Palladium-Catalyzed α-Arylation of Esters: Ideal New Methodology for Discovery Chemistry**

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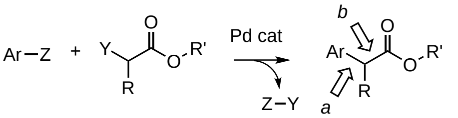
> *"α-Aryl carboxylic acids and α-aryl amino acids are amongst the most important carbonyl compounds."*[1]
>
> *"The synthesis of α-aryl esters and their derivatives is of interest in organic chemistry."*[2]
>
> *"Methylenecarboxy groups are key functionalities in many biologically active compounds".*[3]

These are the opening statements from Hartwig et al.,[1] Buchwald et al.,[2] and Gooßen[3] in their recent disclosures of new methods for generating Ar$-$C(R)H$-$CO$_2$R$'$ units **1** by palladium-catalyzed formation of the Ar$-$C$_\alpha$ bond (bond '*a*', Scheme 1).

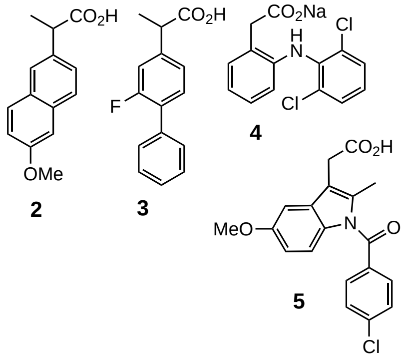


1

Scheme 1. A useful route to α-arylated esters and amino acids (R = NH$_2$), by formation of bond *a*. Most current synthetic methods involve formation of bond *b*.

These overtures are justified: a wide range of substituted arylacetic acids are of significant commercial importance as 'NSAIDs'.[4] Examples include naproxen (**2**), flurbiprofen (**3**), dichlofenac (**4**), and indomethacin (**5**).

The majority of synthetic routes to α-aryl acetic acids **1**[5] and α-aryl α-amino acids[6] involve construction of the '*b*' bond (Scheme 1). Consequently, arylation-type routes (constructing bond *a*, Scheme 1) should be valuable weapons in the synthetic chemists armory. However, the few examples that are known[7] have not been widely adopted; this may be for a variety of reasons including expense, lack of generality, or operational complexity.



2 **3** **4** **5**

Palladium-Catalyzed α-Arylation Reactions

In contrast to other α-arylation routes, the novel methodologies recently reported by the Hartwig, Buchwald, and Gooßen groups are likely to become popular: they proceed in high yield, under simple conditions, and employ readily available substrates and reagents (Scheme 1; Z = BR$_2$ or halide, Y = Br or H); this Highlight focuses on these important developments.

The approach of Hartwig et al., and Buchwald et al. for the generation of **1** is essentially identical and involves the Pd-catalyzed reaction of an aryl halide (**7**) with an ester enolate (**9**; Scheme 2, left-hand half of the catalytic cycle). Common ground with the Gooßen approach (right-hand half) is found in the Pd^0 complex **6** and the proposed palladium–enolate[8] intermediate **10**, generated in an alternative fashion from a bromoacetate (**11**) and an aryl boronate (**13**). In either procedure, reductive elimination in **10** forms the *a* bond of **1** and regenerates the Pd^0 species **6** to facilitate further turnover of the catalytic cycle.

On first inspection, both routes appear simple and promising. However, as is often the case in the rather subtle science of catalysis, both systems presented a number of obstacles that needed to be overcome.

In the Hartwig–Buchwald system, the requisite enolate **9** is generated by deprotonation of the corresponding ester. This

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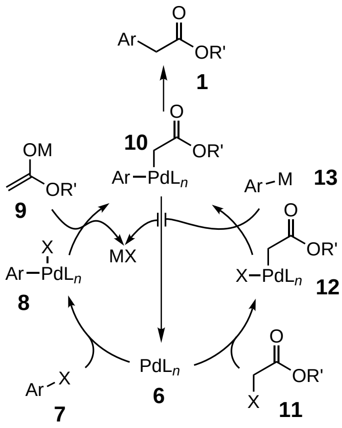
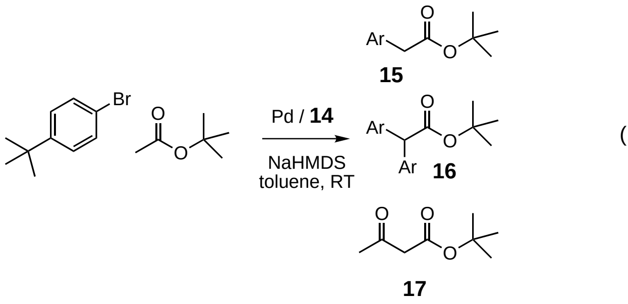


Scheme 2. Potential Pd-catalyzed routes to α-arylated esters **1**. Left-hand of cycle: Hartwig and Buchwald's arylation via enolate (M = Na, Li) trapping of Ar−Pd intermediate (**8**, X = Br, Cl); right-hand of cycle: Gooßen's route involving arylative transmetalation (with **13**, M = $B(OR)_2$) of a Pd−enolate (**12**, X = Br).

method opens the door to an undesired reaction between enolate and ester resulting in Claisen products (acetoacetates). Accordingly, hindered *tert*-butyl esters were employed to suppress nucleophilic attack at the carbonyl carbon atom. As with aryl amination, the choice of ligand and base[9] is crucial and since Na-derived bases had earlier proved superior in amination reactions, NaHMDS (HMDS = 1,1,1,3,3,3-hexamethyldisilazane) was the first choice.

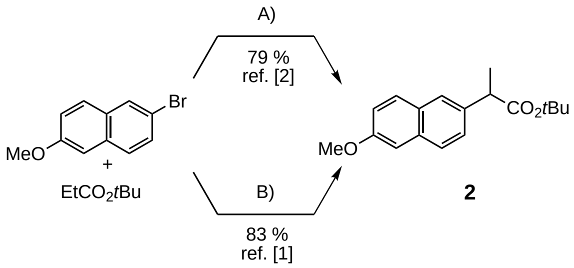
The Buchwald Approach

The Buchwald group employed their biaryl ligand **14** and obtained a 46% yield of mono- and diarylated acetates (**15** and **16**) together with competing Claisen product **17**, on reaction of *tert*-butyl acetate with *p*-*tert*-butyl bromobenzene [Eq. (1)].



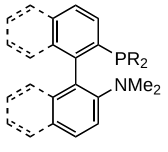
(1)

The mixture of mono- and diarylation represents the second problem: the primary product (here, **15**) is more acidic than the *tert*-butyl acetate and thus the acid−base equilibrium will facilitate a second arylation leading to **16**. This problem was controlled by switching from an Na to an Li counterion (LiHMDS),[10] by using this method a wide range of aryl bromides underwent coupling with *tert*-butyl acetate in toluene at ambient temperature, in yields that ranged from 71−90%. Importantly, the extensively competing Claisen reaction required the use of a large excess of enolate (2.3 equivalents of *tert*-butyl acetate and 2.5 equivalents of LiHMDS) and thus yields based on ester are significantly lower. Propionates and higher homologues also reacted smoothly, although, again a large enolate excess is required. The procedure is very versatile, for example, the *tert*-butyl ester of racemic naproxen (**2**) is obtained in 79% yield after 15 h at ambient temperature (Scheme 3A).

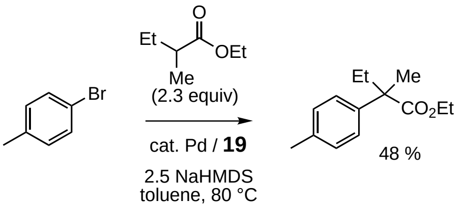


Scheme 3. Buchwald (A) and Hartwig (B) routes to the *tert*-butyl ester of naproxen (**2**). Conditions A) 2.3 equivalents $EtCO_2tBu$; 2.5 equivalents NaHMDS; 3 mol% $Pd(OAc)_2$; 6 mol% **19**; toluene, RT, 15 h. B) 1.1 equivalents $EtCO_2tBu$; 2.3 equivalents NaHMDS; 1 mol% $Pd(dba)_2$; 1 mol% **20**; toluene, RT, 12 h; dba = *trans,trans*-dibenzyldeneacetone.

Often unpredictably, the choice of ligand in Pd-catalyzed reactions can make surprisingly little difference or can open up new avenues. In the current case, the latter situation prevails. There has recently been much attention given to finding methods for the use of cheaper aryl chlorides in place of bromides or iodides in Pd-catalyzed couplings. Using the ligand **14**, poor results were obtained with 4-chloro-aromatics in the ester arylation reaction, but on switching to the tBu_2PAr analogue (**18**) the reaction proved feasible. Furthermore, with the binaphthyl-based ligand **19**, even α-dialkylated acetates could be arylated (albeit only using aryl bromides) so as to generate quaternary carbon centers [Eq. (2)].



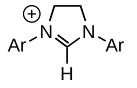
14 benzo, R = Cy
18 benzo, R = *tBu*
19 naphtho, R = *t*Bu



(2)

The Hartwig Approach

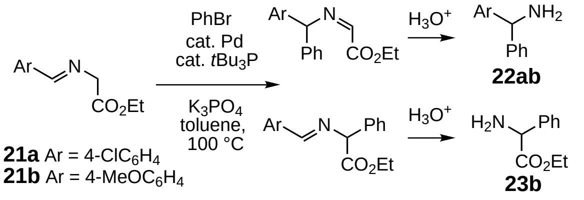
In contrast to the P,C-based ligands (**14**, **18**, and **19**) employed by the Buchwald group, Hartwig et al., chose to use a carbene ligand[11] generated in situ from hindered dihydro imidazolium **20**. Furthermore, they employed an excess of base. In fact a whole extra equivalent of base (Li- or NaHMDS) was added to only 1.1 equivalents of ester so as to deprotonate the product as it is generated. This cunningly solves three problems: first, the Claisen reaction is sup-



20 Ar = 2,6-$iPr_2C_6H_3$

pressed since this requires non-enolized ester coreactant; second, the more reactive (but less acidic) ester reagent can now compete effectively with the product for arylating agent and thus double arylation is suppressed; third, the reaction no longer requires an excess of ester reagent and thus the yields are good based upon both components. The choice of base again proved important: LiHMDS functioned well with acetates whilst NaHMDS worked well with propionates.[12] In both cases, excellent yields (75–98%) were obtained with a range of aryl bromides (Scheme 3B).

By slightly modifying the conditions (employing $t\mathrm{Bu_3P}$ as ligand and K_3PO_4[13] as base) N-protected glycinates undergo analogous arylation. Benzophenone imine proved a suitable protecting group and allowed a large range of glycinates to be arylated. The products are readily hydrolyzed on work-up and thereby facilitate direct access to C-protected α-aryl amino acids. However, the expensive nature of benzophenone imine led Hartwig et al. to explore the use of arylaldimines (**21**). *N*-(4-chlorobenzylidene) glycinate (**21a**) is 'conveniently crystalline', however, reaction with bromobenzene gave two arylated products. The α-aryl-benzylamine (**22a**) was reasoned to arise from arylation of the "wrong" tautomeric enolate, [Eq. (3)]. Electronic tuning of the protecting group (using 4-methoxybenzylidene, see **21b**) shut down this pathway and thus provides, via **23b**, a general route to C-protected α-aryl glycines.[14]

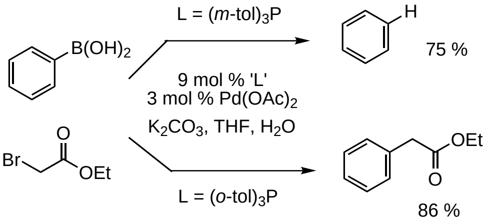


(3)

The Gooßen Approach

The switching of electrophile with nucleophile and vice versa, defines the Gooßen approach. Oxidative addition of a α-halo ester to a Pd^0 species (see **6** in Scheme 1) should generate a neutral Pd^{II}-enolate species **12** bearing a coordinated halide counterion. Transmetallation with aryl–metal compound **13** then generates the requisite aryl–Pd enolate **10** primed for reductive elimination to yield the desired α-aryl ester **1**.

No complications because of acid–base equilibria are expected, a range of aryl boronic acids and α-halo esters are available and thus, in principle, this method appears advantageous. However, there are two problems that are apparent on further consideration. First, competing Pd^0–Pd^{II}–Pd^{IV} cycles are known to facilitate reduction and reductive coupling of aryl boronic acids under analogous conditions[15] and thus Ar–H and Ar–Ar are likely by-products. Second, palladium enolates of esters in which there is a β-hydrogen atom (i.e. propionates) are likely to undergo β-H elimination faster than they transmetallate and thus generate acrylates. The former, but not the latter, turned out to be readily solved by ligand tuning. Relatively bulky triaryl phosphanes facilitate the desired reaction and inhibit biaryl formation. Comparison of the results obtained employing isomeric *meta-* and *ortho*-tritolylphosphane ligands illustrates the case rather well [Eq. (4)].



(4)

Ultimately, the best conditions were found to involve tri-α-naphthylphosphane as the ligand, with THF as solvent, K_3PO_4 as base, and water (2 equiv.) as coadditive (to facilitate boronate formation). Using these conditions, a wide range of aryl boronic acids were coupled in high yield with ethyl bromoacetate. Pd-catalyzed Suzuki–Miyaura type reactions of aryl halides with diboronates ($R_2B{-}BR_2$) or boranes ($R_2B{-}H$) have recently emerged as useful routes to aryl boronic acid derivatives.[16] By connecting the two reactions, Gooßen went on to develop a very effective strategy for the formal hetero-coupling of aryl halides (or pseudohalides) with bromoacetates. The only current limitation with the Gooßen system is the restriction to bromoacetate. As expected, propionates divert by β-H elimination to yield acrylate esters.[17] However, recent results from Fu et al.,[18] suggest that these problems may not be insurmountable.

Summary and Outlook

Two new methods have been recently disclosed for α-arylation of esters. One route also provides ready access to α-arylated amino acids. Both methods are based on Pd catalysis and the choice of ligand is crucial. The two approaches are complimentary with regard to electrophile and nucleophile pairings.

Unless the catalyst efficiencies are increased phenomenally, the current price of Pd will preclude these methods from commercial production processes. Nonetheless, their generality and operational simplicity makes them ideal for discovery chemistry or lead development in the pharmaceutical or agrochemical industries. Since the requisite substrates (acetates and homologues, iminoacetates, aryl halides, and aryl boronates) are often items of commerce or very readily prepared, it should be anticipated that these new synthetic methods will find extensive application in combinatorial-type screening processes.

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[1] S. Lee, N. A. Beare, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 8410–8411.

[2] W. A. Moradi, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7996–8002.

[3] L. J. Gooßen, *Chem. Commun.* **2001**, 669–670.

[4] NSAID = Non-steroidal anti-inflammatory drug. These compounds are cylooxygenase inhibitors and thus affect prostaglandin synthesis.

[5] For example by the Willgerodt reaction on the corresponding acetophenone.

[6] For example by Strecker synthesis from the corresponding benzaldehyde.

[7] For an example and for leading references, see: F. Agnelli, G. A. Sulikowski, *Tetrahedron Lett.* **1998**, *39*, 8807–8810.

[8] The coordination in Pd-enolate complex is likely to be by the carbon atom (rather than by the oxygen atom). For stoichiometric studies involving analogous intermediates and leading references see: D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 5816–5817.

[9] Note that the base employed must not bear a β-hydrogen (because of the potential for undesired Pd^{II} reduction by β-H transfer). *tert*-Butoxide bases proved sluggish whereas hexamethyldisilazide compounds proved useful.

[10] It is not evident why this works, although there is some discussion of M–O (M = Na, Li) covalency. Perhaps surprisingly, given the reduction of diarylation on switching from NaHMDS to LiHMDS, ethyl phenylacetate can be α-arylated in good yield (based on arylating agent) at 80 °C under essentially the same conditions.

[11] With very hindered aryl substrates, Hartwig et al., found that $t\mathrm{Bu}_3\mathrm{P}$ proved to be better than the carbene ligand.

[12] With hindered propionates (those with branching at the α- or β-positions) or glycinates, the ethyl, or methyl ester was preferred over the *tert*-butyl ester.

[13] The higher C–H acidity of ketimine and aldimine derivatives of glycinates allows the weaker base K_3PO_4 to be employed.

[14] Homologues (which require generation of a quaternary center) have not yet been successfully prepared by this method.

[15] M. Moreno-Mañas, M. Pérez, R. Pleixats, *J. Org. Chem.* **1996**, *61*, 2346–2351.

[16] See: M. Murata, T. Oyama, S. Watanabe, Y. Masuda, *J. Org. Chem.* **2000**, *65*, 164–168, and references therein.

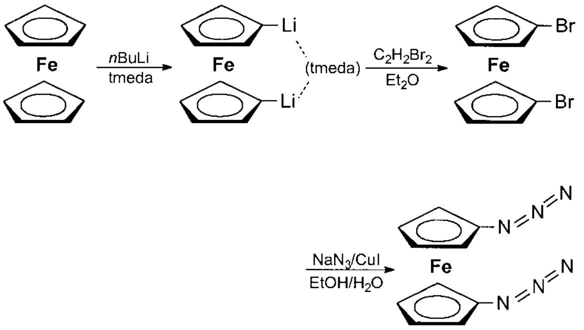
[17] L. J. Gooßen, personal communication.

[18] M. R. Netherton, C. Dai, K. Neuschutz, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100.

1,1′-Ferrocenedi(amido) Chelate Ligands in Titanium and Zirconium Complexes

Max Herberhold*

Although known for more than four decades,[1, 2] the sandwich compound $[Fe(C_5H_4\text{-}NH_2)_2]$ (**1**) ($[fc(NH_2)_2]$; fc = ferrocene-1,1′-diyl),[2, 3] has not really been used either as a building block in polymers or as a chelate ligand in transition metal complexes. Recently, however, an improved synthesis—via 1,1′-di(azido)ferrocene ($[fc(N_3)_2]$;[2] Scheme 1)—has been worked out and the molecular structure of **1** has been determined.[3]



Scheme 1. Synthesis of 1,1′-di(azido)ferrocene; tmeda = tetramethylethylenediamine.

According to the crystal structure analysis of **1**, the lattice contains two (ecliptic) rotamers, that is the 1,1′ and the 1,2′ isomer.[3] The diamine **1** can be protonated, or oxidized (at the iron atom; Scheme 2) to give a green, paramagnetic cation **1a** ($\mu_{\mathrm{eff}} = 2.1\ \mu_B$), of which salts of the type $[fc(NH_2)_2]^+A^-$ (anion $A^- = PF_6^-$, OTf^- or $TCNE^-$ (TCNE = tetracyanoethylene) were obtained.[3]

Starting from the primary diamine **1**, the silylated derivative $[fc(NH\text{-}SiMe_3)_2]$ (**2**) can be prepared,[5] while condensation with benzaldehyde and subsequent hydrogenation generates 1,1′-di(benzylamino)ferrocene, $[fc(NH\text{-}CH_2Ph)_2]$ (**3**).[6]

Titanium and Zirconium Complexes

With regard to the development of new catalysts for the olefin polymerization, during the last few years an increasing number of complexes of the electron-poor transition metals titanium and zirconium with di(amido) chelate ligands has been investigated[5–8] instead of the highly reactive di(cyclopentadienyl)titanium and -zirconium complexes ("metallocene catalysts"). The doubly deprotonated derivatives of the secondary diamines **2**–**4** serve as examples for 1,1′-ferrocenedi(amido) ligands (Scheme 2 and 5).

The use of amino-functionalized 1,1′-ferrocenedi(amido) sandwich compounds as chelate ligands provides two particular advantages:

1) Owing to the rotational mobility of the two cyclopentadienyl rings around the axis which is defined by the ring centers and the iron atom, the bidentate 1,1′-ferrocenedi(amido) ligand can easily adapt to the steric situation in the coordination sphere of the central metal,—as known for $[fc(PPh_2)_2]$.[4b]
2) Owing to the relatively high charge density in the electron-rich ferrocene sandwich, the iron center can be readily oxidized which may also be controlled by cyclovoltammetry.[3, 7]

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