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Dual Ligand-Enabled Non-Directed C–H Olefination of Arenes

Hao Chen[+], Philipp Wedi[+], Tim Meyer, Ghazal Tavakoli, and Manuel van Gemmeren*

This work is dedicated to Prof. Benjamin List on the occasion of his 50th birthday

Abstract: The applicability of the Pd-catalyzed oxidative C–H olefination of arenes, also known as the Fujiwara–Moritani reaction, has traditionally been limited by the requirement for directing groups on the substrate or the need to use the arene in large excess, typically as (co)solvent. Herein we report the development of a catalytic system that, through the combined action of two complementary ligands, enables the use of directing group free arenes as limiting reagents for the first time. The reactions proceed under a combination of both steric and electronic control and enable the application of this powerful reaction to valuable arenes, which cannot be utilized in excess.

The C–H functionalization of arenes constitutes a highly important strategy for the development of novel transformations, which bear great potential in the context of natural product and pharmaceutical synthesis.[1] Numerous approaches have been pursued in order to enable such reactions to occur selectively using various transition metals, with many of these strategies relying on directing groups on the substrate in order to enable the desired reactivity and to control the regiochemistry of the reactions.[2] In parallel to the development of directed arene C–H functionalization reactions, the use of non-directed reactions has been identified as a highly attractive target for method development, since such methods inherently offer complementary regioselectivity patterns and are potentially applicable to a wider range of substrates, since the respective methods would not be limited to substrates containing directing groups, which has for example been demonstrated through the development of Ir-catalyzed arene C–H borylations.[3-5] In this context, Pd-catalyzed reactions have been of particular interest, but the development of efficient catalyst systems has proven to be highly challenging.[3] This is for example reflected by the evolution of approaches for the Fujiwara-Moritani reaction, which enables the oxidative olefination of arenes and can thus be considered a prototypical example of a cross-dehydrogenative coupling reaction (Figure 1).[6] Originally, these reactions were catalyzed by $Pd(OAc)_2$ without the use of additional ligands or directing groups, resulting in low catalytic efficiencies and the need for utilizing the arene coupling partner in a large excess, typically as (co)solvent (Approach 1). These reactions are proposed to proceed through a concerted metalation deprotonation (CMD) mechanism for the key C–H activation step, with the acetate ligand acting as the intramolecular base.[7] Substantial improvements have been achieved by the use of pyridine ligands (Approach 2), where an analogous acetate-based CMD is proposed.[7c] In these systems, the catalytic efficiency is substantially improved, although the arene is still required in substantial excess.[8] Alternatively to the use of pyridine ligands, the use of directing groups on the substrate has been pursued as a strategy towards more efficient Fujiwara-Moritani reactions (Approach 3).[9] Such systems profit from an acceleration through the complex induced proximity effect,[2a] which enables high catalytic efficiencies with the arene as the limiting reagent. In the context of these systems, it has also been found that *N*-acetyl amino acids can be utilized as ligands to modulate the activity and selectivity of the catalyst.[10] In such system, the acetate is replaced by the *N*-acetyl group, which acts as an internal base taking up the proton during the CMD step.[10c, 10d] However, these systems face obvious drawbacks resulting from the use of directing groups, most importantly the limitation to substrates bearing such groups. Furthermore, in this approach the regioselectivity is dictated by the directing group, although specialized directing groups, often called templates, have been developed that enable regioselectivities other than ortho selectivity.[11] Despite these advances, no method has been reported to date, that achieves the non-directed Pd-catalyzed C–H functionalization of arenes as limiting reagents.[12] Such a system would be highly attractive, since it would pave the way for applying the plethora of Pd-catalyzed C–H functionalizations that hitherto require directing groups to the non-directed functionalization of arene substrates, including valuable substrates that cannot be utilized in excess.

Herein we report the development of a Pd-catalyzed non-directed Fujiwara-Moritani reaction, based on the use of two complementary ligands (Approach 4). We reasoned that by combining an amino acid-derived ligand and a pyridine ligand, we might generate a catalyst species that can undergo a CMD through a species that resembles the ones involved in Approach 3, albeit without the linkage between the donor (DG vs. pyridine ligand) and the substrate. We expected that this could result in a catalytic system with the same advantages but without the disadvantages resulting from the use of directing groups. Furthermore, we hypothesized that such a system might even be capable of overriding weak coordinating effects that have previously been utilized to direct arene C–H activation, thereby leading to a complementary selectivity pattern.

We chose phenylacetic acid ester (**1a**) as the model substrate for our studies, since this compound is known to react with poor efficiency and virtually no regioselectivity when subjected to the Fujiwara-Moritani reaction using *N*-acetyl glycine (Ac-Gly-OH) as the ligand.[11e] Using this compound we conducted an extensive optimization of the reaction conditions, leading us to develop the reaction conditions presented in Table 1 (Entry 1).[13]

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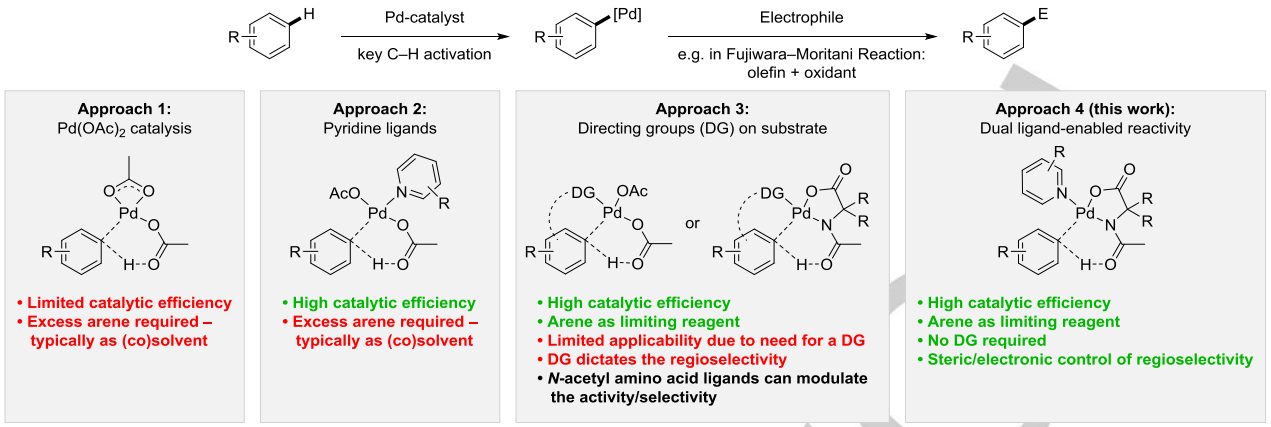
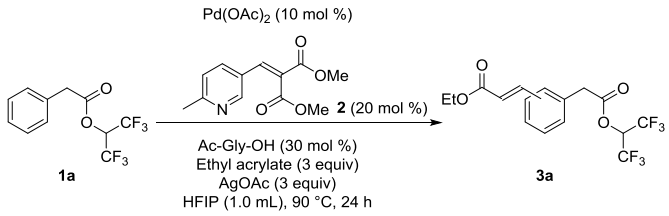


Figure 1. Approaches to the Pd-catalyzed C–H functionalization of arenes such as the Fujiwara–Moritani reaction. Proposed transition state models are shown.

Table 1. Control experiments confirming the necessity of all elements of the catalytic system.

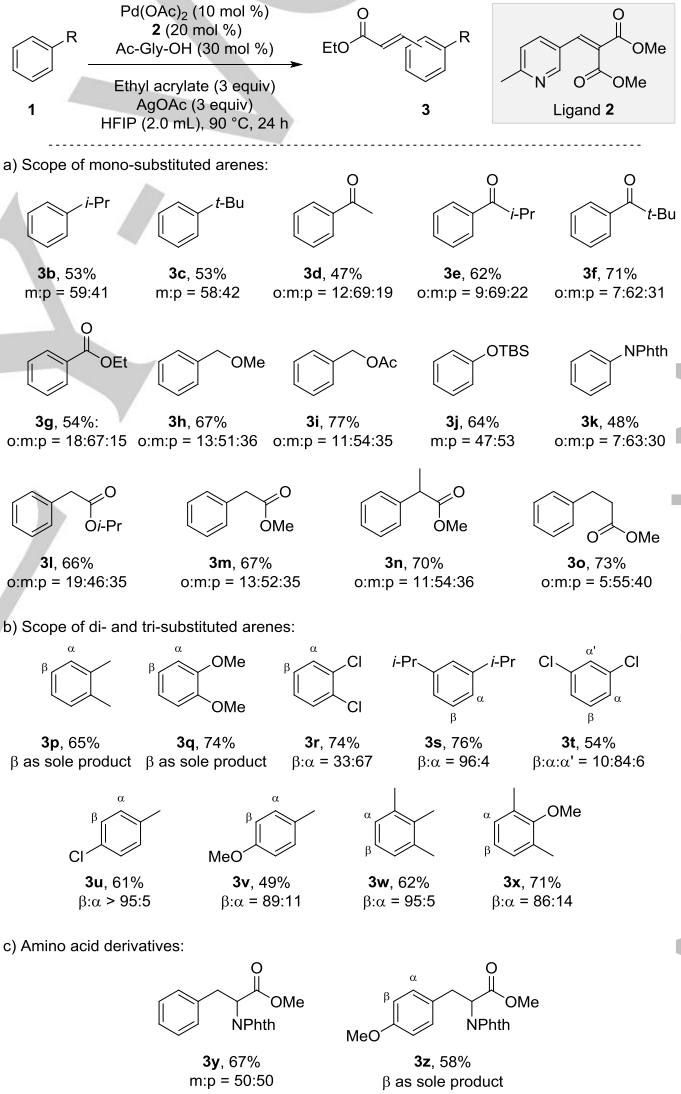


Entry[a]	Deviation from Standard Conditions	GC-Yield (%)[b]	o:m:p[b]
1	None	74 (75)[c]	7:58:35
2	No Ac-Gly-OH	16	9:56:35
3	No ligand **2**	29	27:45:27
4	No $Pd(OAc)_2$	0	-

[a] The reactions in this table were conducted on a 0.1 mmol scale. [b] GC-yields and the o:m:p ratios were determined by GC-FID using 1,3,5-trimethoxybenzene as internal standard [c] The isolated yield on a 0.2 mmol scale is given in parentheses. HFIP = 1,1,1,3,3,3-hexafluoroisopropanol.

Under the optimized conditions, we could obtain our model product **3a** in 75% yield with an ortho:meta:para (o:m:p)-ratio of 7:58:35, which indicates that the reaction proceeds under a combination of both steric and electronic control by the substrate.[14] A control experiment in the absence of *N*-acetyl glycine revealed that this ligand is essential for catalytic activity, but has little influence on the regiochemistry of the reaction (Entry 2). An analogous experiment without the pyridine ligand showed that this ligand is both required for an efficient catalysis and has a substantial influence on the regioselectivity of the process, presumably by increasing the influence of steric factors relative to electronic effects and/or by suppressing a weak directing effect by the electron poor ester functionality (Entry 3). Finally, we confirmed the central role of palladium in the process by demonstrating that no product formation occurs in the absence of $Pd(OAc)_2$ (Entry 4).

Having confirmed the unique performance of our dual ligand-based catalytic protocol, we proceeded to study the generality of the reaction towards various arene substrates (Scheme 1). First, alkyl substituted substrates were tested and the products **3b** and **3c** were both obtained in 53% yield, with the meta-isomer being the major product. Substrates bearing deactivating electron-withdrawing substituents gave the respective products **3d–g** in moderate to good yields and with



Scheme 1. Scope of arene substrates. The structures of the respective starting materials are shown for simplicity.

increased meta selectivity, presumably resulting from the combined effects of both steric and electronic control. Our protocol was also found to be suitable for electron-rich substrates.

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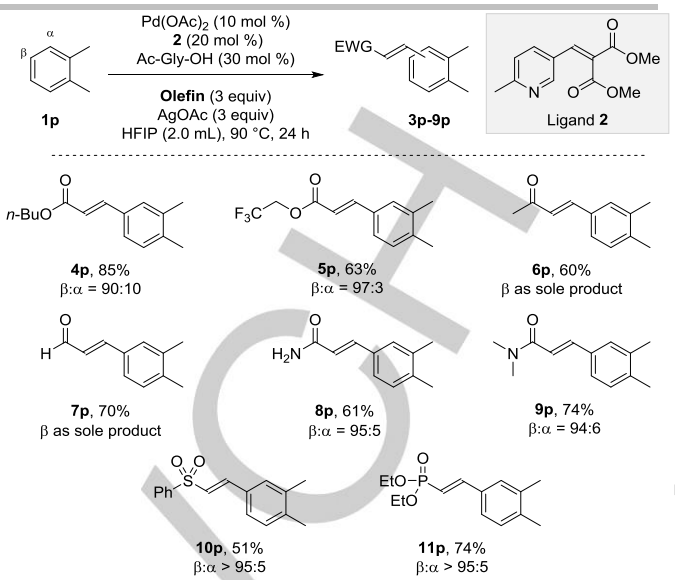
For example, the benzyl alcohol derivatives **3h** and **3i** were both obtained in good yields and the meta isomer as major product. The phenol-derived product **3j** was obtained as an almost even mixture of the meta and para isomers. The formation of the ortho product was not observed, presumably due to steric control, while the ratio between the meta and para product can be rationalized by a superimposition of the statistical factor in favor of the meta position and electronic effects favoring the para position. Remarkably, phthaloyl protected aniline could be converted to product **3k** in 48% yield delivering the meta product as the major isomer, a regioselectivity that clearly differs from what one would predict based on electronic considerations. We next turned our attention to phenylacetic acid and phenylpropionic acid derivatives. We were interested in probing the reactivity of these substrates under our conditions, since such substrates have previously been employed as weak directing groups to induce ortho selectivity.[15] The resulting products **3l–o** were all obtained in good yields and selectivities in favor of the meta product. Notably, while the amount remained low, the products **3l–n** contained a somewhat increased quantity of the respective ortho isomers when compared to the less electron-rich model product **3a**. This effect was not observed for product **3o**, thus indicating that with these substrates a small amount of the product may be formed through a directed pathway. We continued our investigation into the substrate scope of this protocol by studying di- and tri-substituted arene substrates. The electron-rich substrates *ortho*-xylene and veratrole delivered the respective β-isomers as the sole products in good yields (**3p**: 65% and **3q**: 74%). In contrast, when 1,2-dichlorobenzene was utilized, the α-isomer of product **3r** was predominantly formed, albeit again in good yield (74%). The 1,3-dialkylated product **3s** was obtained in 76% yield and with an almost exclusive formation of the β-isomer. When 1,3-dichlorobenzene was employed as starting material, the ortho-directing ability of chlorine already found for product **3r** was again observed, leading to the formation of **3t** in 54% yield as a β:α:α′ = 10:84:6 mixture of isomers. Similarly, when 4-chlorotoluene was employed as a starting material, product **3u** was obtained in 61% yield (β:α >95:5). The product derived from 4-methyl anisole **3v** (49%) was formed with a regioselectivity favoring the position ortho to the more electron donating and sterically less hindered MeO-group (89:11). The tri-substituted products **3w** (62%) and **3x** (71%) were both obtained with the expected regioselectivity in favor of the less hindered position. Finally, in order to demonstrate the synthetic potential of our protocol, we applied the optimized reaction conditions to protected forms of phenylalanine and tyrosine, leading to the formation of the products **3y** (67%, m:p = 50:50) and **3z** (58%, β-isomer exclusively) in good yields and the regioselectivities expected from the previously studied scope.[16]

Having shown the applicability of our protocol to a wide range of arene substrates as limiting reagents, we were interested in probing the generality with respect to the olefinic reaction partner using *ortho*-xylene as a representative yet analytically convenient arene coupling partner (Scheme 2).

The *n*-butyl and 2,2,2-trifluoroethyl esters of acrylic acid delivered the respective products **4p** (85%, β:α = 90:10) and **5p** (63%, β:α = 97:3) with the β-isomer as the major product. When methyl vinyl ketone or acrolein were employed as olefins, the β-isomers were formed exclusively and the products **6p** and **7p** were isolated in 60% and 70% yield respectively. Similarly, acrylamide and *N,N*-dimethylacrylamide as olefins resulted in the formation of **8p**



Scheme 2. Scope of the olefin coupling partners.

(61%, β:α = 95:5) and **9p** (74%, β:α = 94:6) in good yields and with high β-selectivities. Finally, when phenyl vinyl sulfone and diethyl vinylphosphonate were utilized as olefins, the respective products **10p** (51%) and **11p** (74%) were obtained in near complete β-regioselectivity. Overall, our studies on the scope of the protocol reported herein show a broad applicability both with respect to the arene component used as the limiting reagent and to the olefinic coupling partner.

In Summary, we have developed a catalytic method that enables the oxidative C–H olefination of arenes known as the Fujiwara–Moritani reaction to proceed with directing group-free substrates as limiting reagents for the first time. The reaction relies on the combination of *N*-acetyl glycine with a pyridine ligand and was shown to be applicable to a wide range of arenes and olefins. We expect that the synthetic method reported herein will prove to be a valuable tool for the late-stage functionalization of arenes. Furthermore, in light of the many Pd-catalyzed reactions that are currently limited by their need for directing groups, this approach will likely be applicable to the development of further valuable transformations under a non-directed regime.

Experimental Section

General procedure for the non-directed, arene-limited Fujiwara-Moritani reaction: An oven dried 10 mL Schlenk tube was charged with $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol %), ligand **2** (9.4 mg, 0.040 mmol, 20 mol %), *N*-acetyl-glycine (7.0 mg, 0.060 mmol, 30 mol %), AgOAc (100.2 mg, 0.6000 mmol, 3 equiv), arene (0.200 mmol, 1 equiv), olefin (0.600 mmol, 3 equiv), and HFIP (2 mL). The reaction vessel was tightly sealed and placed into an aluminum block with a tightly fitting recess on a magnetic stirrer. The reaction mixture was stirred at room temperature for 2 minutes. The aluminum block was heated to 90 °C and the reaction mixture was stirred at this temperature for 24 h. The reaction mixture was allowed to cool to room temperature, transferred into 50 mL round-bottom flask, and concentrated under reduced pressure. The product was purified by silica gel column chromatography using a gradient of pentane:ethyl acetate = 500:1 to 1:1 as the eluent.

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Keywords: Arenes • C–H Activation • Fujiwara-Moritani Reaction • Olefination • Palladium

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[13] For details regarding the optimization studies, see the Supporting Information.

[14] During our optimization studies we monitored the ortho:meta:para ratio over the course of the reaction using substrates **1a** and **1i** and found that the ratio essentially remains constant over time.

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[16] Compared to the contemporary study by the Yu group (Ref 9), a different major isomer was observed in some instances (products **3a**, **3b**, **3j**, **3r**, and **3t**). Although no comprehensive rationalization can be given at this stage, we hypothesize that a different sensitivity of the two catalytic systems towards competing steric and electronic effects may cause this effect.