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Original article

Pd-catalyzed *ortho*-olefination of aromatic acetyl esters

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ABSTRACT

A Pd(II)-catalyzed *ortho*-olefination of aromatic acetic esters is described which features with an excellent funcitional group tolerance, good yields, mild reaction conditions, good scalability as well as high chemo- and regio-selectivity.

1. Introduction

In the past decade, transition-metal-catalyzed C—H bond functionalization reactions have attracted great attention and significant achievements have been made on these topics. Among them, the application of directing groups show great regio-selectivity and become the most prevalent strategy for efficient C—H activation [1–9]. Ester is a kind of very important and common functional groups in natural products, drug molecules and practical materials. Therefore the development of esters as directing group would be very important and practical. However, there are only very few examples in literature compared to the dominant directing groups like amides, carboxylic acid, pyridine *etc.*, which is probably due to the weak coordinating feature of ester: for instance, Chang and co-workers reported an ester as an efficient directing group in the Rh(III)-catalyzed olefination of aromatic ester [10], and later on the same group developed an Ir (III)-catalyzed direct amidation of aromatic esters [11]. In a related contribution, Graczyk *et al.* disclosed a Ru(II)-catalyzed oxidative alkenylations with aromatic esters [12]. In addition, Shan *et al.* described a Pd(II)-catalyzed regioselective C—H oxygenation of benzoates [13]. Recently, Li *et al.* developed an *ortho*-olefination of phenylacetic Weinreb amides, esters and ketones [14]. Furthermore, a Pd(II)-catalyzed *ortho*-olefination of phenyl acetic and propionic acid esters was described by Hu *et al.* [15]. The *ortho*-olefination product of phenylacetic esters is a key intermediate forthe syntheses of 2-tetralone derivatives, which are usually needed multi-step synthesis in existing methods [16]. Herein, we report a Pd(II)-catalyzed *ortho*-olefination of aromatic acetic esters as complementary protocol to precedent work, which characterizes with a broader substrate scope and less reaction time.

2. Results and discussion

Ibuprofen methyl ester **1a** and methyl acrylate **2a** were chosen as the substrates to test the feasibility (Table 1). Starting with $Pd(OAc)_2$ as the catalyst, Ac-lle-OH as the ligand and $AgNO_3$ as oxidant in HFIP (1,1,1,3,3,3-hexafluoro-2-propanol), to our delight, the desired product **3aa** was formed in 82% GC yield that displayed general mono-selectivity (mono: di = 68:14) (Table 1, entry 1). Further ligand screening suggested that Ac-Ala-OH was the optimal one over Ac-lle-OH, Ac-leu-OH, Ac-gly-OH, Ac-ph-OH and Boc-lle-OH (Table 1, entries 1–6). Control experiment without ligand was performed accordingly, and much lower yield was obtained with poor selectivity, which revealed the importance of ligand for the transformation (entry 7). Subsequently, oxidant optimization demonstrated that $AgNO_3$ was the best one among Ag_2CO_3, AgOAc, Ag_2O, AgOTf, $Cu(OAc)_2$ and O_2 (Table 1, entries 8–13). It is noteworthy that significant improvement of monose-lectivity was observed when the reaction time was decreased from 24 h to 4 h (mono:di up to 70:8), however, the substrate did not completely consumed at 4 h (Table 1, entries 14–16). So we chose 6 h as the optimized reaction time with high yield and better monoselectivity. It is of note that other solvent system, such as DMSO, DMF, *t*-amyl-OH and 2,2,2-trifluoroethanol could not

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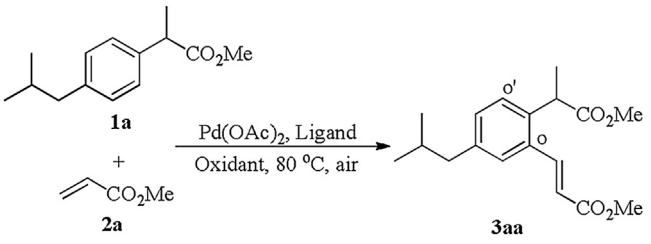
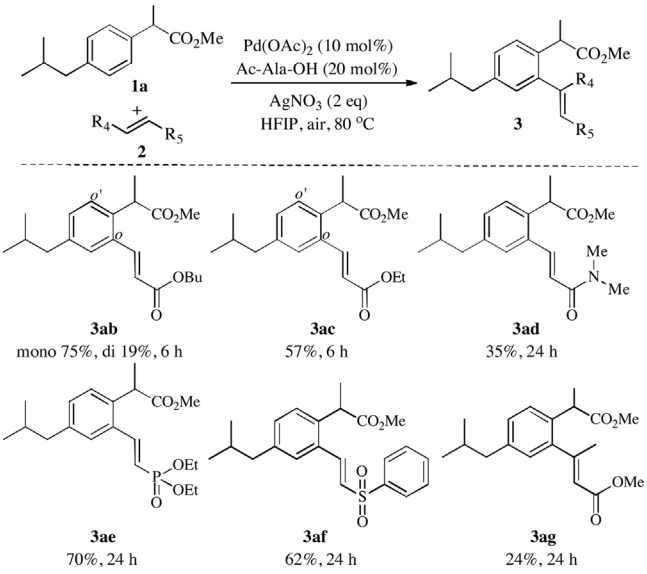
Table 1
Development of optimized conditions for *ortho*-olefination.[a]



Entry	Ligand	Oxidant	Yield (%)[b]	Mono/di
1	Ac-Ile-OH	$AgNO_3$	82	68/14
2	Ac-Leu-OH	$AgNO_3$	97	60/37
3	Ac-Ala-OH	$AgNO_3$	99	69/30
4	Ac-Gly-OH	$AgNO_3$	79	55/24
5	Ac-Ph-OH	$AgNO_3$	14	13/1
6	Boc-Ile-OH	$AgNO_3$	Trace	
7	–	$AgNO_3$	15	13/2
8	Ac-Ala-OH	Ag_2CO_3	33	33/0
9	Ac-Ala-OH	AgOAc	66	60/6
10	Ac-Ala-OH	Ag_2O	3	3/0
11	Ac-Ala-OH	AgOTf	1	1/0
12	Ac-Ala-OH	$Cu(OAc)_2$	0	0
13	Ac-Ala-OH	O_2	1	1/0
14[c]	Ac-Ala-OH	$AgNO_3$	99	76/23
15[d]	Ac-Ala-OH	$AgNO_3$	99	82/17
16[e]	Ac-Ala-OH	$AgNO_3$	78	70/8

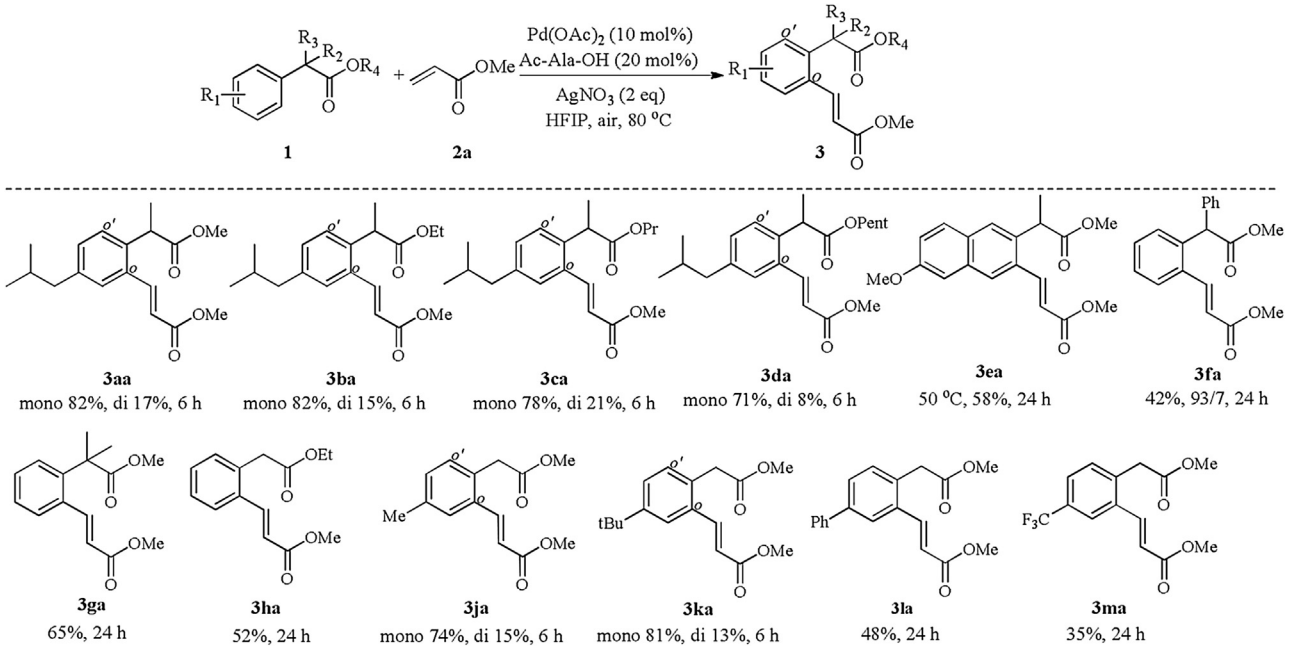
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), oxidant (2 equiv.), solvent HFIP (2 mL), air, 24 h.
[b] GC yield.
[c] 12 h.
[d] 6 h.
[e] 4 h.

facilitate this reaction. It needs to be pointed out that compared with Yu's method [14], our method has obvious advantages, much short reaction time (6 h *vs.* 48 h), better mono/di ratio, mild reaction temperature etc.



Scheme 2. Substrate scope of alkene. Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (10 mol%), Ac-Ala-OH (20 mol%), $AgNO_3$ (2 equiv.), HFIP (2 mL), air, isolated yield.

With the optimized conditions in hand, we next turned our attention to the substrate scope of this palladium-catalyzed *ortho*-olefination. A very broad range of substituted aromatic acetic esters (**1a**–**1m**,Scheme 1) with **2a** could be smoothly converted into the corresponding *ortho*-olefination products with high regioselectivity. Firstly, esters of ibuprofen were demonstrated to be tolerated well under our standard conditions, and methyl, ethyl, propyl and pentyl esters all provided corresponding products in good yields (**3aa**–**3ca**, Scheme 1). Then, naproxen methyl ester (**1e**, Scheme 1) also was a good substrate to participate in *ortho*-olefination with 58% yield. Next, α-position of phenylacetic esters has phenyl (**1f**, Scheme 1) or two methyls (**1g**, Scheme 1) could proceed smoothly to afford *ortho*-olefination product with high regioselectivity. Both



Scheme 1. Substrate scope of aromatic acetic esters. Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (10 mol%), Ac-Leu-OH (20 mol%), $AgNO_3$ (2 equiv.), HFIP (2 mL), air, isolated yield.

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