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Chelation-Assisted Palladium-Catalyzed γ-Arylation of Aliphatic Carboxylic Acid Derivatives

Aniruddha Dey,[+a] Sandeep Pimparkar,[+a] Arghya Deb,[a] Srimanta Guin,[a] and Debabrata Maiti[a,*]

[a] Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai – 400 076, India
Fax: (+91)-022–2576–7152; e-mail: dmaiti@chem.iitb.ac.in

[+] Both of these authors have contributed equally to this work.

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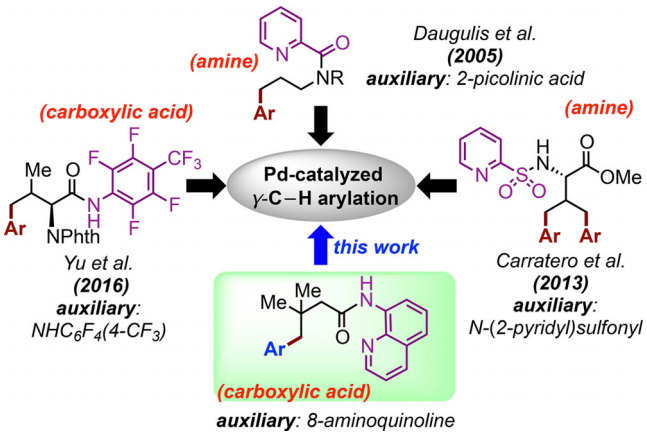
Abstract: A palladium(II)-catalyzed protocol for the highly regioselective remote γ-C–H arylation of aliphatic carboxylic acid has been disclosed. The 8-aminoquinoline moiety as an intramolecular bidentate chelator was found to be suitable for this γ-C–H arylation. Various aryl iodides successfully produced the regioselectively mono-arylated products with negligible diarylation. Functional group tolerance and easy-to-handle reaction conditions make this method attractive.

Keywords: aliphatic γ-C–H arylation; aminoquinolines; carboxylic acids; palladium

The inception of C–H activation in materializing remarkable organic transformations in recent years has revolutionized the modern trend of retrosynthetic disconnections. A series of success stories over the decades serve as representative paradigms in this regard which reflect the immense applicative potential of envisioning a C–H bond as an ideal functional core. This has allowed a superior scope of selective functionalization at sp^2/sp^3 carbon centres in the presence of an organometallic catalyst in complex molecular environments.[1] With reference to the widely known genre of C–H bonds, activation of an sp^3 carbon centre is quite problematic. Asserting the compliance of such a bond, with the absence of a polarizable π-electron cloud and a low-lying σ* orbital, to undergo a metal-catalyzed cleavage is seemingly tedious. A series of strategies implemented over the years has thus helped in the formidable task of making this inert class of C–H bonds participate actively in chemical transformations.

One among these many strategies allowing the formation of a carbon-carbon bond at an unactivated alkyl C–H centre is by the use of a metal-catalyzed chelation approach. Formation of a five-membered metallacycle has led to a highly selective β-C–H functionalization. The efficacy of Daugulis' 8-aminoquinoline directing group in this regard has been beneficial which can be corroborated by recent literature reports.[1g,2] Successful β-C–H arylation/alkylation *via* the chelation approach in the presence of a variety of metal salts has been demonstrated by Chatani, Ge and others.[1d,3] A wish to further the scope of this protocol into taming more distal C–H bonds, *viz.* γ-C–H bonds, to undergo functionalization was foreseeable. Progress on γ-C–H functionalization was thus endeavored by various research groups.[4] γ-C–H arylation of amines by a 2-picolinic acid auxiliary was performed by Daugulis. (Scheme 1).[2a,b] Pioneering reports by Corey on the γ-C–H functionalization of *N*-phthaloyl-α-amino amides as well as by Chen hold

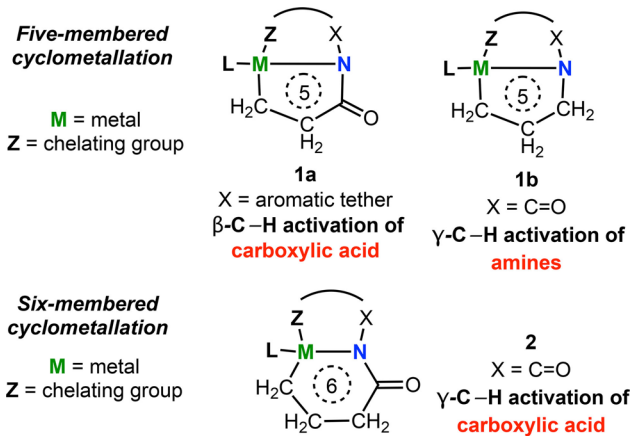


Scheme 1. Auxiliary-assisted palladium-catalyzed γ-C–H arylation protocols.

immense significance concerning their utility in drug research and development.[5] Seminal work by Carratero in performing remote C(sp^3)–H arylation on dipeptides by using an *N*-(2-pyridyl)sulfonamide-based chelating model is noteworthy.[6] In the last few years, Yu made significant advancements in this regard by promoting the effective use of ligand controlled strategy towards highly site selective arylation at both sp^2 and sp^3 carbon centres.[7]

This was demonstrated in a one-pot sequential diarylation of alanine derivatives using a CONHAr$_F$ [Ar$_F$ = C$_6$F$_4$-(4-CF$_3$)] auxiliary at the γ-C–H bond.[8] A stepwise combination of a pyridine and quinolone-based ligand derivatives was used for this reaction. γ-C–H arylation using an amino acid as the directing group had been also reported which was brought about by changes in the design of the ligands used.[9] Very recently, while this work was under progress, Yu made a successful attempt towards the distal γ-C–H arylation of carboxylic acid derivatives using CONHAr$_F$ as the directing group.[10] Arylation was performed selectively at the γ-position of valine, leucine and isoleucine derivatives. An intricate tuning of the ligand helped to overcome the necessity of the sterically bulky phthalimido group, which was primarily required to attain the required metallated intermediate. During this time, activation of the remote aliphatic γ-C–H bond of carboxylic acid derivatives was being investigated in our laboratory. Herein, we independently report a facile protocol to perform a selective arylation at the remote γ-position of aliphatic carboxylic acids using a palladium-catalyzed reaction with 8-aminoquinoline as bidentate chelating auxiliary in which both amine and quinoline nitrogens chelate with the metal.

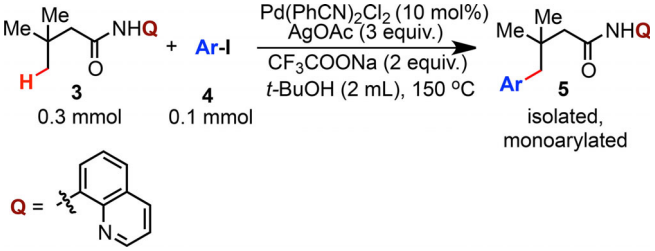
While the γ-C–H activation of amines requires a five-membered metallacycle, the same in case of carboxylic acids would proceed by a six-membered cyclometallation pathway (Scheme 2). The metal pre-



Scheme 2. Formation of metallacycle for β- and γ-C–H activation.

catalyst would undergo an increase in its oxidation state by two while forming the metallacycle. This will require a donor group in the intermediate metallacycle which could stabilize the higher oxidation state of the metal. Use of exogeneous ligands was shown to be useful for this in earlier reports.[10] In this case, the bidentate 8-aminoquinoline was at first tethered to a linear *n*-butyl carboxylic acid through an amide linkage that would provide an active chelation assistance with palladium. Unfortunately, this yielded β-arylated products exclusively. Later, we tethered *tert*-butylacetic acid with 8-aminoquinoline *via* an amide linkage for arylation with 4-nitroiodobenzene as arylating source in presence of Pd(OAc)$_2$ as catalyst and AgOAc as oxidant. Interestingly, regioselective γ-arylation was observed (NMR yield: 50%) with a near exclusive formation of mono-arylated product (*mono*:*di* > 30:1). With these initial results at hand, detailed optimization of the reaction conditions was carried out. A sequential screening of the palladium salts and the oxidants resulted in Pd(PhCN)$_2$Cl$_2$ and AgOAc as the perfect catalyst-oxidant combination for the reaction. Use of a bulky polar hydroxylic solvent like *t*-BuOH was found to be beneficial for the reaction. The presence of a bulky anion like trifluoroacetate was useful for the reaction (Table 1). Inclusion

Table 1. Optimization of catalyst, oxidant and solvent for the reaction condition starting with 0.3 mmol of amide and 0.1 mmol of aryl iodide.

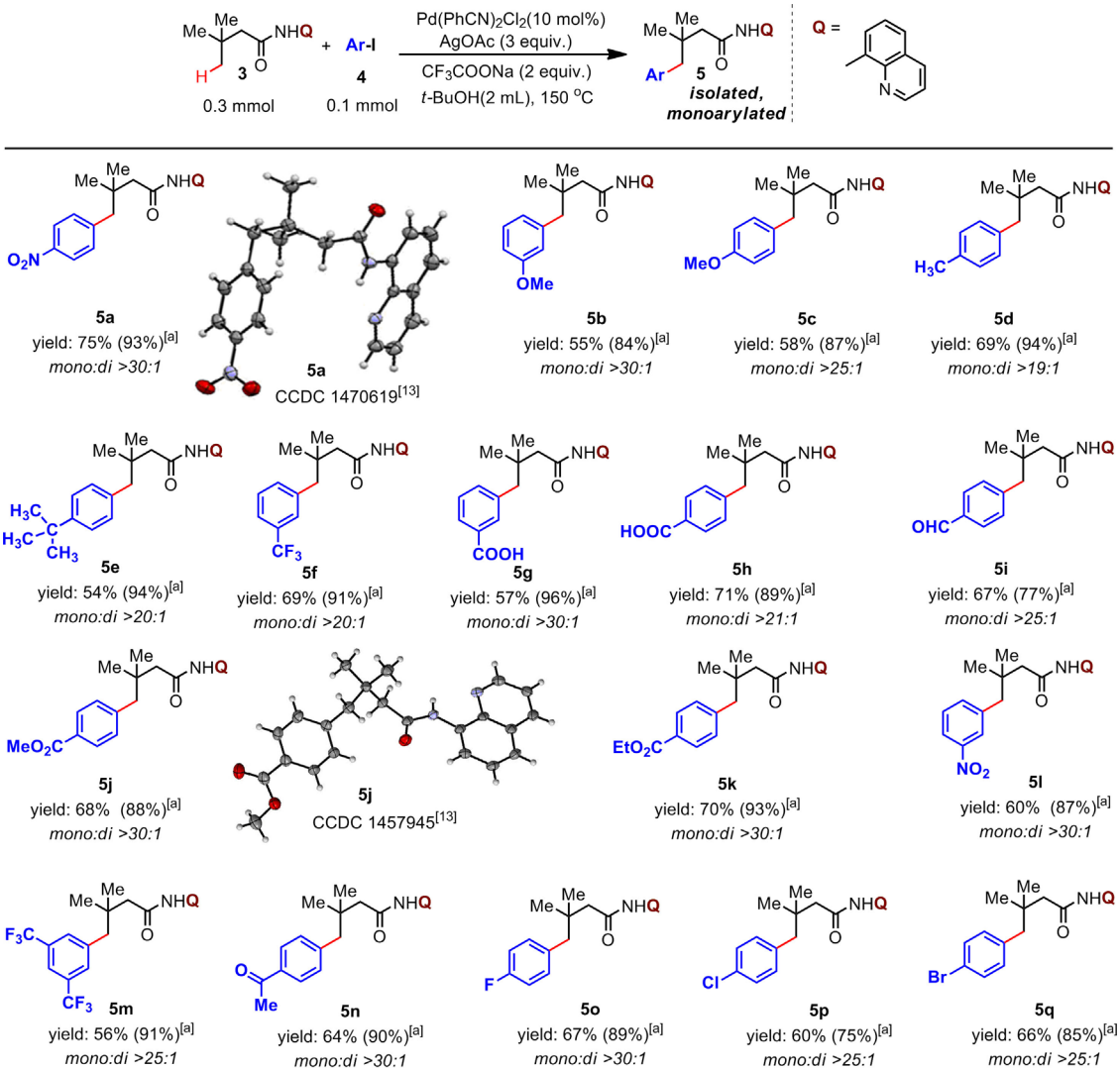


Entry	Pd Catalyst	Oxidant	Solvent (2 mL)	Yield [%][a]
1	Pd(OAc)$_2$	AgOAc	IPA	35[b]
2	Pd(OAc)$_2$	AgOAc	HFIP	40[b]
3	Pd(OAc)$_2$	AgOAc	CF_3CH_2OH	32[b]
4	Pd(OAc)$_2$	AgOAc	*t*-BuOH	50[b]
5	Pd(OAc)$_2$	AgI	*t*-BuOH	20[b]
6	Pd(OAc)$_2$	Ag_2CO_3	*t*-BuOH	45[b]
7	Pd(OAc)$_2$	CuOAc	*t*-BuOH	32[b]
8	Pd(OAc)$_2$	AgOAc	*t*-BuOH	70[c,d]
9	$PdCl_2$	AgOAc	*t*-BuOH	50[c,d]
10	Pd(CH$_3$CN)$_2$Cl$_2$	AgOAc	*t*-BuOH	60[c,d]
11	*trans*-Pd(PhCN)$_2$Cl$_2$	AgOAc	*t*-BuOH	75[c,d]

[a] For mono-arylated product.
[b] 2 equiv. oxidant were used.
[c] In the presence of CF_3CO_2Na.
[d] 3 equiv. of oxidant were used. See the Supporting Information for more details.

of an exogeneous ligand failed to provide any additional improvements on the reaction conditions. The importance of ligand design was emphasized by Yu in his recent report on γ-arylation. Moreover, γ-arylation of carboxylic acids was confirmed to be unknown in absence of any ligands to date and therefore had remained as a challenge.[10] However, a prudent choice of the directing group has allowed this target to be achievable. The reaction conditions employed in our case completely nullified the requirement of any exogeneous ligands. This ensured an enhanced atom-economical catalytic conversion and easier reaction conditions without any compromise of the yield and mono-selectivity. Bidentate chelation by the tethered 8-aminoquinoline ensured an apt placement of the palladium catalyst in order to maintain the required six-membered metallacycle (Scheme 2). The presence of this directing group provided a strong coordination mode that helped in stabilizing the intermediary high oxidation states of palladium. Addition of an exogeneous bulky ligand therefore did not help in improving the yield as much since it might hinder the intramolecular chelation by the 8-aminoquinoline group.[11] This led to a facile activation of the remote γ-C–H bond of the aliphatic carboxylic acid and the imminent γ-arylation with impressive mono-selectivity.

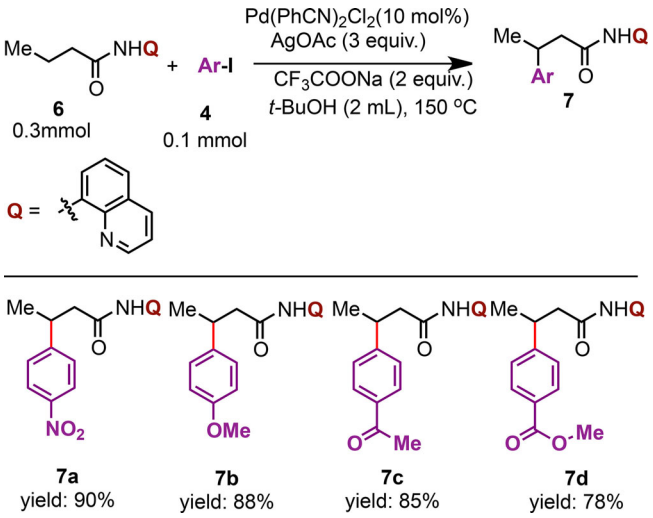
With the optimized conditions in hand, we went on to contemplate the scope of the substrates (Scheme 3). Both electron-donating and electron-withdrawing aryl iodides were found to be effective for the regioselective γ-arylation in moderate to good yields. Electron-rich arenes containing substituents like 3-methoxy (**5b**), 4-methoxy (**5c**), 4-methyl (**5d**) as well as 4-*tert*-butyl groups (**5e**) underwent successful γ-arylation with an excellent ratio in favour of mono-arylated products relative to di-arylation. Aryl iodides



[a] Yield based on recovered starting material.

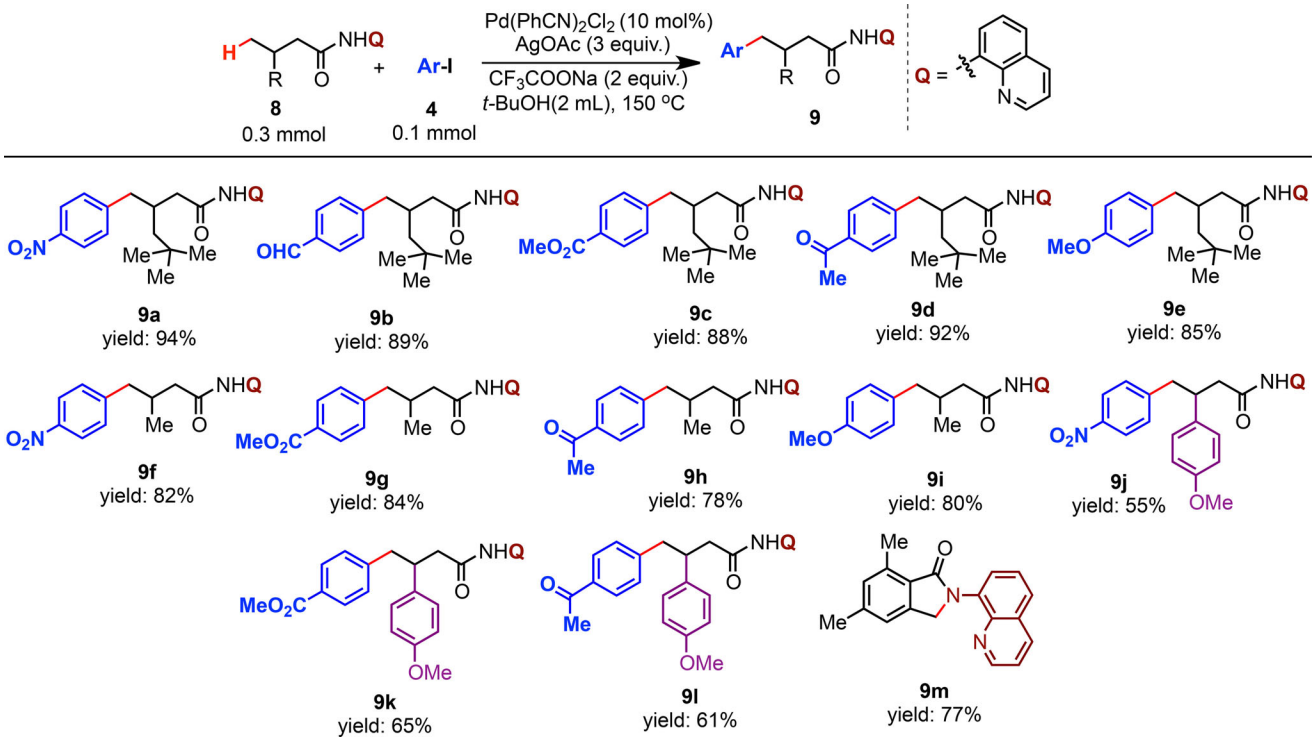
Scheme 3. Arene scope for γ-C–H arylation of carboxylic acid derivatives. Isolated yields are reported.

containing electron-withdrawing groups such as trifluoromethyl, carboxyl, formyl, esters and keto groups were also found to be effective (**5f**–**5n**). Fluorine-containing aryl groups have been found to be important in agrochemicals and pharmaceuticals. Notably, 4-fluorophenyl iodide gave mono-arylated product (**5o**) with excellent selectivity and moderate yields when subjected to the above reaction conditions. Parallel to this, other halogen like chloro and bromo substituted phenyl iodides also provided γ-mono-arylated products with enhanced selectivity (**5p** and **5q**). However, iodo derivatives of heteroarenes, phenol and benzyl alcohols failed to undergo the arylation reaction as suitable coupling partners. Initial attempts for arylation with *n*-butylamides had led to the exclusive formation of β-arylated products with a variety of aryl iodides (Scheme 4, **7a**–**7d**). However, substrates with a β-alkyl/aryl substituent (Scheme 5, **9a**–**9l**) showed high γ-regioselectivity for arylation. Although the role of the β-substituents is not clear at this stage, their role could be accredited towards rendering support in formation of the six-membered metallacycle required for γ-C–H arylation of carboxylic acids (**2** in Scheme 2). Mono-selective arylated products **9a**–**9e** were obtained without any percentage of di-arylation (Scheme 4). Substrates like isovaleric acid were also tested which yielded mono-γ-arylated products (**9f**–**9i**). Furthermore, using the initially obtained β-arylated products, γ-arylation was performed. Gratifyingly, exclusive formation of mono-γ-arylated products was obtained (**9j**–**9l**). Interestingly, γ-cyclization was obtained for mesitoic acid amide which proceeded *via* intramolecular cyclization (**9m**).

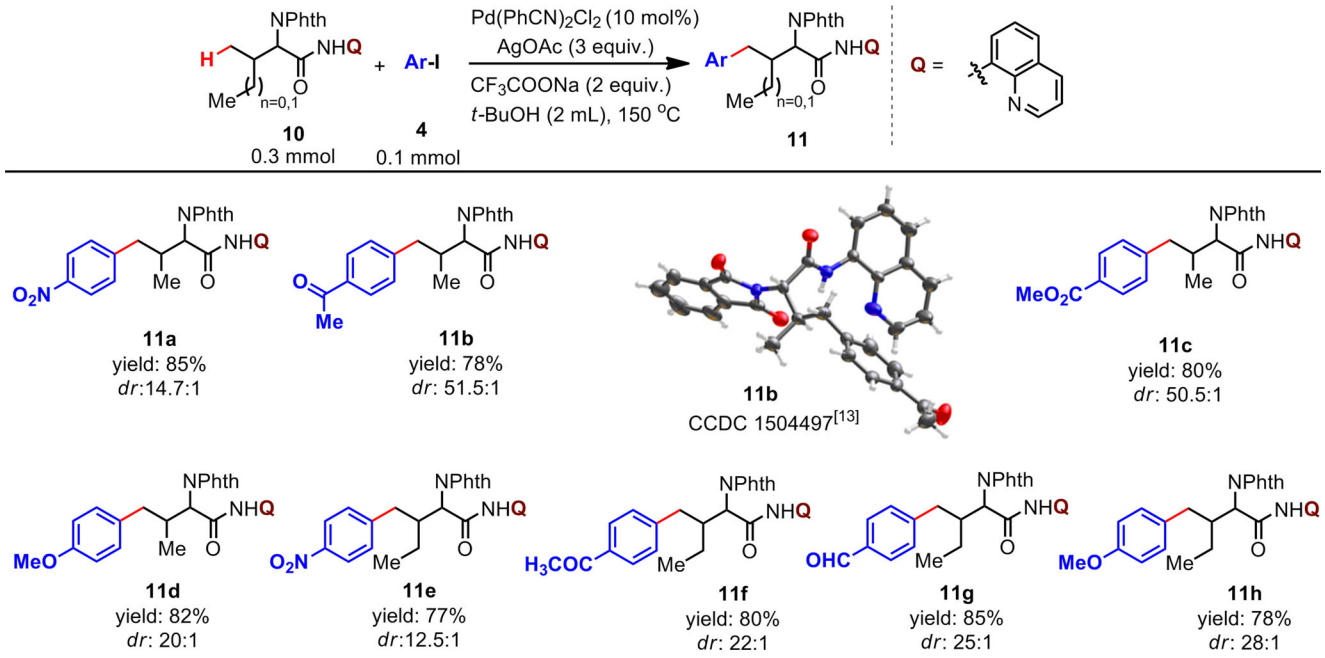


Scheme 4. β-Arylation with linear carboxylic acids.

Examination of the carboxylic acid scope was then carried out with *N*-protected amino acids such as L-valine and L-isoleucine. Despite the presence of a β-hydrogen, both amino acids underwent successful γ-arylation in good to excellent yields (Scheme 6, **11a**–**11h**). Careful ^{1}H NMR analysis revealed that products were formed in a good diastereomeric ratio (see the



Scheme 5. Scope of various β-unprotected carboxylic acids for γ-C–H arylation.

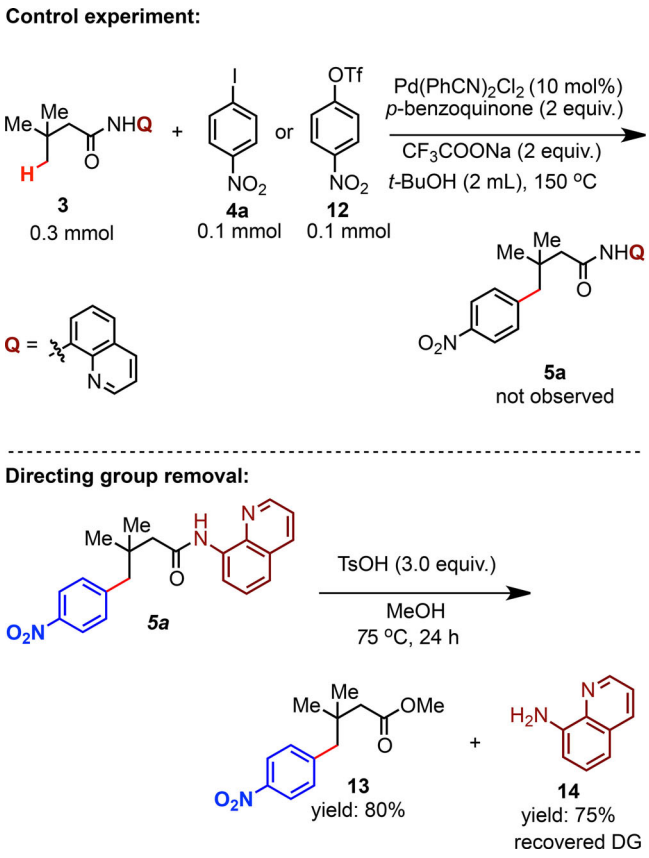


Scheme 6. Scope of *N*-protected amino acids for γ-C–H arylation.

Supporting Information). Aryl iodides with electron-donating or electron-withdrawing substituents underwent the transformation with exceptional mono-selectivity.

Control experiments were performed to understand the role of AgOAc. In an independent set of reactions, replacement of AgOAc either by air, oxygen or N_2 did not give corresponding product. Replacing AgOAc with *p*-benzoquinone as an oxidant with 4-nitroiodobenzene (**4a**) as coupling partner did not yield any product. Also replacing 4-nitroiodobenzene (**4a**) with 4-nitrophenyl triflate (**12**) and using *p*-benzoquinone as the oxidant failed to produce **5a**. Thus, the aryl halide is a potent arylating source for this protocol. (Scheme 7). Moreover, AgOAc exhibits a dual role by probably acting as halide scavenger as well as reoxidant. These facts point towards a tentative Pd(II)/Pd(IV) catalytic pathway.[12] Further application of the protocol was demonstrated by the facile removal of the 8-aminoquinoline directing group that furnished the free ester (Scheme 7, **13**) in 80% yield along with recovery of the 8-aminoquinoline moiety (**14**) in 75% yield. The latter could be reinstalled again to achieve the γ-arylation of other substrates.

In summary, a palladium-catalyzed protocol for selective γ-C–H arylation of carboxylic acids has been developed. This strategy utilizes the chelating potential of the 8-aminoquinoline-based directing group for the site selective C–H activation. Prudent application of a suitable directing group has eliminated the necessity of expensive exogeneous ligands for γ-C–H arylation rendering the protocol cost effective and economical. A detailed mechanistic investigation about the protocol and the involved catalytic process is ongoing in our laboratory.



Scheme 7. Control experiments to study the role of AgOAc; removal and concomitant recovery of the directing group.

Experimental Section

General Procedure for γ-Arylation of 8-Aminoquinoline Amide

In a clean, oven-dried screw-cap reaction tube containing magnetic stir-bar, 3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (**3**) (0.3 mmol), iodoarene (**4**) (0.1 mmol), $Pd(PhCN)_2Cl_2$ (10 mol%, 0.01 mmol), AgOAc (3 equiv., 0.3 mmol), CF_3CO_2Na (2 equiv., 0.2 mmol) were added. Solid reagents were weighed before the liquid reagents. Then *t*-BuOH (2.0 mL) was added and the tube was tightly closed by a screw cap fitted with a rubber septum. Finally, the reaction tube was placed in a preheated oil bath at 150 °C and the mixture stirred vigorously (900 rpm) for 24 h. After completion, the reaction mixture was cooled to room temperature and filtered through pad of Celite and ethyl acetate (15 mL). This filtrate was concentrated under reduced pressure and purified by column chromatography through silica gel using petroleum ether/ethyl acetate as eluent.

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[13] CCDC 1470619 (**5a**), CCDC 1457945 (**5j**) and CCDC 1504497 (**11b**) contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. Please see the Supporting Information for more details.