VIP C–H Functionalization

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Palladium-Catalyzed β Arylation of Carboxylic Esters**

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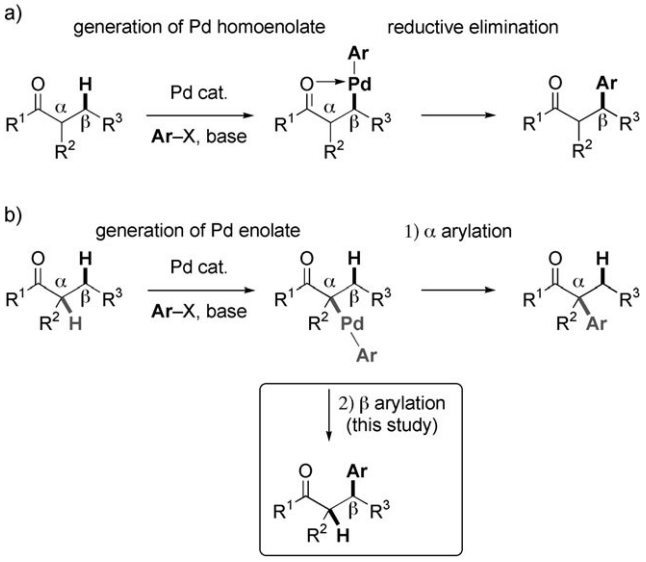
The direct functionalization of C–H bonds is an atom- and step-economical alternative to more traditional synthetic methods based on functional-group transformations, which often require multistep sequences.[1] In particular, transition-metal catalysis has emerged as a powerful tool for the functionalization of otherwise unreactive C(sp^2)–H and C(sp^3)–H bonds. These advances have enabled the construction of a variety of carbon–carbon and carbon–heteroatom bonds with great efficiency and selectivity, even in structurally complex organic molecules.[2] In this context, we previously investigated the intramolecular arylation of unactivated C(sp^3)–H bonds under palladium(0) catalysis.[3] Intermolecular C(sp^3)–H arylation reactions have also been developed through the use of palladium(II)[4] or palladium(0)[5] catalysis and the assistance of a coordinating group, such as a carbonyl group (Scheme 1 a).[6] This group directs arylation in the β position through the formation of a chelated palladium homoenolate.

The palladium(0)-catalyzed C–H arylation α to an electron-withdrawing functional group (Scheme 1 b, path 1) has also been established as a powerful method for the construction of C(sp^3)–C(sp^2) bonds. An enantioselective reaction is also possible with a chiral catalyst.[7] This reaction takes advantage of the acidity of the C–H bond α to the electron-withdrawing group—in general a carbonyl group—to generate a palladium enolate, which is converted into the α-arylated product by reductive elimination. Herein, we describe a diversion from this mechanism and the development of a straightforward and conceptually new β-C–H arylation method (Scheme 1 b, path 2). Because this new type of β arylation is related mechanistically to α arylation, it is complementary to directing-group-controlled β arylation reactions. In this regard, it presents a few interesting features; for example, simple carboxylic esters can be used as substrates at mild temperatures, and no polyarylation products are formed. We also describe the proof of concept of an enantioselective variant with a chiral catalyst and propose a reaction mechanism on the basis of DFT calculations.



Scheme 1. a) Directing-group strategy for the palladium-catalyzed β arylation of carbonyl compounds. b) Palladium-catalyzed α and β arylation of enolates generated in situ.

Our initial studies focused on the palladium-catalyzed arylation of the lithium enolate of *tert*-butyl isobutyrate (**2a**) with *ortho*-, *meta*-, and *para*-fluorobromobenzene (**1a–c**; Table 1; the lithium enolate was formed in situ from **2a** and lithium dicyclohexylamide (Cy_2NLi)).[8] The palladium catalyst was composed of tris(dibenzylideneacetone)dipalladium(0) ($[Pd_2(dba)_3]$) and 2-dicyclohexylphosphanyl-2′-(*N*,*N*-dimethylamino)biphenyl (davephos).[9] The reaction of the lithium enolate of **2a** with *para*- and *meta*-fluorobromobenzene in toluene at 28 °C gave an approximately 1:1 mixture of α-arylation (compounds **3a**,**b**) and β-arylation products (compounds **4a**,**b**; Table 1, entries 1 and 2). In contrast, the reaction with *ortho*-fluorobromobenzene (**1c**) gave only the β-arylation product **4c**, which was isolated in 63 % yield (Table 1, entry 3). Similarly, the reaction of methyl isobutyrate **2b** with **1c** gave only the β-arylation product **4d** (Table 1, entry 4). A slightly higher temperature (50 °C) was required for complete conversion in the reaction of bromide **1c** with ester **2a** than for other reactions, and the product **4c**

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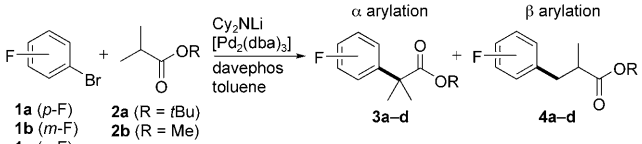
Table 1: Effect of the substitution of the aryl bromide on the arylation pathway (α versus β).[a]



1a (*p*-F) **1b** (*m*-F) **1c** (*o*-F) **2a** (R = *t*Bu) **2b** (R = Me) **3a–d** **4a–d**

Entry	1	2	*T* [°C]	Product(s)	α/β[b]	Yield [%][c]
1	**1a**	**2a**	28	**3a** + **4a**	47:53	91
2	**1b**	**2a**	28	**3b** + **4b**	47:53	95
3	**1c**	**2a**	50	**4c**	<2:98	63 (77)[d]
4	**1c**	**2b**	28	**4d**	<2:98	69
5[e]	**1c**	**2a**	50	**3c** + **4c**	85:15	55

[a] Reaction conditions: ester (2.0 equiv), Cy_2NLi (2.2 equiv), toluene; then aryl bromide (1.0 equiv), $[Pd_2(dba)_3]$ (5 mol%), davephos (10 mol%), 2 h. [b] The ratio of the products of α and β arylation was determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [c] Yield of the isolated product (entries 3 and 4) or of the mixture of products (entries 1, 2, and 5). [d] The product was obtained in 77% yield when the reaction was carried out at 110°C. [e] $PtBu_3$ was used instead of davephos as the ligand.

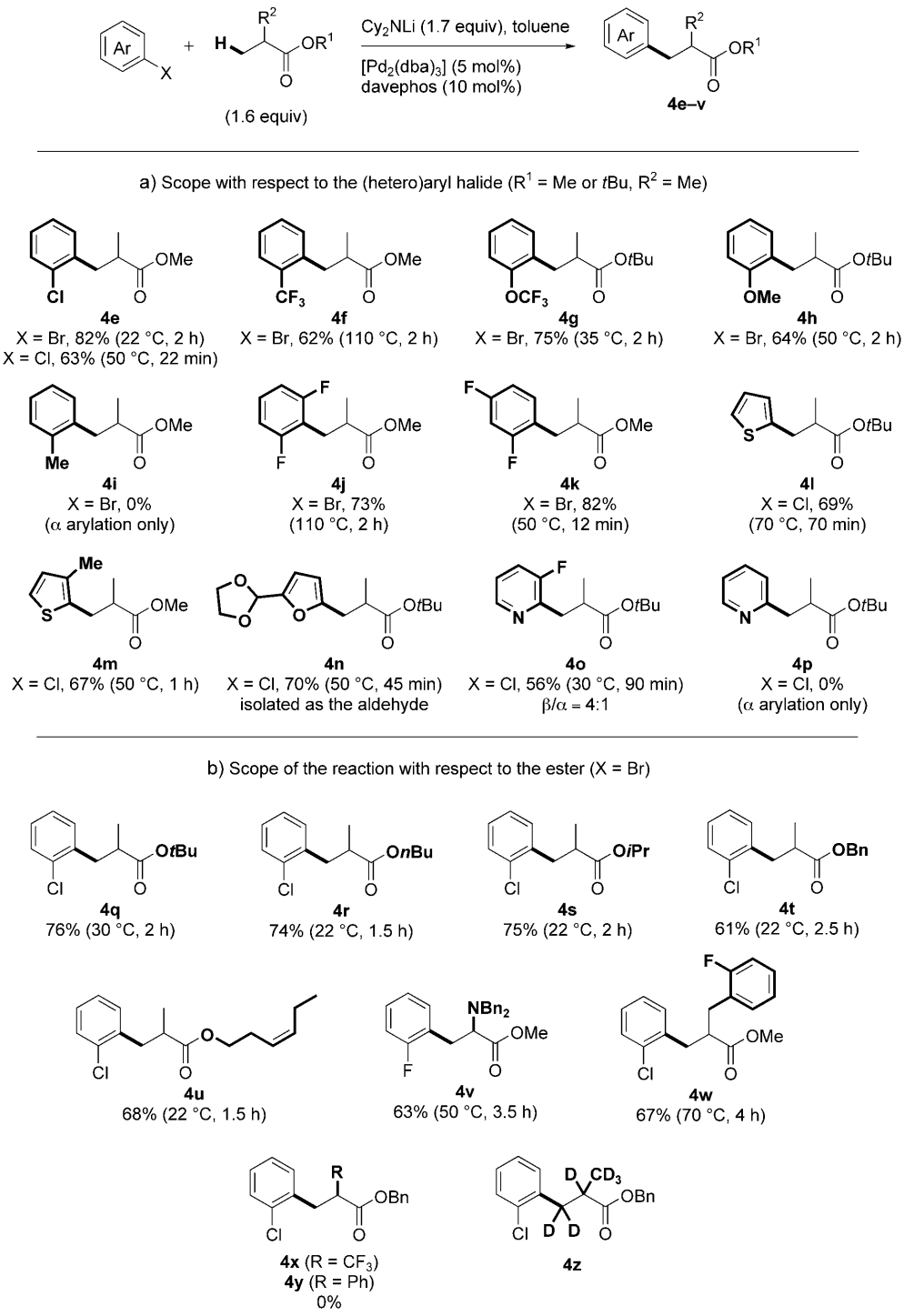
was formed in higher yield (77%) when the reaction mixture was heated at reflux (Table 1, entry 3). Other bases, solvents, Pd sources, and ligands were screened in the reaction of aryl bromide **1c** with methyl ester **2b**,[10] but the conditions described in Table 1 were found to give the highest yield of **4d**. To the best of our knowledge, β arylation has been reported only once as a side reaction during α-arylation studies.[8b] In the present study, the structure of both the aryl halide and the palladium ligand was found to be key to the high selectivity observed in favor of β arylation. For example, with $P(tBu)_3$ as the palladium ligand instead of davephos, the ratio of α- to β-arylation products was reversed (Table 1, entry 5).

We carried out a few control experiments to gain a better understanding of this new process. Control reactions between **1c** and **2b** in the absence of a base or catalyst failed to give any of the coupling product. Furthermore, the reaction of **1c** with the nonenolizable ester methyl pivalate ($tBuCO_2Me$) failed to give any of the β-arylation product. This result shows that the present β arylation does not occur through a directing-group controlled mechanism (Scheme 1a). Finally, a similar reactivity was observed between the isolated lithium enolate formed from **2b** and the lithium enolate formed in situ from **2b** in reactions with Cy_2NLi. These results show again that this enolate is most probably the reactive species and that dicyclohexylamine, which is liberated in the in situ procedure, has no influence on the course of the reaction.

We next examined the scope of the β arylation of carboxylic esters with aryl and heteroaryl halides (Scheme 2). In agreement with the above observations, the reaction was more efficient and more selective with aryl bromides bearing an electronegative group in the *ortho* position, such as a chlorine (product **4e**) or fluorine atom (product **4j**,**k**), or a trifluoromethyl (product **4f**), trifluoromethoxy (product **4g**), or methoxy group (product **4h**; Scheme 2a). Other functional groups in the *ortho* position, such as a methyl group (desired product **4i**), only gave rise to the more usual α-arylation product. Thus, electronegative groups in *ortho* positions clearly favor β arylation. Remarkably, aryl chlorides also proved competent coupling partners, as demonstrated by the β arylation of methyl ester **2b** with *ortho*-dichlorobenzene to furnish **4e** in 63% yield. Only a slightly higher temperature (50°C) was required in this case. Interestingly, a few heteroaryl chlorides, such as 2-chlorothiophenes (products **4l**,**m**), a functionalized 2-chlorofuran (product **4n**), and 2-chloro-3-fluoropyridine (product **4o**), were also employed successfully in this reaction; the corresponding β-arylated products were obtained in good yields. Furan **4n** was isolated as the corresponding aldehyde as a result of acetal cleavage during workup. In the reaction to form pyridine **4o**, the α-arylation product was also observed as a minor product (β/α 4:1); however, **4o** could be separated and isolated in pure form (56% yield). In contrast, 2-chloropyridine furnished only the α-arylation product rather than the β-arylation product **4p**. This result highlights the effect of the *ortho* electronegative fluorine atom on the α/β selectivity.

We also examined the scope of the reaction with respect to the ester component (Scheme 2b). Different alkoxy groups were tolerated well in the β arylation with 2-chlorobromobenzene (products **4q–u**). We next attempted the reaction of carboxylic esters containing other main carbon chains. The presence of an α tertiary carbon atom ($R^2 \neq H$) was found to be compulsory: propionic esters ($R^2 = H$) furnished neither the α- or the β-arylation product under these conditions. Remarkably, the protected phenylalanine analogue **4v** was obtained in 63% yield from the reaction of the corresponding protected alanine derivative with 2-fluorobromobenzene. Thus, this method provides a route to novel nonproteinogenic amino acids, which are difficult to access by other methods. Compound **4e**, synthesized as described above by the β arylation of methyl isobutyrate (**2b**) with 2-chlorobromobenzene, was subjected to a second β arylation with 2-fluorobromobenzene. The reaction was slower, presumably for steric reasons, and required a higher temperature (70°C) to reach completion. Nevertheless, the desired bisarylated product **4w** was isolated in 67% yield. Esters bearing a trifluoromethyl or phenyl group in the α position proved unreactive under these conditions, presumably as a result of excessive steric hindrance at this position, and the corresponding products **4x**,**y** were not isolated. Finally, the reaction of the deuterated ester $(CD_3)_2CHCO_2Bn$ gave rise to product **4z** with complete deuterium transfer from the β to the α position. This result indicates that the β-arylation product does not undergo deprotonation under the reaction conditions. In other words, the lithium enolate of the starting ester, which was added in slight excess with respect to the aryl halide, is not sufficiently basic to deprotonate the product. This experiment is key to the development of an asymmetric version of this reaction. Indeed, the asymmetric β arylation of symmetrical esters, such as isobutyrates, would yield a chiral product containing a stereogenic center α to the ester. This center should not epimerize under the reaction conditions.

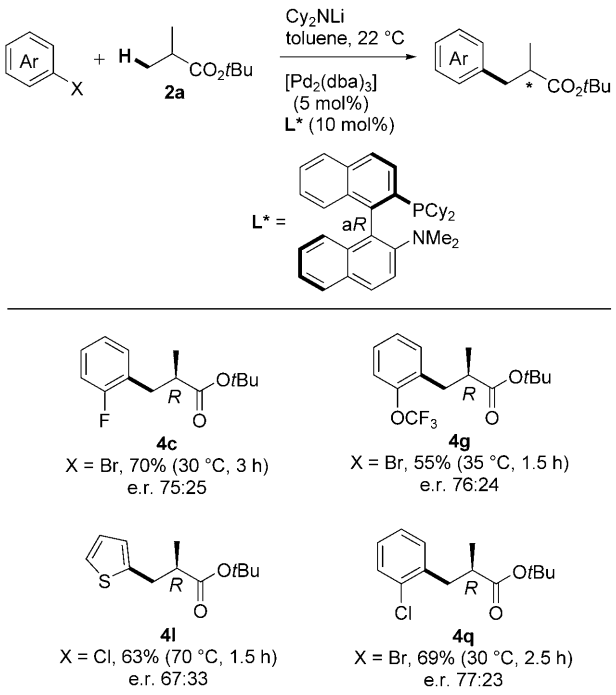
Encouraged by these preliminary results, we next investigated the enantioselective β arylation of *tert*-butyl isobuty-



Scheme 2. Scope of the Pd^0-catalyzed β arylation with respect to a) the (hetero)aryl halide and b) the ester. Bn = benzyl; yields refer to the isolated β-arylation product.

rate (**2a**) with various (hetero)aryl halides (Scheme 3).[11,12] In this study, *tert*-butyl ester **2a** was the preferred ester substrate because it tended to give less of the Claisen condensation by-products and thus cleaner reaction mixtures. As the first type of chiral palladium ligands considered for this reaction, we logically turned our attention to the chiral version of davephos, **L***, which was prepared as described by Buchwald and co-workers.[13] Gratifyingly, products **4c**, **4g**, **4l**, and **4q** were obtained in good yields with enantiomeric ratios (e.r.) between 67:33 and 77:23 in the presence of the chiral catalyst formed in situ from [Pd_2(dba)$_3$] and the a*R*-configured ligand **L***. The absolute configuration of all major enantiomers was determined to be *R* by reduction of the *tert*-butyl ester group to the primary alcohol and formation of an α-methoxy-α-trifluoromethylphenylacetyl (MTPA) ester.[14] Although the enantioselectivities were only moderate, the asymmetric transformation constitutes a proof of concept and provides a blueprint for the development of more efficient chiral catalysts.

We addressed the competition between α and β arylation computationally with DFT(B3PW91) calculations[10] of the corresponding reaction mechanisms from the C-enolate complex [Pd(Ar)(PCy_3)($C(Me)_2$-(CO_2Me))] (Ar = 2-F-C_6H_4, Figure 1). Tricyclohexylphosphane, which was shown experimentally to give similar results,[10] was used as a model for structurally more complex davephos. The initial palladium–C-enolate complex results from the C–Br oxidative addition of the bromoarene to [Pd(PCy_3)], followed by bromide substitution with the ester enolate. The preferred pathway (blue in Figure 1) involves the following sequence of steps: 1) β-H elimination from an agostic C–H bond of one β-methyl group ($\Delta G^{\ddagger} = 10.6$ kcal mol^{-1}), 2) 180° rotation of the coordinated olefin ($\Delta G^{\ddagger} = 8.4$ kcal mol^{-1}), 3) insertion of the olefin into the Pd–H bond with the formation of a Pd–C_β bond ($\Delta G^{\ddagger} = 1.2$ kcal mol^{-1}), and 4) reductive elimination of the β-arylation product ($\Delta G^{\ddagger} = 10.3$ kcal mol^{-1}).[15] From the product of β-H elimination, dissociation of the olefin was computed to be



Scheme 3. Enantioselective β arylation. For the determination of enantiomeric ratios and the absolute configuration of the major enantiomers, see the Supporting Information.

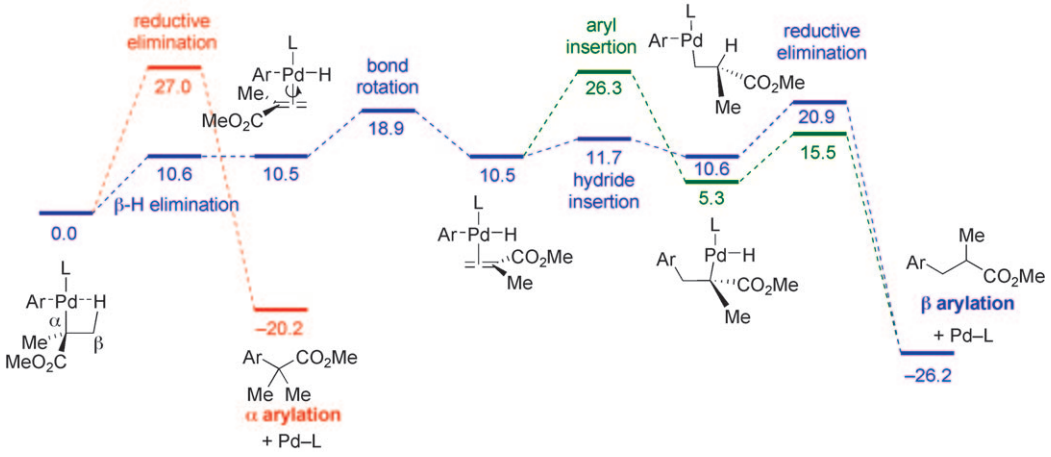


Figure 1. Gibbs free energy (kcal mol^{-1}) diagram for the α- and β-arylation pathways (L = PCy_3, Ar = 2-fluorophenyl).

more difficult than rotation of the olefin ($\Delta G^{\ddagger} = 14.4$ versus 8.4 kcal mol^{-1}). Such a dissociated olefin was observed in small amounts in some β-arylation experiments, in agreement with the computational data. After rotation of the olefin, insertion into the Pd–H bond and C–Ar reductive elimination to give the β-arylation product (blue pathway) were computed to be preferred over olefin insertion into the Pd–Ar bond ($\Delta G^{\ddagger} = 15.8$ kcal mol^{-1}), followed by C–H reductive elimination (green pathway). From the initial C-enolate complex, the transition state for Ar–C reductive elimination to form the α-arylation product (red pathway) is 6.1 kcal mol^{-1} higher than the highest point along the pathway for the formation of the β-arylation product; thus, any kinetic formation of the α-arylation product is ruled out. Moreover the β-arylation product is 6 kcal mol^{-1} more stable than the α-arylation product; therefore, the former is both the kinetic and the thermodynamic product of the reaction. Although these calculations explain many of the experimental observations in this study, further investigations into the influence of the *ortho* electronegative group of the bromoarene on the selectivity for β/α arylation are under way.

In conclusion, we have developed a mild and efficient intermolecular arylation of unactivated C(sp^3)–H bonds β to carboxylic esters on the basis of a novel concept. The reaction gives a range of synthetically useful functionalized carboxylic esters, such as phenylalanine analogues and new fluorinated building blocks.[16] In an asymmetric version with a chiral palladium ligand related to davephos, β-arylated products were obtained with enantiomeric ratios up to 77:23. Computational studies indicated that the mechanism involves a β-hydride elimination/Pd–η^2(C=C) bond rotation/hydride insertion/reductive elimination manifold, and that β arylation is kinetically favored over α arylation with the substrates and catalyst studied. Our current research includes the generalization of this β functionalization to other enolates and electrophiles, as well as the improvement of enantioselectivities.

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