SCIENCE CHINA
Chemistry

• ARTICLES •

September 2010 Vol.53 No.9: 1927–1931
doi: 10.1007/s11426-010-4096-7

Direct palladium/copper oxidative cross-coupling of α-methylstyrene with acrylates

AL-MAKSOUD Walid, DJAKOVITCH Laurent*, JAHJAH Mohamad & PINEL Catherine

Université de Lyon, CNRS, UMR 5256, IRCELYON, Institut de recherches sur la catalyse et l'environnement de Lyon,
2 avenue Albert Einstein, F-69626 Villeurbanne, France

Received April 28, 2010; accepted June 14, 2010

Fully palladium/copper catalytic oxidative cross-coupling of acrylates with α-methylstyrene was performed in a DMSO/AcOH (1:1) mixture at 60 °C in the air. This improves previous procedures which employed stoichiometric amounts of copper and oxygen. Thus various acrylates were effectively coupled to α-methylstyrene giving the expected compounds in moderate to good yields (44%–65%) as a mixture of *E* and *Z* isomers.

direct cross-coupling, oxidative couplings, palladium, copper, catalytic procedures, olefin cross-coupling

1 Introduction

The cross-coupling reactions have become one of the most powerful methods for the construction of carbon-carbon bonds in organic syntheses including naturally occurring compounds and pharmaceuticals [1] for two decades. However, one of the main limitations is related to the use of activated reagents, generally as halogenated or metallic derivatives that are linked to the co-production of undesirable wastes.

In order to solve such limitation, several research groups have investigated both direct and oxidative cross-coupling reactions. In these reactions, one takes advantages of the natural reactivity of C–H bonds affording good alternative to the use of halide or metallic compounds. However, these procedures based on C–H activation are generally limited to heterocycles [2–7].

For alkene substrates, the main difficulty in such C–H activation based protocols concerns generally the rate at which the catalytic system performs of each elementary steps of the cross-coupling reaction (i.e. C–H activation, cross-coupling, elimination of product) before substrate decomposition [8, 9].

There were few studies due to the difficulties in solving such issue. Ishii *et al.* reported an elegant Pd(II)-catalysed oxidative cross-coupling of acrylates with vinyl carboxylates in presence of vanadomolybdophosphonic acids (2 mol%) under oxygen in 2004. Thus, working in acetic acid at 90 °C with 10 mol% $Pd(OAc)_2$ associated to $H_4PMo_{11}VO_{40}$ (2 mol%) under oxygen, good to high conversion (65%–90%) leading to useful yields (45%–76%) for the coupling reaction of various acrylates (i.e. methyl, ethyl, butyl, *iso*-butyl) with vinyl acetate were achieved [10]. Lately, Loh *et al.* reported the direct cross-coupling between α-methylstyrene and *tert*-butylacrylate using 20 mol% $Pd(OAc)_2$ in the presence of 2 equiv $Cu(OAc)_2$ under oxygen (1 atm) in DMSO/AcOH (1:1) at 60 °C. Thus target compounds were obtained in moderate to good yields (33%–87%) [11].

In our ongoing research, we developed several catalytic systems applied to the direct cross-coupling of indoles with olefins under oxidative conditions [3, 5]. Generally, using a catalytic system based both on palladium and copper in a DMF/H_2O/AcOH mixture, high conversions and good isolated yields were achieved for the coupling of the indole nucleus with the *n*-butylacrylate. Therefore, we planned to

---

*Corresponding author (email: Laurent.Djakovitch@ircelyon.univ-lyon1.fr) adapt these systems to the oxidative direct coupling of olefins.

2 Experimental

2.1 General experimental

The qualitative and quantitative analysis of the reactants and the products were made by gas chromatography (GC). Conversions and yields were determined by GC based on the relative area of GC signals referred to an internal standard (biphenyl) calibrated to the corresponding pure compound.

Liquid NMR spectra were recorded on a Bruker AC-250 spectrometer. All chemical shifts were measured relative to residual ^{1}H resonances in the deuterated solvents: $CDCl_3$, d 7.25 ppm for ^{1}H.

Flash chromatography was performed at a pressure slightly greater than atmospheric pressure using silica (Merck Silica Gel 60, 230–400 mesh). Thin layer chromatography was performed on Fluka Silica Gel 60 F254. The compounds are generally obtained as a mixture of two isomers [*trans*/*trans*: *cis*/*trans*], noticed hereafter [*EE*:*ZE*].

GC analyses were performed on a HP 4890 chromatograph equipped with a FID detector, a HP 6890 autosampler and a HP-5 column (cross-linked 5% phenyl-methylsiloxane, 30 m × 0.25 mm i.d. × 0.25 μm film thickness). Nitrogen is used as carrier gas. The mass spectra were obtained by a Shimadzu GC-MS-QP2010S equipped with a Sulpelco SLB-5MS column (95% methylpolysiloxane + 5% phenyl-polysiloxane, 30 m × 0.25 mm × 0.25 μm) with He as carrier gas was used. The experimental error was estimated to be ± 5%.

2.2 General procedure for the catalytic tests

A 5 mL dry round bottom flask was charged sequentially with a stirring bar, $Pd(OAc)_2$ (mol%), $Cu(OAc)_2$ (mol%), mixed solvents DMSO/HOAc (*v*/*v* 1/1) (1 mL). The α-methylstyrene (2 equiv, 1 mmol) and acrylate (1 equiv, 0.5 mmol) were added into the solution in sequence. The reaction mixture was stirred at 60 °C under atmospheric pressure for 24 h. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with distilled water and brine. The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated to give the crude product which was directly applied to a flash column chromatography (EtOAc/Hexanes mixtures).

*(2E)-Butyl 5-phenylhexa-2,4-dienoate (**3a**)*

This compound was prepared by the procedure described above and was obtained as a mixture (*EE*:*ZE* = 80:20) as a colourless oil. Yield = 78%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.7–7.8 (dd, *J* = 12.1, 14.7 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 2H), 7.15–7.30 (m, 3H), 6.45 (d, *J* = 11.9 Hz, 1H), 5.85 (*J* = 15.1 Hz, 2H), 4.10 (t, *J* = 7.5 Hz, 2H), 2.20 (s, 3H), 1.65 (qn, *J* = 6.8 Hz, 2H), 1.45 (sx, *J* = 7.8 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). Data agree with those reported for this compound; CAS [943613-81-8].

*(2E)-tert-Butyl 5-phenylhexa-2,4-dienoate (**3b**)*

This compound was prepared by the procedure described above and was obtained as a mixture (*EE*:*ZE* = 90:10) as a colourless oil. Yield = 49%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.6–7.75 (dd, *J* = 11.7, 15.0 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.29–7.35 (m, 3H), 6.51 (d, *J* = 11.6 Hz, 1H), 5.90 (d, *J* = 15.4 Hz, 2H), 2.28 (s, 3H), 1.50 (s, 9H). Data agree with those reported for this compound; CAS [1110610-05-3].

*(2E)-tert-Butyl 5-phenylhexa-2,4-dienoate (**3c**)*

This compound was prepared by the procedure described above and was obtained as a mixture (*EE*:*ZE* = 87:13) as a colourless oil. Yield = 38%. ^{1}H NMR (250 MHz, CDCl3) δ 7.6–7.75 (dd, *J* = 11.7, 15.0 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.29–7.35 (m, 3H), 6.51 (d, *J* = 11.6 Hz, 1H), 5.90 (d, *J* = 15.4 Hz, 2H), 3.76 (s, 3H), 2.28 (s, 3H). Data agree with those reported for this compound; CAS [131070-56-9].

3 Results and discussion

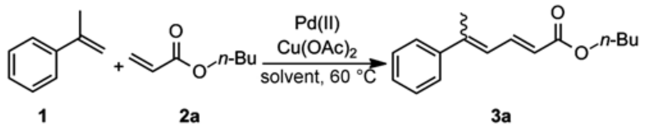
The influence of the nature of palladium source, solvent and atmosphere were studied for the cross-coupling of α-methylstyrene with acrylate esters.

Table 1 summarized the representative results for the reaction of the α-methylstyrene **1** (2 equiv) with *n*-butyl acrylate **2a** (1 equiv) in the presence of different Pd-salts/complexes and $Cu(OAc)_2$ under various solvent and reaction conditions. The desired product, i.e. the *n*-butyl 5-phenylhexa-2,4-dienoate, was formed in 59% isolated yield in the mixed solvent system DMSO/HOAc (*v*/*v* 1/1) when using 20 mol% $Pd(OAc)_2$ at 60 °C (Table 1, entry 4). By contrast, when applying the reaction conditions described by Loh *et al.* [11], i.e. under O_2 atmosphere, **3a** was obtained in slightly lower 48% yield (Table 1, entry 7). When the $Pd(OAc)_2$ loading was decreased to 10 mol%, the yield in **3a** decreased to 38% (Table 1, entry 5), and 15% with 5 mol% of $Pd(OAc)_2$ (Table 1 entry 6). Moving from DMSO to apolar *iso*-octane resulted in moderate yield (50%); however after longer reaction time (i.e. 48 h) (Table 1, entry 2). Poor yields were observed in pure H_2O (Table 1, entries 1 and 10) or H_2O/HOAc (1:1) mixture (Table 1, entries 3, 9 and 11) whatever the palladium precursor used. This can be attributed to low solubility of styrene derivatives in aqueous medium.

The nature of palladium source also played a significant role on the yield of **3a**. Under identical conditions, the Herrmann palladacycle did not exhibited activities (Table 1, entry 11), while 9% and 28% yields were achieved with [12] and $PdCl_2$, respectively (Table1, entries 8 and 9).

Next, we optimised the reaction conditions working with

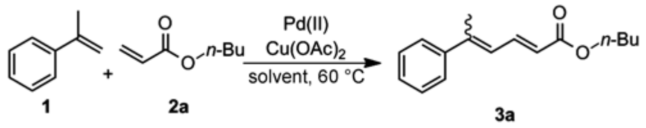
Table 1 Direct cross-coupling reaction of α-methyl styrene with *n*-butyl acrylate



Entry	Pd(II) (mol%)	Solvent	Yield a)
1	$Pd(OAc)_2$/20	H_2O	11
2	$Pd(OAc)_2$/20	isooctane/HOAc	50 c)
3	$Pd(OAc)_2$/20	H_2O/HOAc	26
4	$Pd(OAc)_2$/20	DMSO/HOAc	59
5	$Pd(OAc)_2$/10	DMSO/HOAc	38
6	$Pd(OAc)_2$/5	DMSO/HOAc	15
7 b)	$Pd(OAc)_2$/20	DMSO/HOAc	48
8	$Pd(NH_3)_4Cl_2$/10	DMSO/HOAc	9
9	$PdCl_2$/10	DMSO/HOAc	28
10	$PdCl_2$/10	H_2O	16
11	palladacycle/10	DMSO/HOAc	–

Reaction conditions unless otherwise specified: **1** (2 equiv), **2a** (1 equiv, 0.5 M) and oxidant: $Cu(OAc)_2$ (1 equiv) at 60 °C in the mixture solvent (1:1), 24 h. a) Isolated yields as a mixture of isomers (ratio [*trans*/*trans*:*cis*/*trans*] = 80:20). b) $Cu(OAc)_2$ (1 equiv.) + O_2. c) Reaction time: 48 h.

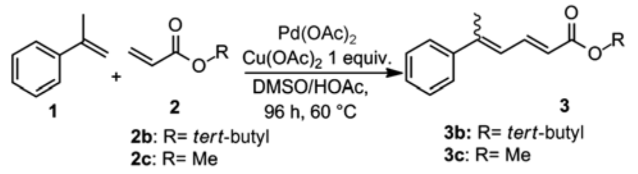
Table 2 $Pd(OAc)_2$ catalyzed direct cross-coupling reaction of α-methyl styrene with *n*-butyl acrylate



Entry	$Pd(OAc)_2$ (mol%)	Yield a)
1	5	77
2 b)	5	13
3 c)	5	52
4	2	62
5 d)	2	57
6 e)	5	79
7 e)	2	72
8 e, g, f)	2	62
9 f)	2	22

Reaction conditions unless otherwise specified: **1** (2 equiv), **2a** (1 equiv, 0.5 M) and oxidant (1 equiv $Cu(OAc)_2$) at 60 °C in the mixture solvent DMSO/HOAc (1:1), 4 days. a) Isolated yields as a mixture of isomers (ratio [*trans*/*trans*:*cis*/*trans*] = 80:20). b, c) The reaction was performed at 25 °C (b) and 80 °C (c). d) $Cu(OAc)_2$ (1 equiv.) + O_2. e) 1 equiv of **1** and 1 equiv of **2a**. f) 1 equiv of **1** and 2 equiv of **2a**. g) The concentration of **2a** is 0.25 M.

Table 3 Direct cross-coupling reaction of α-methyl styrene with various acrylates catalyzed by $Pd(OAc)_2$



Entry	2	$Pd(OAc)_2$ (mol%)	Oxidant	Yield a
1	**b**	$Pd(OAc)_2$/2	$Cu(OAc)_2$	42 (90:10)
2	**c**	$Pd(OAc)_2$/5	$Cu(OAc)_2$	38 (87:13)
3	**c**	$Pd(OAc)_2$/2	$Cu(OAc)_2$	21 (87:13)
4	**c**	$Pd(OAc)_2$/5	$Cu(OAc)_2 + O_2$	36 (87:13)

Optimized reaction conditions: **1** (1 equiv), **2** (1 equiv, 0.5 M) and oxidant $Cu(OAc)_2$ (1 equiv) at 60 °C for 96 h in the mixture solvent: DMSO/HOAc (1:1). a) Isolated yields as a mixture of isomers (ratio [*trans*/*trans*:*cis*/*trans*] is given in brackets).

lower $Pd(OAc)_2$ loading. With a longer reaction time (4 days), the coupling reactions afforded the desired product in good yield (77%) using only 5 mol% $Pd(OAc)_2$ (Table 2, entry 1). Under these conditions, working even at low loading as 2 mol% resulted to useful yields (62%, Table 2, entry 4). Furthermore, no influence of the atmosphere (i.e. air or pure O_2) was observed (Table 2, entry 5).

With these new conditions (i.e. 5 mol% $Pd(OAc)_2$) we were able to decrease the substrates ratio to an equimolar mixture of **1**:**2a** that afforded high product yield (i.e. 79%) (Table 2, entry 6). This could be further optimised by using only 2 mol% $Pd(OAc)_2$ (Table 2, entry 8).

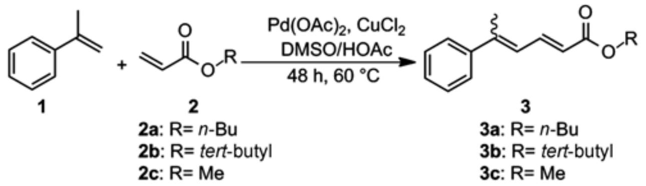
At room temperature, the reaction proceeded very slowly as only 13% yield was obtained even after prolonged stirring (Table 2, entry 2). However, higher reaction temperature (i.e. 80 °C) resulted in decreased 52% yield due to the formation of numerous side products because of the oxidation of α-methylstyrene and acrylate decomposition (Table 2, entry 3).

With the optimized conditions ($Pd(OAc)_2$ (2–5 mol%), $Cu(OAc)_2$ (1 equiv), DMSO/HOAc (1:1), 60 °C), we evaluated various olefins as coupling partners. However, besides acrylates (Table 3), all other evaluated olefins (i.e. 1-octen, cycloocten, 2-vinylpyridine, cyclohexen, 3-methylcyclohexen) failed to couple.

The reaction between α-methylstyrene **1** and *tert*-butyl acrylate **2b** afforded the corresponding product in 42% yield using 2 mol% $Pd(OAc)_2$ (Table 3, entry 1). Under the same conditions, the methyl acrylate **2c** gave only the desired product in 21% yield (Table 3, entry 3). Again, no influence of O_2 pressure on chemical yields was observed (Table 3, entry 2 versus 4).

Having demonstrated the applicability of the protocol for the catalyzed direct cross-coupling of α-methylstyrene with acrylates, we explored the possibility to perform it in a fully catalytic procedure (i.e. both for palladium and copper) using copper salts as co-catalyst to re-oxidise the palladium species under air. Table 4 summarized the representative results for this study using α-methylstyrene **1** (1 equiv) and

Table 4 Direct cross-coupling reaction of α-methyl styrene with various acrylates catalysed by $Pd(OAc)_2$



Entry	2	$Pd(OAc)_2$ (mol%)	CuX_2/mol%	Yield [a]
1	**a**	20	$Cu(OAc)_2$/1 equiv	48 (80:20)
2	**a**	5	$Cu(OAc)_2$/5 mol%	–
3 [b]	**a**	5	$Cu(OAc)_2$/5 mol%	–
4	**a**	5	$Cu(OAc)_2$/40 mol%	8 (nd)
5	**a**	2	$CuCl_2$/1 equiv	5 (nd)
6 [c]	**a**	2	$CuCl_2$/2 mol%	15 (80:20)
7	**a**	10	$CuCl_2$/1 equiv	25 (80:20)
8	**a**	10	$CuCl_2$/10 mol%	58 (80:20)
9	**a**	10	$CuCl_2$/2 mol%	65 (80:20)
10	**b**	10	$CuCl_2$/10 mol%	20 (90:10)
11	**b**	10	$CuCl_2$/2 mol%	46 (90:10)
12	**c**	10	$CuCl_2$/10 mol%	28 (87:13)
13	**c**	10	$CuCl_2$/2 mol%	44 (87:13)

Reaction conditions: **1** (1 equiv), **2** (1 equiv, 0.5 M) and $Pd(OAc)_2$ at 60 °C for 48 h in the mixture solvent: DMSO/HOAc (1:1). a) Isolated yields as a mixture of isomers (ratio [*trans*/*trans*:*cis*/*trans*] is given in brackets). b) With air bubbling. c) Time = 96 h.

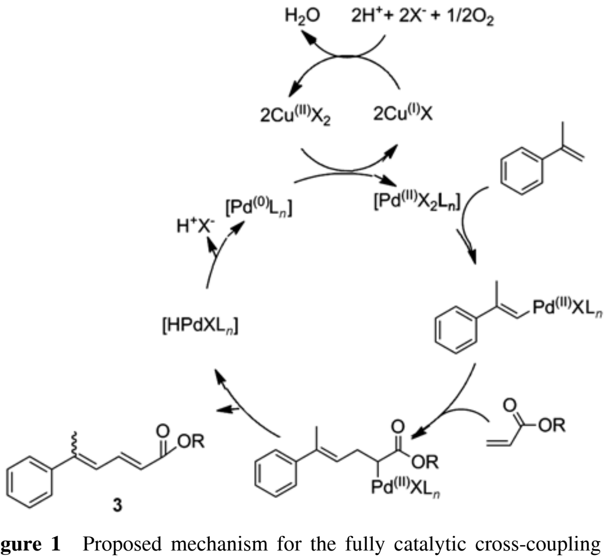


Figure 1 Proposed mechanism for the fully catalytic cross-coupling of α-methylstyrene with acrylates.

different acrylates **2a–c** (1 equiv) in the presence of $Pd(OAc)_2$ and copper salts as the catalytic system.

It was observed that while the reaction proceed smoothly when using copper acetate in stoichiometric amount (Table 4, entry 1), it failed when using this salt as co-catalyst (Table 4, entries 2–4), whatever the reactions were conducted under oxygen atmosphere or continuous air bubbling (Table 4, entry 3). Surprisingly, while the copper chloride used as oxidant is somewhat ineffective (Table 4, entries 5 and 7), it was found valuable when used in catalytic amount and working under air. To date, the best explanation accounting for these observations is related to a possible poisoning of palladium species (i.e. mainly palladium colloids and aggregates) by metallic copper surrounding when copper chloride is used in high concentration. Such palladium particles poisoning by copper was previously observed when engaging supported metallic palladium in presence of copper salts ($CuCl_2$, CuI) [13]. Thus optimisation of the conditions led to a new fully catalytic protocol working with $Pd(OAc)_2$ (10 mol%) and $CuCl_2$ (2 mol%) at 60 °C. These conditions led to useful product yields, up to 65% depending on the acrylate. Interestingly, these conditions did not modify the selectivity of the cross-coupling reaction (i.e. *E*/*Z*, noticed *trans*/*trans*:*cis*/*trans*) that depend essentially on the nature of the acrylate according to previous reports [10, 11].

4 Conclusions

In this paper we described an improved protocol for the oxidative direct cross-coupling of α-methylstyrene with acrylates. We demonstrated that the use of $Pd(OAc)_2$ (10 mol%) associated to $CuCl_2$ (2 mol%) allowed to convert almost fully the starting material used in a ratio (1:1) toward the expected compounds within 48 h. working in a DMSO/AcOH (1:1) mixture at 60 °C , with yields ranging from 44 to 65%. Though Loh's procedure previously reported was already an efficient one, it is shown that a fully catalytic system in both copper and palladium could be used, and that air can be simply used. Current investigations are in progress to extend the method to other olefins and environmentally friendly solvents.

The authors gratefully acknowledge the National Agency of Research (CATAQ N° ANR-07-CP2D-0167-01/02) for funding. MJ and WAL thank ANR for a grant.

1 For recent reviews related to this area see special issues: *Adv Synth Catal*, 2004, 346 dedicated to cross-coupling reactions and *Acc Chem Res*, 2008, 41 dedicated to recent advances in cross-coupling methodologies

2 Joucla L, Djakovitch L. Transition metal-catalysed, direct and site-selective N1-, C2- or C3-arylation of the indole nucleus: 20 Years of improvements. *Adv Synth Catal,* 2009, 351: 673–714

3 Djakovitch L, Rouge P. Environmentally friendly [Pd/Cu]-catalysed C3-alkenylation of free NH-indoles. *Catal Today*, 2009, 140: 90–99

4 Stuart DR, Villemure E, Fagnou K. Elements of regiocontrol in palladium-catalyzed oxidative arene cross-coupling. *J Am Chem Soc,* 2007, 129: 12072–12073

5 Djakovitch L, Rouge P. New homogeneously and heterogeneously [Pd/Cu]-catalysed C3-alkenylation of free NH-indoles. *J Mol Catal A: Chem,* 2007, 273: 230–239

6 Dwight TA, Rue NR, Charyk D, Josselyn R, DeBoef B. C–C bond formation via double C–H functionalization: Aerobic oxidative coupling as a method for synthesizing heterocoupled biaryls. *Org Lett,* 2007, 9: 3137–3139

7 Stuart DR, Fagnou K. The catalytic cross-coupling of unactivated arenes. *Science,* 2007, 316: 1172–1175

8 José da Silva M, Ailton Gonçalves J, Brondi Alves R, Howarth OW, Gusevskaya EV. Palladium catalyzed transformations of monoterpenes: Stereoselective deuteriation and oxidative dimerization of camphene. *J Organomet Chem,* 2004, 689: 302–308

9 Kohll CF, Vanhelde R. Oxidative coupling of vinyl acetate with palladium acetate – Synthesis of 1,4-diacetoxy-1,3-butadiene. *Recl Trav Chim Pays-Bas,* 1967, 86: 1930

10 Hatamoto Y, Sakaguchi S, Ishii Y. Oxidative cross-coupling of acrylates with vinyl carboxylates catalyzed by a $Pd(OAc)_2/HPMoV/O_2$ system. *Org Lett,* 2004, 6: 4623–4625

11 Xu Y-H, Lu J, Loh T-P. Direct cross-coupling reaction of simple alkenes with acrylates catalyzed by palladium catalyst. *J Am Chem Soc,* 2009, 131: 1372–1373

12 Okumura K, Matsui H, Sanada T, Arao M, Honma T, Hirayama S, Niwa M. Generation of the active Pd cluster catalyst in the Suzuki-Miyaura reactions: Effect of the activation with H_2 studied by means of quick XAFS. *J Catal,* 2009, 265: 89–98

13 Gruber M, Chouzier S, Koehler K, Djakovitch L. Palladium on activated carbon: A valuable heterogeneous catalyst for one-pot multi-step synthesis. *Appl Catal A: Gen,* 2004, 265: 161–169