C–C Coupling

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Synthesis of Aromatic α-Aminoesters: Palladium-Catalyzed Long-Range Arylation of Primary C_{sp^3}–H Bonds**

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Aromatic noncoded α-amino acids are very important building blocks for natural product synthesis and drug discovery.[1–2] Figure 1 shows representative examples (**1**–**4**) of

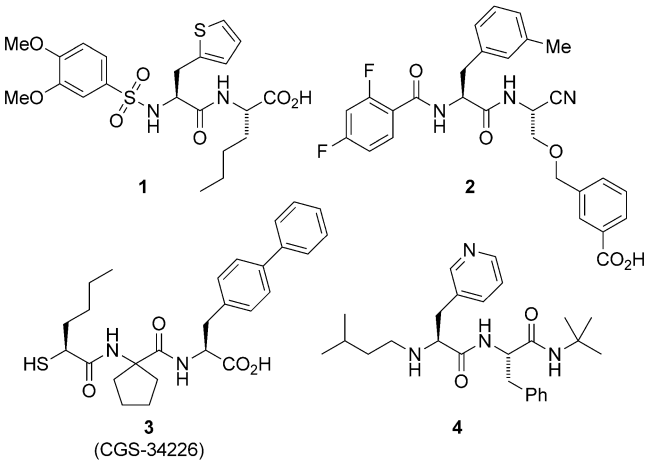
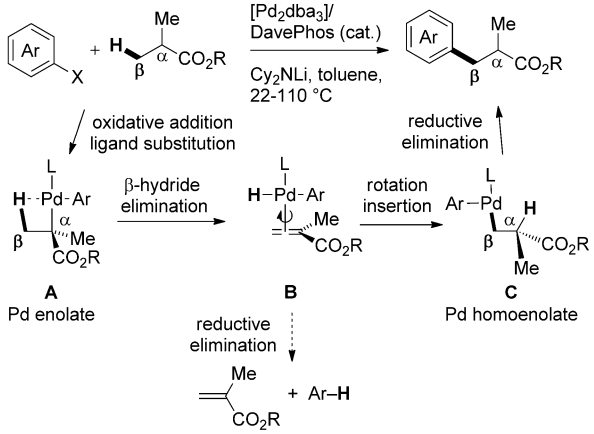


Figure 1.

bioactive molecules, containing a noncoded (hetero)arylalanine fragment, which have been recently developed by pharmaceutical companies. In light of the interest for these compounds, there is a great need for direct preparation methods that avoid multistep sequences.[3]

We recently reported the intermolecular palladium(0)-catalyzed C_β–H arylation of ester enolates as an extension of the more established α-arylation reaction (Scheme 1).[4–6] This reaction was shown to proceed by rearrangement of the



Scheme 1. The β arylation of ester enolates. dba = dibenzylideneacetone.

palladium enolate **A** to the palladium homoenolate **C**, from which reductive elimination occurs more readily.[4] However, the reaction was found to be limited to aryl halides containing an electronegative substituent at the *ortho* position. Other substitution patterns provided unproductive mixtures of α- and β-arylated products. Herein, we report a much more general β arylation of a protected alanine ester, a reaction that gives rise to a range of synthetically useful (hetero)arylalanine building blocks. In addition, we report the extension of this reaction to longer-range (γ to ζ) arylations at the terminal position of a linear alkyl chain on the amino ester.[7]

We first examined the reactivity of various α-amino acid precursors that were previously used in α arylations such as imines and azlactones,[8] but none of them provided any substantial amount of the β-arylated product. Gratifyingly, the readily available benzyl-protected alanine methyl ester **5a** was found to be the best arylalanine precursor (Scheme 2). Indeed, when the in situ generated lithium enolate of **5a** was reacted with *p*-fluorobromobenzene under reoptimized reaction conditions using [Pd(dba-3,5,3′,5′-OMe)$_2$] as the palladium source[9] and DavePhos (**L1**) as the ligand in toluene at 70 °C,[10] the compound **6a** was isolated as the sole arylation product in 67% yield. Interestingly, the reaction of the NBnMe-substituted ester **5b** also gave the β-arylated product **6b** efficiently, whereas the NMe_2-substituted ester **5c** failed to undergo arylation, apparently because of the degradation of its lithium enolate under the reaction conditions. These results stand in sharp contrast to our previous observation that *p*-fluorobromobenzene gives an approximately 1:1 mixture of α- and β-arylated products from isobutyric esters (i.e., with Me instead of NR^1R^2),[4] thus showing that the presence

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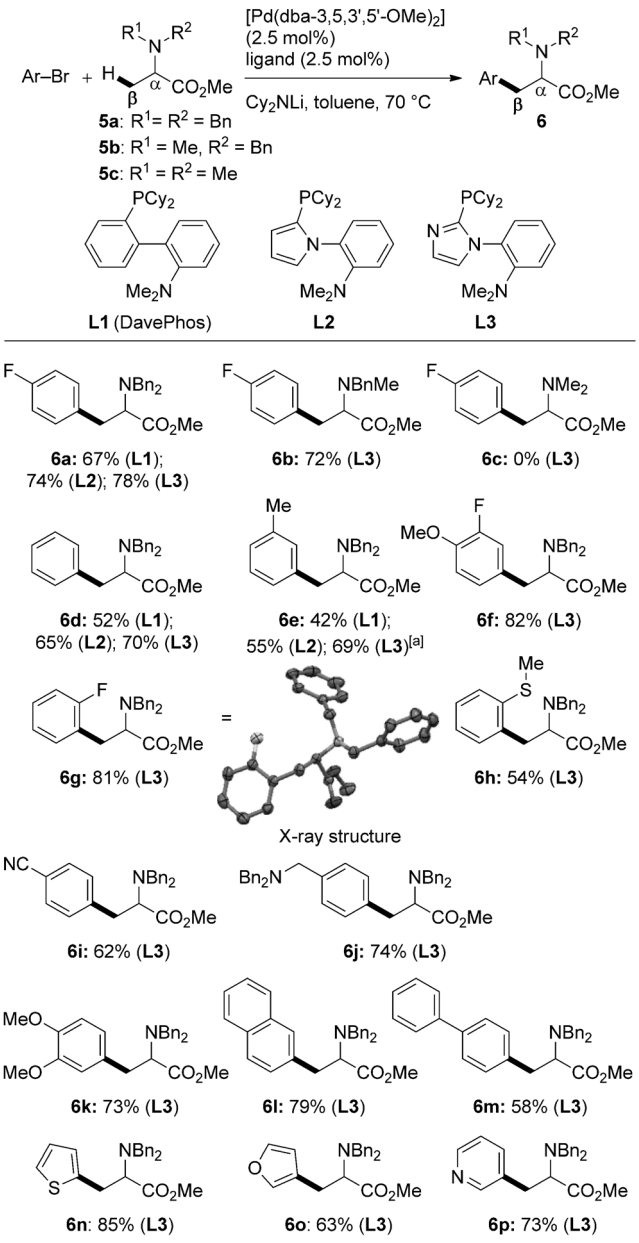
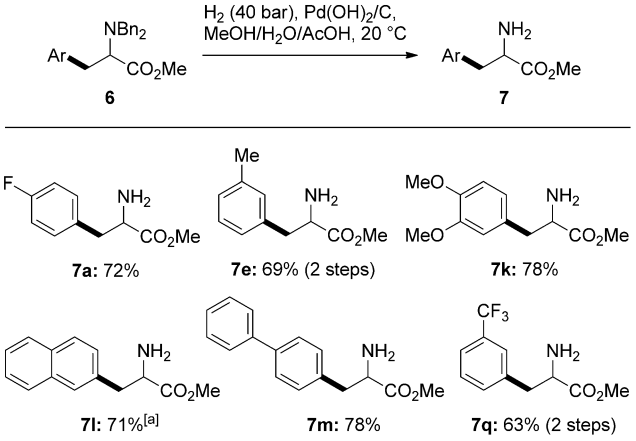


Scheme 2. The β arylation of α-amino esters. Reaction conditions: ester **5a** or **5b** (1.6 equiv), Cy_2NLi (1.6 equiv), toluene, 0°C, then [Pd(dba-3,5,3′,5′-OMe)$_2$] (2.5 mol%), ligand (2.5 mol%), aryl bromide (1 equiv), 70°C. The yield of the isolated product is given for each compound. [a] Yield of the isolated product after two steps, that is after hydrogenolysis (see Scheme 3). Cy = cyclohexyl.

of a tertiary α-amino group strongly favors β arylation. This remarkable β-arylation selectivity was also evidenced with other aryl and heteroaryl halides (Scheme 2), for which exclusive β arylation was observed. However, to improve the yield, new analogues of DavePhos were synthesized and tested.[10] In particular, we found that replacing the phosphine-bearing aromatic group with a nitrogen heterocycle such as a pyrrole (**L2**) and especially imidazole (**L3**) had a positive impact on the yield for various aryl bromides (**6a, 6d**, **6e**).[11] Scheme 2 shows selected examples of β-arylated products (**6a**–**p**) which were obtained efficiently by using **L3** as the ligand. In particular, the following products are precursors of aryl- and heteroarylalanines found in drugs or drug candidates: **6a**, **6e** (found in **2**; see Figure 1), **6j**, **6k** (found in L-DOPA), **6l** (found in the drug Nafarelin), **6m** (found in **3**), **6n** (found in **1**), and **6p** (found in **4**). Recrystallization of **6g** furnished crystals suitable for X-ray diffraction analysis.[12] In all cases, the α-arylated product was not observed, regardless of the substitution pattern, which is in contrast to our previous results with isobutyric esters,[4] and exclusive monoarylation was achieved.

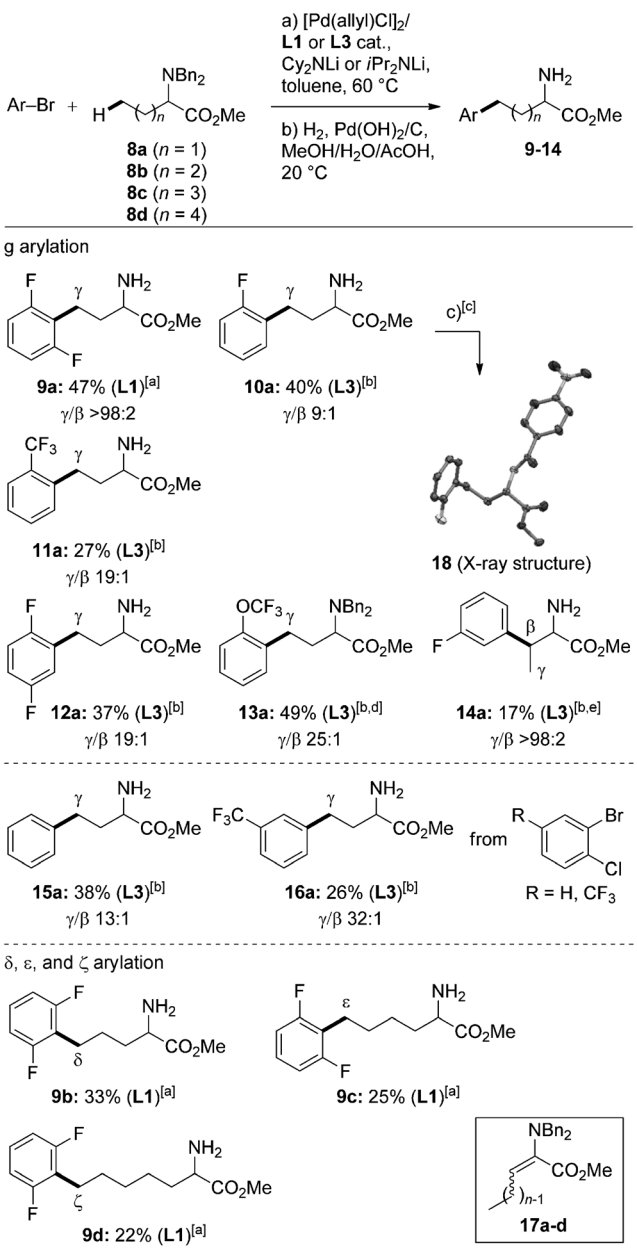
Following intermolecular arylation, the benzyl groups were successfully cleaved (debenzylation yield ca. 70–80%) in selected cases by hydrogenolysis (Scheme 3). The addition



Scheme 3. Deprotection of the β-arylated α-amino esters. [a] Reaction performed at 1 atm H_2.

of acetic acid[13] and a sufficient pressure (40 bar) of hydrogen were found to be crucial to ensure complete deprotection, except for the naphthalene derivative **6l** which was hydrogenated more smoothly to give **7l**.

As an extension to the preceding results, we examined the reactivity of α-amino acids bearing other linear alkyl chains. We hoped that, under similar reaction conditions, intermolecular arylation would occur preferentially at the terminal C_{sp^3}–H bond to yield useful arylalanine homologues.[14] The anticipated selectivity would result from palladium migration along the alkyl chain and more favorable reductive elimination from the primary carbon atom (see Scheme 1). However, we were aware that the arylation selectivity could be also influenced by the electronic properties of the aryl bromide.[4] Therefore, we first studied the reaction of the amino ester **8a** with 1-bromo-2,6-difluorobenzene, which is a priori the most favorable aryl bromide for palladium migration (γ arylation section of Scheme 4). Indeed, both *ortho* fluorine atoms should induce a very strong Ar–Pd bond[15] and therefore disfavor reductive elimination, thus allowing palladium migration to occur by the β-hydride elimination/rotation/olefin insertion manifold. Gratifyingly, **8a** underwent exclusive γ arylation at the terminal carbon atom of the ethyl chain upon reaction with 1-bromo-2,6-difluorobenzene, thus providing the amine **9a** in 47% yield



Scheme 4. Long-range (γ to ζ) arylation of amino esters. Reaction conditions for step a): ester **8a–d** (2.0 equiv), Cy_2NLi or iPr_2NLi (2.0 equiv) toluene, 0 °C, then [{Pd(η³-allyl)Cl}₂] (5 mol%), **L1** or **L3** (10 mol%), aryl bromide (1 equiv), 60 °C. The yield of the isolated major arylation product is given for two steps, except for **13a**. [a] With Cy_2NLi as the base. [b] With iPr_2NLi as the base (which gave slightly superior results to Cy_2NLi in these cases). [c] Reaction conditions: *p*-$NO_2C_6H_4COCl$, *i*PrNEt₂, DMF, 0 °C (92%). [d] Isolated pure as the dibenzylamine. [e] Mixture of diastereoisomers; d.r. 65:35. DMF = *N*,*N*′-dimethylformamide.

upon isolation after hydrogenolysis. With this aryl bromide, optimal arylation conditions involved DavePhos (**L1**) as the phosphine ligand in combination with [{Pd(η³-allyl)Cl}₂] as the palladium source.[10] With other aryl bromides containing only one electron-withdrawing *ortho* substituent (F, CF_3, OCF_3), the imidazole-based ligand **L3** was found to provide much higher γ/β-arylation ratios than **L1** and **L2**, thus paralleling the reactivity trend observed in β arylation (Scheme 2). For instance, the following γ/β-arylation ratios were obtained with *ortho*-fluorobromobenzene: 1:2.2 for **L1**, 4:1 for **L2**, and 9:1 for **L3**. Thus, by using **L3**, the products **10a–13a** were obtained with high γ selectivity in 27–40% yield after two steps (49% yield for one step in the case of **13a**). In all cases, the minor β-arylated product could be separated by chromatographic purification after hydrogenolysis. The γ-arylated amino ester **10a** was further derivatized to the *p*-nitrobenzamide **18**, thus furnishing single crystals suitable for X-ray diffraction analysis (Scheme 4).[12] The moderate yields obtained for the compounds **9a–13a** (average yield per step is 49–63%) should be put into perspective with the unprecedented and straightforward character of this transformation which employs an unfunctionalized substrate (**8a**).[7,16] A noteworthy amount of the olefin **17a** ($n = 1$) was observed in all cases, thereby impairing the arylation efficiency. This olefin arises from the reductive elimination of palladium/olefin intermediates (see intermediate **B**, Scheme 1) which are formed during both palladium migrations (α-to-β, then β-to-γ) along the alkyl chain.[17] With *m*-fluorobromobenzene as the aryl donor, the β-arylated product **14a** was obtained as a diastereoisomeric mixture in low yield after hydrogenolysis. This β/γ-arylation selectivity trend observed with differently substituted aryl bromides (compare **10a** and **14a**) mirrors the α/β-arylation selectivity trend previously observed with isobutyric esters,[4] with aryl bromides bearing an *ortho* electronegative group favoring palladium migration, and thus arylation at the terminal position. Arylation was also achieved selectively from aryl bromides bearing an *ortho* chlorine atom, and the corresponding products underwent concomitant dechlorination upon hydrogenolysis (Scheme 4, compounds **15a** and **16a**). Although the overall efficiency of this sequence still has to be improved (average yield per step is 51–62%), it provides a direct access to useful γ-aryl amino esters without an *ortho* electron-withdrawing group, which are not accessible in the absence of the orienting chlorine atom. For instance, the homophenylalanine ester **15a** is a structural constituent of the antihypertensive drug Enalapril.[2]

We next examined the arylation of the amino esters **8b–d**, bearing longer linear alkyl chains, with the most favorable aryl bromide, that is, 1-bromo-2,6-difluorobenzene under the same reaction conditions as used with **8a** (δ, ε, and ζ arylation section of Scheme 4). Again, arylation occurred exclusively at the terminal carbon atom of the alkyl chain, thus providing δ-, ε-, and even ζ-arylated products (**9b–d**) in progressively lower yields as the length of the chain increased. These lower yields can again result from the formation of the olefins **17b–d** (and olefin isomers), which accumulate as the number of palladium migrations along the chain increases (there are five 1,2-migrations of palladium to form the ζ-arylated product **9d**). With other aryl bromides, unproductive mixtures of arylated isomers were obtained.[18]

In conclusion, we have described a general palladium-catalyzed long-range intermolecular arylation of α-amino esters with aryl bromides, which occurs selectively at the terminal position of linear alkyl chains to give rise to synthetically useful (hetero)arylalanines and higher homo-

logues after debenzylation. All products obtained in this study are racemic, but might be resolved by enzymatic methods to obtain enantiomerically pure amino acids.[16i] Alternatively, an efficient asymmetric version using chiral ligands remains to be developed.[4a]

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