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Direct Cross-Coupling Reaction of Simple Alkenes with Acrylates Catalyzed by Palladium Catalyst

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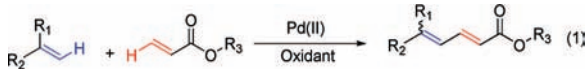
The cross-coupling reaction catalyzed by Pd has been shown to be one of the most powerful methods for the construction of C−C bonds.[1] Accordingly, it has been applied extensively for the synthesis of a wide variety of natural products and pharmaceuticals.[2] One of the most challenging problems associated with this method is the need to use halogenated substrates or/and organometallics.[3] Therefore, many research groups have focused on exploring the Pd-catalyzed coupling reaction through C−H bond activation.[4] However, direct cross-coupling reactions using simple alkenes to form dienes have not been well studied. This is due to the difficulty in activating the alkenyl C−H bond.[5] Self-coupling products of the Pd catalyzed oxidation of monoterpenes[6] and vinyl acetate[7] have been reported. In 2004, Ishii et al. elegantly demonstrated the feasibility of the Pd(II)-catalyzed oxidative cross-coupling reaction of acrylates with vinyl carboxylates in the presence of vanadomolybdophospholic acids under O_2.[5] However, as far as we know, a direct cross coupling reaction between simple alkenes and acrylates has not been reported. Herein, we report that a direct cross-coupling reaction between simple olefins and acrylates could be achieved in high efficiency using catalytic amounts of Pd (eq 1).

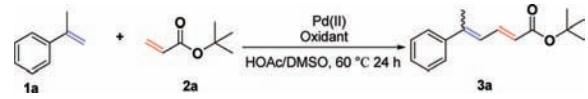


Initially, the reaction of α-methylstyrene with *tert*-butyl acrylate was carried out in the presence of Pd complexes under various reaction conditions. Table 1 summarized the representative results for the reaction of **1a** (2 equiv) with **2a** (1 equiv). The desired product, *tert*-butyl 5-phenylhexa-2,4-dienoate, was formed in 71% isolated yield and with moderate regioselectivity (*E*/*Z* 87/13), when the mixed solvent system DMSO/HOAc (v/v 1/1) was selected as solvent in the presence of 20 mol% $Pd(OAc)_2$ at 60 °C (Table 1, entry 1). When $Pd(OAc)_2$ was increased to 30 mol%, the yield of the product increased slightly to 78% (Table 1, entry 2), while only 33% yield of the product was obtained with 10 mol% loading of the catalyst (Table 1, entry 3). Other catalysts such as $Pd(TFA)_2$ (Table 1, entry 4) and $PdCl_2$ (Table 1, entry 6) afforded the product in only 16% and 21% yields, respectively. However, $Pd(PPh_3)_2Cl_2$ failed to give any product (Table 1, entry 5). We proposed that the stronger electron-donating ligands may block the catalytic cycle by coordinating to the Pd(II) center, thereby decreasing its electrophilicity. At room temperature, the reaction proceeded very slowly. Only 22% yield of the desired product was obtained even after prolonged stirring (Table 1, entry 8).

With the optimized conditions in hand (20 mol % of $Pd(OAc)_2$, $Cu(OAc)_2$ (1 equiv) in mixed solvent of DMSO and HOAc), we then examined the scope of this method. The results were summarized in Table 2. Substrates with various substitution patterns all gave the expected products in moderate to good yields. Substitution at the *para*-, *meta*-, or *ortho*-positions of the α-methylstyrene were tolerated (Table 2, entries 2−4), but the substituent on the *ortho*-position (Table 2, entry 4) decreased the yield slightly. Both electron-poor (Table 2, entry 5) and -rich (Table 2, entries 6−8) substrates could be efficiently alkenylated, although in the former case the yield was lower. Internal alkenes (Table 2, entries 9 and 10) were also successfully employed for the cross-coupling reaction, and the 5-methoxy-3-methy-1*H*-indene afforded **3j** in 87% yield. It appeared that the steric property of the substituents on the double bonds had a very obvious influence on the reaction yields (Table 2, entries 11, 14, and 15). α-Ethyl styrene reacted with *tert*-butyl acrylate to furnish **3k** in moderate yield (Table 2, entry 11). However the reaction of α-methyl styrene with methyl *trans*-2-pentenoate or methyl methacrylate only afforded the corresponding products in 33% and 34% yields, respectively (Table 2, entries 14 and 15). In addition, the direct cross-coupling reaction of *aliphatic* olefins with *tert*-butyl acrylate were screened, when ethyl 4-methyl-4-pentenoate and 2-methylhexene were allowed to react with *tert*-butyl acrylate under the same catalytic conditions, dienoates **3l** and **3m** were obtained in 41% and 36% yields, respectively (Table 2, entries 12 and 13).

Mechanistically, it was unclear why only 2-substituted olefins could proceed smoothly in our reactions. To answer this question, α-methylstyrene-methyl-d_3 (94% atom D) was reacted with *tert*-butyl acrylate under the same reaction conditions. Interestingly, the product **5** was obtained as a mixture of geometrical isomers (*E*/*Z* 89/11) with the retention of the amount of the deuterated methyl group in the product (94% atom D). Based on this information, we

Table 1. Direct Cross-Coupling Reaction of α-Methyl Styrene with *tert*-Butyl Acrylate

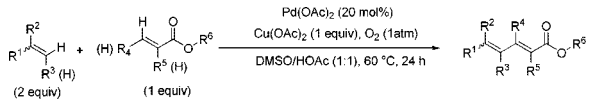


entry[a]	oxidant	Pd(II) (mol %)	time (h)	yield[b] (mol %)
1	$Cu(OAc)_2 + O_2$	$Pd(OAc)_2$/20	24	71
2	$Cu(OAc)_2 + O_2$	$Pd(OAc)_2$/30	24	78
3	$Cu(OAc)_2 + O_2$	$Pd(OAc)_2$/10	24	33
4	$Cu(OAc)_2 + O_2$	$Pd(TFA)_2$/20	24	16
5	$Cu(OAc)_2 + O_2$	$Pd(PPh_3)Cl_2$/20	24	0
6	$Cu(OAc)_2 + O_2$	$PdCl_2$/20	24	21
7[c]	$Cu(OAc)_2 + O_2$	$Pd(OAc)_2$/20	24	53
8[d]	$Cu(OAc)_2 + O_2$	$Pd(OAc)_2$/20	48	22

[a] Reaction conditions unless otherwise specified: **1a** (2 equiv), **2a** (1 equiv, 0.5 M), Pd(II) (0.2 equiv), and oxidant (1 equiv) at 60 °C in the mixture solvent of DMSO/HOAc (1:1). Except the desired product, the homocoupling product of **1a** was found in 8% yield. 1-Phenylvinyl acetate (3% yield), acetophenone (3% yield), and (*E*)-*tert*-butyl 3-acetoxyacrylate (4% yield) as byproducts also were obtained in this reaction. [b] Isolated yields of the mixture of isomers. [c] The concentration of **2a** is 0.25 M. [d] The reaction was performed at 25 °C. HOAc: acetic acid; TFA: trifluoroacetate.

10.1021/ja8084548 CCC: $40.75

Table 2. Direct Cross-Coupling of Various Aromatic Alkenes with *tert*-Butyl Acrylate Catalyzed by $Pd(OAc)_2$



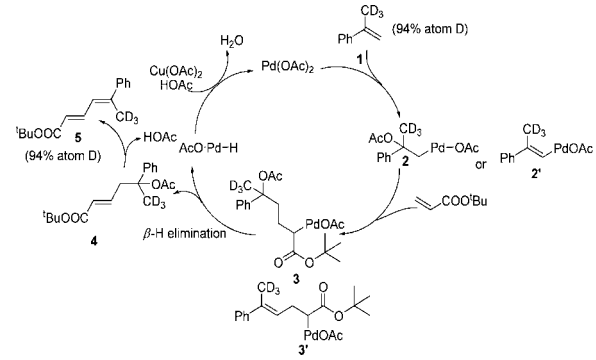
entry	reactants	products	yield (%)[a] (*E*/*Z*)[b]
1[c]	1a, 2a	3a	71 (87:13)
2	1b, 2a	3b	74 (88:12)
3	1c, 2a	3c	68 (90:10)
4	1d, 2a	3d	52 (62:38)
5	1e, 2a	3e	51 (90:10)
6	1f, 2a	3f	78 (91:9)
7	1g, 2a	3g	83 (90:10)
8	1h, 2a	3h	67 (89:11)
9	1i, 2a	3i	83 (>99:1)
10	1j, 2a	3j	87 (>99:1)
11	1k, 2a	3k	65 (84:16)
12	1l, 2a	3l	41 (68:32)
13	1m, 2a	3m	36 (60:40)
14	1a, 2b	3n	33 (84:16)
15	1a, 2c	3o	34 (83:17)

[a] Isolated yields of the mixture of isomers. [b] *E:Z* indicated the ratio of regioselectivity of the disubstituents of olefin in products which was determined by crude NMR spectroscopy. [c] Different electron-deficient coupling partner were also screened for the reaction with α-methylstyrene under optimized reaction conditions: methyl acrylate afforded the corresponding product in 62% yield; ethyl acrylate only gave the desired product in 25% yield; *N*-phenylacrylamide furnished the product in 48% yield; as for acrylonitrile or styrene, no desired product were obtained.

proposed two possible mechanisms as shown in Scheme 1. At this moment, we were not able to distinguish whether direct C−H activation of the vinyl proton occurred to form intermediate **2** or the formation of intermediate **2′**.

In summary, we have developed an efficient method for the Pd(II)-catalyzed direct cross-coupling reaction of simple olefins with acrylates under very mild reaction conditions. This method potentially enlarges the scope of coupling reactions which provides a direct entry to dienoates which are important building blocks in many natural products. Efforts to design more active Pd catalysts

Scheme 1. Proposed Catalytic Cycle for Direct Cross-Coupling Reaction of Olefins



as well as to apply this method to the synthesis of natural products are in progress.

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Supporting Information Available: Additional experimental procedure, chromatogram, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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