Selective Pd-Catalyzed Oxidative Coupling of Anilides with Olefins through C-H Bond Activation at Room Temperature

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General Information. Experiments were carried out under air atmosphere using magnetic stirring unless otherwise noted. Solvents were purchased from commercial suppliers used without further purification. *n*-Butylacrylate was purchased from Aldrich and used as received. Anilides were obtained from commercial suppliers (Acros) or synthesized by reaction of the corresponding aniline with acetic anhydride. $[(C_6H_4NHC(O)CH_3)Pd(II)(OAc^-)]_2$ was prepared as reported by Fujiwara.[1] ^{1}H NMR spectra were recorded on a Varian Mercury 300 (300.1 MHz) in $CDCl_3$ and are reported in ppm using tetramethylsilane as external standard. Data are reported as follows: (b – broad, s – singlet, d – doublet, t – triplet, q – quartet, m – multiplet; integration; coupling constant(s) in Hz; assignment). ^{13}C NMR spectra were recorded on the same spectrometer (75.5 MHz) in proton decoupled mode. GC measurements were performed on a Shimadzu GC-17A, equipped with a F.I.D. detector and a BPX35 column with an internal diameter of 0.22 mm and a film thickness of 0.25 µm. GC/MS measurements (E.I. detection) were performed on a HP 5890/5971 apparatus, equipped with a ZB-5 column (5% cross-linked phenyl polysiloxane) with an internal diameter of 0.25 mm and film thickness of 0.25 µm. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were performed at the Department of Microanalysis at the Rijksuniversiteit Groningen, The Netherlands.

Parallel Screening Experiments. Rapid screening experiments were carried out using a commercially available automated parallel synthesis Chemspeed ASW 2000 apparatus. The reactions were performed under an inert atmosphere of nitrogen. Each reaction vessel was charged with 0.02 mmol (1 mol%) of the desired catalyst, 0.25 mL of dihexylether as internal standard and, if required, 216 mg (2.0 mmol) of benzoquinone (BQ), followed by 2.0 mL of a stock solution of the aniline-substrate (1.0 M) in the desired solvent. Next, the alkene was added (2.0 mmol), the reaction mixture heated to 80 °C and subsequently stirred under vortex agitation for 16 hrs. Samples of the resulting reaction mixtures were diluted with hexanes and analyzed by GC/MS. See the figure on the last page for details on the reactions screened.

General Procedure for the Coupling of Acetanilide Derivatives with *n*-Butylacrylate. In a typical experiment, 3.0 mmol anilide, 13.5 mg (0.06 mmol) of $Pd(OAc)_2$, 324 mg (3.0 mmol) of BQ and 286 mg (1.5 mmol) of *p*-toluenesulfonic acid monohydrate are weighed into a one-neck roundbottom flask charged with a stirring bar. Next, 4.5 mL acetic acid is added, followed by a solution of 0.42 mL (3.0 mmol) *n*-butylacrylate in 2.25 mL of toluene. The flask is capped with a rubber septum, and the mixture is stirred overnight. Aliquots of the mixture are taken and diluted in diethyl ether, washed with a saturated $NaHCO_3$-solution, dried over $MgSO_4$, followed by GC or GC/MS analysis. After 16 hrs., the reaction mixture is diluted with 15 mL of ether, and carefully neutralized with a 2.5 M NaOH solution. After extraction of the aqueous phase with 15 mL ether, the combined organic phases are washed with water (15 mL), dried ($MgSO_4$) and evaporated in vacuo. The resulting solids are purified by column chromatography to yield the corresponding product as a white powder. Recrystallization provided analytically pure product (except for **15**).

(*E*)-3-(2-acetylamino-phenyl)-propenoic acid butyl ester (4). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, 1H, *J* = 15.7 Hz, olefinic H), 7.73 (d, 1H, *J* = 8.4 Hz, ArH), 7.54 (d, 1H, *J* = 7.8 Hz, ArH), 7.40-7.37 (m, 2H, ArH), 7.20 (m, 1H, ArH), 6.39 (d, 1H, *J* = 15.7 Hz, olefinic H), 4.19 (t, 2H, *J* = 6.6 Hz, C(O)OC*H*$_2$), 2.22 (s, 3H, NHC(O)C*H*$_3$), 1.71-1.62 (m, 2H, OCH$_2$C*H*$_2$), 1.45-1.42 (m, 2H, CH$_2$C*H*$_2$CH$_3$), 0.95 (t, 3H, *J* = 7.5 Hz, CH$_2$CH$_2$C*H*$_3$). (The N-*H* resonance is not observed); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 167.2, 139.5, 136.1, 131.0, 127.9, 127.3, 126.2, 125.6, 120.8, 64.9, 30.9, 24.4, 19.4, 14.0. Mp: 86 °C. Calcd. (%) for $C_{15}H_{19}NO_3$: C 68.94, H 7.33, N 5.36; found: C 68.96, H 7.40, N 5.34.

(*E*)-3-(2-acetylamino-5-methylphenyl)-propenoic acid butyl ester (13). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, 1H, *J* = 16.0 Hz, olefinic H), 7.65 (bs, 1H, N-*H*), 7.55 (d, 1H, *J* = 8.2 Hz, ArH), 7.36 (s, 1H, ArH), 7.19 (d, 1H, *J* = 8.2 Hz, ArH), 6.38 (d, 1H, *J* = 16.0 Hz, olefinic H), 4.19 (t, 2H, *J* = 6.6 Hz, C(O)OC*H*$_2$), 2.33 (s, 3H, NHC(O)C*H*$_3$), 2.14 (s, 3H, ArC*H*$_3$), 1.70-1.63 (m, 2H, OCH$_2$C*H*$_2$), 1.46-1.38 (m, 2H, CH$_2$C*H*$_2$CH$_3$), 0.96 (t, 3H, *J* = 7.3 Hz, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.5, 167.3, 139.9, 136.0, 133.7, 131.8, 128.3, 127.5, 126.1, 120.1, 64.8, 30.9, 24.1, 21.2, 19.4, 14.0. Mp: 97 °C. Calcd. (%) for $C_{16}H_{21}NO_3$: C 69.79, H 7.69, N 5.09; found: C 69.65, H 7.82, N 5.08.

(*E*)-3-(2-acetylamino-4-methylphenyl)-propenoic acid butyl ester (14). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (bs, 1H, N-*H*) 7.74 (d, 1H, *J* = 15.9 Hz, olefinic H), 7.40-7.35 (m, 2H, ArH), 6.94 (d, 1H, *J* = 8.0 Hz, ArH), 6.27 (d, 1H, *J* = 15.9 Hz, olefinic H), 4.12 (t, 2H, *J* = 6.6 Hz, C(O)OCH_2), 2.27 (s, 3H, NHC(O)CH_3), 2.15 (s, 3H, ArCH_3), 1.64-1.59 (m, 2H, OCH_2CH_2), 1.40-1.35 (m, 2H, $CH_2CH_2CH_3$), 0.91 (t, 3H, *J* = 7.3 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 167.4, 141.7, 139.6, 136.0, 127.2, 127.0, 126.2, 125.2, 119.4, 64.8, 30.9, 24.3, 21.7, 19.4, 14.0. Mp: 127-128 °C. Calcd. (%) for $C_{16}H_{21}NO_3$: C 69.79, H 7.69, N 5.09; found: C 69.77, H 7.74, N 5.08.

(*E*)-3-(2-acetylamino-3-methylphenyl)-propenoic acid butyl ester (15). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, 1H, *J* = 15.9 Hz, olefinic H), 7.74 (bs, 1H, N-*H*), 7.30-7.22 (m, 3H, ArH), 6.38 (d, 1H, *J* = 15.9 Hz, olefinic H), 4.18 (t, 2H, *J* = 6.5 Hz, C(O)OCH_2), 2.30 (s, 3H, NHC(O)CH_3), 2.20 (s, 3H, ArCH_3), 1.71-1.67 (m, 2H, OCH_2CH_2), 1.46-1.39 (m, 2H, $CH_2CH_2CH_3$), 0.95 (t, 3H, *J* = 7.4 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.8, 167.3, 140.7, 136.8, 134.7, 130.7, 129.9, 127.9, 123.9, 120.0, 64.7, 30.9, 23.3, 19.4, 18.6, 14.0. Compound contains a significant amount of starting compound (**7**), which could not be separated from the product.

(*E*)-3-(2-acetylamino-5-methoxyphenyl)-propenoic acid butyl ester (16). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 1H, *J* = 15.7 Hz, olefinic H), 7.48 (d, 1H, , *J* = 8.8 Hz, ArH), 7.08-7.05 (m, 2H, N-*H* and ArH overlapping), 6.95-6.91 (m, 1H, ArH), 6.38 (d, 1H, *J* = 15.7 Hz, olefinic H), 4.19 (t, 2H, *J* = 6.6 Hz, C(O)OCH_2), 3.80 (s, 3H, OCH_3), 2.20 (s, 3H, NHC(O)CH_3), 1.69-1.61 (m, 2H, OCH_2CH_2), 1.46-1.38 (m, 2H, $CH_2CH_2CH_3$), 0.92 (t, 3H, *J* = 7.4 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 167.1, 157.9, 139.7, 130.4, 129.3, 128.2, 120.5, 117.0, 111.3, 64.8, 55.8, 30.9, 23.9, 19.4, 14.0. Mp: 128-129 °C. Calcd. (%) for $C_{16}H_{21}NO_4$: C 65.96, H 7.27, N 4.81; found: C 66.04, H 7.29, N 4.85.

(*E*)-3-(2-benzoylamino-phenyl)-propenoic acid butyl ester (20). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (bs, 1H, N-*H*), 7.88-7.81 (m, 4H, ArH + olefinic H), 7.59-7.38 (m, 5H, ArH), 7.25-7.20 (m, 1H, ArH), 6.40 (d, 1H, *J* = 15.9 Hz, olefinic H), 4.13 (t, 2H, *J* = 6.6 Hz, C(O)OCH_2), 1.65-1.58 (m, 2H, OCH_2CH_2), 1.41-1.33 (m, 2H, $CH_2CH_2CH_3$), 0.90 (t, 3H, *J* = 7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 166.3, 139.4, 136.1, 134.4, 132.4, 131.0, 129.1, 128.4, 127.5, 126.3, 125.6, 121.1, 64.8, 30.9, 19.4, 14.0. Mp: 145 °C. Calcd. (%) for $C_{20}H_{21}NO_3$: C 74.28, H 6.55, N 4.33; found: C 73.98, H 6.48, N 4.40.

Kinetic Competition Experiments. These were performed as described above for the general catalysis procedures, but with a total Pd-loading of 34 mg (0.15 mmol; 5 mol%), equimolar amounts of competitive substrates (3.00 mmol in total) and at a reaction temperature of 40 °C. The conversion in acetanilide was determined by GC/MS using dihexylether as internal standard.

The kinetic data resulting from the competition experiments using *para*-substituted acetanilides give a Hammett-Brown plot as depicted in figure 1. From this correlation it follows that $\rho^+ \approx -2.2$, supporting a reaction pathway which involves attack of the electrophilic Pd^+ species on the arene π-system, resulting in a Wheland-type (arenium ion) intermediate.[2,3]

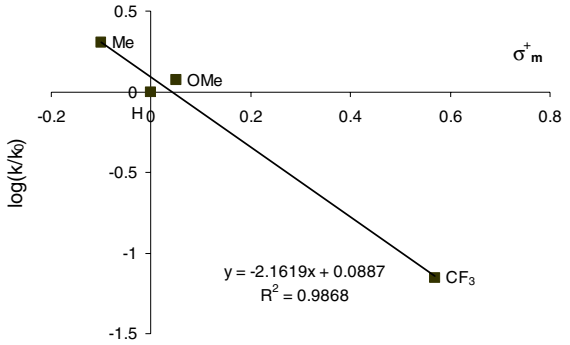

Figure 1. Hammett-Brown plot for the reaction of *para*-substituted acetanilides with *n*-butylacrylate.[4]

The kinetic isotope effect was determined by division of the observed rate-constants (k_{obs}) obtained using acetanilide and 2,3,4,5,6-acetanilide-d_5 (see figure 2). The reaction follows pseudo first-order kinetics for both acetanilide-h_5 and acetanilide-d_5 as can be seen from figure 2. The values of k_{obs} relate to the values of the 'true' k'_{obs} according to the equation:

$$v = k'_{obs} * [acetanilide][Pd] = k_{obs} * [acetanilide] \quad (3)$$

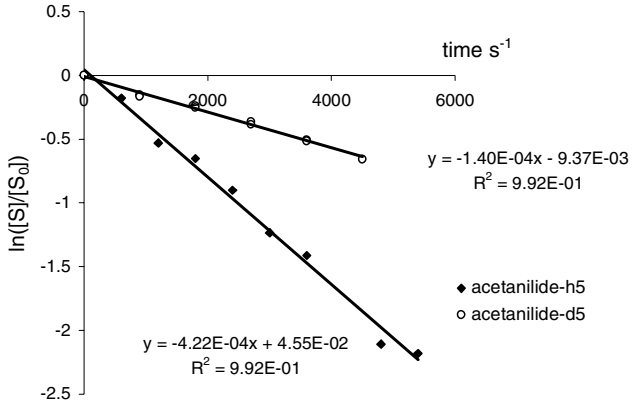

Figure 2. Logarithmic plot of the reaction rate for the reaction of acetanilide-h_5/d_5 with *n*-butylacrylate.

The observed kinetic isotope effect has a value ($k_H/k_D = 3$) similar to values reported in other systems. [5] The fact that a small isotope effect is present (instead of having a value of zero) can arise from the partitioning effect.[6]

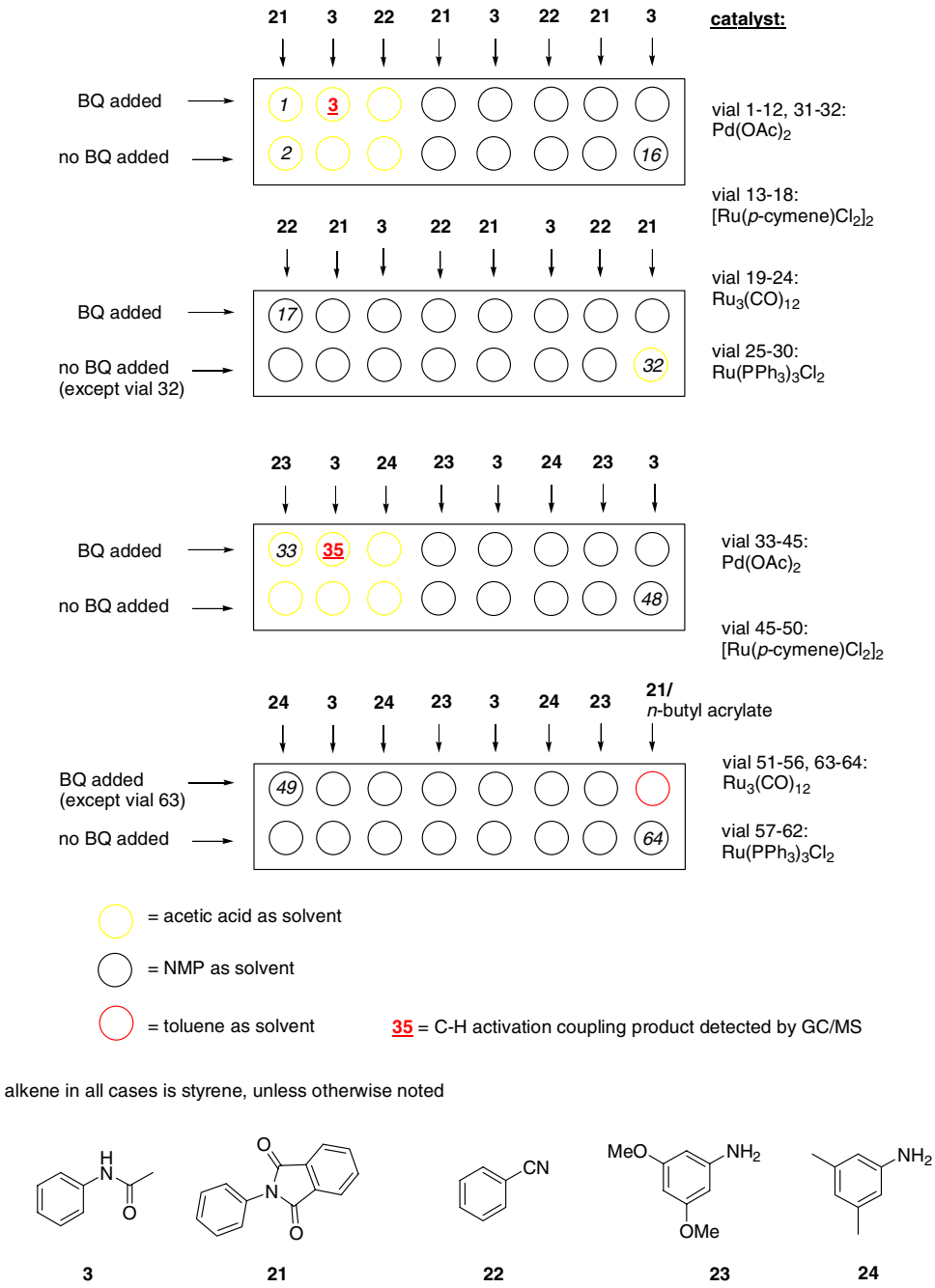

Figure 3. Schematic representation of the reactions performed using the rapid screening setup.

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[1] Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166-7169.
[2] similar ρ^+ values have been reported for other aromatic substitution reactions by electrophilic metal species, see for example (a) Fujiwara, Y.; Asano, R.; Moritani, I.; Teranishi, S. *J. Org. Chem.* **1976**, *41*, 1681-1683.
[3] However, Milstein proposed a mechanism without direct involvement of the π system, see: Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc*. **2001**, *123*, 337-338 and references therein.
[4] σ_m^+ values were taken from March, J. Advanced Organic Chemistry, 3rd ed.; John Wiley & Sons: New York, 1985; p 280.
[5] see for example: (a) Shul'pin, G. B.; Nizova, G. V.; Nikitaev, A. T. *J. Organomet. Chem.* **1984**, *276*, 115-153; (b) reference 2.
[6] March, J. Advanced Organic Chemistry, 3rd ed.; John Wiley & Sons: New York, 1985; pp. 502-504.