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Ligand-Controlled C(sp³)-H Arylation and Olefination in Synthesis of Unnatural Chiral α -Amino Acids

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The use of ligands to tune the reactivity and selectivity of transition metal catalysts for C(sp³)-H bond functionalization is a central challenge in synthetic organic chemistry. Herein, we report a rare example of catalyst-controlled C(sp³)-H arylation using pyridine and quinoline derivatives: The former promotes exclusive monoarylation, whereas the latter activates the catalyst further to achieve diarylation. Successive application of these ligands enables the sequential diarylation of a methyl group in an alanine derivative with two different aryl iodides, affording a wide range of β -Ar- β -Ar'- α -amino acids with excellent levels of diastereoselectivity (diastereomeric ratio > 20:1). Both configurations of the β -chiral center can be accessed by choosing the order in which the aryl groups are installed. The use of a quinoline derivative as a ligand also enables C(sp³)-H olefination of a protected alanine.

Over the past decade, substantial progress has been achieved in the palladium-catalyzed activation of the inert β -C(sp³)-H bonds of aliphatic carboxylic acid derivatives using chiral oxazolines (1), the 8-aminoquinoline auxiliary (2, 3), and a variety of weakly coordinating amide directing groups (4, 5). In particular, the synthesis of unnatural amino acids via the direct β -functionalization of α -amino acids has been an area of extensive research since a seminal report by Reddy *et al.* (6). We envisioned that a sequential diarylation of alanine with two different aryl iodides could potentially provide an efficient route for the preparation of β -Ar- β -Ar'- α -amino acids containing a β -chiral center (Fig. 1). Although the more strongly coordinating 8-aminoquinoline auxiliary developed by Zaitsev *et al.* (2) is a powerful directing group for the β -arylation of alanine, this auxiliary provides predominantly β,β -homo-diarylated products, which prevents the sequential installation of two different aryl groups. It is possible to use a specifically designed 2-methylthioaniline auxiliary to achieve monoarylation of alanine in moderate yield and then use a different auxiliary to perform the secondary C(sp³)-H arylation with a distinct aryl iodide (Fig. 1A) (7). However, this hypothetical route has not yet been used for preparing β -Ar- β -Ar'- α -amino acids because the removal and installation of the second auxiliary would add three synthetic steps to the sequence. In addition, the basic reaction conditions used in the first arylation step partially racemize the amino acid to 90% enantiomeric excess (7).

We reasoned that a ligand-controlled strategy could provide an ideal solution for the synthesis of β -Ar- β -Ar'- α -amino acids. Specifically, we envisioned the application of two different ligands: one that would selectively promote primary β -C(sp³)-H arylation [without further arylating the remaining, now secondary, β -C(sp³)-H bonds] and another that would enable further secondary β -C(sp³)-H arylation, thereby introducing both aryl substituents successively onto a single substrate in one pot (Fig. 1B). This re-

action sequence provides an alternative synthetic disconnection to the existing asymmetric hydrogenation method for the synthesis of chiral β -Ar- β -Ar'- α -amino acids (Fig. 1C) (8–11). Fundamentally, the development of appropriate ligands to confer selectivity for primary or secondary β -C(sp³)-H bonds on a weakly coordinating substrate can greatly improve C(sp³)-H activation reactions (12–20).

Herein, we report the discovery that a pyridine-based ligand promotes monoarylation of primary β -C(sp³)-H bonds exclusively and that a second, quinoline-based ligand enables introduction of a distinct aryl group via subsequent secondary β -C(sp³)-H activation in one pot. The reactions proceed with excellent levels of diastereoselectivity with respect to the starting configuration at the α carbon (Fig. 1B). As such, both configurations at the new β -stereogenic center can be constructed by simply choosing the order of aryl group installation. We further demonstrate that the use of the quinoline-based ligand enables the C(sp³)-H olefination of an alanine-derived substrate to afford olefin-substituted chiral α -amino acids.

A Ligand for Monoarylation

Our first challenge in the development of a versatile method for the preparation of stereo-defined β -Ar- β -Ar'- α -amino acids from alanine (Fig. 1B) was to achieve selective monoarylation of primary C(sp³)-H bonds without further arylating the secondary C(sp³)-H bonds. Our group has recently focused on the development of simple auxiliaries, such as *N*-methoxyamides and

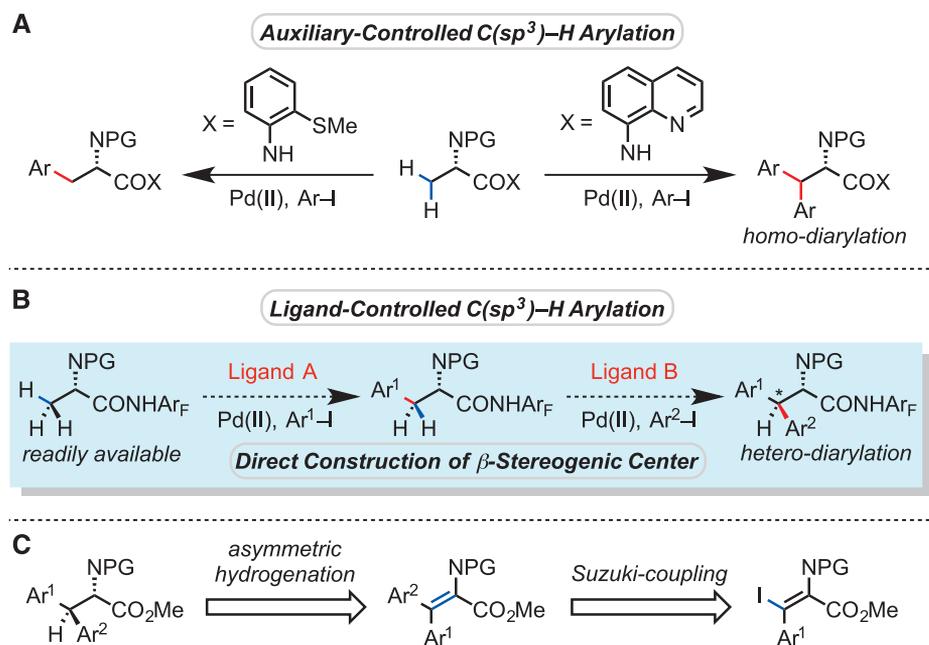


Fig. 1. Methods for synthesizing chiral β -Ar- β -Ar'- α -amino acids. (A) C(sp³)-H activation using substrate-bound auxiliaries to govern selectivity. NPG, protected amino groups; COX, amides; Me, methyl. **(B)** C(sp³)-H activation using catalyst-bound ligands to govern selectivity. **(C)** Asymmetric hydrogenation.

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perfluorinated arylamides, to direct a wide range of $C(sp^3)\text{-H}$ activation reactions by weak coordination to palladium catalysts (4, 5). However, to date we have found that these auxiliaries are incompatible with the functionalization of the $C(sp^3)\text{-H}$ bonds of α -amino acids (4, 5). We recently demonstrated that the use of an alkoxyridine ligand can match the weak coordination of the amide auxiliary (CONHAr_F) and facilitate secondary $C(sp^3)\text{-H}$ activation (albeit, with only simple aliphatic amides) (21), indicating that pyridine-based ligands are capable of lowering the transition state energy of $C(sp^3)\text{-H}$ activation. This finding prompted us to test a diverse array of monodentate pyridine-derived ligands for their ability to selectively pro-

mote primary $C(sp^3)\text{-H}$ activation, thereby allowing for highly monoselective arylation of alanine-derived amide **1**.

To obtain preliminary information regarding the reactivity of the CONHAr_F amide auxiliary with amino acid substrates, we initiated our experimental efforts by studying $C(sp^3)\text{-H}$ arylation of **1** under a variety of different reaction conditions in the absence of an ancillary ligand. Through extensive screening, we found that the use of 20 mol % trifluoroacetic acid (TFA) prevented substrate decomposition, which had been observed with **1** under previously developed basic conditions (21). Under the best conditions from this initial screen, monoarylated product **2** could be obtained in 47% yield, along with

full recovery of the remaining starting material (Fig. 2A). Additional attempts to fine-tune various reaction parameters, including increasing the catalyst loading to 30 mol %, failed to improve the reaction conversion. The low conversion was found to result primarily from product inhibition (see supplementary materials: table S2, entry 16). Alternative aryl iodide coupling partners reacted in even lower yields (Fig. 2A, **2m** to **2p**). These findings point to the need for the identification of a ligand that will promote the activation of primary $\beta\text{-C}(sp^3)\text{-H}$ bonds exclusively but not the secondary $\beta\text{-C}(sp^3)\text{-H}$ bonds in the product. Hence, a library of pyridine ligands was tested for their efficiency of promoting monoarylation in the presence of TFA. Pyridine and 4-dimethylaminopyridine (**L1** and **L2**) are highly selective for monoarylation, but neither enhances conversion substantially relative to the ligand-free catalyst. In contrast, we found that 2,6-dimethoxy-pyridine, acridine, 2,6-lutidine, and 2-picoline (**L4** to **L7**) promote substantially higher conversion, though the use of **L4** to **L6** leads to appreciable quantities of the undesired diarylated product **3** as well. The 2-picoline ligand (**L7**) seems to possess an optimal balance of steric and electronic properties to provide **2** in high yield with an excellent level of selectivity for monoarylation [nuclear magnetic resonance (NMR) yield of 94%]. The monoarylation reaction also proceeded in the presence of 5 mol % of Pd(TFA)₂ and 10 mol % of **L7** to give the desired product **2** in 79% yield (table S2, entry 4).

The applicability of this ligand-controlled monoarylation protocol in the preparation of diverse chiral $\beta\text{-Ar}\text{-}\beta\text{-Ar}'\text{-}\alpha$ -amino acids is shown in Fig. 2A: Phenylalanine derivatives with electron-rich or electron-poor groups in the ortho, meta, or para positions can be synthesized in high yields. This reaction is tolerant of halide substituents and a wide range of polar functional groups. Arylation with 4-methylthiophenyl iodide also proceeds to give the arylated product (**2p**) in a synthetically useful yield, indicating that the pyridine ligand is able to out-compete the methylthio group for coordination at Pd(II). The reaction of **1** with 2-iodonaphthalene to give **2q** is particularly useful, as the resulting product could be applied to synthesis of bioactive peptides that block cell cycle progression in HeLa cells (22). Arylation with disubstituted aryl iodides is also efficient, giving **2r** to **2t** in >85% yields.

When conducted at 100°C, these reactions are typically complete within 20 hours, and no racemization of the α -chiral center is observed. Subsequent removal of the auxiliary can be accomplished under mild conditions without loss of enantiomeric purity (Fig. 2B), and the monoarylated products are readily converted to the corresponding *N*-fluorenylmethylxycarbonyl-protected unnatural amino acids following literature procedures (see supplementary materials). The auxiliary 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline is readily prepared from octafluorotoluene (\$0.47/g) on a 100-g scale or purchased directly from Aldrich.

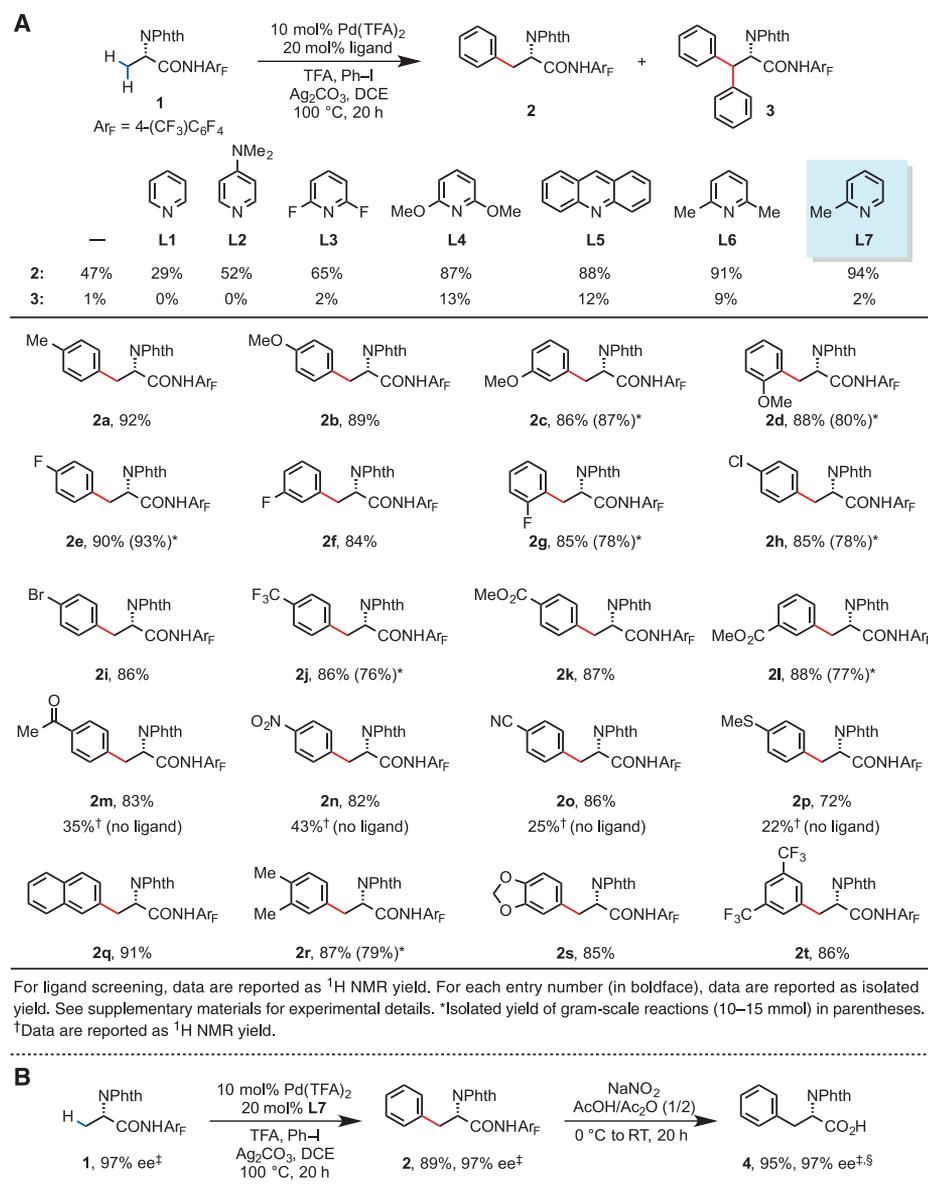


Fig. 2. Palladium-catalyzed arylation of primary $C(sp^3)\text{-H}$ bonds. (A) Ligand-promoted monoarylation of auxiliary-substituted alanine. Phth, phthalimido; DCE, 1,2-dichloroethane **(B)** Removal of amide auxiliary and determination of enantiomeric purity of *N*-Phth-protected chiral α -amino acid. Ac, acetyl; RT, room temperature; ee, enantiomeric excess; HPLC, high-performance liquid chromatography.

Due to these practical advantages, we have prepared a variety of monoarylated alanines on a 10-mmol scale to facilitate peptide drug discovery in collaboration with Bristol-Myers Squibb (**2c** to **2e**, **2g**, **2h**, **2j**, **2l**, and **2r**).

A Ligand for Diarylation

We next sought to identify a second ligand that could promote the subsequent arylation of the secondary β -C(sp³)-H bonds. As previously mentioned, our recently disclosed procedure for the ligand-promoted arylation of secondary C(sp³)-H bonds under basic reaction conditions (**2l**) is not compatible with amino acid substrates. However, the formation of minor amounts of the diarylated product **3** from amide **1** with ligand **L4** (13% yield, Fig. 2A) suggested that these new conditions could be effective for secondary β -C(sp³)-H bond arylation with an appropriate ligand. We were pleased to find that the arylation of phenylalanine-derived amide **2**, in the presence of ligand **L4**, afforded the desired product **3** in 47% yield. The modest success of this ligand and our previously reported 2-alkoxyquinoline ligand **L9** (**2l**) led us to explore a variety of electron-rich 2-alkoxypyridine and 2-alkoxylquinoline ligands for this secondary C(sp³)-H bond arylation.

A substantial improvement in reaction efficiency using ligand **L8** or **L9** suggested that the 2-substituted quinoline motif possesses favorable steric and electronic properties that promote C(sp³)-H activation. Next, we examined the impact of further increasing the electron-donating ability of the alkoxy group by synthesizing the tricyclic ligand **L10**, in which the conformation of the lone pairs on the oxygen atom is rigidified to favor π -conjugation with the pyridine ring. The use of this new ligand led to a dramatic improvement in reaction efficiency, affording product **3** in 92% yield (90% isolated yield). Further modifications of **L10** to weaken or strengthen the coordinating ability of the quinoline led to a decrease in product yield (**L11** and **L12**).

Under these optimized reaction conditions, phenylalanine-derived amide **2** can be arylated with a broad range of electron-rich and electron-poor aryl iodides in high yields (Fig. 3A). Despite the known steric hindrance associated with the arylation of secondary C(sp³)-H bonds (**3j**), ortho-substituted aryl iodides are also compatible with this reaction. To demonstrate the generality of this ligand effect for secondary C(sp³)-H activation, we also performed the arylation of four representative open-chain and cyclic alkyl amino acids. Amide substrates derived from lysine, L-2-aminobutyric acid, 1-aminocyclobutane-1-carboxylic acid, and 1-aminocyclopropane-1-carboxylic acid were successfully arylated using ligand **L10** to give the corresponding β -alkyl- β -aryl- α -amino acid derivatives in good to excellent yields (Fig. 3B). These arylation reactions all proceeded with high levels of diastereoselectivity. These aliphatic secondary C(sp³)-H bonds are less reactive than benzylic C(sp³)-H bonds, and

the use of ligand **L10** is crucial to achieve this reactivity.

One-Pot Diarylation

Ligands **L7** and **L10**, which enable the arylation of primary and secondary β -C(sp³)-H bonds, respectively, can be employed for the sequential one-pot incorporation of two distinct aryl groups onto the β carbon of alanine-derivative **1** (Fig. 4). Thus, after the completion of the monoarylation of **1** with an aryl iodide using **L7**, we can add **L10** and a second aryl iodide to provide a β -Ar- β -Ar'- α -amino acid. The aryl iodide (1.5 equivalents) used in the first step is mostly incorporated into the product, with small amount being con-

verted to the biaryl (**23**). The remaining aryl iodide is outcompeted by a large excess of the second aryl iodide (3 equivalents), thus avoiding participation in a second arylation event. This one-pot procedure is successfully applied with both electron-rich and electron-deficient aryl iodides to prepare a variety of diarylated amino acids (**7a** to **7f**) in good yields with excellent levels of diastereoselectivity (**24**). By simply switching the order of the addition of the two different aryl iodides, the inverse configuration at the β -stereogenic center can be obtained, as shown with **7e** and **7f** (absolute configuration of **7f** was confirmed by x-ray crystallography). When the sequential hetero-diarylation of **1** was conducted

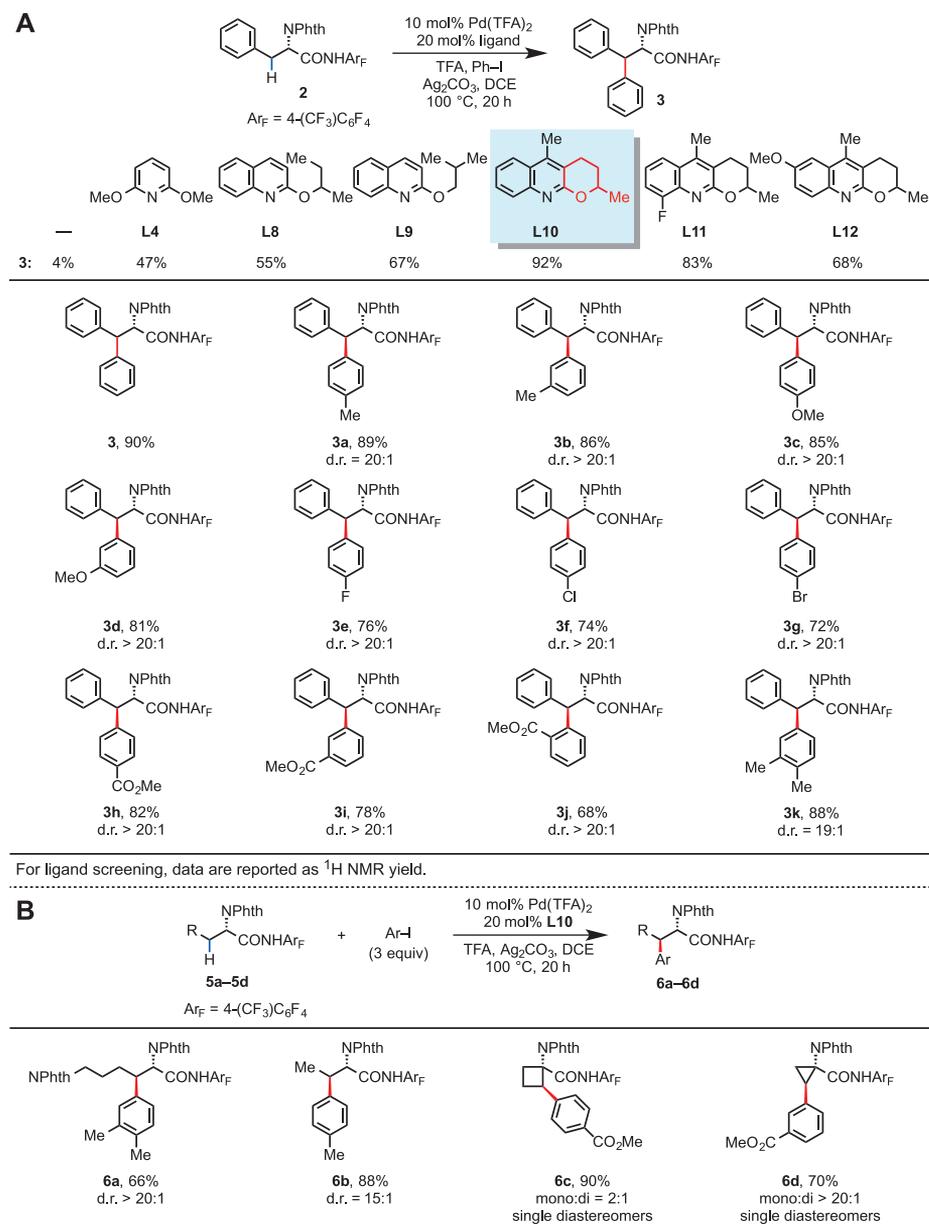


Fig. 3. Palladium-catalyzed arylation of secondary C(sp³)-H bonds. (A) Ligand-promoted arylation of phenylalanine-derived substrate. d.r., diastereomeric ratio. (B) Arylation of alkyl amino acid derivatives. R, alkyl.

in one pot on a 5-mmol scale (2.2 g), the desired product **7b** was isolated in 60% yield.

The superior reactivity of ligand **L10** prompted us to revisit previously unsuccessful arylation with heteroaryl iodides. Although secondary C(sp³)-H arylation of **2** with heteroaryl iodides proved inefficient, primary C(sp³)-H arylation of **1** with pyridyl, indolyl, and thiophenyl iodides

afforded synthetically useful yields (Fig. 5A). These heteroaryl-containing unnatural amino acids are especially desirable for developing peptide drug molecules.

Olefination with Ligand L10

We also examined the feasibility of using ligand **L10** to effect the olefination of alanine-derived

substrate **1**, and we observed efficient reactivity under slightly modified reaction conditions. The subsequent lactamization in situ also ensured the monoselectivity of the reaction. With the use of established procedures, lactam **8** is converted to *N*-Boc-protected product **10** (Fig. 5B). Further improvement of this olefination reaction could lead to a useful method for the preparation of β -olefinated α -amino acids that is complementary to the asymmetric hydrogenation route (25). The olefinated product **10** can be subjected to cross metathesis to afford olefinated products **11** and **12** with high levels of *E/Z* selectivity or hydrogenated to provide the corresponding alkylated product **13** (Fig. 5C).

Mechanistic Studies

Whereas C(sp³)-H arylation with aryl iodides likely proceeds via a Pd(II)/Pd(IV) catalytic cycle, olefination probably proceeds via a Pd(II)/Pd(0) redox manifold. The considerable ligand effect observed in these distinct reaction pathways implicates the intimate involvement of the ligand in the C(sp³)-H cleavage step as the common step. This is further substantiated by the intramolecular kinetic isotope effect observed in the arylation reaction, which showed a noticeable and consistent dependence on the ligand (without ligand, intramolecular isotope effect value $k_H/k_D = 6.0$; with **L7**, $k_H/k_D = 8.1$; with **L10**, $k_H/k_D = 10.7$; see supplementary materials).

To obtain further insights into the coordination of the substrate and ligands at the Pd(II) centers, we have successfully characterized the C-H insertion intermediates (intermediate **A** and intermediate **B**), formed via primary and secondary C(sp³)-H activation, respectively (Fig. 6A). The formation of these C(sp³)-H insertion intermediates

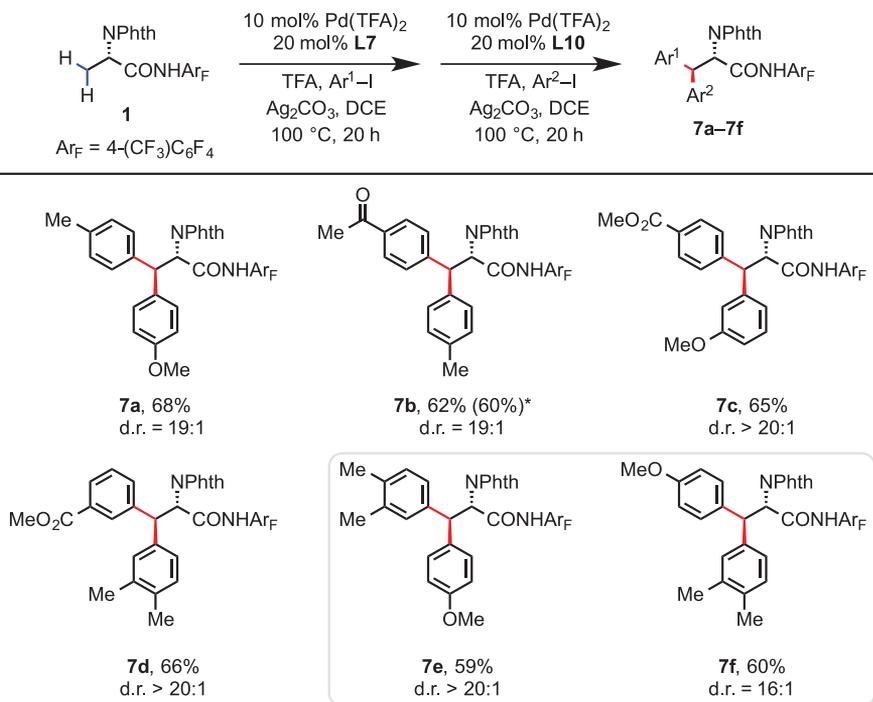


Fig. 4. Synthesis of β -Ar- β -Ar'- α -amino acids via sequential C(sp³)-H arylations in one pot.

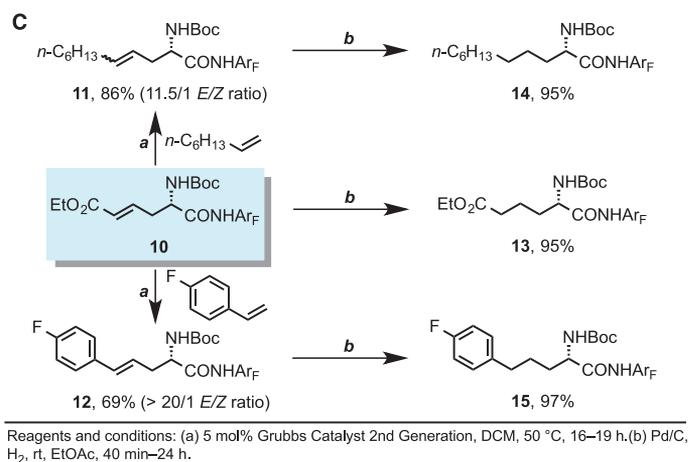
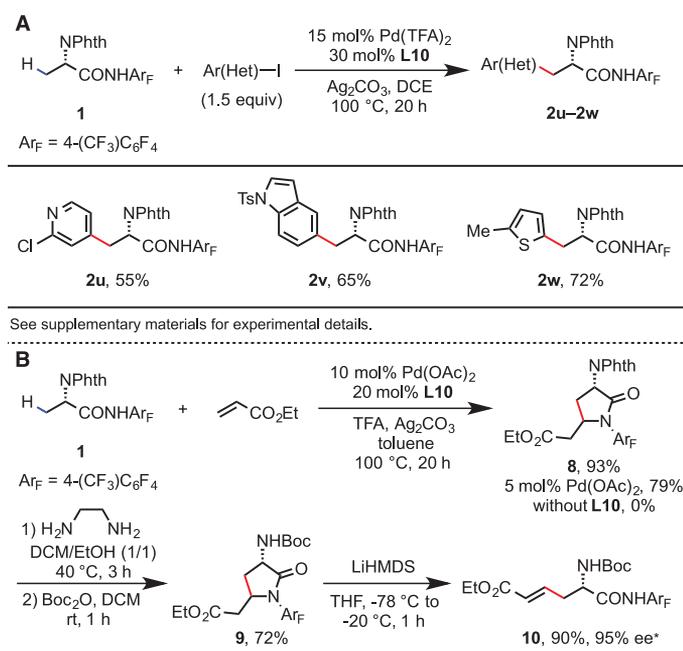
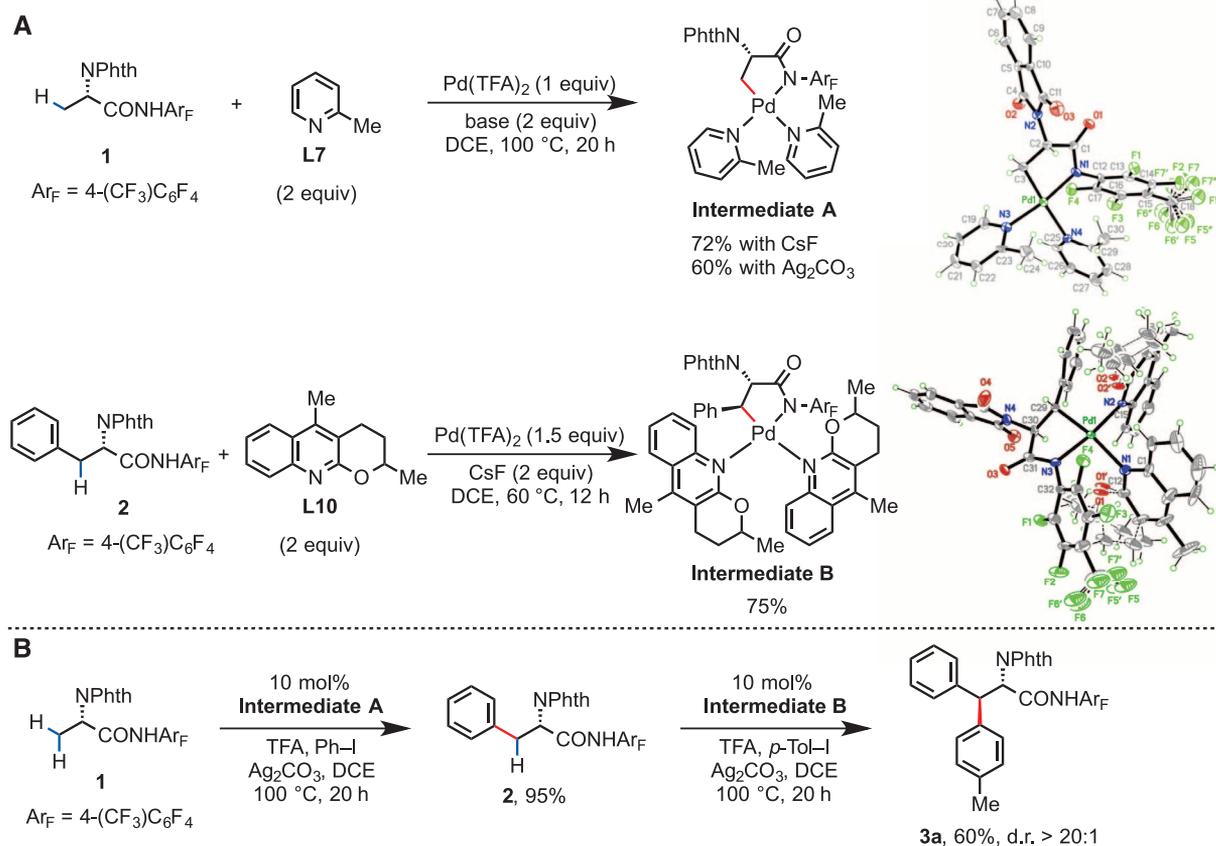


Fig. 5. Further applications of Pd catalysis with **L10**. (A) Ligand-enabled C(sp³)-H arylation with heteroaryl iodides. (B) C(sp³)-H olefination of alanine derivatives. DCM, dichloromethane; Et, ethyl; Boc, *tert*-butoxycarbonyl; HMDS, hexamethyldisilazide. (C) Unnatural α -amino acid elaboration.

*The ee values were determined by chiral HPLC.



For each entry number (in boldface), data are reported as isolated yield. See supplementary materials for experimental details.

Fig. 6. Mechanistic studies. (A) Synthesis and crystallography of primary and secondary C(sp³)-H activation intermediates. Oak Ridge thermal ellipsoid plots (30% probability ellipsoids) of intermediate **A** and intermediate **B** are shown. (B) Catalytic reactivity of intermediates in C(sp³)-H arylation reactions.

in the absence of aryl iodides is consistent with the Pd(II)/Pd(IV) pathway in which Pd(II) cleaves the C-H bond first and subsequently undergoes oxidative addition with an aryl iodide (26). We have found that intermediate **A** reacts with iodobenzene stoichiometrically to provide **2** (see supplementary materials). However, the addition of TFA is required for this transformation, presumably to facilitate the dissociation of one of the pyridine ligands. These intermediates are viable precatalysts for primary and secondary C(sp³)-H arylation, respectively (Fig. 6B). These rare and valuable C(sp³)-H insertion intermediates provide a promising platform for further kinetic and computational study of elementary steps in a well-defined manner.

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Supplementary Materials

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 Supplementary Text
 Figs. S1 to S3
 Tables S1 to S6
 NMR Spectra
 References (27–31)

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