JOC The Journal of Organic Chemistry

NOTE

pubs.acs.org/joc

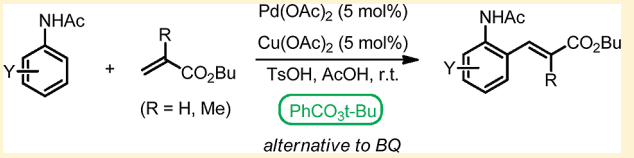
Alternative to Benzoquinone for Room-Temperature Fujiwara−Moritani Reactions

Xinzhu Liu and King Kuok (Mimi) Hii*

Department of Chemistry, Imperial College London, Exhibition Road, South Kensington, London SW7 2AZ, United Kingdom

Supporting Information

ABSTRACT: *tert*-Butyl perbenzoate is a substitute for benzoquinone for mild (room-temperature) Fujiwara−Moritani reactions between acetanilides and butyl acrylate under homogeneous conditions. The system was enhanced further by including $Cu(OAc)_2$ as a cocatalyst. Methyl methacrylate can be activated toward coupling under these conditions.

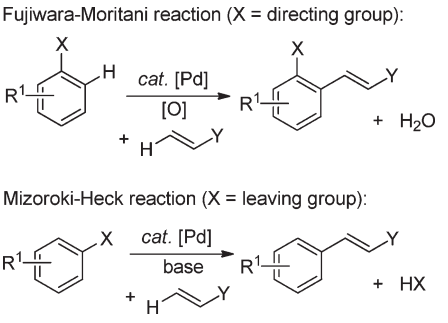


Bond formation between two sp^2 carbons is most effectively achieved by metal catalysis, notably by palladium. For the substitution of an alkenyl C−H bond with an aryl group, the Fujiwara−Moritani (FM)[1,2] and Mizoroki−Heck[3] reactions are both very attractive methodologies (Scheme 1). In the FM reaction, bond formation between two C−H moieties requires an oxidant to promote catalyst turnover. In comparison, the aryl moiety in the Mizoroki−Heck reaction is preactivated by a suitable leaving group (X), which requires a base to regenerate the catalyst precursor. Although the FM reaction was discovered before the Mizoroki−Heck reaction, the latter was adopted more readily by the synthetic community,[4,5] largely due to its better regio- and chemoselectivity attainable by the judicious choice of X. In contrast, the selectivity of the FM reaction is dependent upon the presence of certain functional ("directing") groups. Nevertheless, interest in these reactions was revived in recent years, driven by the potential economic and environmental benefits that can be afforded by mild C−H activation reactions.[6]

The archetypal FM reaction is often represented by the *ortho*-olefination of acetanilide derivatives by butyl acrylate using $Pd(OAc)_2$ as a catalytic precursor (Table 1).[7] The reaction has been reported to proceed at room temperature in moderately good yields (entry 1).[8] Subsequently, improvements to the reaction protocol include electrochemical regeneration of oxidant during the reaction (entry 2)[9] and conditions that allowed the reaction to be performed "on water" (entry 3).[10] Very recently, potassium persulfate can be used to replace 1,4-benzoquinone (BQ) as an oxidant for the room-temperature process (entry 4).[11]

The productive catalytic cycle of this particular reaction has been delineated in a recent study by Brown et al. (Scheme 2).[12] Kinetic experiments showed the rate of the reaction to be first order in anilide and $Pd(OAc)_2$, but independent of [BQ]. Thus, it was concluded that the formation of the palladacycle **II** is the overall rate-limiting step. In earlier work, we have also found that the reaction pathway can be diverted toward an oxidative amination reaction by switching the aromatic reactants from anilides to benzamides.[13] Given that a stoichiometric amount of BQ is required in the absence of any co-oxidants, it is generally accepted that it participates directly in the process as a 2-proton, 2-electron acceptor. However, the precise mechanism of the catalyst regeneration step from the palladium hydride **IV** by the oxidant is not well-understood.[14]

Scheme 1. Comparison between Fujiwara−Moritani and Mizoroki−Heck Reactions

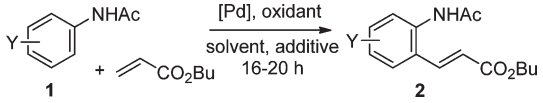


The primary aim of this work is to develop a "greener" and environmentally more sustainable set of conditions for the FM reaction that can be realized under ambient and homogeneous conditions while avoiding hazards associated with handling toxic BQ[15] and hydroquinone (HQ).[16] An initial screen of various organic oxidants (Table 2, entries 2−5) revealed *tert*-butyl hydrogen peroxide (TBHP) and *tert*-butyl perbenzoate (TBPB) are just as effective as BQ (entry 1). The use of TBHP and TBPB as oxidants for the FM reaction has been previously reported by Fujiwara[17] and Tsuji,[18] respectively, but only at elevated temperatures (80−100 °C).

In the current work, TBPB was selected for further studies as it was considered to be a safer alternative to TBHP.[19] Lowering the amount of alkene increased the product yield, chiefly by suppressing the formation of the disubstituted product **3c** and also by increasing the amount of TsOH (entries 5−7). It has been previously suggested that TBPB regenerates Pd(II) from palladium hydrides by O−O bond cleavage via a six-membered

Received: June 10, 2011
Published: August 12, 2011

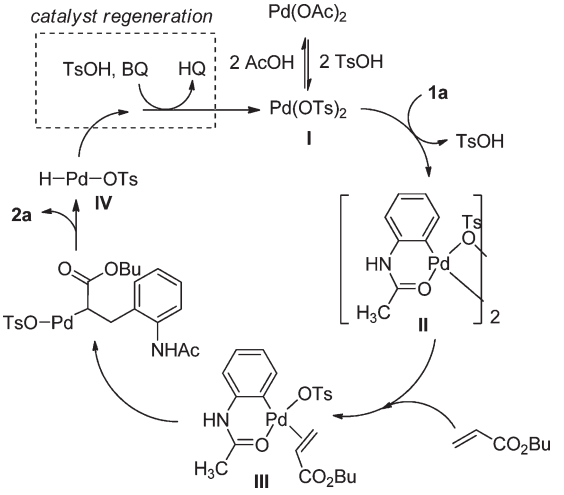
Table 1. Survey of Conditions for Room-Temperature FM Reactions



entry	Y	Pd (concn, mol %)	conditions	yield, %	ref
1	H	$Pd(OAc)_2$ (2)	BQ (1 equiv), AcOH/toluene, TsOH (0.5 equiv), 20 °C	72[a]	8
2	3-Me	$Pd(OAc)_2$ (10)	BQ (0.1 equiv),[c] Bu_4NBF_4 (electrolyte), AcOH (0.5 equiv), 22 °C	82[b]	9
3	3-MeO	$[Pd(MeCN)_4](BF_4)_2$ (10)	BQ (1 equiv), $AgNO_3$ (2 equiv), 2 wt % PTS[d], H_2O, rt	85[a]	10
4	H	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (1 equiv), TFA/CH_2Cl_2, 25 °C	80[a]	11

[a] Isolated yield. [b] Yield determined by ^1H NMR spectroscopy. [c] Oxidant was regenerated electrochemically at a C anode, applying a constant current of 220 mA (with H^+ converted to H_2 at a Ni cathode). [d] PTS = poly(oxyethanyl α-tocopheryl sebacate).

Scheme 2. Mechanism of the Fujiwara−Moritani Reaction



transition state (Scheme 3); i.e., the regeneration of the catalyst can occur without involving a Pd[0] intermediate, predisposing it to deactivate by the formation of metal clusters.[18] Nevertheless, in the present work, the deposition of a small amount of Pd black was visible even at ambient temperature, suggesting that the reductive decomposition of the catalyst is still a competitive process under these conditions. Thus, $Cu(OAc)_2$ was added as a cocatalyst (5 mol %) in an attempt to reoxidize Pd(0) to Pd(II). Indeed, this led to a further increase in product yield to 86% (Table 2, entry 8), which did not improve further with further amount of the perbenzoate (entry 9). On the other hand, lowering the amount of TBPB to substoichiometric levels led to a corresponding decrease in the product yield (entries 10 and 11). Notably, more than 50% product can be obtained using $\leq$0.5 equiv of the peroxy reactant, so it is likely that the catalyst is regenerated by both TBPB and a Cu-mediated process, with O_2 as the terminal oxidant (entry 2).

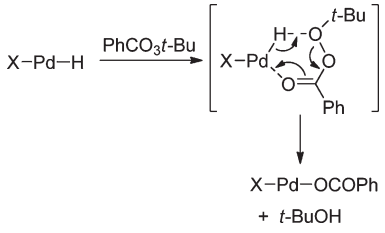
Subsequently, the optimized reaction conditions were applied to the reaction of different acetanilides **1a**−**e** with butyl acrylate (Table 3). Small amounts of the disubstituted products **3a**−**c** were observed as byproducts in these reactions. Otherwise, the results were comparable to, if not better, than those of previous reactions performed using BQ as an oxidant.[8] The pattern of reactivity is similar: higher yields were obtained with electronically neutral or rich anilides (entries 1−3), while the reaction with the electron-poor aromatic substrate was sluggish (entry 4).

Table 2. Identification of Alternative Oxidants and Selected Optimization Studies[a]

entry	oxidant (amt, equiv)	amt of TsOH (equiv)	amt of alkene (equiv)	yield,[b] %
1	BQ (1)	0.25	2	48
2	O_2[c]	0.25	2	0
3	$Cu(OAc)_2$ (1)	0.25	2	20
4	TBHP (1)	0.25	2	48
5	$PhCO_3Bu$ (1)	0.25	2	52
6	$PhCO_3Bu$ (1)	0.25	2.5	37[d]
7	$PhCO_3Bu$ (1)	1	1	61
8	$PhCO_3Bu$ (1), $Cu(OAc)_2$ (0.05)	1	1	86
9	$PhCO_3Bu$ (1.2), $Cu(OAc)_2$ (0.05)	1	1	85
10	$PhCO_3Bu$ (0.5), $Cu(OAc)_2$ (0.05)	1	1	74
11	$PhCO_3Bu$ (0.25), $Cu(OAc)_2$ (0.05)	1	1	60

[a] General reaction conditions: 4-methoxyacetanilide (**1c**; 0.25 mmol, 1 equiv), $Pd(OAc)_2$ (5 mol %), oxidant, TsOH, *n*-butyl acrylate, AcOH (1 mL), rt, 16 h. [b] Calculated from ^1H NMR integration. [c] 1 atm of O_2. [d] 12% disubstituted product **3c** observed in ^1H NMR spectroscopy.

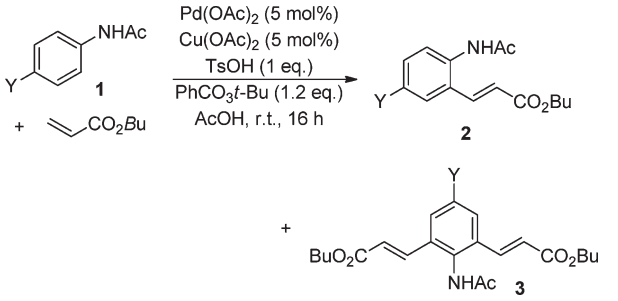
Scheme 3. Regeneration of Catalyst by *tert*-Butyl Perbenzoate As Proposed by Tsuji



Using 2,5-dimethoxy-substituted acetanilide (**1e**) as a substrate, an inseparable mixture of isomers was obtained. Upon hydrogenation, two reduced regioisomers, **2e** and the *para*-substituted **4**, were isolated after column chromatography (Scheme 4). The observation of **5** is particularly noteworthy, as it shows that uncatalyzed electrophilic substitution can be competitive with

dx.doi.org/10.1021/jo201164m |J. Org. Chem. 2011, 76, 8022–8026

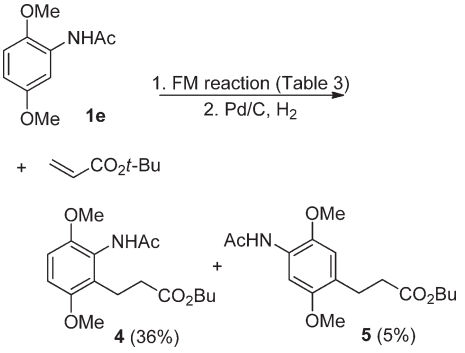
Table 3. Reaction of Acetanilides with *n*-Butyl Acrylate[a]



entry	Y	R	yield of **2**,[b] %	yield of **3**,[b] %	reported yield,[8,b] %
1	H (**a**)	Bu	78	7	72
2	Me (**b**)	Bu	86	7	85
3	OMe (**c**)	Bu	75	5[c]	62
4	Cl (**d**)	Bu	32	0	0

[a] Reaction conditions: acetanilides **1a**−**d** (0.75 mmol), $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (5 mol %), TBPB (0.9 mmol), TsOH (0.9 mmol), *n*-butyl acrylate (0.9 mmol), AcOH (3 mL), rt, 16 h. [b] Isolated yield. [c] Not isolated.

Scheme 4. Competitive Electrophilic Olefination Reactions of 2,5-Dimethoxyacetanilide



electron-rich aromatic rings, even under these mild reaction conditions.

A major limitation of the FM reaction is its rather narrow scope, particularly toward alkene substrates. For the coupling with acetanilides, reactions are largely performed with acrylates. Styrene was sometimes reported as a substrate, but gave typically low yields in Pd-catalyzed processes with acetanilide as the coupling partner (<40%).[9,20] With this in mind, we examined a number of other alkenes. No product formation was afforded by styrene, nor by methyl cyclohex-1-enecarboxylate, chalcone, or acrylonitrile. Conversely, a low yield of product (up to 16%) was obtained with methyl crotonate at elevated temperatures (80 °C).[21] More encouragingly, positive results were obtained with methyl methacrylate *at room temperature*. Due to an unselective β-hydride elimination process, the reaction yielded a complex mixture of at least three double bond isomers, from which only **7c** could be isolated in low yield. By subjecting the crude product to hydrogenolysis, **6a**−**c** could be obtained in low to moderate yields over two steps (Scheme 5, Table 4). As far as we can ascertain, this is the first time methacrylate has been utilized successfully as a substrate for the FM reaction under such mild reaction conditions.[22]

Scheme 5. FM Reaction of Acetanilides with Methyl Methacrylate

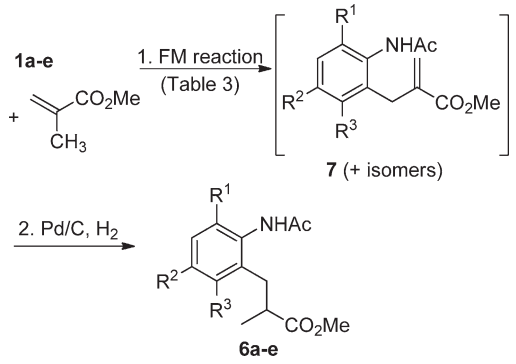


Table 4. FM Reactions of Acetanilides with Methyl Methacrylate[a]

entry	R^1	R^2	R^3	product	yield,[b] %
1	H	H	H	**6a**	43
2	H	Me	H	**6b**	57
3	H	OMe	H	**6c**	46
4	H	Cl	H	**6d**	
5	OMe	H	OMe	**6e**	5[c]

[a] Reaction conditions: (1) FM reaction, as described in Table 3, substituting butyl acrylate with methyl methacrylate; (2) Pd/C, H_2, MeOH, 4 h. [b] Isolated yield of **6**, over two steps. [c] Product was not isolated.

To conclude, TBPB is a viable oxidant for room-temperature Fujiwara−Moritani reactions.[23] This obviates exposure to toxic benzoquinone and the need to aerate flammable organic reactants and solvents at elevated temperature. The new protocol also allows methyl methacrylate to be utilized as an olefin substrate under mild reaction conditions. The study suggests that the scope of FM reactions may be dependent on the choice of the oxidant, which will warrant further investigation.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all precursors and reagents were procured commercially and used as received. Palladium salts were provided by a commercial supplier. ^1H and ^{13}C NMR spectra were recorded with ^1H at 400 MHz and ^{13}C at 100.6 MHz. Chemical shifts are reported in δ (ppm), referenced to residual protons (7.26 ppm) and ^{13}C signals of deuterated chloroform (77 ppm). Multiplicity is abbreviated to s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Melting points were uncorrected. Infrared spectra were recorded on an FT-IR spectrometer equipped with a beam-condensing accessory. Column chromatography was performed using flash silica gel. Acetanilide derivatives **1a**−**e** were prepared in 95−99% yield by the acetylation of the corresponding aniline.[24]

General Procedure for the Intermolecular FM Reaction. All reactions were assembled under aerobic conditions with reagent-grade solvents. A reaction vial was charged with a stir bar, the appropriate acetanilide (0.75 mmol), *tert*-butyl perbenzoate (171 μL, 0.9 mmol), *p*-toluenesulfonic acid monohydrate (142.5 mg, 0.75 mmol), $Pd(OAc)_2$ (8.4 mg, 0.038 mmol), $Cu(OAc)_2$ (7.0 mg, 0.038 mmol), and acetic acid (2.5 mL). A solution of *n*-butyl acrylate (120 μL, 0.75 mmol) or methyl methacrylate (80.2 μL, 0.75 mmol) in acetic acid (0.5 mL) was added with stirring over 3 min. The vial was then capped with a rubber septum,

dx.doi.org/10.1021/jo201164m |J. Org. Chem. 2011, 76, 8022–8026

and the mixture was stirred at room temperature for 16 h (an O_2 balloon may be fixed to the septum, if required). The solvent was evaporated under vacuum, and the residue was dissolved in EtOAc (100 mL). The solution was washed with saturated Na_2CO_3 (2 × 15 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting solids were purified by column chromatography to yield the product as a white solid.

General Procedure for the Hydrogenation Reaction. Pd/C (5 wt %, 0.075 mmol, 159 mg) was placed in a 20 mL two-neck round-bottomed flask to which a solution of the alkene substrate (0.75 mmol) in EtOH (7.5 mL) was added. H_2 was passed through the mixture for 10 min, before it was left to stir under a H_2 atmosphere for 4 h. Catalyst was removed from the reaction mixture by filtering through a short silica gel pad, which was rinsed with a little EtOH. The filtrate was evaporated to furnish the product.

Data for (*E*)-3-(2-(acetylamino)phenyl)propenoic acid butyl ester (2a): yield 160 mg, 82% as a white solid; mp 81−82 °C (lit.[8] mp 86 °C); R_f = 0.3, hexane/EtOAc (2/3); υ_{max}/cm^{-1} 3258, 1710, 1665, 1633, 1527, 1264, 1171, 760; δ_H 7.82 (d, *J* = 15.9, 1H), 7.67−7.65 (m, 1H), 7.55−7.53 (m, 1H), 7.52 (br s, 1H),7.37−7.34 (m, 1H), 7.20−7.17 (m, 1H), 6.39 (d, *J* = 15.9, 1H), 4.18 (t, *J* = 6.6, 2H), 2.21 (s, 3H), 1.71−1.64 (m, 2H), 1.47−1.38 (m, 2H), 0.95 (t, *J* = 7.4, 3H); δ_C 169.3, 166.9, 139.6, 136.0, 130.7, 127.9, 126.9, 125.9, 125.6, 120.1, 64.6, 30.7, 23.9, 19.2, 13.7; *m*/*z* (EI) 261 (M^+, 43), 219 (32), 146 (100), 118 (91), 43 (39).

Data for (*E*)-butyl 3-(2-acetamido-5-methylphenyl)acrylate (2b): yield 178 mg, 86% as a white solid; mp 93−94 °C (lit.[25] mp 97 °C); R_f = 0.25, hexane/EtOAc (1/1); υ_{max}/cm^{-1} 3240, 1710, 1663, 1634, 1520, 1264; δ_H (400 MHz, $CDCl_3$) 7.78 (d, *J* = 15.8, 1H), 7.58 (br s, 1H), 7.51 (d, *J* = 8.3, 1H), 7.34 (d, *J* = 2.2, 1H), 7.16 (dd, *J* = 8.3, 2.2, 1H), 6.37 (d, *J* = 15.8, 1H), 4.16 (t, *J* = 6.7, 2H), 2.31 (s, 3H), 2.18 (s, 3H), 1.70−1.63 (m, 2H), 1.44−1.38 (m, 2H), 0.94 (t, *J* = 7.4, 3H); δ_C 169.2, 167.0, 139.6, 135.8, 133.5, 131.6, 128.0, 127.3, 125.8, 119.9, 64.6, 30.7, 23.9, 21.0, 19.2, 13.7; *m*/*z* (EI) 275 (M^+, 42), 233 (23), 160 (100), 132 (78).

Data for (*E*)-butyl 3-(2-acetamido-5-methoxyphenyl)acrylate (2c): yield 163 mg, 75% as a white solid; mp 129−130 °C (lit.[8] mp 128−129 °C); R_f = 0.25, $CHCl_3$; υ_{max}/cm^{-1} 3256, 1707, 1651, 1639, 1529, 1242, 980, 729; δ_H 7.78 (d, *J* = 15.9, 1H), 7.45 (d, *J* = 8.8, 1H), 7.44 (br s, 1H), 7.05 (d, *J* = 2.8, 1H), 6.93 (dd, *J* = 8.8, 2.8, 1H), 6.39 (d, *J* = 15.9, 1H), 4.20 (t, *J* = 6.7, 2H), 3.82 (s, 3H), 2.20 (s, 3H), 1.72−1.65 (m, 2H), 1.48−1.39 (m, 2H), 0.97 (t, *J* = 7.4, 3H); δ_C 169.7, 166.9, 157.7, 139.6, 130.2, 129.1, 128.0, 120.0, 116.4, 111.0, 64.6, 55.6, 30.7, 23.6, 19.2, 13.7; *m*/*z* (EI) 291 (M^+, 9), 165 (78), 123 (76), 108 (100), 84 (57).

Data for (*E*)-butyl 3-(2-acetamido-5-chlorophenyl)acrylate (2d): yield 72.6 mg, 32% as a white solid; mp 137−138 °C (lit.[25] mp 140−141 °C); R_f = 0.55, hexane/EtOAc (3/1); υ_{max}/cm^{-1} 3261, 1713, 1663, 1519, 1315, 1175; δ_H 8.03 (br s, 1H), 7.67 (d, *J* = 15.8, 1H), 7.54 (d, *J* = 8.7, 1H), 7.44 (d, *J* = 1.7, 1H), 7.22 (d, *J* = 8.7, 1.7, 1H), 6.32 (d, *J* = 15.8, 1H), 4.14 (t, *J* = 6.1, 2H), 2.15 (s, 3H), 1.66−1.60 (m, 2H), 1.42−1.36 (m, 2H), 0.93 (t, *J* = 7.4, 3H); δ_C 169.3, 166.6, 138.1, 134.5, 131.3, 130.4, 129.3, 126.8, 126.6, 121.3, 64.7, 30.6, 23.9, 19.2, 13.7; *m*/*z* (EI) 295 (M^+, 48), 253 (47), 180 (100), 152 (54), 43 (51).

Data for (2*E*,2′*E*)-dibutyl 3,3′-(2-acetamido-1,3-phenylene)diacrylate (3a): yield 18 mg, 7% as a white solid; mp 141−142 °C; R_f = 0.5, hexane/EtOAc (2/3); υ_{max}/cm^{-1} 3248, 1716, 1665, 1635, 1279, 1172; δ_H 7.77 (d, *J* = 15.9, 2H), 7.67 (d, *J* = 7.8, 2H), 7.36 (t, *J* = 7.8, 1H), 7.22 (br s, 1H), 6.42 (d, *J* = 15.9, 2H), 4.19 (t, *J* = 6.6, 4H), 2.29 (s, 3H), 1.72−1.6 (m, 4H), 1.49−1.39 (m, 4H), 0.96 (t, *J* = 7.4, 6H); δ_C 169.6, 166.7, 139.5, 134.6, 133.2, 128.5, 128.1, 121.0, 64.6, 30.7, 23.2, 19.2, 13.7; *m*/*z* (EI) 387 (M^+, 5), 272 (18), 91 (48), 198 (39), 170 (100); HRMS *m*/*z* (EI) calcd for $C_{22}H_{29}NO_5$ (M^+) 387.2046, found 387.2046. Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 68.29; H, 7.69; N, 3.66.

Data for (2*E*,2′*E*)-Dibutyl 3,3′-(2-acetamido-5-methyl-1,3-phenylene)diacrylate (3b): yield 18 mg, 7% as a white solid; mp 122−123 °C; R_f = 0.4, hexane/EtOAc (1/1); υ_{max}/cm^{-1} 3261, 1710, 1659, 1637, 1458, 1283, 1177, 981; δ_H (400 MHz, $CDCl_3$) 7.74 (d, *J* = 16.0, 2H), 7.49 (s, 2H), 7.06 (br s, 1H), 6.43 (d, *J* = 16.0, 2H), 4.19 (t, *J* = 6.7, 4H), 2.38 (s, 3H), 2.28 (s, 3H), 1.72−1.66 (m, 4H), 1.46−1.38 (m, 4H), 0.96 (d, *J* = 7.4, 6H); δ_C 169.9, 166.8, 139.7, 137.7, 132.9, 132.4, 129.1, 120.5, 64.6, 30.7, 23.1, 21.1, 19.2, 13.7; *m*/*z* (EI) 401 (M^+, 34), 358 (35), 286 (61), 212 (63), 184 (100), 57 (36); HRMS *m*/*z* (EI) calcd for $C_{23}H_{31}NO_5$ (M^+) 401.2202, found 401.2201. Anal. Calcd for $C_{23}H_{31}NO_5$: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.88; H, 7.69; N, 3.53.

Data for butyl 3-(2-acetamido-3,6-dimethoxyphenyl)propanoate (4): yield 87 mg, 36% as a white solid; mp 91−92 °C; R_f = 0.4, hexane/EtOAc (1/3); υ_{max}/cm^{-1} 3254, 1729, 1660, 1486, 1256, 1082; δ_H 7.85 (br s, 1H), 6.76−6.72 (m, 2H), 4.01 (t, *J* = 6.7, 2H), 3.78 (s, 3H), 3.78 (s, 6H), 2.86 (t, *J* = 6.7, 2H), 2.66 (t, *J* = 6.7, 2H), 2.22 (s, 3H), 1.57−1.51 (m, 2H), 1.36−1.29 (m, 2H), 0.89 (t, *J* = 7.4, 3H); δ_C 174.9, 169.4, 151.9, 149.2, 127.3, 125.6, 109.7, 108.9, 64.5, 56.3, 55.7, 33.1, 30.6, 23.4, 21.1, 19.1, 13.7. *m*/*z* (EI) 323 (M^+, 68), 281 (46), 207 (73), 192 (100); HRMS *m*/*z* (EI) calcd for $C_{17}H_{25}NO_5$ (M^+) 323.1733, found 323.1733. Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.16; H, 7.79; N, 4.28.

Data for butyl 3-(4-acetamido-2,5-dimethoxyphenyl)propanoate (5): yield 16 mg, 5% as a white solid; mp 94−95 °C; R_f = 0.6, hexane/EtOAc (1/3); υ_{max}/cm^{-1} 3325, 1730, 1678, 1526, 1216; δ_H 8.07 (s, 1H), 7.71 (br s, 1H), 6.70 (s, 1H), 4.06 (t, *J* = 6.7, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 2.86 (t, *J* = 6.7, 2H), 2.57 (t, *J* = 6.7, 2H), 2.19 (s, 3H), 1.63−1.56 (m, 2H, overlapped with water peak), 1.36−1.31 (m, 2H), 0.91 (t, *J* = 7.4, 3H); δ_C 173.5, 168.1, 151.4, 141.2, 126.5, 122.4, 112.3, 103.6, 64.2, 56.3, 55.9, 34.4, 30.5, 26.1, 24.9, 19.1, 13.7; *m*/*z* (EI) 323 (M^+, 100), 266 (55), 208 (80), 166 (79); HRMS *m*/*z* (EI) calcd for $C_{17}H_{25}NO_5$ (M^+) 323.1733, found 323.1736. Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.17; H, 7.72; N, 4.43.

Data for methyl 3-(2-acetamidophenyl)-2-methylpropanoate (6a): yield 76 mg, 43% over two steps, as a white solid; mp 79−80 °C; R_f = 0.1, hexane/EtOAc (1/1); υ_{max}/cm^{-1} 3263, 1733, 1662, 1525, 1451, 753; δ_H 8.49 (br s, 1H), 7.76−7.74 (m, 1H), 7.26−7.22 (m, 1H), 7.18−7.16 (m, 1H), 7.13−7.08 (m, 1H), 3.62 (s, 3H), 3.01 (dd, *J* = 9.6, 14.1, 1H), 2.80−2.74 (m, 1H), 2.57 (dd, *J* = 4.5, 14.1, 1H), 2.23 (s, 3H), 1.32 (d, *J* = 7.2, 3H); δ_C 178.2, 168.8, 135.5, 131.2, 130.4, 127.2, 125.2, 124.7, 52.2, 41.8, 34.4, 24.3, 18.6; *m*/*z* (EI) 235 (M^+, 43), 162 (29), 132 (34), 106 (100). HRMS *m*/*z* (EI) calcd for $C_{13}H_{17}NO_3$ (M^+) 235.1208, found 235.1205. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.44; H, 7.34; N, 5.90.

Data for methyl 3-(2-acetamido-5-methylphenyl)-2-methylpropanoate (6b): yield 106.5 mg, 57% over two steps, as a white solid; mp 91−92 °C; R_f = 0.3, CH_2Cl_2/EtOAc (1/2); υ_{max}/cm^{-1} 3265, 1733, 1659, 1520, 1168; δ_H 8.37 (br s, 1H), 7.58 (d, *J* = 8.2, 1H), 7.03 (dd, *J* = 8.2, 2.3, 1H), 6.95 (d, *J* = 2.3, 1H), 3.62 (s, 3H), 2.98 (dd, *J* = 14.1, 9.8, 1H), 2.80−2.73 (m, 1H), 2.53 (dd, *J* = 14.1, 4.4, 1H), 2.28 (s, 3H), 2.22 (s, 3H), 1.32 (d, *J* = 7.1, 3H); δ_C 178.2, 168.8, 134.8, 132.8, 131.3, 130.8, 127.8, 124.9, 52.1, 41.8, 34.4, 21.2, 20.8, 18.6; *m*/*z* (EI) 249 (M^+, 52), 175 (70), 146 (43), 120 (100); HRMS *m*/*z* (EI) calcd for $C_{14}H_{19}NO_3$ (M^+) 249.1365, found 249.1366. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.47; H, 7.70; N, 5.58.

Data for methyl 3-(2-acetamido-5-methoxyphenyl)-2-methylpropanoate (6c): yield 91 mg, 46% over two steps, as a white solid; mp 92.5−93.5 °C; R_f = 0.08, hexane/EtOAc (1/1); υ_{max}/cm^{-1} 3255, 1736, 1657, 1502, 1230; δ_H 8.19 (br s, 1H), 7.52 (d, *J* = 8.8, 1H), 6.77 (dd, *J* = 8.8, 2.9, 1H), 6.68 (d, *J* = 2.9, 1H), 3.77 (s, 3H), 3.62 (s, 3H), 2.98 (dd, *J* = 14.0, 9.7, 1H), 2.79−2.74 (m, 1H), 2.51 (dd, *J* = 14.0, 4.7, 1H), 2.21 (s, 3H), 1.31 (d, *J* = 7.2, 3H); δ_C 178.0, 169.0, 157.1, 133.7, 128.5, 126.9, 115.6, 112.3, 55.4, 52.1, 41.7, 34.6, 24.0, 18.6; *m*/*z* (EI) 265 (M^+, 89), 233 (44), 192 (36), 136 (100); HRMS *m*/*z* (EI)

calcd for $C_{14}H_{19}NO_4$ (M^+) 265.1314, found 265.1312. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.64; H, 7.51; N, 5.36.

Data for methyl 2-(2-acetamido-5-methoxybenzyl)acrylate (7c): isolated as one of the FM products from the reaction of **1c** with methyl methacrylate (Table 4); yield 35.5 mg, 18% as a white solid; mp 126–127 °C; R_f = 0.45, CH_2Cl_2/pentane/MeOH (40/10/1); υ_{max}/cm^{-1} 3266, 1718, 1658, 1522, 1502, 1437, 1284, 1254, 1138, 1040, 803; δ_H 8.44 (br s, 1H), 7.61 (d, J = 8.8, 1H), 6.79 (dd, J = 2.9, 8.8, 1H), 6.71 (d, J = 2.9, 1H), 6.23 (d, J = 0.7, 1H), 5.79 (d, J = 0.7, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.53 (s, 2H), 2.21 (s, 3H); 168.3, 167.1, 156.4, 138.5, 131.9, 127.9, 126.8, 125.9, 114.9, 111.8, 54.8, 51.8, 33.4, 23.4; m/z (EI) 263 (M^+, 100), 190 (58), 174 (61), 114 (77), 84 (75), 49 (73); HRMS m/z (EI) calcd for $C_{14}H_{17}NO_4$ (M^+) 263.1158, found: 263.1160. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.69; H, 6.53; N, 5.29.

■ ASSOCIATED CONTENT

Supporting Information. Description of optimization studies and copies of ^1H and ^{13}C NMR spectra of compounds **2**–**7**. This material is available free of charge via the Internet at http://pubs.acs.org/.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: mimi.hii@imperial.ac.uk.

■ ACKNOWLEDGMENT

We thank CVCP and Imperial College London for studentship support (to X.L.) and Johnson Matthey plc for the loan of Pd salts.

■ REFERENCES

(1) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119.
(2) Moritani, I.; Fujiwara, Y. *Synthesis* **1973**, 524.
(3) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.
(4) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.
(5) Heravi, M. M.; Fazeli, A. *Heterocycles* **2010**, *81*, 1979.
(6) Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* **2010**, 1399.
(7) Rh- and Co-catalyzed FM reactions are known, but require higher reaction temperatures. For example, see: (a) Patureau, F. W.; Besset, T.; Gloruis, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1064. (b) Park, S.; Kim, J. Y.; Chang, S. *Org. Lett.* **2011**, *13*, 2372. (c) Ilies, L.; Chen, Q.; Zeng, X. M.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 5221. (d) Rakshit, S.; Grohmann, C.; Besset, T.; Gloruis, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350.
(8) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. *J. Am. Chem. Soc.* **2002**, *124*, 1586.
(9) Amatore, C.; Cammoun, C.; Jutand, A. *Adv. Synth. Catal.* **2007**, *349*, 292.
(10) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 1972.
(11) Kim, B. S.; Jang, C.; Lee, D. J.; Youn, S. W. *Chem.—Asian J.* **2010**, *5*, 2336.
(12) Rauf, W.; Thompson, A. L.; Brown, J. M. *Dalton Trans.* **2010**, *39*, 10414.
(13) Liu, X.; Hii, K. K. *Eur. J. Org. Chem.* **2010**, 5181.
(14) It is worth noting that BQ has been implicated as a ligand to facilitate the reoxidation of Pd[0] by O_2 in reactions of NHC-ligated palladium complexes: (a) Decharin, N.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 5732. (b) Konnick, M. M.; Decharin, N.; Popp, B. V.; Stahl, S. S. *Chem. Sci.* **2011**, *2*, 326.
(15) (a) Das, A.; Chakrabarty, S.; Choudhury, D.; Chakrabarti, G. *Chem. Res. Toxicol.* **2010**, *23*, 1054. (b) Lindsey, R. H.; Bromberg, K. D.; Felix, C. A.; Osheroff, N. *Biochemistry* **2004**, *43*, 7563.
(16) (a) Andersen, F. A.; Bergfeld, W. F.; Belsito, D. V.; Hill, R. A.; Klaassen, C. D.; Liebler, D. S.; Marks, J. G.; Shank, R. C.; Slaga, T. J.; Snyder, P. W. *Int. J. Toxicol.* **2010**, *29*, 274S. (b) McGregor, D. *Crit. Rev. Toxicol.* **2007**, *37*, 887.
(17) Jia, C. G.; Lu, W. J.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097.
(18) Tsuji, J.; Nagashima, H. *Tetrahedron* **1984**, *40*, 2699.
(19) TBHP is known to be mutagenic in vitro. The toxicity of TBPB has been extensively studied with mice and rats, where it was found that "systematic toxicity is not observed in either species with oral doses as high as 1112 mg/kg": Matthews, H. B. *NTP Technical Report on Toxicity Studies of tert-Butyl Perbenzoate*; NIH Publication No. 92-3134; National Institutes of Health: Bethesda, MD, July 1992.
(20) Wang, J. R.; Yang, C. T.; Liu, L.; Guo, Q. X. *Tetrahedron Lett.* **2007**, *48*, 5449.
(21) A low yield was also observed (ca. 40%) using persulfate as the oxidant; see ref 11.
(22) There is only one previous example of the substitution of benzene by ethyl methacrylate under oxidative palladium catalysis. Reactions were conducted at 90 °C to give 24% combined yield of regioisomers; see ref 17.
(23) Classified as an organic peroxide, due care is still required to minimize explosive hazards of TBPB by shock, friction, or contact with sources of ignition.
(24) Harwood, L. M.; Moody, C. J.; Percy, J. M. *Experimental Organic Chemistry*, 2nd ed.; Blackwell Publishing: Malden, MA, 1999; p 272.
(25) Lee, G. T.; Jiang, X. L.; Prasad, K.; Repic, J.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 1921.