

C–H Arylation

Palladium-Catalyzed Direct C–H Arylation of Enamides with Simple Arenes**

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The realm of transition-metal-catalyzed cross-coupling reactions^[1] has traditionally depended on prefunctionalized substrates for both reactivity and selectivity. The quest for improved atom economy and efficiency has brought forward revolutionary changes and important advances especially in the palladium-catalyzed direct C–H functionalization^[2,3] where one or ideally both coupling partners could be replaced with simple arenes/alkenes.^[3,4] A vast majority of these tandem C–H activation reactions are devoted on the synthesis of biaryl motifs. Direct oxidative coupling of unactivated arenes with olefins,^[3a,5] the Fujiwara–Moritani reactions^[6,7] are comparatively under-explored in terms of the olefinic substrate scope and selectivity.^[8] Given the synthetic and economic potential of these reactions, development of new olefin functionalities that could be coupled with simple arenes is much warranted. Enamides are stable enamine surrogates and important synthetic intermediates having tunable reactivity and potential usage in various transformations.^[9] Development of effective and direct olefin functionalization^[10,11] of these compounds is highly desirable, because it provides access to multisubstituted amines and olefins, which are scaffolds that are pivotal in natural products as well as in molecular materials.^[12] Absolute stereocontrol of the double bond in these type of transformations is quite challenging, particularly when *Z*-enamides are required.^[13] Herein we present our results on the palladium-catalyzed direct arylation of enamides by using unactivated arenes through double C–H functionalization. To our knowledge, this is the first report^[14] on the catalytic direct arylation of enamides and provides cost-effective and efficient access to highly substituted enamides with perfect *Z* selectivity.

The initial screening studies were carried out using the enamide substrate **1** (Table 1, entry 1). Benzene was chosen as the model arene partner and used as the solvent, too. Sodium

Table 1: Effect of various nitrogen-protecting groups on the reactivity of enamides towards direct arylation.^[a]

Entry	Enamide	R	X	t [h]	Product	Yield [%]
1	1	Me	H	24	decomposed	–
2 ^[b]	2	Me	Me	36	2 a	59
3	3	Me	Ac	24	decomposed	–
4 ^[b]	4 ^[d]	Me	Bn	26	4 a	91
5 ^[b]	5	Me	PMB	26	5 a	90
6 ^[c]	6		Bn	30	6 a	78

[a] Unless otherwise specified, the reaction conditions are as follows: enamide **1–6** (0.1 mmol), benzene (0.5 mL), Pd(OAc)₂ (1 equiv), Na(OAc) (2 equiv) at 80 °C. [b] *Z* configuration of the product was confirmed by NMR spectroscopy. [c] *E/Z* mixture (60:40). [d] Enamide **4** in this scheme is the *p*-methoxyphenyl derivative of the general enamide **4** in Scheme 1. PMB = *p*-methoxybenzyl.

acetate was employed as a base and a stoichiometric amount of palladium acetate was used for the initial studies to avoid any side reactions that may happen with a terminal oxidant. Enamide **1** decomposed to the corresponding ketone under the reaction temperature of 80 °C (no reaction was observed at room temperature). We assumed that protecting the nitrogen atom of the enamide would increase the chemical stability of the enamide under the reaction conditions, and accordingly the *N*-methylated substrate **2** (Table 1, entry 2) was tested next. Significantly the substrate underwent a clean conversion and 59 % of the desired arylated product **2 a** was isolated as a single stereoisomer (*Z* configuration as evidenced by NOESY, see the Supporting Information). The doubly acylated enamide **3** responded poorly under the reaction conditions (Table 1, entry 3). We reasoned that the electron density of the double bond is crucial for the coupling reaction and switched to the benzyl-protected substrate **4**. Gratifyingly the product **4 a** was isolated in 91 % yield in 26 h solely as the *Z* isomer (Table 1, entry 4, see the Supporting Information for the NMR proof for the *Z* configuration). Further increase of the electron density through a *p*-methoxy benzyl protection (enamide **5**) did not alter the reaction profile (Table 1, entry 5). The carbonyl ligand on the nitrogen atom was also modified (enamide **6**), but an *E/Z* mixture of the product **6 a** was isolated in a yield of 78 % (Table 1, entry 6).

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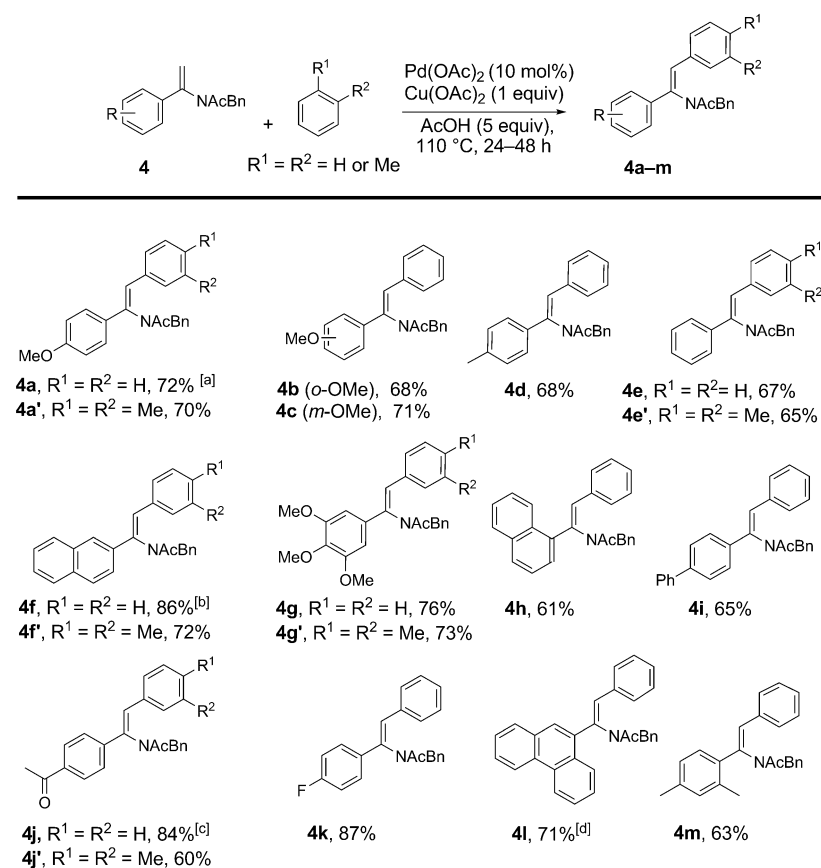
Having found the right substitution (enamide **4**), we went on to develop the catalytic variant of this transformation. Several palladium catalysts, oxidants, and acid/base additives were screened (see the Supporting Information for details), and finally one equivalent of copper acetate was found to be the best terminal oxidant for a catalytic loading of 10 mol % palladium acetate at a reaction temperature of 110 °C. Acid additives were imperative, and five equivalents of acetic acid were found to be optimal (notably zero conversion was observed in the absence of the palladium catalyst). The product **4a** was isolated in 72 % yield under the optimized catalytic conditions (Scheme 1).

For practical purposes, the reaction could be conducted with the arene (40 equiv) in dioxane as the solvent with a slightly longer reaction time (Scheme 1).

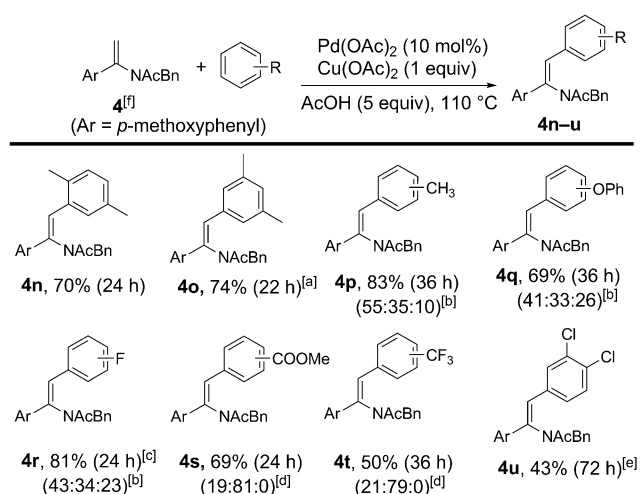
Having the optimized conditions in hand, we investigated the scope of various enamides for the arylation using benzene and *o*-xylene as the arene partners. Pleasingly enamides that display a variety of functional motifs could be selectively arylated (Scheme 1, compounds **4a–m**). The alkenes were formed with absolute regio- and stereoselectivity (*Z* configuration, see below) and functional groups like methoxy and carbonyl groups as well as fluorine were tolerated (Scheme 1,

compounds **4a**, **4b**, **4c**, **4g**, **4j**, and **4k**). The results demonstrated that the electronic nature of the substituents on the enamide moiety played a negligible role in the reaction kinetics as both electron-rich and electron-poor substrates underwent the coupling with comparable ease (Scheme 1, compare **4a**, **4b**, **4c**, and **4g** with **4j** and **4k**). Steric effects adjacent to the reaction center had a significant influence on the reaction profile as evidenced by the lower reactivity of enamides having substituents in the *ortho* positions (Scheme 1, compounds **4b**, **4h**, **4l**, and **4m**). The lower reactivity of *o*-xylene compared to benzene (Scheme 1, compare **4a'**, **4e'**, **4f'**, **4g'** and **4j'** with their benzene analogues) could also be attributed to the increased steric bulk of the former. The *Z* configuration of the alkenes were confirmed from the NOESY spectra (see the Supporting Information for details) of the representative product **4g** (Scheme 1). Further proof was obtained by comparing the ¹H NMR spectra of the product **4e** (Scheme 1) with its authentic *E* isomer (see the Supporting Information for details).

The generality of this arylation protocol with respect to the arene partner was tested for a range of electronically different arenes with the benzyl-protected *p*-methoxyphenyl-substituted enamide **4** as the model substrate. Pleasingly electronically different arenes could be accommodated under this procedure (Scheme 2, compounds **4n–u**), although regioisomers were observed when monosubstituted arenes were employed. Homocoupling of the arenes was not observed, and the reactions exclusively furnished *Z*-alkenes (see above). The *para*- and *meta*-xylenes were equally effective (Scheme 2, compounds **4n**, **4o**), though the latter produced a regioisomeric mixture. Toluene furnished the coupling product in 83 % yield (Scheme 2, compound **4p**). Diphenyl ether, an electron-rich arene gave the arylation product in 69 % yield (Scheme 2, compound **4q**). Significantly the electron-poor fluorobenzene could also be coupled, and the product was isolated in 81 % yield (Scheme 2, compound **4r**). More-electron-deficient arenes like methyl benzoate, (Scheme 2, compound **4s**), trifluoromethyl benzene (Scheme 2, compound **4t**), and 1,2-dichlorobenzene (Scheme 2, compound **4u**) were also suitable partners under the reaction conditions, though the efficiency of arylation decreased with increasing electron deficiency of the arenes. Monosubstituted electron-deficient arenes preferentially formed *meta* isomers (Scheme 2, compounds **4s**, **4t**), whereas their electron-rich analogues (Scheme 2, compounds **4p**, **4q**) and fluorobenzene (Scheme 2, compound **4r**) did not have any appreciable regioselectivity.

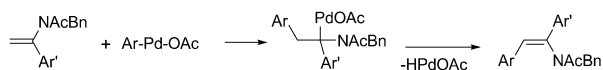


Scheme 1. Exploration of the scope of various enamides in the direct arylation. Unless noted otherwise, the reactions were carried out as follows: enamide **4** (0.1 mmol), arene (0.5 mL), Pd(OAc)₂ (10 mol %), Cu(OAc)₂ (1 equiv), and AcOH (5 equiv) at 110 °C. [a] 70 % (30 h) with arene (0.36 mL, 40 equiv) in dioxane (0.5 mL), 69 % (32 h) with catalyst (5 mol %) in arene (1 mL, 110 equiv) and AcOH (10 equiv). [b] 70 % (48 h) with arene (0.36 mL, 40 equiv) in dioxane (0.5 mL). [c] 80 % (48 h) with arene (0.36 mL, 40 equiv) in dioxane (0.5 mL). [d] 20 mol % of Pd(OAc)₂ was used.



Scheme 2. Scope of various arenes in the direct arylation of the model enamide **4**. Unless noted otherwise, the typical reaction was done as follows: enamide **4** (0.1 mmol), arene (0.5 mL), Pd(OAc)₂ (10 mol%), Cu(OAc)₂ (1 equiv), AcOH (5 equiv) at 110 °C till the starting material was consumed. [a] 20% of the *ortho* isomer was also formed as determined by NMR spectroscopy. [b] Ratio of regioisomers, which could not be assigned and are thus given in no particular order (determined by NMR spectroscopy). [c] 75% (36 h) with arene (0.36 mL, 40 equiv) in dioxane (0.5 mL). [d] *p/m/o* ratio of isomers determined by NMR spectroscopy. [e] 20 mol% of Pd(OAc)₂ was used. [f] Enamide **4** in this scheme is the *p*-methoxyphenyl derivative of the general enamide **4** in Scheme 1.

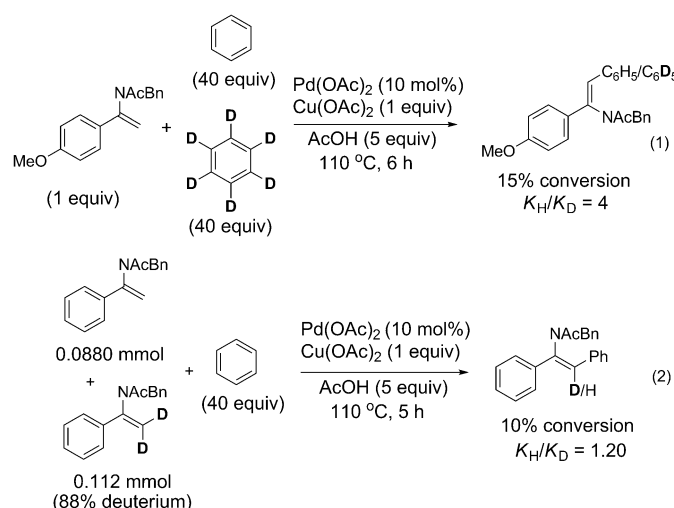
The finite mechanistic possibilities for this transformation warrant detailed investigation. Based on the preliminary studies and observations, an electrophilic palladation pathway involving a σ -aryl Pd complex is postulated (Scheme 3). The formation of this species under acidic conditions is well-known from the arylation reactions described by Fujiwara



Scheme 3. Plausible mechanism for the palladium-catalyzed direct arylation of enamides.

and co-workers.^[6, 7a, 15] Insertion of this aryl–palladium species on the enamide double bond and subsequent β -hydride elimination furnish the arylated product. The terminal oxidation of the resulting palladium hydride or palladium(0) by the sacrificial oxidant (copper acetate) complete the catalytic cycle. The fact that the reaction is slowed down in the absence of acetic acid and the diminished reactivity of electron-deficient arenes support this carbopalladation mechanism.

To gain further mechanistic insights, isotope effect studies were conducted on both the enamide and the arene partners (Scheme 4). The significant primary kinetic isotope effect ($K_{\text{H}}/K_{\text{D}} = 4$, calculated from ¹H NMR spectra) that was observed in the intermolecular competition reaction between benzene and [D₆] benzene hints at a rate-limiting C–H bond

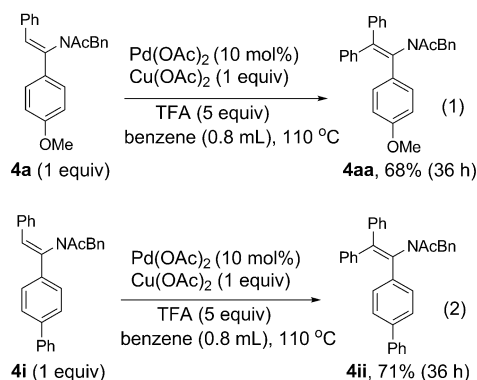


Scheme 4. Intermolecular kinetic isotope effect (KIE) studies.

cleavage^[16] (Scheme 4, Eq. (1)). The absence of a KIE ($K_{\text{H}}/K_{\text{D}} = 1.20$, calculated from ¹H NMR spectra) in the competition reaction of the deuterated and the protonated enamides towards direct arylation with benzene (Scheme 4, Eq. (2)) further serves to discard the possibility of a cyclopalladation^[17] mechanism directed by the N-acetyl fragment.^[11] Supplementary proof in favor of the oxidative pathway can be found in the Supporting Information on page 11.

We have sought to extend the scope of this methodology further by performing a sequential double arylation. The monoarylated product was unreactive under the proposed reaction conditions. But when acetic acid was replaced with the more acidic trifluoroacetic acid (TFA) the tetrasubstituted enamide products were obtained in good yields (Scheme 5, Eq. (1), (2)).

The key to this double arylation strategy lies in exploiting the robustness of the monoarylation product in TFA (the terminal enamide decomposes in TFA, see the optimization studies in the Supporting Information), an acid that is known to generate a highly electrophilic palladium cation,^[7a] thereby



Scheme 5. Synthesis of tetrasubstituted enamides through second arylation of monoarylation products. Product **4aa** was obtained in 55% yield (72 h) and **4ii** was obtained in 62% yield (72 h) when the reactions were carried out in a one-pot manner starting from the respective terminal enamides.

pursuing the less reactive monoarylated enamide towards further arylation. The double arylation could be done in a sequential manner in the same pot by adding a fresh batch of catalyst, oxidant, and TFA once the monoarylation is completed (albeit with a slight decrease in yield; see Scheme 5).

In summary, we have developed an efficient and environmentally benign synthetic route towards arylated enamides through double C–H functionalization. The *Z/E* selectivity of the monoarylation is absolute, and the molecular complexity of the products can be further endowed by a sequential second arylation. Investigation on the origin of *Z* selectivity and possible functional transformations of these products are currently underway and will be reported in due course.

Experimental Section

General procedure for the direct monoarylation of enamides: The terminal enamide (0.1 mmol, 1 equiv) was dissolved in the arene (0.50 mL) in a screw cap vial. Palladium acetate (2.30 mg, 0.01 mmol, 10 mol %), copper acetate (18 mg, 0.1 mmol, 1 equiv), and acetic acid (31 mg, 0.5 mmol, 5 equiv) were added to the solution, and the vial was heated at 110 °C till the starting material was consumed. The solution was concentrated in vacuum, and the product was isolated through flash column chromatography (*n*-hexane/ethyl acetate) to furnish the monoarylated product.

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