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Ligand-Enabled β-C−H Arylation of α-Amino Acids Using a Simple and Practical Auxiliary

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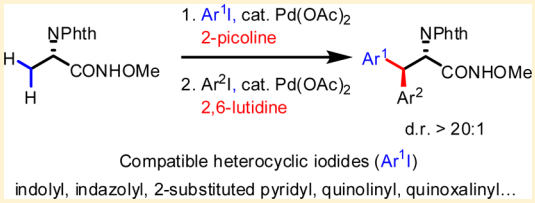
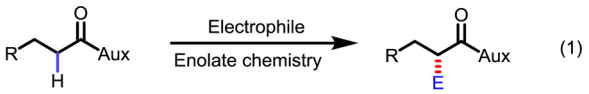
Supporting Information

ABSTRACT: Pd-catalyzed β-C−H functionalizations of carboxylic acid derivatives using an auxiliary as a directing group have been extensively explored in the past decade. In comparison to the most widely used auxiliaries in asymmetric synthesis, the simplicity and practicality of the auxiliaries developed for C−H activation remains to be improved. We previously developed a simple *N*-methoxyamide auxiliary to direct β-C−H activation, albeit this system was not compatible with carboxylic acids containing α-hydrogen atoms. Herein we report the development of a pyridine-type ligand that overcomes this limitation of the *N*-methoxyamide auxiliary, leading to a significant improvement of β-arylation of carboxylic acid derivatives, especially α-amino acids. The arylation using this practical auxiliary is applied to the gram-scale syntheses of unnatural amino acids, bioactive molecules, and chiral bis(oxazoline) ligands.



1. BACKGROUND

Aliphatic acids belong to an important class of useful building blocks due to their availability and the diverse reactivity of the carboxyl group. Among many methods for the preparation of α- or β-substituted carboxylic acids, α-enolate chemistry using chiral auxiliaries[1] and asymmetric conjugate additions[2] are the most powerful tools (eqs 1 and 2). To seek an alternative



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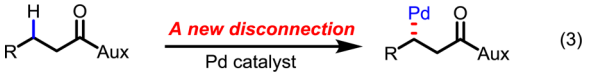
synthetic disconnection, we initiated a research program centered on the β-C−H activation and subsequent carbon−carbon and carbon−heteroatom bond-forming reactions in 2002 (eq 3). Our early studies employed an oxazoline auxiliary as a



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directing group[3] to investigate the reactivity and mechanism of β-C−H insertion by Pd(II) (Figure 1). We utilized the stereochemistry obtained in the C−H insertion step to deduce the pretransition-state structure of directed C−H insertions using chiral oxazoline auxiliaries. With hindsight and recent in-depth computational and kinetic studies,[4] the primitive, but important insights, we obtained from these studies regarding the conformation and structure of the C−H insertion precursors paved the way for our subsequent design of more efficient auxiliaries (Figure 1). In the past decade, while Daugulis' bidentate 8-aminoquinoline auxiliary has emerged as a powerful directing group,[5] we have focused on the development of monodendate simple amide auxiliaries, hoping to achieve ligand-accelerated and -controlled β-C−H functionalization reactions.

Due to the moderate reactivity of sodium or potassium carboxylates in β-C−H arylation,[6] we developed an *N*-methoxyamide auxiliary to mimic the carboxylate while allowing improved coordination with Pd(II).[7] The simple rationale behind this design was to best mimic the conformation of the coordination structure of Pd(II) with carboxylates while at the same time slightly increase the binding strength. This new auxiliary (CONHOMe) displayed excellent efficiency in directing β-C−H activation (Figure 1). For example, β-arylation of the amide derived from pivalic acid with Ph−I using this auxiliary proceeds at room temperature. We have also successfully exploited this reactivity to accomplish an unprecedented coupling of β-C−H bonds with alkyl boronic acids.[7] Numerous applications of this powerful auxiliary in directed C(sp^2)−H activation have also been reported with Pd(II), Rh(III), and Ru(II) catalysts.[8] Unfortunately, C(sp^3)−H activation of aliphatic acids using this auxiliary has been limited to substrates containing α-quaternary centers under current

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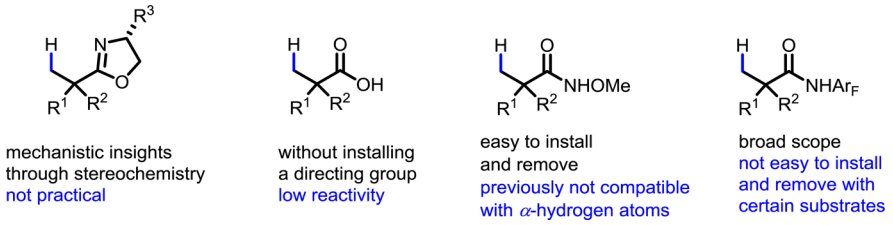


Figure 1. Advantages and disadvantages of different directing groups developed in our laboratory.

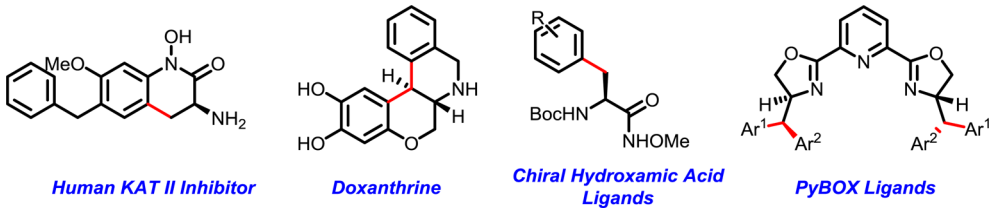


Figure 2. Synthetic applications.

conditions. Apart from the known Thorpe−Ingold effect in cyclopalladation, we suspected that the acidic α-hydrogen of aliphatic acid substrates could be responsible for the lack of reactivity. This reasoning has led us to develop another acidic amide auxiliary ($CONHAr_F$, $Ar_F = p\text{-}CF_3C_6F_4$) that is compatible with aliphatic acid substrates containing α-hydrogen atoms (Figure 1).[9] Despite the broad utility of this new directing group, the simplicity of CONHOMe[10] in terms of installation and removal prompted us to develop new conditions that may overcome the limitation of this potentially broadly useful auxiliary. Our recent collaboration with Bristol-Myers Squibb to establish a robust and scalable method for the preparation of a wide range of unnatural amino acids through C−H functionalization of readily available amino acids such as alanine provided a further incentive for this endeavor.

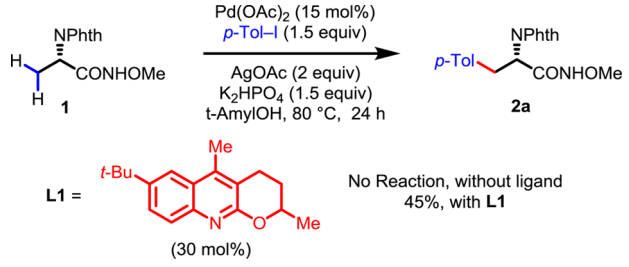
Herein we report the development of pyridine-type ligands that promote selective mono- and di-β-arylation of a broad range of carboxylic acids using a simple *N*-methoxyamide auxiliary as the directing group. 2-Picoline ligand (**L7**) promotes the selective monoarylation of primary C(sp^3)−H bonds, and 2,6-lutidine ligand (**L13**) enables the subsequent arylation of secondary C(sp^3)−H bonds in one pot. Sequential arylation of alanine derivatives with two different aryl iodides using these ligands enables the introduction of two distinct aryl groups to produce a variety of β-Ar-β-Ar′-α-amino acids with excellent levels of diastereoselectivity. Arylation of the *N*-methoxyamide derived from alanine with a variety of heterocyclic aryl iodides on gram scales to make various unnatural amino acids was also demonstrated. These unnatural amino acid intermediates were further transformed to drug molecules such as a human kynurenine aminotransferase (KAT) II inhibitor[11] and Doxanthrine[12] as well as chiral hydroxamic acid ligands[13] and a variety of new chiral pyridine-2,6-bis(oxazolines) (PyBOX) ligands[14] (Figure 2).

2. RESULTS AND DISCUSSION

2.1. β-Monoarylation Directed by *N*-Methoxyamide.

β-C−H functionalizations of amino acid derivatives using various auxiliaries have been extensively studied since the first report from the Corey group.[15,16] It was established in this early study that the use of the phthalimide protecting group was crucial for achieving β-C−H activation.[15a] Recently, we have discovered that pyridine- and quinoline-based ligands promote activation of the C(sp^3)−H bonds in alanine using $CONHAr_F$ (Ar_F = $p\text{-}CF_3C_6F_4$) auxiliary as the directing group.[17] While the precise mechanistic origin of the ligand effects remains to be elucidated, a recent computational study suggests that the ligand is involved in every step of the catalytic cycle including the C−H activation step.[18] This new development encouraged us to revisit whether a simpler *N*-methoxyamide auxiliary, with the assistance of a ligand, can accommodate substrates derived from carboxylic acids containing α-hydrogen atoms. Thus, phthaloyl alanine amide **1** was reacted with 1.5 equiv of *p*-Tol−I using $Pd(OAc)_2$ and ligand **L1** under various conditions. We found that the monoarylation proceeded under the conditions shown in Scheme 1 to give the arylated products as a mixture of amide

Scheme 1. Preliminary Discovery for Ligand-Promoted C−H Arylation



2a and the corresponding ester in 45% yield. A substantial amount of the starting material was converted to corresponding unreactive ester. The conversion of the *N*-methoxyamide to the corresponding ester via a radical process is known to be promoted by silver salts.[10] A control experiment showed that ligand **L1** was required for the formation of the arylated product.

Prior to undertaking further ligand screening, we needed to identify conditions under which the known decomposition of the *N*-methoxyamide to the unreactive ester via a radical process[10a−c] was minimized (Table 1). The use of (2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) to inhibit the radical process led to a slight drop in product yield (Table 1, entry 2). The reaction did not proceed at a lower temperature of 60 °C (Table 1, entry 3). Switching to a range of commonly used solvents did not reduce the decomposition or improve the yields (Table 1, entries 4−8). We were pleased to find that the decomposition of the

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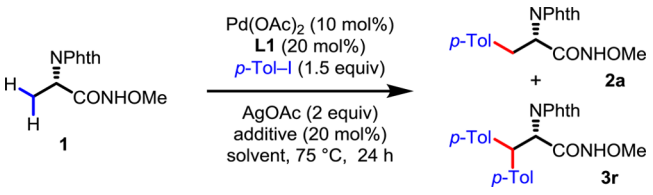
Table 1. Evaluation of Reaction Conditions[a]



entry	solvent	additive	% yield of 2a[b]
1	*t*-AmylOH	no	45
2	*t*-AmylOH	TEMPO	40
3[c]	*t*-AmylOH	no	N.R.
4	toluene	no	30
5	CH_3CN	no	35
6	1,4-dioxane	no	50
7	DCE	no	43
8	DMF	no	40
9	CF_3CH_2OH	no	60
10	HFIP	no	76(86)[d]
11	DCE	TFA	75

[a]Conditions: Substrate **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), *p*-Tol–I (0.15 mmol), ligand **L1** (20 mol %), solvent (1.0 mL), 75 °C, 24 h. [b]Determined by ^{1}HNMR analysis of the crude product using CH_2Br_2 as an internal standard, and the yield is based on the amide and ester. [c]Reaction run at 60 °C. [d]Combined 76% mono- and 10% diarylated products determined by crude ^{1}HNMR.

N-methoxyamide was effectively prevented by using acidic solvents, such as 2,2,2-trifluoroethanol (CF_3CH_2OH) or hexafluoro-2-propanol (HFIP) (Table 1, entries 9–10). Arylation proceeded in HFIP to give the monoarylated product in 76% yield and the diarylated product in 10% yield (Table 1, entry 10). Running the reaction in 1,2-dichloroethene (DCE) in the presence of 20 mol % trifluoroacetic acid (TFA) also significantly improved the yield to 75% (Table 1, entry 11).

While further ligand screening using DCE/TFA solvent system did not provide noticeable improvement, dramatic ligand effects were observed for this reaction in HFIP (Table 2). A variety of quinoline-based ligands (**L2**-**L4**) afforded moderate to good yields (up to 83%). Further optimizations of quinoline-based ligands were not fruitful. We found a wide range of pyridines as suitable ligands for this reaction. 2-Picoline ligand (**L7**) was found to be highly effective affording both excellent yield (90%) and monoselectivity (99%). Replacing the 2-methyl group by other substituents in 2-substituted pyridines (**L8**-**L12**) resulted in lower yields. Among the disubstituted and trisubstituted pyridines (**L13**-**L18**), **L16** and **L17** containing a 2-methyl group performed well with good yields (84% and 83%) and monoselectivity. Interestingly, the use of 2,6-lutidine (**L13**) resulted in some loss of monoselectivity affording the monoarylated product **2a** in 70% yield and the diarylated product **3r** in 10% yield. Arylation in the absence of ligand under these new conditions gave the desired product in 36% yield, thus confirming the significant ligand acceleration effect. Mechanistically, the comparison of the most effective ligand **L7** with the less effective ligands **L10** and **L11** is informative. The decrease in binding strength of the ligands via either electronic or steric effects reduces the efficiency of the catalysts.

A broad range of variously substituted aryl iodides are compatible with this ligand-promoted β-C–H arylation reaction (Table 3). Aryl iodides containing methyl, phenyl, and methoxy groups react with substrate **1** under the standard conditions to give the desired products in good to excellent yields (**2a**–**f**). Fluoro, chloro, bromo, and iodo substituents are all tolerated, and moderate to good yields are obtained (**2g**-**k**). Aryl iodides containing highly electron-withdrawing groups including acetyl and methoxycarbonyl are excellent coupling partners affording the arylation products in 71–82% yields (**2l**–**p**). Di- and trisubstituted aryl iodides display similar reactivity to the monosubstituted ones (**2q**–**t**). Most importantly, aryl iodides containing well-known directing groups such as acetamide, phosphonate, and hydroxyls are also reactive coupling partners (**2u**–**x**), thus overcoming some limitations of previous protocols.[16,17] These unnatural amino acids have been widely used as building blocks for the preparation of bioactive peptides.[19,20] For example, the corresponding amino acid of **2v** was used to replace tyrosine in a peptide to afford an improved β_2 adrenergic receptor,[19] while a tetrapeptide containing the corresponding amino acid of **2w** has been evaluated as a tyrosine kinase inhibitor.[20]

2.2. Arylation with Heteroaryl Iodides. Heteroatoms in heterocycles coordinate strongly to Pd(II) catalysts and result in catalyst poisoning. This detrimental effect often prevents the use of heteroaryl iodides as coupling partners in C–H activation reactions. We reasoned that the acidic solvent HFIP used in our new protocol could weaken the coordinating ability of the heterocycles. Furthermore, the pyridine-type ligand picoline could potentially also outcompete the coordination of the heteroaryl iodides. We thus proceeded to investigate the reactivity of a wide range of heterocyclic iodides under the standard conditions. We found that aryl iodides containing dioxane and chromonyl moieties were coupled with alanine substrate **1** successfully to give the desired products **4a** and **4b** in 76% and 70% yields, respectively (Table 4). Tosyl-protected indolyl and indazolyl iodides also afforded **4c**–**f** in synthetically useful yields (58–65%). These unnatural amino acids containing heteroaryls are not readily accessible via other methods[21] and are often desirable in medicinal chemistry.

However, arylation with the more coordinative pyridyl iodide gave poor yields (<10%). Considering that a halogen substituent at the 2-position of a pyridine can be readily removed or transformed to other functional groups, we tested the reactivity of 2-fluoro, 2-chloro and 2-bromopyridyl iodides. These coupling partners reacted with substrate **1** to give the desired products in approximately 20% yields under the standard conditions. Through further ligand screening, 2,6-lutidine was identified as a more efficient ligand. Thus, arylation with a range of pyridyl iodides was carried out under the optimized conditions (Table 5). Although 4-pyridyl iodide gave poor yield (**4g′**), all 2-halo-pyridyl iodides afford synthetically useful yields (**4h′**-**4m′**). The arylated products were obtained as a mixture of amides and esters which are treated with $PhI(OAc)_2$ in one pot to give the pure esters as the isolated products. Arylation with pyridyl iodides containing 2-CF_3, 2-Me, and 2-OMe substituents proceeded to give the desired products in 42–66% yields. The presence of 3-CH_2OH group reduced the yield to 32% (**4r′**). Various quinolinyl and quinoxalinyl iodides are also compatible with protocol affording heterocycle-containing amino acids (**4s′**–**4v′**) in moderate yields.

2.3. Removal of the Auxiliary. Since *N*-alkoxyamides are used as masked esters, a number of deprotection procedures based on radical pathways have been developed (eq 4).[10,22]

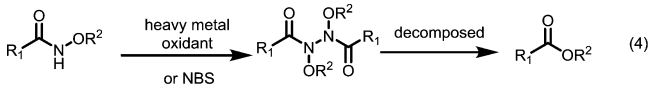


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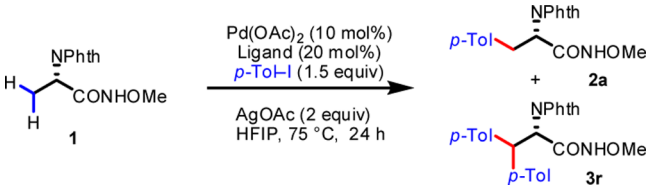
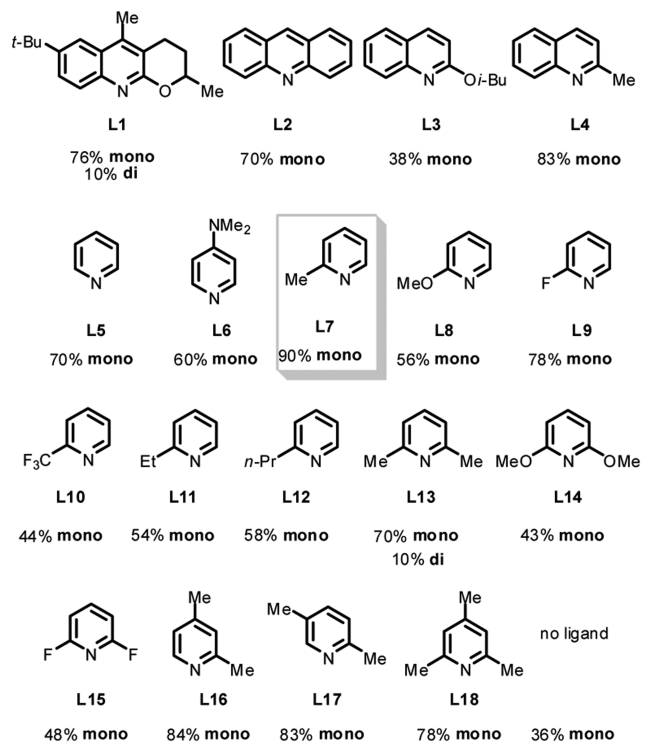
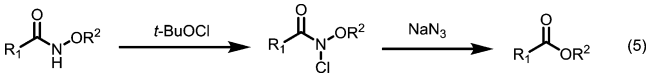
Table 2. Ligand Screening[a,b]





[a]Conditions: Substrate **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), *p*-Tol–I (0.15 mmol), ligand (20 mol %), HFIP (1.0 mL), 75 °C, 24 h. [b]The yields were determined by ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard. The mono:di ratio was determined by ^1H NMR.

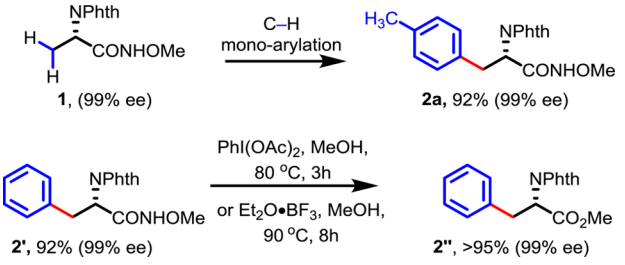
N, *N*-Bis-heteroatom-substituted amides formed from *N*-alkoxyamides can thermally decompose to give the corresponding esters. A wide range of metal oxidants including silver oxide (Ag_2O), nickel(IV) peroxide hydrate ($NiO_2{\cdot}H_2O$), ceric ammonium nitrate (CAN), and lead(IV) acetate [$Pb(OAc)_4$] have been used to convert *N*-alkoxyamides into esters.[10] One-step conversion of *N*-alkoxyamides to esters by reacting with *N*-bromosuccinimide (NBS) in toluene has also been reported.[22] *N*-Chlorohydroxamates generated from *N*-alkoxyamides can be converted to the esters by treating with sodium azide via Heron rearrangement (eq 5).[23] However, all of these protocols convert



(5)

the amino acid-derived amides to esters in only moderate yields. We found that reacting *N*-methoxyamides with iodosobenzene diacetate [$PhI(OAc)_2$] in methanol at 80 °C afforded esters in excellent yields excluding indole-containing amides (**4c**, **4d**) which suffered from partial intramolecular radical lactamization. Lewis acid boron trifluoride diethyl etherate ($Et_2O{\cdot}BF_3$) was also identified as an efficient reagent to convert *N*-methoxyamides into esters in methanol at 90 °C. This latter protocol is also compatible with the indole-containing amides. Importantly, no racemization of the α-chiral center was observed during the C–H arylation and the subsequent removal of the auxiliary (Scheme 2).

Scheme 2. Removal of the Directing Group



2.4. Arylation of Methylene C–H Bonds. Following the development of monoarylation of the primary $C(sp^3)$–H bonds directed by *N*-methoxyamide, we began to search for ligands that would promote further arylation of the methylene C–H bonds. The formation of 10% of the diarylated product with the quinoline ligand **L1** (Table 1) led us to investigate whether these conditions can be optimized for arylation of methylene C–H bonds (Table 6). Considering the previously observed significant effects of inorganic bases on the β-C–H functionalizations of *N*-methoxyamides,[7] we investigated the arylation with a wide range of base additives. Among the various potassium, sodium, and lithium salts, monohydrogen phosphate (Table 6, entries 5 and 8) and dihydrogen phosphate (Table 6, entries 6, 9–11) significantly improved the yields of the arylation. Sodium dihydrogen phosphate was especially effective, affording the arylated product in 50% yield (Table 6, entries 9, 10). Increasing the amount of sodium dihydrogen phosphate monohydrate ($NaH_2PO_4{\cdot}H_2O$) to three equivalents improved the yield to 72% (Table 6, entry 15).

With this promising result in hand, we began to further improve the arylation of phenylalanine **2′** by screening ligands (Table 7). The dependence of this reaction on ligand was confirmed by the complete loss of reactivity in the absence of a ligand. While other quinoline-based ligands (**L2**, **L3**, **L19**) were all inferior to **L1**, 2,6-lutidine (**L13**), and 2,4,6-trimethylpyridine (**L18**) proved to be superior ligands, affording the desired product in 92% and 86% yields, respectively.

The scope of this newly developed methylene C–H arylation was examined with a board range of electron-rich and electron-poor aryl iodides (Table 8). Aryl iodides containing electron-donating substituents at the *ortho*-, *meta*-, and *para*-positions served as efficient coupling partners, affording the β-arylated phenylalanine products in good to excellent yields (**3a–f**). Arylation of **2′** with fluoro- and chloro-substituted aryl iodides proceeded to afford the desired products in 70–75% yields (**3g–i**). This reaction is also compatible with aryl iodides containing electron-withdrawing groups (**3j–m**). Arylation with naphthalene iodide and disubstitued aryl iodides also afforded synthetically useful yields (**3n–p**). In all cases, this arylation reaction affords excellent diastereoselectivity which can be explained by a previously isolated C–H cleavage intermediate from a related amide substrate.[17]

The removal of the auxiliary from the β-diaryl alanine products using $PhI(OAc)_2$ resulted in the formation of a substantial

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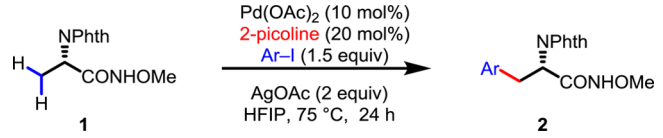
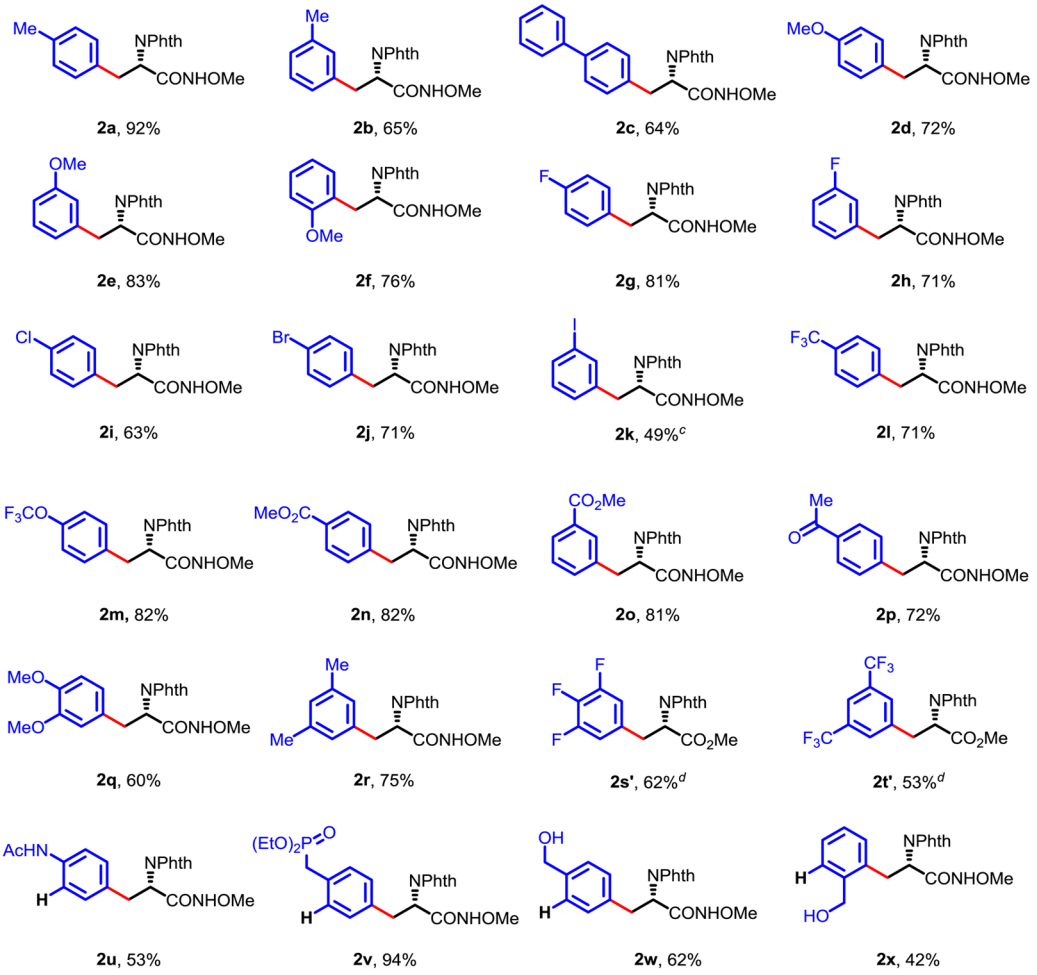
Table 3. Substrate Scope of Aryl Iodides of Monoarylation[a,b]





[a]Conditions: Substrate **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), Ar–I (0.15 mmol), 2-picoline (20 mol %), HFIP (1.0 mL), 75 °C, 24 h. [b]Isolated yields are shown. [c]Ar–I (0.3 mmol). [d]After C–H activation, the reaction mixture was subjected to $PhI(OAc)_2$ (0.1 mmol), MeOH (1 mL), 80 °C, 3 h. Yields for two steps.

amount of a lactamization side product. The use of Lewis acid $Et_2O{\cdot}BF_3$ proved to be effective in removing the auxiliary in high yields. Importantly, the enantiopurity of the α-chiral center was retained during both the C–H arylation step and the subsequent conversion of the amide to the corresponding ester (Scheme 3).

2.5. Homodiarylation of Alanine. The recently identified 2,6-lutidine ligand was also applied to the arylation of alanine substrate **1** to obtain homodiarylation products in one pot (Table 9). Various β-diaryl-α-amino acids (**3q–t**) were synthesized in 63–75% yields. Considering the steric hindrance on the β-carbon of these diarylated amino acids, we anticipate that the corresponding chiral amino alcohols are highly valuable for the synthesis of bulky chiral bis(oxazoline) ligands.

2.6. One-Pot Sequential Heterodiarylation of Alanine. The exclusive monoselectivity of 2-picoline-promoted β-arylation of primary C–H bonds provides a possibility for achieving sequential arylation of alanine substrate **1** with two different aryl iodides in one pot. Thus, **1** was subjected to the monoarylation conditions with 1.2 equiv of 4-iodotoluene. After **1** was completely arylated as shown by thin-layer chromatography (TLC), 3 equiv of phenyl iodide (Ph–I) as well as other reagents (2,6-lutidine, AgOAc, $NaH_2PO_4{\cdot}H_2O$) required for the methylene C–H activation were added to the reaction to initiate the second arylation (Table 10). This one-pot procedure afforded the heterodiarylated product **3u** in 71% yield. The formation of homoarylated product with 4-iodotoluene was not observed, suggesting that the remaining aryl iodide from the first step was outcompeted by the excess phenyl iodide introduced in the second step. This protocol is also compatible with other combinations of a variety of aryl iodides, affording diverse range of heterodiarylated products in 43–71% yields with excellent diastereoselectivity (**3u–ab**). The switching of the arylation order to access different diastereomers was also demonstrated with the preparation of **3w** and **3x**. Given the availability of both enantiomers of the starting amino acids, all four diasteromeric products can be obtained by switching the order of addition

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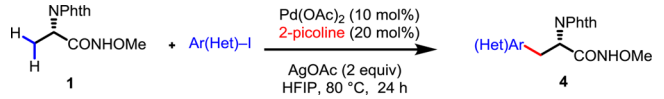
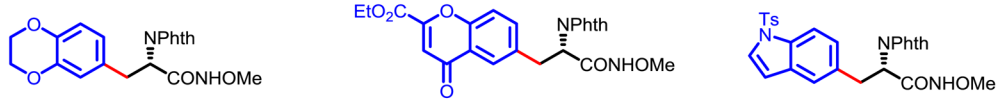
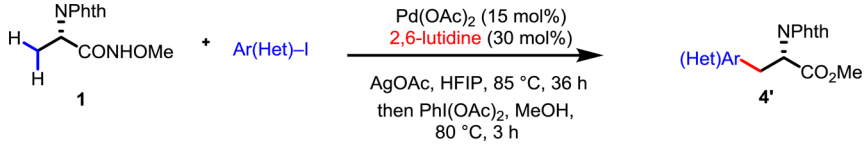
Table 4. Scope of Heteroaryl Iodides[a,b]

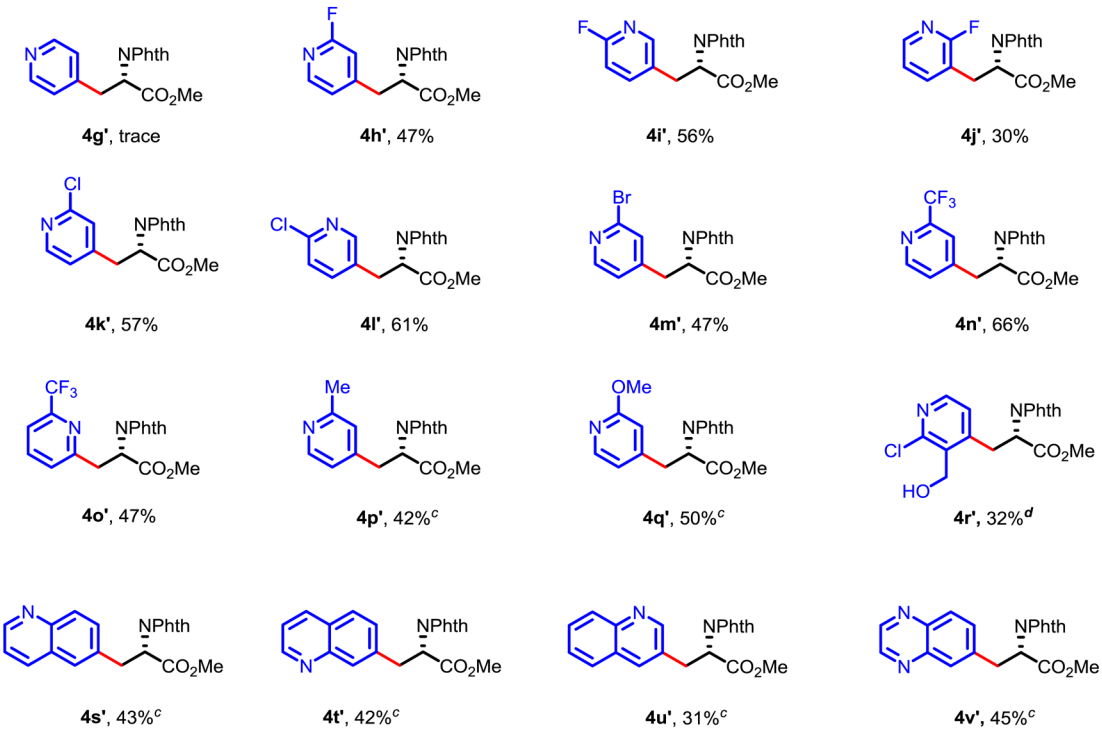




[a]Conditions: Substrate **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), Ar–I (0.15 mmol), 2-picoline (20 mol %), HFIP (1.0 mL), 80 °C, 24 h. [b]Isolated yields are shown. [c]$Pd(OAc)_2$ (15 mol %), 2-picoline (30 mol %). [d]Yields based on the amide and ester.

Table 5. Expanding the Scope of Heteroaryl Iodides[a,b]





[a]Conditions: Substrate **1** (0.1 mmol), $Pd(OAc)_2$ (15 mol %), AgOAc (0.2 mmol), Ar–I (0.15 mmol), ligand (30 mol %), HFIP (1.0 mL), 85 °C, 36 h, and then $PhI(OAc)_2$ (0.1 mmol), MeOH (1 mL), 80 °C, 3 h. [b]Isolated yields are shown. [c]Substrate **1** (0.2 mmol), Ar–I (0.1 mmol), yield based on the Ar–I. [d]Lactone was first formed, then was converted to **4r′** with $MeSO_3H$. For details, see Supporting Information.

of the two different aryl iodides. Overall, this protocol offers a highly versatile approach for the preparation of chiral *β*-Ar-*β*-Ar′-*α*-amino acids. A sequential heterodiarylation using a strongly coordinating bidentate directing group has also been

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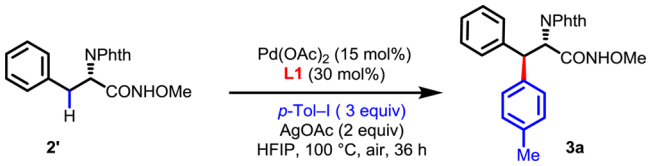
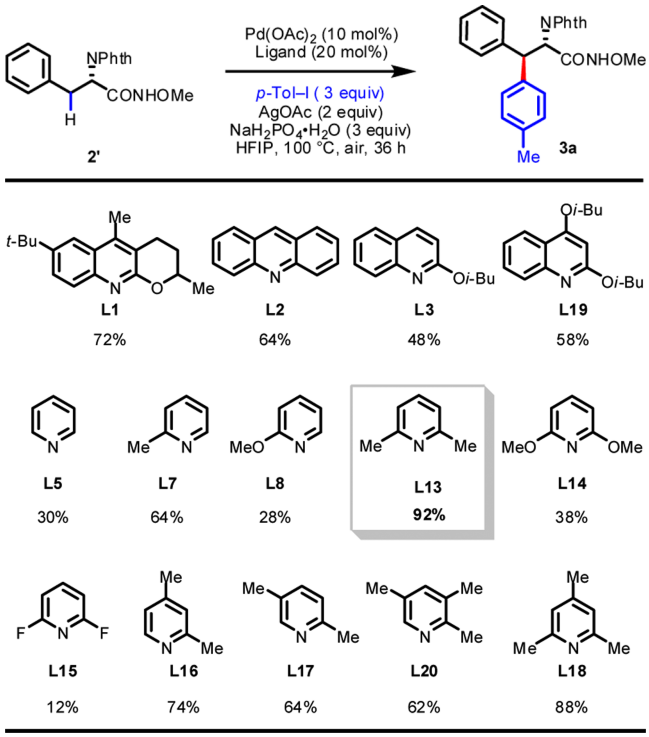
Table 6. Additive Screening in the Arylation of Phenylalanine[a,b]



entry	additives (equiv)	% yield
1	no (1)	10
2	K_2CO_3 (1)	0
3	$KHCO_3$ (1)	8
4	K_3PO_4(0.5) (1)	14
5	K_2HPO_4 (1)	40
6	KH_2PO_4 (1)	30
7	KF (1)	16
8	Na_2HPO_4 (1)	32
9	$NaH_2PO_4{\cdot}H_2O$ (1)	50
10	NaH_2PO_4 (1)	49
11	LiH_2PO_4 (1)	36
12	LiOAc (1)	0
13	$NaH_2PO_4{\cdot}H_2O$ (1.5)	56
14	$NaH_2PO_4{\cdot}H_2O$ (2)	66
15	$NaH_2PO_4{\cdot}H_2O$ (3)	72
16	$NaH_2PO_4{\cdot}H_2O$ (4)	70

[a]Conditions: Substrate **2'** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), *p*-Tol–I (0.3 mmol), **L1** (20 mol %), HFIP (1.0 mL), 100 °C, 36 h. [b]Determined by ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard.

Table 7. Ligand Screening[a,b]



[a]Conditions: Substrate **2'** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), *p*-Tol–I (0.3 mmol), ligand (20 mol %), HFIP (1.0 mL), 100 °C, 36 h. [b]Determined by ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard.

demonstrated,[16a] although the monoarylated product needs to be isolated and subjected to different conditions to perform the second arylation. A recent report[24] on an improved synthesis of differentially substituted dehydro-*β*,*β*-diarylalanine derivatives and subsequent asymmetric hydrogenation also speaks to the need for efficient methods for preparing chiral *β*-Ar-*β*-Ar′-*α*-amino acids.

2.7. Arylation of Other Carboxylic Acids. To demonstrate the generality of *N*-methoxyamide as a directing group for the arylation of C(sp^3)–H bond, we also examined the arylation of other aliphatic acid substrates. Under the conditions for the *β*-arylation of primary C–H bonds using 2-picoline as the ligand, amides derived from 2-methyl butyric acid, *β*-hydroxy acid, *β*-amino acid, and 2-aminoisobutyric acid afforded the arylated products in 53–72% yields (Table 11, **6a–d**). Interestingly, arylation of the cyclobutyl C–H bonds in the amide substrate derived from 1-aminocyclobutane-1-carboxylic acid afforded 86% yield under these conditions (**6g**). As expected, *β*-arylation of amide substrates derived from tyrosine and L-2-aminobutyric acid only proceeded under the conditions developed for methylene C–H bonds (**6e–f**). To our surprise, cyclopropyl C–H bond in **5h** is less reactive under these conditions and requires the use of ligand **L1** to allow the arylation to proceed in moderate yield (45%).

2.8. Gram-Scale Syntheses of Unnatural Amino Acids. The use of *N*-methoxyamide auxiliary has important advantages for gram-scale preparation of unnatural amino acids. First, methoxyamine hydrochloride is inexpensive and has a low molecular weight. Second, the installation involves treatment of carboxylic acid with oxalyl chloride and methoxyamine hydrochloride at room temperature to afford the *N*-methoxyamides in nearly quantitative yields. Notably, the installation of other amide directing groups such as $CONHAr_F$ (Ar_F = *p*-$CF_3C_6F_4$) often requires refluxing conditions or proceeds in low yields. Furthermore, the removal of this auxiliary using $Et_2O{\cdot}BF_3$ or $PhI(OAc)_2$ is highly reliable and high yielding with retention of stereochemistry at the acidic *α*-carbon center.

In response to needs for bioactive peptides from Bristol-Myers Squibb, alanine substrate **1** was coupled with fluorinated and trifluoromethylated aryl iodides (20 mmol scale) using 2-picoline as the ligand to give the monoarylated products in excellent yields (Scheme 4). The resulting crude products were treated with $PhI(OAc)_2$ in methanol to afford the esters in 85–98% yields over two steps. The phthalimide group was removed in the presence of ethylenediamine to generate the free amines that were subsequently converted to Fmoc-protected amino esters. Finally, the esters were hydrolyzed in the presence of lithium hydroxide to give 7.5–9.0 g of the desired amino acids (**7–9**) in 50–55% overall yields. The less reactive heteroaryl iodides and trifluoro-aryl iodide were also successfully coupled with alanine **1** using 2,6-lutidine. Following a similar procedure, 1.1–6.0 g of these desired Fmoc-protected amino acids were prepared (**10–13**) (Scheme 5; for details, see Supporting Information).

2.9. Diverse Synthetic Applications. The practical advantage of the *N*-methoxyamide auxiliary is further demonstrated by its versatile transformations to various biologically active compounds (Scheme 6). Radical cyclization of **2e** with [bis(trifluoroacetoxy)iodo]benzene (PIFA) led to a lactam,[25] and subsequent deprotection of the phthalamide using ethylenediamine afforded **14** as a key intermediate for the synthesis of glycogen phosphorylase inhibitors.[26] Conversion of **2e** to carboxylic acid and subsequent treatment with oxalyl chloride and aluminum trichloride gave the 2-amino-1-indanone **15**,[27] a key intermediate of α_1-adrenoceptor antagonists.[28] The amino

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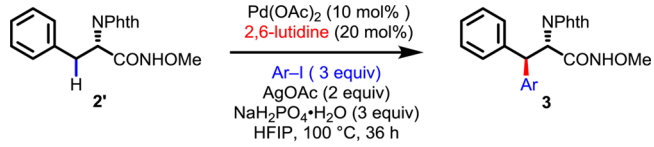
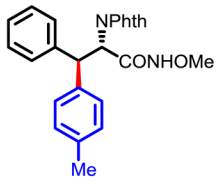
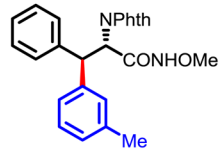
Table 8. Substrate Scope of Aryl Iodides in the Arylation of Phenylalanine[a,b]

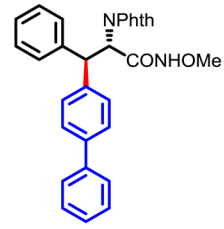




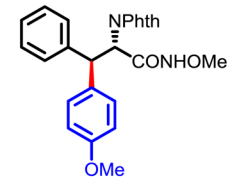
3a, 81%
d.r. > 20:1



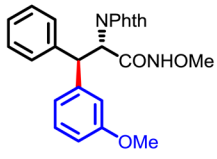
3b,82%
d.r. > 20:1



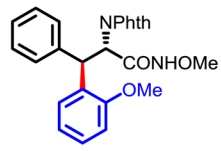
3c, 78%
d.r. > 20:1



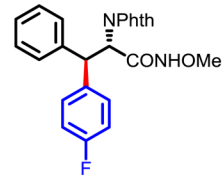
3d, 80%
d.r. > 20:1



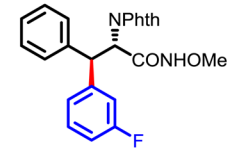
3e, 75%
d.r. > 20:1



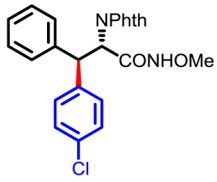
3f, 59%
d.r. > 20:1



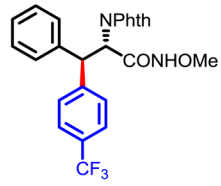
3g, 72%
d.r. > 20:1



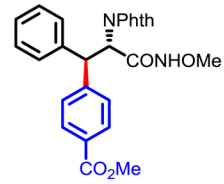
3h, 70%
d.r. > 20:1



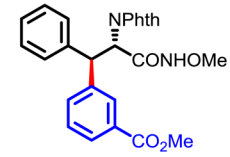
3i, 75%
d.r. > 20:1



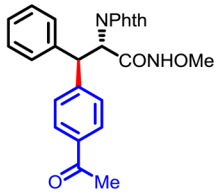
3j,75%
d.r. > 20:1



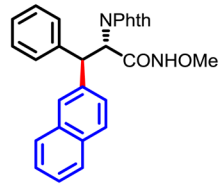
3k, 76%
d.r. > 20:1



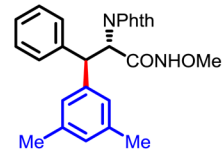
3l, 83%
d.r. > 20:1



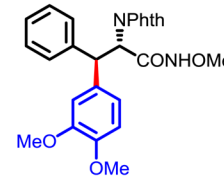
3m, 55%
d.r. > 20:1



3n, 61%
d.r. > 20:1



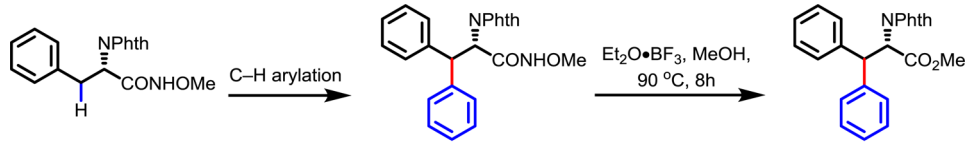
3o, 75%
d.r. > 20:1



3p, 69%
d.r. > 20:1

[a]Conditions: Substrate **2′** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), Ar–I (0.3 mmol), 2,6-lutidine (20 mol %), $NaH_2PO_4 \cdot H_2O$ (0.3 mmol), HFIP (1.0 mL), 100 °C, 36 h. [b]Isolated yields are shown.

Scheme 3. Removal of the Directing Group



2', (99% ee) **3q**, 82% (99% ee) **3q'**, 90% (98% ee)

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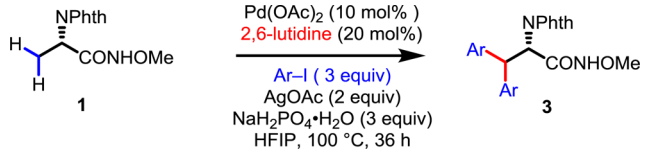
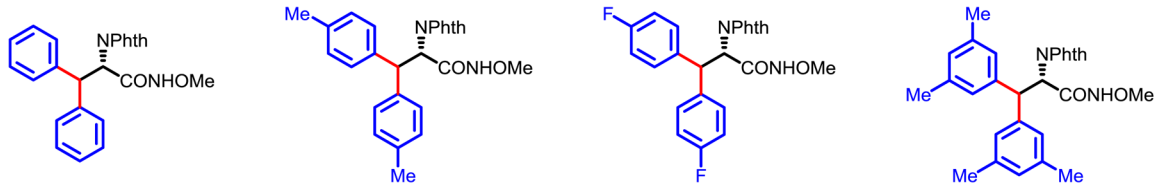
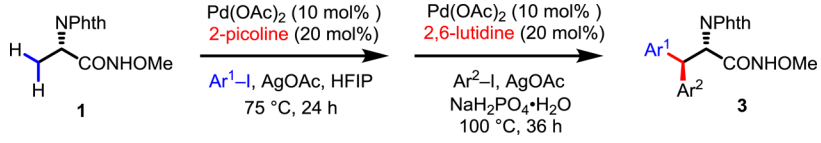
Table 9. Homodiarylation of Alanine Substrate[a,b]

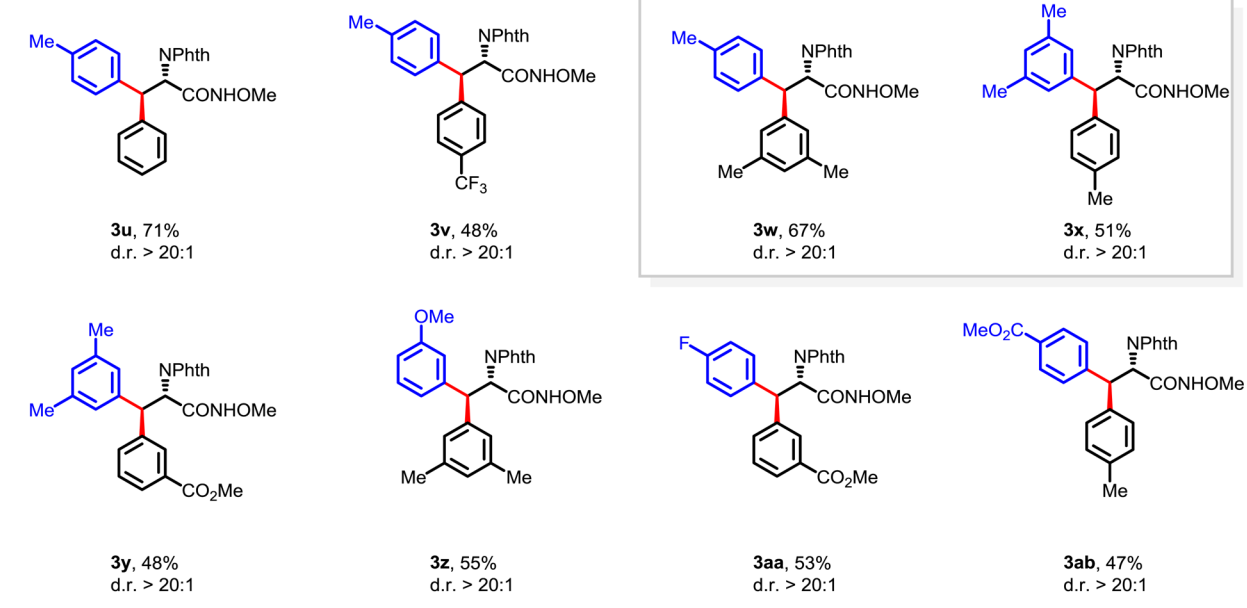




[a]Conditions: Substrate **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), Ar–I (0.3 mmol), 2,6-lutidine (20 mol %), $NaH_2PO_4 \cdot H_2O$ (0.3 mmol), HFIP (1.0 mL), 100 °C, 36 h. [b]Isolated yields are shown.

Table 10. Heterodiarylation of Alanine Substrate[a,b]





[a]Conditions: Substrate **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), Ar^1–I (0.12 mmol), 2-picoline (20 mol %), HFIP (1.0 mL), 75 °C, 24 h. Then $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), Ar^2–I (0.3 mmol), 2,6-lutidine (20 mol %), $NaH_2PO_4 \cdot H_2O$ (0.3 mmol), 100 °C, 36 h. [b]Isolated yields are shown.

ester **16** derived from **2e** was readily converted to Fmoc-protected unnatural amino acid **17** as a useful building block for peptide synthesis. Through the Pictet–Spengler reaction, **16** could be also converted to a chiral tetrahydroisoquinoline **18**, a known *N*-methyl-D-aspartate (NMDA) agonist.[29] A chiral bioactive indoline **19**[30] could also be synthesized via our previously developed intramolecular C–H amination reaction of sulfonyl protected **16**.[31]

The *N*-methoxyamide auxiliary also gives access to *N*-hydroxy-3-amino-3,4-dihydroquinolinone class of compounds. First reported by Davis and co-workers over 30 years ago, they were shown to exhibit antibacterial activity.[32] More recently, similar scaffolds have been identified as potent inhibitors of KAT II, an enzyme currently being investigated as a therapeutic target for cognitive impairment associated with schizophrenia, among other disorders.[11] Using the above protocols, arylation followed by a known radical cyclization, medicinally important analogues of *N*-methoxy-3-amino-3,4-dihydroquinolines **14′** and **20–22** were prepared in a straightforward manner (Table 12).

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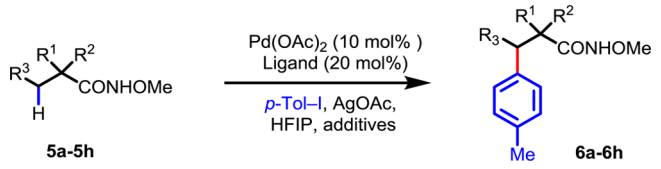
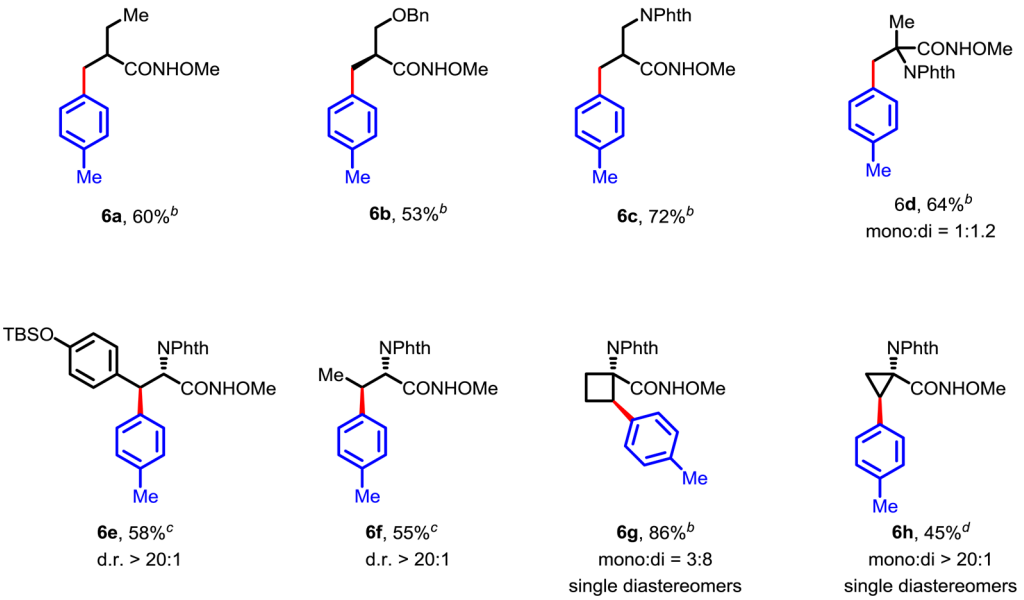
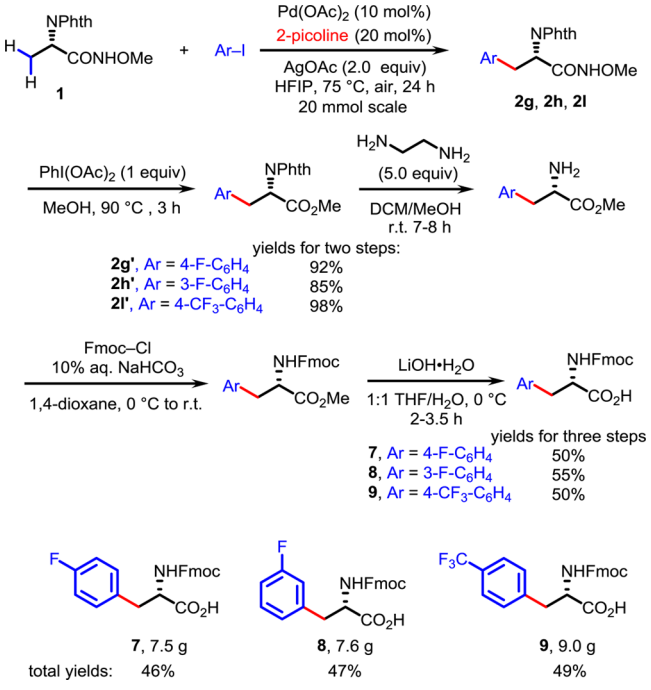
Table 11. Arylation of Other Amino Acids and Carboxylic Acids[a]





[a]Isolated yields are shown. [b]Conditions: Substrate (0.2 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.4 mmol), *p*-Tol–I (0.3 mmol), 2-picoline (20 mol %), HFIP (2.0 mL), 80 °C, 24 h. [c]Conditions: Substrate (0.1 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), *p*-Tol–I (0.3 mmol), 2,6-lutidine (20 mol %), $NaH_2PO_4{\cdot}H_2O$ (0.3 mmol), HFIP (1.0 mL), 90 °C, 36 h. [d]Substrate (0.1 mmol), $Pd(OAc)_2$ (15 mol %), AgOAc (0.2 mmol), *p*-Tol–I (0.3 mmol), **L1** (30 mol %), TFA (20 mol %), DCE (1.0 mL), 85 °C, 36 h.

Scheme 4. Gram-Scale Synthesis of Unnatural Amino Acids 7–9



Chiral amino alcohols derived from chiral amino acids are essential building blocks for the preparation of chiral ligands. For example, the sterically hindered chiral amino alcohol derived from *tert*-leucine is a key precursor for the synthesis of one of the most effective chiral oxazoline ligands in asymmetric catalysis. β-Ar-β-Ar′-α-amino acids prepared via the recently developed procedure can be readily reduced to the corresponding chiral amino alcohols containing two chiral centers that are previously difficult to make (Scheme 7). Thus, employing our heterodiarylation protocol above, **3z** was obtained in moderate yields via a two step, one-pot procedure on a 10 mmol scale. Hydrolysis of the amide group to ester followed by removal of the phthalimide protecting group led to the amino ester **24** which was reduced to the amino alcohol **25** in 75% yield. From this common intermediate **25**, PyBox ligand **26** and Box ligand **27** were successfully prepared.[33] We anticipate that these novel chiral bis(oxazoline) ligands will display interesting and useful properties in asymmetric catalysis. The potential impact of the additional chiral centers of ligands **26** and **27** on asymmetric catalysis is also intriguing.

3. CONCLUSION

During the past decade-long efforts to develop a simple and practical auxiliary or directing group for β-C–H fucntionalizations of carboxylic acids, we have focused on the use of relatively weak coordination from the substrates to direct metalation and match this weak coordination with ligand development to enhance the reactivity. The simple *N*-methoxyamide group, initially used as a masked ester, has been reinvented as a broadly useful directing group for β-C–H arylation with the assistance

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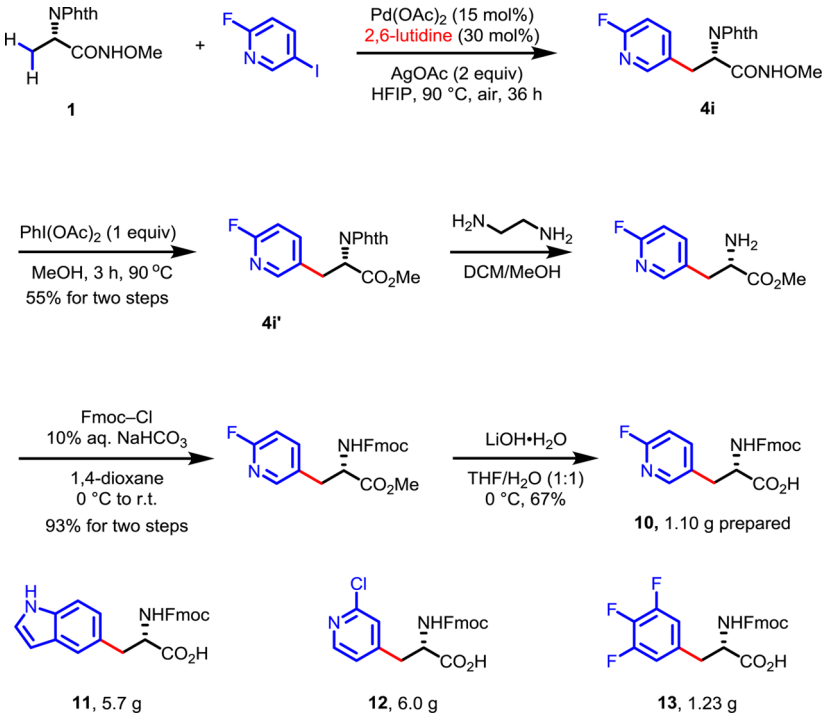
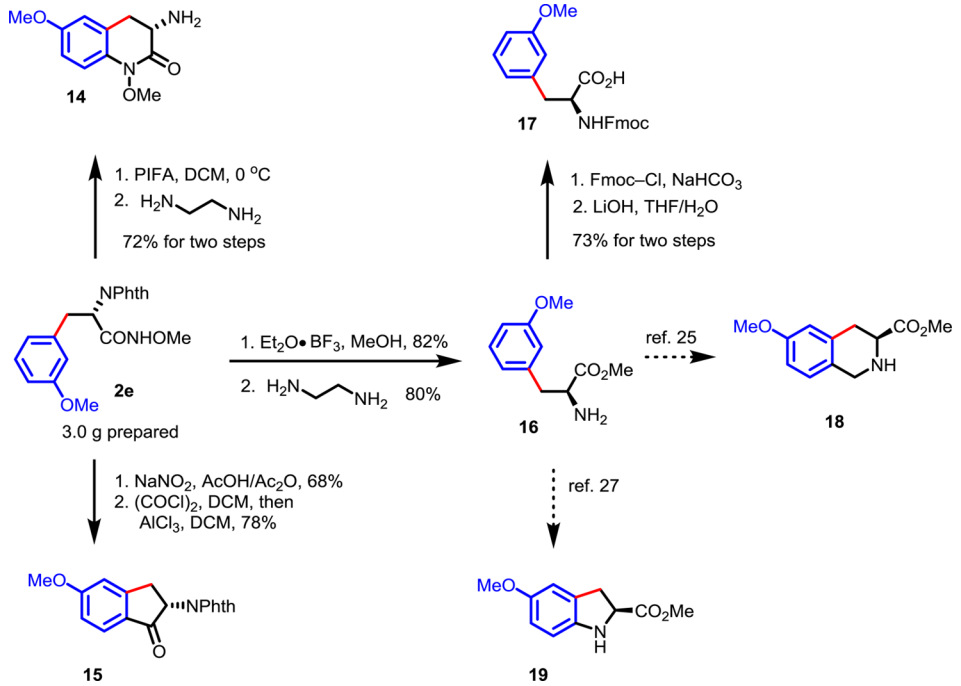
Scheme 5. Gram-Scale Synthesis of Unnatural Amino Acids 10−13



Scheme 6. Application to Synthesis of a Variety of Biologically Active Compounds



of two pyridine-type ligands. 2-Picoline promotes the monoselective arylation of primary C(sp^3)−H bonds, while 2,6-lutidine enables the subsequent arylation of secondary C(sp^3)−H bonds in one pot. This new method is extensively applied to gram-scale synthesis of novel, unnatural amino acids as well as bioactive compounds and chiral bis(oxazoline) ligands.

4. EXPERIMENTAL SECTION

4.1. General Procedure for Monoarylation with Aryl Iodides (Table 3). The starting material **1** (0.1 mmol, 24.8 mg), $Pd(OAc)_2$ (10 mol %, 2.2 mg), and AgOAc (0.2 mmol, 33.4 mg) were weighed in air and placed in a sealed tube (10 mL) with a magnetic stir bar. To the reaction mixture, aryl iodide (0.15 mmol), 2-picoline (20 mol %, 2 μL), HFIP (1.0 mL) were added. The reaction mixture was first stirred at room temperature for 10 min and then heated to 75 °C for 24 h under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature, filtered with Celite, and washed with DCM. The solvents were removed under reduced pressure, and the resulting mixture was purified by a silica gel-packed flash chromatography column using DCM/EtOAc (1/0 to 4/1 to 2/1) as the eluent.

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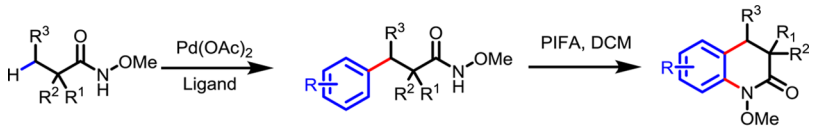
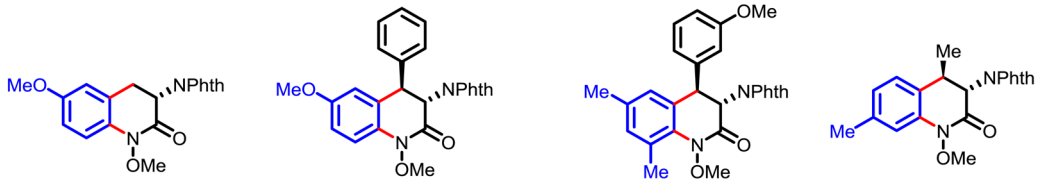
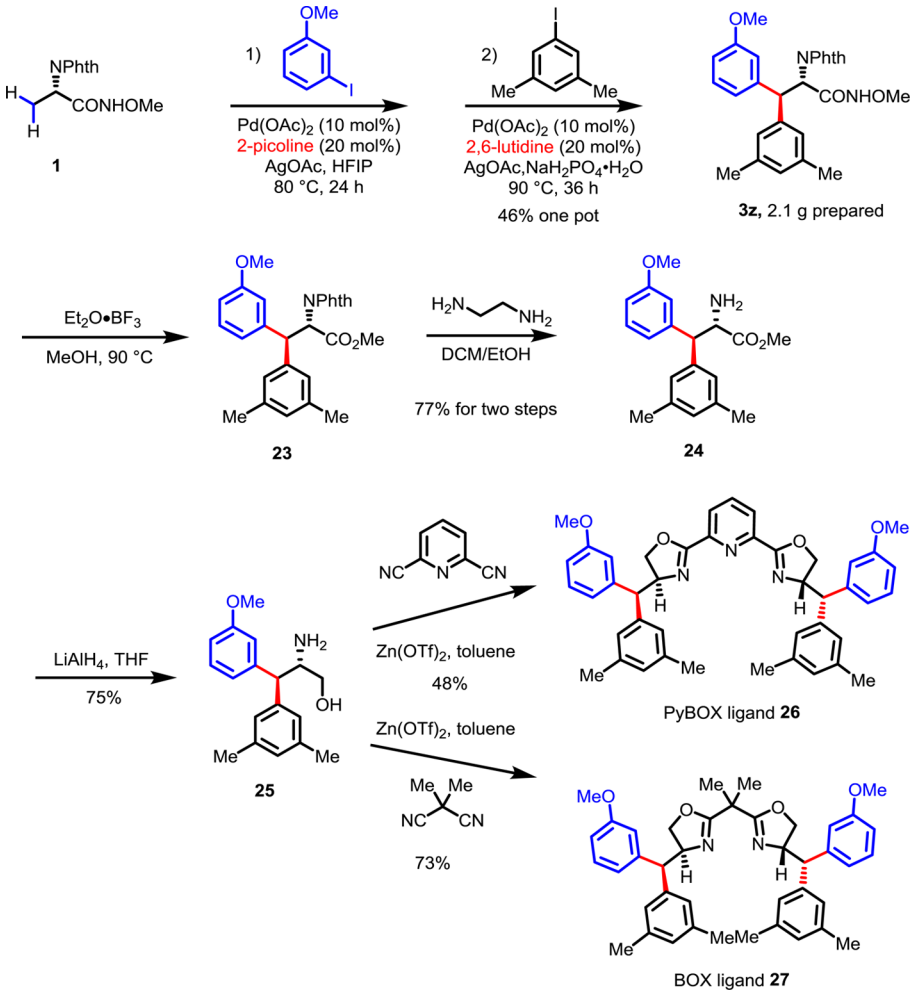
Table 12. Lactamization of Different Substrates[a,b]





[a]Conditions for cyclization: Substrate, PIFA (2 equiv), DCM, 0 °C to rt. [b]Isolated yields are shown.

Scheme 7. Synthesis of PyBox and Box Ligands



4.2. General Procedure for Monoarylation with Heterocyclic Iodides (Schemes 4 and 5). *Method A.* (Table 4) The starting material **1** (0.1 mmol, 24.8 mg), $Pd(OAc)_2$ (10 mol %, 2.2 mg), and AgOAc (0.2 mmol, 33.4 mg) were weighed in air and placed in a sealed tube (10 mL) with a magnetic stir bar. To the reaction mixture, aryl iodide (0.15 mmol), 2-picoline (20 mol %, 2 μL), and HFIP (1.0 mL) were added. The reaction mixture was first stirred at room temperature for 10 min and then heated to 80 °C for 24 h under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature, filtered with Celite, and washed with DCM. The solvents were removed under reduced pressure, and the resulting mixture was purified by a silica gel-packed flash chromatography column using DCM/EtOAc (1/0 to 4/1 to 2/1) as the eluent.

Method B. (Table 5) The starting material **1** (0.1 mmol, 24.8 mg), $Pd(OAc)_2$ (15 mol %, 3.3 mg), and AgOAc (0.2 mmol, 33.4 mg) were weighed in air and placed in a sealed tube (10 mL) with a magnetic stir

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bar. To the reaction mixture, aryl iodide (0.15 mmol), 2,6-lutidine (30 mol %, 3 μL), and HFIP (1.0 mL) were added. The reaction mixture was first stirred at room temperature for 10 min and then heated to 80 °C for 36 h under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature, filtered with Celite, and washed with DCM. The solvents were removed under reduced pressure, and the resulting mixture was added $PhI(OAc)_2$ (0.1 mmol, 32.2 mg) and MeOH (1 mL) in a sealed tube (10 mL) with a magnetic stir bar. The reaction mixture was heated to 80 °C for 3 h. Upon completion, the reaction mixture was cooled to room temperature, filtered with Celite, and washed with DCM. The solvents were removed under reduced pressure, and the resulting mixture was purified by a silica gel-packed flash chromatography column using hexanes/EtOAc (5/1 to 4/1 to 2/1) as the eluent.

Method C. (Table 5). The starting material **1** (0.2 mmol, 49.6 mg), $Pd(OAc)_2$ (15 mol %, 3.3 mg), and AgOAc (0.2 mmol, 33.4 mg) were weighed in air and placed in a sealed tube (10 mL) with a magnetic stir bar. To the reaction mixture, aryl iodide (0.1 mmol), 2,6-lutidine (30 mol %, 3 μL), and HFIP (1.0 mL) were added. The reaction mixture was first stirred at room temperature for 10 min and then heated to 80 °C for 36 h under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature, filtered with Celite, and washed with DCM. The solvents were removed under reduced pressure, and the resulting mixture was added $PhI(OAc)_2$ (0.1 mmol, 32.2 mg) and MeOH (1 mL) in a sealed tube (10 mL) with a magnetic stir bar. The reaction mixture was heated to 80 °C for 3 h. Upon completion, the reaction mixture was cooled to room temperature, filtered with Celite, and washed with DCM. The solvents were removed under reduced pressure, and the resulting mixture was purified by a silica gel-packed flash chromatography column using hexanes/EtOAc (5/1 to 4/1 to 2/1) as the eluent.

4.3. General Procedure for Arylation of Phenylalanine (Table 8). The substrate **2′** (0.1 mmol, 32.4 mg), $Pd(OAc)_2$ (10 mol %, 2.2 mg), $NaH_2PO_4{\cdot}H_2O$ (0.3 mmol, 42 mg), and AgOAc (0.2 mmol, 33.4 mg) were weighed in air and placed in a sealed tube (10 mL) with a magnetic stir bar. To the reaction mixture, aryl iodide (0.3 mmol), 2,6-lutidine (20 mol %, 2 μL), and HFIP (1 mL) were added. The reaction mixture was first stirred at room temperature for 10 min and then heated to 100 °C for 36 h under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature, filtered with Celite, and washed with DCM. The solvents were removed under reduced pressure, and the resulting mixture was purified by a silica gel-packed flash chromatography column using hexanes/EtOAc (5/1 to 3/1 to 2/1) as the eluent.

4.4. General Procedure for Large Scale of Monoarylation Step. The starting material **1** (10.0 mmol, 2.48 g), $Pd(OAc)_2$ (1.50 mmol, 337 mg), and AgOAc (20.0 mmol, 3.34 g) were weighed in air and placed in a sealed tube (350 mL) with a magnetic stir bar. To the reaction mixture, aryl iodide (15 mmol), ligand (3.00 mmol), and HFIP (100 mL) were added. The reaction mixture was first stirred at room temperature for 10 min and then heated to 90 °C for 36 h under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature. The solvents were removed under reduced pressure and recovered for next time use. The resulting mixture was added $PhI(OAc)_2$ (10 mmol, 3.22 g) and MeOH (100 mL) in a sealed tube (350 mL) with a magnetic stir bar. The reaction mixture was heated to 80 °C for 3 h. Upon completion, the reaction mixture was cooled to room temperature, filtered with Celite, and washed with DCM. The solvents were removed under reduced pressure, and the resulting mixture was purified by a silica gel-packed flash chromatography column using hexanes/EtOAc (5/1 to 4/1 to 2/1) as the eluent.

4.5. General Procedure for One Pot Synthesis of β-Ar-β-Ar′-α-Amino Acids (Table 10). The starting material (0.1 mmol, 24.8 mg), $Pd(OAc)_2$ (10 mol %, 2.2 mg), and AgOAc (0.2 mmol, 33.4 mg) were weighed in air and placed in a sealed tube (10 mL) with a magnetic stir bar. To the reaction mixture, the first aryl iodide (0.12 mmol), 2-picoline (20 mol %, 2 μL), and HFIP (1.0 mL) were added. The reaction mixture was first stirred at room temperature for 10 min and then heated to 75 °C for 24 h under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature, and $Pd(OAc)_2$ (0.01 mmol, 2.2 mg), $NaH_2PO_4{\cdot}H_2O$ (0.3 mmol, 42 mg), AgOAc (0.2 mmol, 33.4 mg) the second aryl iodide (0.3 mmol) and 2,6-lutidine (0.2 mmol, 2 μL) were added. The reaction mixture was first stirred at room temperature for 10 min and then heated to 100 °C for 36 h under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature, filtered with Celite, and washed with DCM. The solvents were removed under reduced pressure, and the resulting mixture was purified by a silica gel-packed flash chromatography column using hexanes/EtOAc (5/1 to 3/1 to 2/1) as the eluent.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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