Palladium-Catalyzed Reactions, 3†

Stereoselective Palladium-Catalyzed *C-C* Coupling Reactions with a Diazabicyclo[2.2.1]heptene

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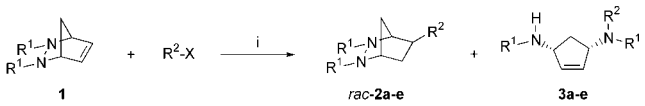
One of the most important goals in contemporary synthetic chemistry is the development of stereoselective *C-C* coupling reactions providing a broadly applicable method to synthesize complex structures from simple precursors. Among transition metal-catalyzed coupling reactions, especially the palladium-catalyzed Heck-type reactions have gained much attention during the last years.[1] The reductive arylation of bicyclic alkenes using palladium catalysts has been well studied,[2] but there is nothing known on the hydroarylation of 2,3-diazabicyclic alkenes, which provide a potential internal point of fracture with the *N-N* bond. Against this background, we have carried out coupling reactions on the 2,3-diazabicyclo[2.2.1]hept-5-ene **1** with different organic halides. The results of our investigations along with some reactions of the resulting primary products are presented below.

The diazabicyclic alkene **1** is easily accessible by a Diels-Alder reaction of cyclopentadiene with diethyl azodicarboxylate (DEAD) in a good yield.[3] Its reaction with aryl or β-styryl halides (Scheme 1) in the presence of an *in situ* generated palladium catalyst, stabilized by triphenylarsine, afforded exclusively the *exo*-configurated hydroarylation (**2 a–d**) and hydrovinylation products (**2 e**) in good yields (Table 1). Recently, triphenylarsine has been introduced as a highly efficient ligand in the hydroarylation of 7-heterobicyclo[2.2.1]heptenes.[2c]

Scope and some limitations of this *C-C* coupling reaction are presented in Table 1. The yield of the main product is usually high, independent of the structure of the halide (phenyl, pyridyl, β-styryl). It decreases, though in case of additional halogen substituents, probably due to reduction processes. The side product **3** is strongly increasing in case of electron-deficient aromatic systems like chloroiodopyridine (26%) or chlorofluoroiodobenzene (21%).



$R^1 = CO_2Et$, R^2 = Aryl, ß -styryl

Scheme 1. Hydroarylation and hydrovinylation of the diazabicyclo[2.2.1]alkene **1**.
(i) 2.5 mol % $Pd(OAc)_2$, 11.0 mol % $AsPh_3$, 3.5 equiv. NEt_3, 3.0 equiv. HCO_2H, DMF, 65 °C, 16 h.

The products were characterized on the basis of their spectral data. In the ^1H NMR spectrum, generally the proton at C-5 resonates at δ = 3.2 to 3.3 ppm as a broad

Table 1. Results of the hydroarylation and hydrovinylation of **1**.

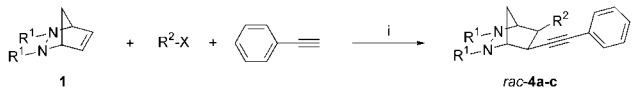
Entry	Main Product	R^2	X	Yield [%] *rac* **2a-e**	Yield [%] **3a-e**
1	**2a**		I	77	5
2	**2b**		I	52	21
3	**2c**		I	77	8
4	**2d**		I	46	26
5	**2e**		Br	86	2

† Part 2: B. Schilling, D. E. Kaufmann, *Eur. J. Org. Chem.* **1998**, 701–709.

  1615-4150/01/34301-177–180 $ 17.50-.50/0

singlet. Temperature-dependent NMR-experiments of **2 a** clearly indicate the *exo*-stereochemistry of the phenyl group, where the proton resonates as a double doublet at δ = 3.23 (*J* = 7.0, 6.7 Hz).[4] The formation of the side product **3** can be explained by a competitive addition of the *R-Pd-X* species to the *N-N* bond, followed by reductive cleavage of the newly formed *Pd-N* bond.[5] The palladium-catalyzed *N*-arylation of a urethane moiety has been reported.[6] The structures of all products were further confirmed on the basis of their mass and high resolution mass spectra.

Moreover, it is possible to substitute the hydride reagent in a hydroorganylation reaction by the nucleophilic phenylacetylene[7] as it is shown in Scheme 2, resulting in a domino *C-C* coupling reaction of **1**.



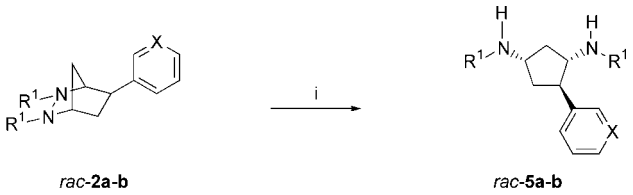
R^1 = CO_2Et, R^2 = Aryl, ß -styryl, Benzyl

Scheme 2. Sequential *C-C* coupling of diazabicyclo-[2.2.1]alkene **1**.
(i) 2.5 mol % $Pd(OAc)_2$, 11.0 mol % $AsPh_3$, 3.5 equiv. NEt_3, DMF, 65 °C, 16 h.

The results are presented in Table 2, starting with phenyl, benzyl, and β-styryl halides.

The bis-*exo*-configuration of the substituents at C-5 and C-6 was established on the basis of temperature-dependent proton NMR spectra and COSY experiments. In the ^{1}H NMR spectrum of **4a** at 353 K, the 5-H and 6-H-protons resonated at δ = 3.66 (d, *J* = 8.6 Hz) and 3.52 (d, *J* = 8.9 Hz), respectively. The low yields are due to undesired side-reactions such as *Sonogashira*-type and homo-coupling products[8,9] that are also formed.

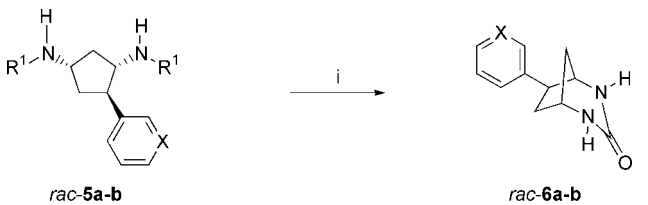
As an extension of this work, we have carried out the reductive cleavage of the *N-N* bond, which leads to urethane derivatives of synthetically interesting cyclic *cis*-1,3-diamines.[10] The reactions of **2 a** and **2 b** with lithium in liquid ammonia yielded the *cis*-1,3-diaminocyclopentane derivatives **5 a–b** with an aryl substituent in the *trans*-position (Scheme 3); other reduction methods[11] have failed so far.



R^1 = CO_2Et, X = CH, N

Scheme 3. Reductive *N-N* cleavage of the cyclic hydrazines **2 a–b**.
(i) 1.3 equiv. lithium/liquid NH_3, 3 h, **5 a**: X = CH, 78%, **5 b**: X = N, 27%.

The stereodefined geometry of the racemic products **5 a–b** was assigned on the basis of their spectral data. The high resolution mass spectra also support the structures. Treatment of the urethane-protected diamines **5 a–b** with ethanolic KOH under reflux conditions afforded the cyclic ureas **6 a–b** in good yields as shown in Scheme 4. Cyclic ureas are important subunits of many biologically active heterocycles like hydantoic and barbituric acid derivatives.



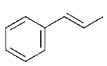
R^1 = CO_2Et, X = CH, N

Scheme 4. Formation of the cyclic ureas **6 a–b**.
(i) 5 equiv. KOH, EtOH, reflux, 24 h, **6 a**: X = CH, 74%, **6 b**: X = N, 51%.

Both the formation of these cyclic ureas and the proton NMR spectra of **6 a–b** clearly indicate the assigned stereochemisty of **5 a–b**.

In summary, we have investigated the palladium-catalyzed reductive Heck-type reaction and the sequential *C-C* coupling with a 2,3-diazabicyclic alkene. The *N-N* bond cleavage of these products afforded stereoselectively *cis*-1,3-diamino-*trans*-4-cyclopentane derivatives, which are otherwise not easy to obtain. Further work is in progress.

Table 2. Results of the sequential *C-C* coupling of **1**.

Entry	Product	R^2	X	Yield [%] *rac*-**4a-c**
1	**4a**		I	52
2	**4b**		Br	18
3	**4c**		Cl	12

Experimental Section

All reactions were carried out in oven-dried 10-mL Schlenk-tubes under a nitrogen atmosphere. NMR spectra were recorded on a Bruker AMX 400 spectrometer (^{1}H: 400 MHz, ^{13}C: 100 MHz) with tetramethylsilane as internal standard; δ values are given in ppm, *J* values in Hz. Multiplicities of ^{13}C NMR signals were determined by the DEPT sequence and are reported as follows: + for CH or CH_3, – for CH_2, and o for C. Mass spectra were obtained with a Hewlett Packard 5898B (at 70 eV); high-resolution mass spectra were recorded with a Varian MAT 311 A spectrometer with pre-selected molecular ion peak matching at R ≫ 10000 to be within ±2 ppm of the exact masses. Melting points are uncorrected. Solvents were dried by standard procedures. Column chromatography was performed on Macherey and Nagel M 60 silica gel (40–63 μm).

N,N′-Diethoxycarbonyl-*exo*-5-(4′-chloro-3′-fluorophenyl)-2,3-diazabicyclo[2.2.1]heptane (2b) and *N*-(4′-Chloro-3′-fluorophenyl)-*cis*-*N,N′*-di(ethoxycarbonylamino)cyclopent-4-ene (3b)

Palladium(II) acetate (5.6 mg, 25 μmol) and triphenylarsine (33.7 mg, 110 μmol) were dissolved in 3 mL of dry DMF under nitrogen and heated at 65 °C. After stirring for 15 minutes to complete the catalyst-formation, 240 mg (1.0 mmol) of alkene **1**, 385 mg (1.5 mmol) of 3-fluoro-4-chloro-iodobenzene, 354 mg (3.5 mmol) NEt_3, and 138 mg (3.0 mmol) of formic acid were added and stirred for 16 h. After cooling to r.t. 50 mL of brine was added to the reaction mixture which was then extracted with ethyl acetate and dried over $MgSO_4$. The solvent was removed and the products were purified by column chromatography (ethyl acetate/petroleum ether 40–60 °C, 1:9) affording **2b** (193 mg, 52%) and **3b** (77 mg, 21%) as colorless, viscous liquids.

2b: ^{1}H NMR (25 °C, $CDCl_3$): δ (ppm) = 1.32 (t, ^3J = 7.1 Hz, 6 H; $-OCH_2CH_3$), 1.75 and 2.33 (br s, 3 h and br s, 1 H; 6-$H_{exo/endo}$ and 7-$H_{syn/anti}$), 3.32 (br s, 1 H, 5-H_{endo}), 4.26 (q, ^3J = 7.0 Hz, 4 H; $-OCH_2CH_3$), 4.56 and 4.68 (br s, 1 H; 1-H and 4-$H_{bridgehead}$), 6.93–7.02 (m, 2 H; 2′-H_{aryl} and 6′-H_{aryl}), 7.35 (t, *J* = 8.2 Hz, 1 H; 5′-H_{aryl}); ^{13}C NMR (25 °C, $CDCl_3$): δ (ppm) = 14.5 (+, 2 C; $-OCH_2CH_3$), 33.0, 35.6 (–, 2C; C-6, C-7), 44.3 (+; C-5), 60.3 (+; C-4$_{bridgehead}$), 62.5 (–, 2C; $-OCH_2CH_3$), 65.0 (+; C-1$_{bridgehead}$), 115.2 (+, d, $^2J_{C,F}$ = 20.8 Hz; C-2′), 119.1 (o, d, $^2J_{C,F}$ = 17.3 Hz; C-4′), 123.4 (+; C-6′), 130.7 (+; C-5′), 142.5 (o; C-1′), 159.1 (o; 2C$_{carboxyl}$), 159.3 (o, d, $^1J_{C,F}$ = 249.0 Hz; C-3′); MS (EI): *m/z* (%) = 371 (40) [M^+ + 1], 325 (6), 298 (10), 253 (2), 225 (2), 169 (10), 157 (12), 141 (68); calcd. for $C_{17}H_{20}ClFN_2O_4$: 370.1096; found: 370.1096 (MS).

3b: ^{1}H NMR (25 °C, $CDCl_3$): δ (ppm) = 1.09 (br s, 3 H; $-OCH_2CH_3$), 1.30 (t, ^3J = 7.1 Hz, 3 H; $-OCH_2CH_3$), 2.50–2.70 (m, 2 H; 2-H), 4.02 (br s, 3 H; $-OCH_2CH_3$ and 3-H), 4.23 (q, ^3J = 6.6 Hz, 2 H; $-OCH_2CH_3$), 4.71 (br s, 1 H; 1-H), 5.64–5.67 (m, 1 H; 4-H_{alkene}), 5.89–5.91 (m, 1 H; 5-H_{alkene}), 6.60 (br s, 1 H; N′-*H*), 7.03–7.13 (m, 2 H; 2′-H_{aryl}, 6′-H_{aryl}), 7.30 (t, ^3J = 7.1 Hz, 1 H; 5′-H_{aryl}): ^{13}C NMR (25 °C, $CDCl_3$): δ (ppm) = 14.2 and 14.4 (+; $-OCH_2CH_3$), 35.0 (–; C-2), 53.1 (+; C-3), 62.3 and 62.6 (–; $-OCH_2CH_3$), 66.9 (+; C-1), 115.6 (+, d, $^2J_{C,F}$ = 21.4 Hz; C-2′), 118.7 (o, d, $^2J_{C,F}$ = 17.1 Hz; C-4′), 124.0 (+; C-6′), 130.0 (+; C-5′), 130.7 (+; C-5$_{alkene}$), 131.6 (+; C-4$_{alkene}$), 144.6 (o; C-1′), 155.8 and 157.0 (o; 2C$_{carboxyl}$), 158.0 (o, d, $^1J_{C,F}$ = 248.5 Hz; C-3′); MS (EI): *m/z* (%) = 371 (42) [M^+ + 1], 299 (5), 210 (16), 194 (100); calcd. for $C_{17}H_{20}ClFN_2O_4$: 370.1096; found: 370.1096 (MS).

N,N′-Diethoxycarbonyl-*exo*-5-phenyl-*exo*-6-(phenylethinyl)-2,3-diazabicyclo[2.2.1]heptane (4a)

The procedure is the same as in **2b** except for exchanging the formic acid by phenylacetylene. The product was purified by column chromatography on reversed phase silica gel (Merck RP-18, MeOH/H_2O, 8:2) affording **4a** (323 mg, 52%) as a white solid; mp 61 °C; ^{1}H NMR (25 °C, $CDCl_3$): δ (ppm) = 1.29 (t, ^3J = 7.2 Hz, 3 H; $-OCH_2CH_3$), 1.36 (t, ^3J = 7.2 Hz, 3 H; $-OCH_2CH_3$), 1.96 (d, *J* = 10.7 Hz, 1 H; 7-H_{anti}), 2.46 (d, *J* = 10.7 Hz, 1 H; 7-H_{syn}), 3.58 and 3.62 (br s, 2 H; 5-H_{endo}, 6-H_{endo}), 4.21–4.35 (m, 4 H; $-OCH_2CH_3$), 4.65 (br s, 1 H; 1-H$_{bridgehead}$), 4.90 (br s, 1 H; 4-H$_{bridgehead}$), 6.86–6.88 (m; 2 H$_{aryl}$), 7.12–7.21 (m, 5 H$_{aryl}$), 7.26–7.29 (m; 1 H$_{aryl}$), 7.33–7.37 (m; 2 H$_{aryl}$); ^{13}C NMR (25 °C, $CDCl_3$): δ (ppm) = 14.4 and 14.6 (+; $-OCH_2CH_3$), 36.2 (–; C-7), 41.0 (+; C-6), 49.6 (+; C-5), 62.6 and 62.8 (–; $-OCH_2CH_3$), 63.1 (+; C-4$_{bridgehead}$), 64.1 (+; C-1$_{bridgehead}$), 77.1 (o; C-9), 86.9 (o; C-8), 122.7 (o; C-1″), 126.7 (+; C-4′), 127.9 (+; C-4″), 128.0 (+; 2 C$_{aryl}$), 128.2 (+; 2 C$_{aryl}$), 128.3 (+; 2 C$_{aryl}$), 131.3 (+, 2 C; C-2″, C-6″) 138.8 (o; C-1′), 158.0 (o; 2C$_{carboxyl}$); MS (EI): *m/z* (%) = 418 (20) [M^+], 373 (4), 329 (4), 244 (10), 203 (22), 141 (54), 115 (56), 91 (10), 69 (100); calcd. for $C_{25}H_{26}N_2O_4$: 418.1893; found: 418.1893 (MS).

cis-1,3-Diethoxycarbonylamino-*trans*-4-phenylcyclopentane (5a)

To a solution of 7 mg (1.0 mmol) of lithium in 40 mL of liquid ammonia **2a** (318 mg, 1.0 mmol) was added. The reaction mixture was stirred for 3 h at –78 °C. The excess lithium was destroyed by adding ammonium chloride and the ammonia was allowed to boil off. The residue was extracted with CH_2Cl_2, the solvent was evaporated and the product purified by column chromatography (ethyl acetate/petroleum ether 40–60 °C, 3:7) to afford 249 mg (78%) of **5a** as a white solid; mp 100–102 °C; ^{1}H NMR (25 °C, $CDCl_3$): δ (ppm) = 1.19 (br s, 3 H; $-OCH_2CH_3$), 1.28 (t, ^3J = 7.0 Hz, 3 H; $-OCH_2CH_3$), 1.64 (br s, 1 H; 5-H), 2.09 (br s, 2 H; 2-H), 2.62–2.70 (m, 1 H; 5-H), 3.27 (br s, 1 H; 1-H), 3.82 (br s, 1 H; 3-H), 4.01–4.21 (m, 5 H; $-OCH_2CH_3$ and 4-H), 4.98 (br s, 1 H; N*H*), 5.67 (br s, 1 H; N*H*), 7.21–7.24 (m; 3 H$_{aryl}$), 7.29–7.33 (m; 2 H$_{aryl}$); ^{13}C NMR (25 °C, $CDCl_3$): δ (ppm) = 14.4 and 14.6 (+; $-OCH_2CH_3$), 38.8 (–; C-5), 40.1 (–; C-2), 48.5 (+; C-1), 49.7 (+; C-4), 58.2 (+; C-3), 60.6 (–, 2 C; $-OCH_2CH_3$), 126.6 (+; C-4′), 127.2 (+, 2 C; C-3′, C-5′), 128.5 (+, 2 C; C-2′, C-6′), 141.7 (o; C-1′), 156.1 (o; 2C$_{carboxyl}$); MS (EI): *m/z* (%) = 321 (100) [M^+ + 1], 275 (33), 231 (10), 176 (20), 142 (68), 96 (14); calcd. for $C_{17}H_{24}N_2O_4$: 320.1736; found: 320.1736 (MS).

exo-6-Phenyl-2,4-diazabicyclo[3.2.1]octan-3-one (6a)

To a solution of 320 mg (1.0 mmol) of **5a** in 5 mL of ethanol 280 mg (5.0 mmol) of KOH was added. After refluxing the re-

action mixture overnight, it was allowed to cool to room temperature and filtered. The solvent was evaporated and the product purified by column chromatography (MeOH/$CHCl_3$, 2:98) to afford 150 mg (74%) **6a** as a white solid; mp 201–203 °C; ^{1}H NMR (25 °C, DMSO-d_6): δ (ppm) = 1.73 (m, 1H; 8-H), 1.88 (m, 2H; 7-H and 8-H), 2.40 (m, 1H; 7-H), 3.40 (m, 1H; 6-H), 3.47 (m, 1H; 5-H), 3.69 (m, 1H; 1-H), 6.41 (s, 1H; N–H), 6.55 (s, 1H; N–H), 7.19–7.34 (m, 5H; Ar); ^{13}C NMR (25 °C, DMSO-d_6): δ (ppm) = 32.8 (–; C-8), 44.2 (–; C-7), 51.7 (+; C-1), 54.0 (+; C-5), 57.8 (+; C-6), 126.2 (+; C-4′), 126.9 (+, 2C; C-3′, C-5′), 128.6 (+, 2C; C-2′, C-6′), 144.4 (o; C-1′), 155.7 (o; $C_{carbonyl}$); MS (EI): *m/z* (%) = 202 (4) [M^+], 149 (4), 111 (8), 101 (100), 97 (57); calcd. for $C_{12}H_{14}N_2O$: 202.1106; found: 202.1106 (MS).

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