C–H Activation

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Palladium-Catalyzed Direct Functionalization of 2-Aminobutanoic Acid Derivatives: Application of a Convenient and Versatile Auxiliary**

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The last decade has witnessed great progress on transition-metal-catalyzed C–H bond functionalization.[1,2] Although many synthetically useful methods for regioselective functionalization of the C(sp^2)–H bond of arenes and heteroarenes have been discovered,[3] direct functionalization of C(sp^3)–H bonds in common alkyl groups is still challenging.[4] This challenge arises from the inert nature of most C(sp^3)–H bonds and the difficulty in controlling regioselectivity. A promising approach is to use directing groups which can bind to metal centers and selectively deliver the catalyst to a proximal C–H bond. For this strategy to be synthetically useful, an ideal directing group should be readily available, easily introduced and removed under mild reaction conditions, and even applicable for further chemical manipulations to afford desired functional groups. To date, a considerable number of auxiliaries derived from carboxylic acids have been demonstrated to have the directing ability to promote metal-catalyzed C(sp^3)–H bond activation, and include amides derived from 8-aminoquinoline,[5] *O*-methyl hydroxyamine,[6] 2-methylthioaniline,[5c,d,7] 2,3,4,5,6-pentafluoro-aniline,[8a–c] or 4-trifluoromethyl-2,3,5,6-tetrafluoro-aniline,[8d,e] oxazoline,[9] esters,[10] and even carboxylic acid[11] itself. However, only three structurally similar directing groups derived from amines have been discovered (Figure 1).[5a,12,13] In 2005, Daugulis and co-workers reported that palladium-catalyzed γ arylation of amine derivatives could be achieved by employing a picolinamide auxiliary as the directing group.[5a] The difficulty in removing this amide auxiliary prompted Chen, He and co-workers to employ 3-[(*tert*-butyldimethylsilyloxy)-methyl]picolinamide as a modified directing group, which can be removed through intramolecular acyl transfer under acidic conditions, although it is not conveniently available.[12] Recently, Carretero and co-workers described that *N*-(2-pyridyl)sulfamide could serve as the directing group for palladium-catalyzed γ arylation of amino acid derivatives.[13] The auxiliary could be easily removed in this case by treatment with zinc/NH_4Cl. However, their arylation step needed relatively high reaction temperatures (ca. 150 °C) to ensure satisfactory conversion, and led to the desired arylation product being isolated in a low yield (44%) when a 2-aminobutanoic acid derivative was used as the substrate.

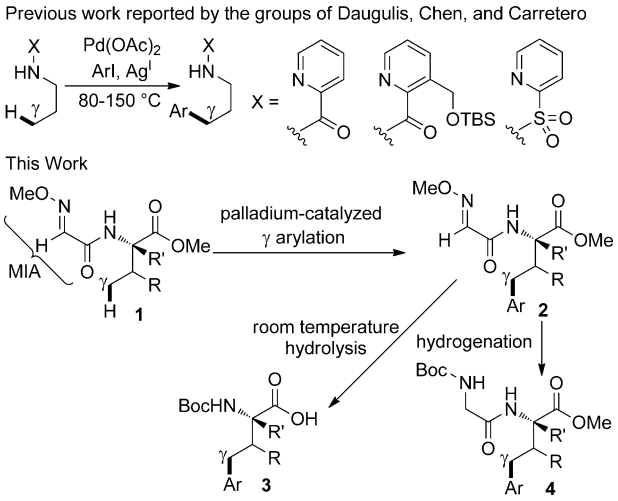

Figure 1. Auxiliary-directed γ arylation of C(sp^3)–H bond. Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl.

Herein, we wish to report 2-methoxyiminoacetyl (MIA) as a powerful auxiliary for promoting palladium-catalyzed functionalization of the C(sp^3)–H bonds of amines. The corresponding amides, derived from substituted aminobutanoic acids, can couple with aryl iodides in the presence of $Pd(OAc)_2$ at 60–100 °C to afford the γ-arylation products **2** in good yields. The amides **2** can be hydrolyzed at room temperature and hydrogenated to deliver the substituted homophenylalanines **3** and homophenylalanine-embodied peptides **4**, respectively. Noteworthy is that substituted homophenylalanines have been frequently used in developing peptidomimetics which possess important biological activities.[14] This effort has led to the discovery of several marketed drugs such as the antihypertensives enalapril and quinapril,[15] and the antitumor agent carfilzomib[16] (Figure 2). Thus, synthetic methods for quick assembly of substituted homophenylalanines are highly desirable so as to fully explore the structure–activity relationship of homophenylalanine-embodied peptidomimetics.

As indicated in Table 1, we started our exploration by conducting the direct arylation of **1a**, which was derived from methyl (2*S*)-aminobutanate and 2-methoxyiminoacetic acid by condensation. To our delight, reaction of **1a** with 4-iodoanisole in the presence of 10 mol% $Pd(OAc)_2$ and

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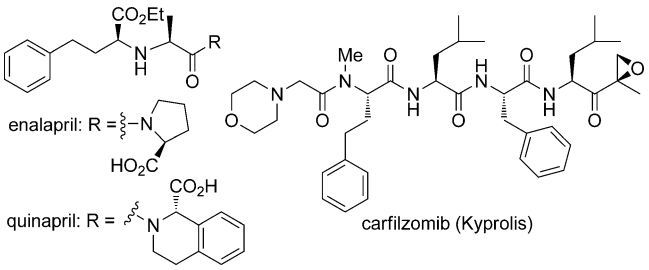
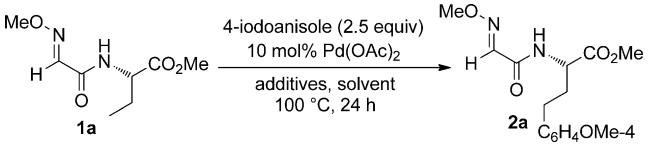


Figure 2. Drugs containing the homophenylalanine moiety.

Table 1: Reaction conditions for the arylation of **1a**.[a]



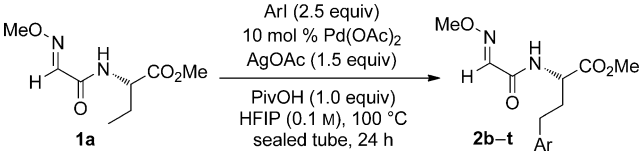
Entry	Additives (equiv)	Solvent	Yield [%][b]
1	AgOAc (1.0)	neat	15
2	AgOAc (2.0)	neat	15
3	AgOAc (1.5)	toluene	11
4	AgOAc (1.5)	*t*AmylOH	26
5	AgOAc (1.5)	*t*BuOH	23
6	AgOAc (1.5)	HFIP	58
7	Ag_2CO_3 (1.5)	HFIP	6
8	AgOAc/PivOH (1.5:1.0)	HFIP	62
9[c]	AgOAc/PivOH (1.5:1.0)	HFIP	74 (67)[d]

[a] All of the screening reactions were carried out in a 5 mL Teflon cap-sealed tube on a 0.5 mmol scale ([**1a**] = 0.5 M) unless otherwise specified. [b] The yields were determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as the internal standard. [c] A diluted reaction system was applied ([**1a**] = 0.1 M) and was carried out in a 15 mL Teflon cap-sealed tube. [d] Yield of isolated product; 99% *ee*. Piv = pivaloyl, HFIP = hexafluoroisopropanol.

AgOAc[5a] provided the desired arylation product **2a** successfully at 100 °C, however the yield (15%) was poor because of a low conversion (entry 1). Increasing the loading of AgOAc and using toluene as the solvent failed to give any improvement (entries 2 and 3). However, increased yields were observed when reaction was carried out in *t*BuOH and *t*AmylOH (entries 4 and 5). Further improvement could be achieved by using hexafluoroisopropanol (HFIP)[7,13] as the solvent (entry 6) and employing pivalic acid (PivOH) as another additive (entry 8).[17] The best result (67% yield) was obtained when the reaction was run as a dilute solution (entry 9). More importantly, the high enantiopurity of **2a** (99% *ee*) indicated that no racemization occurred during the reaction course. It is notable that changing the silver salt to Ag_2CO_3 led to a poor conversion (entry 7).

With the optimal reaction conditions in hand, we next examined the reaction scope by varying aryl iodides and the results are summarized in Table 2. Gratifyingly, a wide range of aryl iodides bearing either electron-donating or electron-withdrawing groups worked well, thus giving the corresponding arylation products in 54–88% yield upon isolation. The reaction chemoselectivity between aryl iodides and aryl bromides was achieved, as is evident from the fact that **2i** and **2j** were obtained in good yields. Particularly interesting

Table 2: Direct arylation of **1a** with aryl iodides.[a]



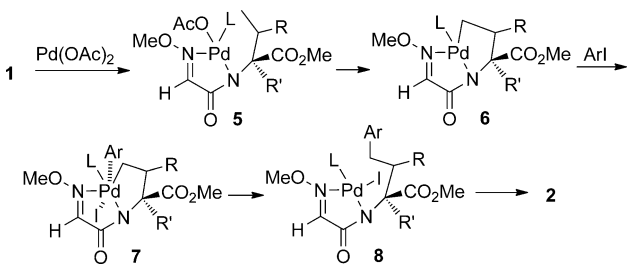
Entry	Ar	Product	Yield [%][b]
1	3-$MeOC_6H_4$	**2b**	68
2	4-$CF_3OC_6H_4$	**2c**	69
3	4-PhC_6H_4	**2d**	69
4	2-naphthyl	**2e**	54
5	4-ClC_6H_4	**2f**	71
6	4-FC_6H_4	**2g**	63
7	3,4-$F_2C_6H_3$	**2h**	69
8	4-BrC_6H_4	**2i**	75
9	3-BrC_6H_4	**2j**	64
10	4-$CF_3C_6H_4$	**2k**	64
11	3-$CF_3C_6H_4$	**2l**	70
12	4-$MeO_2CC_6H_4$	**2m**	74
13	3-$MeO_2CC_6H_4$	**2n**	74
14	2-$MeO_2CC_6H_4$	**2o**	87
15	4-$O_2NC_6H_4$	**2p**	69
16	3-$O_2NC_6H_4$	**2q**	70
17	2-$O_2NC_6H_4$	**2r**	88
18	2-$O_2NC_6H_4$	**2r**	80[c]
19	4-$MeOCC_6H_4$	**2s**	67
20	3-$MeOCC_6H_4$	**2t**	74

[a] Reaction was carried out on a 0.5 mmol scale. [b] Yields of isolated products. [c] Reaction was conducted on a 5 mmol scale, at 110 °C for 36 h.

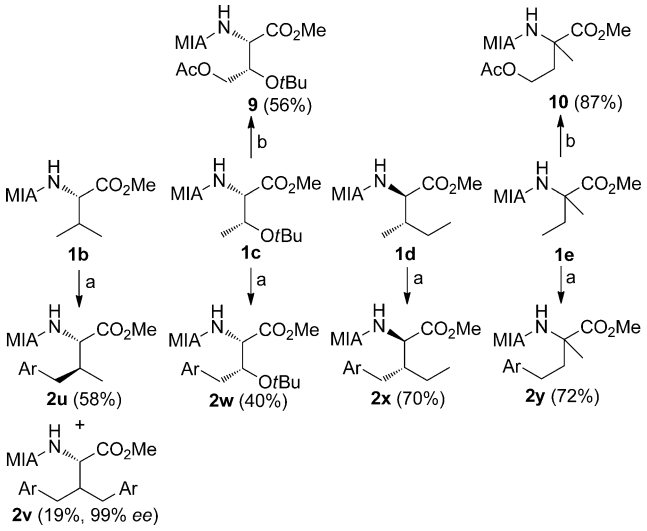
was that *ortho*-substituted aryl iodides provided better yields than the corresponding *para*- and *meta*-substituted aryl iodides (compare **2m–o**, and **2p–r**), presumably because of the additional binding to palladium complexes provided by ester and nitro groups. This advantage allows assembly of conformationally rigid cyclic homophenylalanine analogues.

Although a detailed mechanistic investigation of the present arylation awaits further experimentation, tentative proposals are outlined in Scheme 1. Based on the studies by Daugulis and co-workers,[5a–d] we believed that an MIA-generated amide might react with $Pd(OAc)_2$ to form the palladium amidate **5** and therefore facilitate a subsequent C–H insertion to give the double five-membered palladium chelate **6**. After oxidative addition of **6** to aryl iodide, the resultant complex **7** would undergo reductive elimination to deliver **2** through the intermediate **8**.

We next moved our attention to other substituted 2-aminobutanoic acid derivatives. As shown in Scheme 2, direct arylation of the L-valine derivative **1b** afforded the γ-



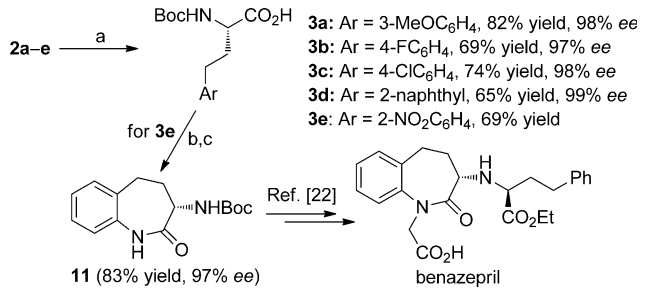
Scheme 1. Possible reaction mechanism.



Scheme 2. Reagents and conditions: a) 10 mol% $Pd(OAc)_2$, 4-iodoanisole (2–3 equiv), AgOAc (1.5 equiv), HFIP, 60–80°C, 24 h. b) 10 mol% $Pd(OAc)_2$, $PhI(OAc)_2$ (2.0 equiv), toluene, 90°C, 10 h. Ar = 4-methoxyphenyl, MIA = 2-methoxyiminoacetyl.

monoarylated product **2u** and γ,γ'-biarylated product **2v** in a combined yield of 77% under very mild reaction conditions (60°C). Notably, **2u** was isolated as a single diastereoisomer, thus indicating that the arylation occurred exclusively at the pro-*S* methyl of **1b**. The L-threonine derivative **1c** gave **2w** in only 40% yield, probably because of its steric hindrance. The D-allo-isoleucine derivative **1d** provided the desired **2x** in 70% yield. Additionally, the α-quaternary amino acid derivative **1e** is compatible with these conditions, thus leading to formation of **2y** in 72% yield. Besides γ-arylation, acetoxylation at the same position was also found to be feasible using $PhI(OAc)_2$ as the oxidant. Accordingly, oxidation of **1c** and **1e** afforded the γ-acetoxylated products **9** (55%) and **10** (87%), respectively.

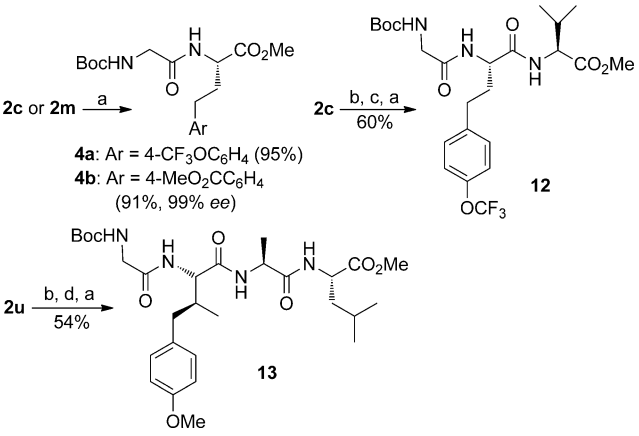
To demonstrate the synthetic utility of the present direct arylation reaction, we conducted further transformations of the arylation products. As depicted in Scheme 3, we were pleased to find that the MIA auxiliary could be simply removed by hydrolysis of **2** with 1N KOH in dioxane at room temperature, and the resultant amino acids were protected with $(Boc)_2O$ to afford **3a–e** with good yields and excellent enantiopurity. Noteworthy is that **3a–d** have been used in the



Scheme 3. Reagents and conditions: a) 1M KOH, 1,4-dioxane, RT; then $(Boc)_2O$. b) Pd/C, H_2. c) EDCI, HOAt, DIPEA. DIPEA = diisopropylethylamine, EDCI = 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide.

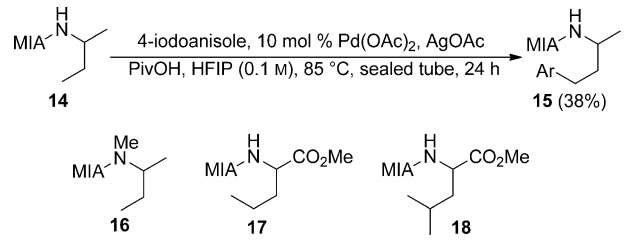
preparation of anthranil amino acid derivatives possessing anticholecystokinin activity,[18] novel α-amino-γ-lactams as β-secretase inhibitors,[19] propionamide derivatives as endopeptidase inhibitors,[20] and small peptides for controlling Wnt activity.[21] Compound **3e** was easily converted into the lactam **11**, a promising intermediate for preparing antihypertensive drug benazepril.[22]

Additionally, we found that the MIA auxiliary could be conveniently transformed into a glycine moiety which could be used in peptide synthesis, and is illustrated by formation of the dipeptides **4a** and **4b** from the corresponding arylation products **2c** and **2m** by hydrogenation and subsequent protection (Scheme 4). Interestingly, selective hydrolysis of the ester moiety in **2** could be achieved by treatment of **2** with 1.5 equivalents of LiOH in dioxane, and the resultant acids were condensed with another protected amino acid or peptide to synthesize oligopeptides, as indicated by formation of the tripeptide **12** and tetrapeptide **13**.



Scheme 4. Reagents and conditions: a) Pd/C, H_2, $(Boc)_2O$. b) aq LiOH, 1,4-dioxane. c) $ClCO_2iBu$, *N*-ethylmorpholine; then H-Val-OMe·HCl. d) $ClCO_2iBu$, *N*-ethylmorpholine; then H-Ala-Leu-OMe·TFA. TFA = trifluoroacetic acid.

Additional investigations demonstrated that the amino ester moiety is necessary for this arylation, as evidenced from the generation of **15** in 38% yield from the MIA-protected 2-butylamine **14** under our typical reaction conditions (Scheme 5). However, *N*-methyl 2-butylamine, methyl 2-aminopentanoate, and methyl 2-amino-4-methylpentanoate-derived substrates **16–18** did not give any arylation products even at 120°C, thus indicating that secondary amides are not suitable substrates and γ arylation of the methylene unit and δ arylation of the terminal CH_3 group cannot occur under the



Scheme 5. Functionalization with other substrates.

present conditions. These results are consistent with those reported by the groups of Daugulis, Chen, and Carretero.[5a,12,13]

In summary, we have developed an effective protocol for palladium-catalyzed direct γ arylation of substituted 2-aminobutanates by employing MIA as the amine auxiliary. The synthetic utility of this method has been illustrated by assembly of a variety of substituted homophenylalanines and peptides. More importantly, the routinely high yields and selectivity observed in direct functionalization of substituted 2-aminobutanates, coupled with its ease of introduction, removal, and further transformation makes MIA a powerful amine auxiliary for palladium-catalyzed C(sp^3)–H bond functionalization. Application of this auxiliary for other coupling reactions involving C(sp^3)–H bond activation is being actively pursued in our group and the results will be disclosed in due course.

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