aryl iodides (see SI for

details).[5c, 19a] The performance of auxiliaries slightly fluctuates depending on the β-aryl groups. In general, substituents on the meta and para positions of aryl groups were well tolerated (see **4**, **8**). *Ortho*-substituted or electron-deficient aryl groups gave significantly lower yield and ee (**14**, **11**, **15**). As exemplified by **13**, intramolecular amination of the unactivated C(sp^3)-H bond gave very low yield and moderate ee under the standard conditions.[24]



Scheme 2. Substrate scope of β-C(sp^3)-H amidation. Isolated yield of lactam products/^{1}H-NMR yield of arylation products on a 0.1 mmol scale under standard conditions **B**.

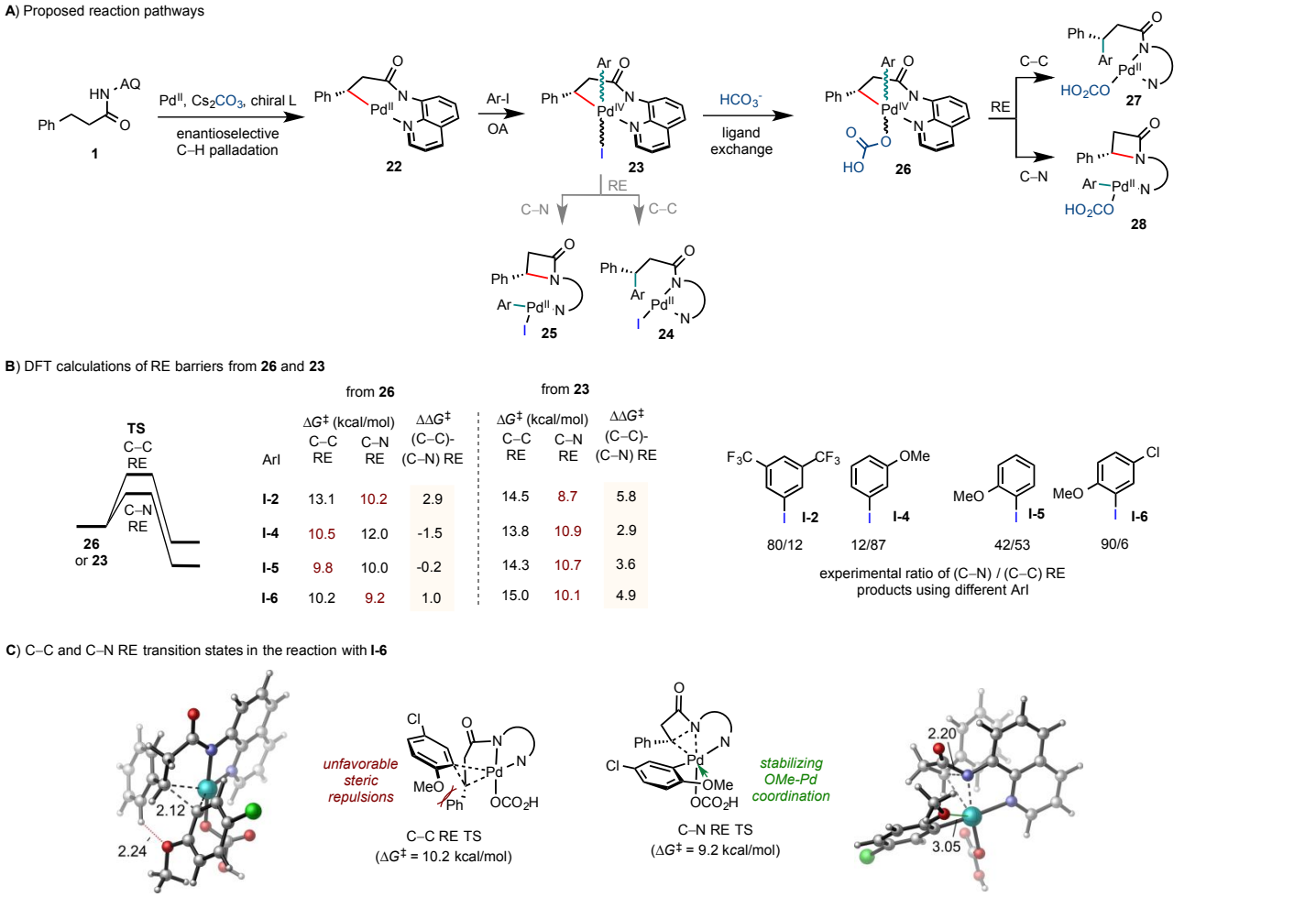
As shown in Scheme 3A, Pd-catalyzed mono-selective β C-H arylation of MQ-coupled propenamide **16** with PhI and subsequent β C-H amination gave compound **2b**. Removal of the MQ group of **2b** by the treatment of cerium ammonium nitrate (CAN) in acetonitrile and water gave the NH-free β-lactam product **17** in 75% yield and with 87% ee.[21,25] As exemplified by **19**, the Ar'' group on the C5 position of AQ can be readily installed by Cu-mediated regioselective iodination[26]and Pd-catalyzed Suzuki coupling with the corresponding aryl boronic acid. Pd-catalyzed PQ-directed β C-H arylation and β C-H amination gave compound **2c**. Interestingly, the PQ group can also be removed by the treatment of CAN to give **17** in moderate yield[27] and with 94% ee. The ee value of **17** was increased to 99% after one recrystallization in hexanes and ethyl acetate. Amide activation of **17** by Boc and cleavage with LiOH gave phenyl substituted β-amino acid **20** in good yield and 99% ee.[28] Hartwig-Buchwald coupling of **17** with aryl iodide gave **21** in 90% yield.



Scheme 3. Synthetic transformations. Isolated yield on a 0.2 mmol scale. a) ee of **20** was measured by HPLC analysis of its benzyl ester (See SI).

Mechanistic study. This Pd-catalyzed aminoquinoline-directed intramolecular C-H amidation reaction is believed to follow the main sequence of C-H palladation, oxidative addition (OA), and reductive elimination (RE) (Scheme 4A). As in the previously reported Pd^{II}-catalyzed C(sp^3)-H functionalization reactions,[5,6] C-H palladation under the asymmetric control of either BINOL-based phosphate or di-F-BINOL ligand is likely the enantio-determining step of this reaction, forming an enantioenriched Pd^{II}-palladacycle (**22**). Following the OA with ArI, Pd^{IV} intermediate **23** can undergo either C-C or C-N RE to give the arylated or cyclized products **24** and **25** respectively. Protodepalladation and dissociation of I^- ligand regenerates the active Pd^{II} catalyst. To understand the roles of the ArI oxidant on the chemoselectivity, density functional theory (DFT)

calculations were performed to study the C-C and C-N RE transition states (TS) in reactions of model substrate **1** with various ArIs.[29-32] Since previous computational studies of the Pd-catalyzed directed C-H arylation with ArI suggested the I^--bound Pd^{IV} intermediate may undergo anionic ligand exchange prior to the RE,[31c] we expect that **23** may react with HCO_3^- generated in situ to form a new Pd^{IV} intermediate **26**. Therefore, RE from both **23** and **26** were considered computationally. As shown in Scheme 4B, the calculated chemoselectivity of C-C vs C-N RE of **26** agreed well with the experimental product ratios. In comparison, the calculated chemoselectivity of RE of the I^--bound **23**, particularly with **I-4**, notably deviated from the observed ratios. Similar to the C_6F_5-I



Scheme 4. Mechanistic studies.

(**I-1**) oxidant used in Wu's racemic system, reagent **I-2** bearing two strongly electron-withdrawing CF_3 groups promotes the lactam formation by disfavouring C-C RE of Pd^{IV} through electronic effects. The enhanced selectivity for lactam products with electron-rich ArIs bearing *ortho*-methoxyl groups (**I-5** and **I-6**) is likely due to the steric repulsions between the *ortho*-OMe group of ArI and the β-Ph that destabilize the C-C RE transition state (Scheme 4C). A weak *o*-OMe–Pd coordination in the C-N RE transition state may further promote the C-N bond formation. Addition of an electron-withdrawing Cl group at C5′ of **I-5** fine-tuned the electronic property of **I-6** and the selectivity for C-N RE. The above computational analysis suggests that the good chemoselectivity for lactam with the use of *ortho*-methyl substituted **I-10** is due to similar steric effects that suppress the C-C RE. However, reaction with **I-10** suffers from low reactivity, which is probably caused by the difficulty of the initial OA to palladacycle.[33]

Conclusion

In summary, we have developed the first Pd^{II}-catalyzed enantioselective intramolecular C(sp^3)–H amidation reaction with up to 94% ee. It offered a streamlined method for the asymmetric synthesis of β-aryl β-lactams from propanoic acid and aryl iodides precursors. The identification of 2-methoxy-5-chlorophenyl iodide oxidant is critical to achieve high chemoselectivity. Mechanistic studies suggest that

both steric and electronic effects of the unconventional aryl iodide oxidant are responsible for controlling the competing C-N vs C-C reductive elimination pathways of Pd^{IV} intermediate. The quinoline auxiliary group of the lactam products can be removed under mild conditions. Other Pd-catalyzed bidentate auxiliary-directed enantioselective C(sp^3)–H functionalization reactions are under current investigation.

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The authors declare no competing financial interest.

ASSOCIATED CONTENT

Detailed synthetic procedures, compound characterization, NMR spectra, X-ray crystallographic data, and computational details are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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