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Annulated Ring-Systems by Domino-Heck-Aldol-Condensation and Domino-Heck-Michael-Addition Processes

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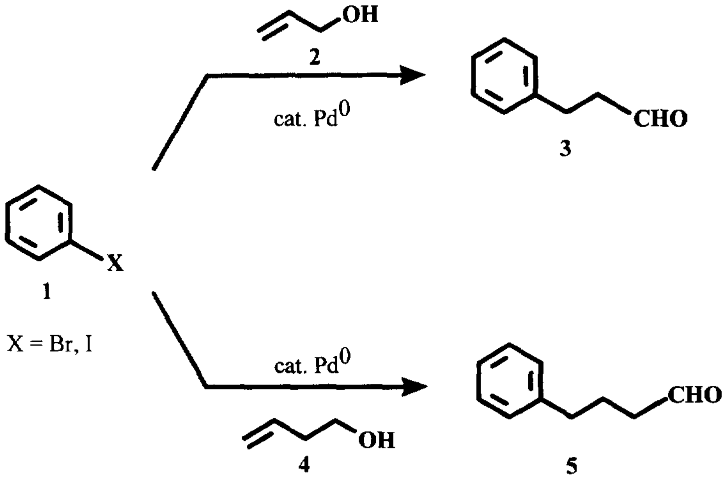
Abstract: A palladium catalyzed coupling process of functionalized aryl bromides with allylic alcohols results in 5-membered ring annulation, whereas with homoallylic alcohols 6-membered rings are formed.

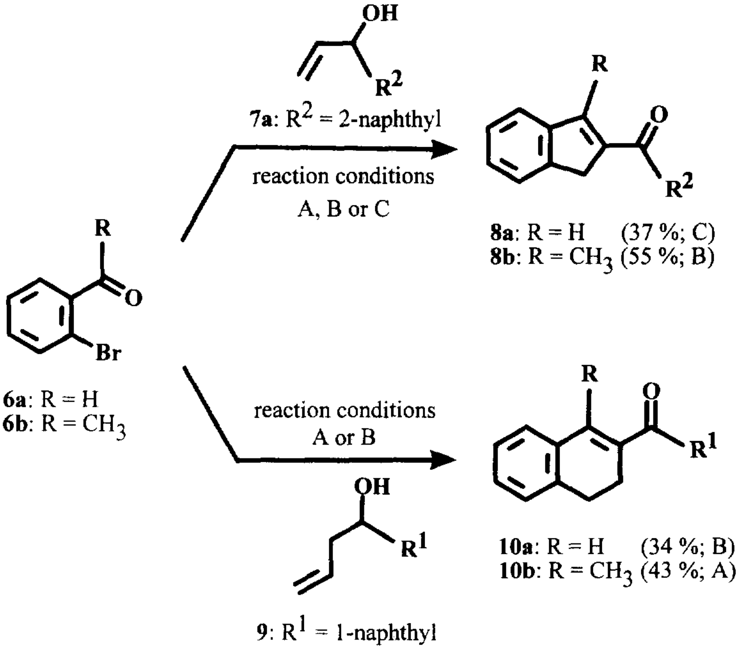
The Heck-type coupling of aryl halides with allylic or homoallylic alcohols is a facile entry to various aldehydes and ketones[1-5] as illustrated by the simple examples in scheme 1.



Scheme 1

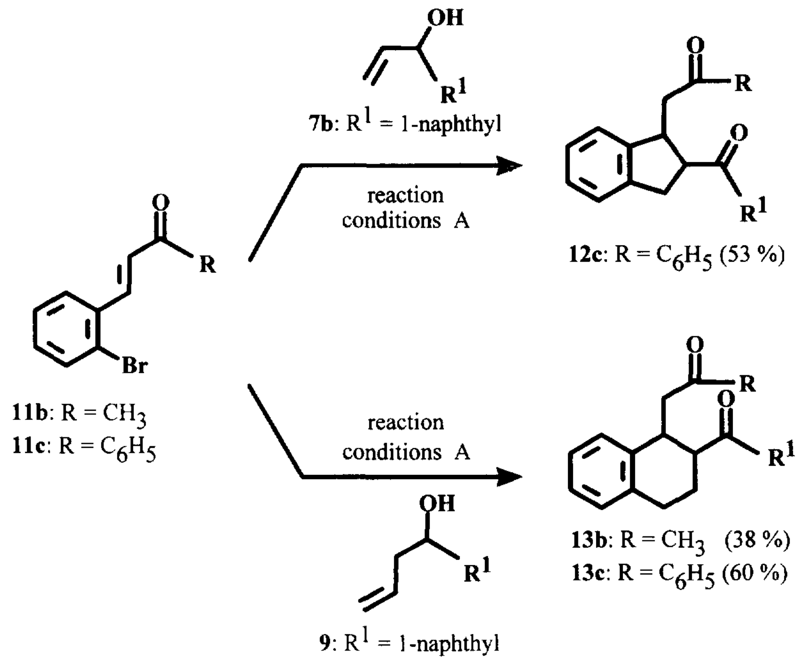
The formation of the carbonyl compound presumably proceeds via palladium-complexed enols[4]. These intermediates should be capable of carrying out intramolecular aldol condensations and Michael reactions with appropriate substrates[6]. We wish to report our preliminary results on the synthesis of annulated ring systems by *domino-Heck-aldol-condensation* and *domino-Heck-Michael-addition* processes[7].

Functionalized aryl bromides of type **6** and **11** turned out to be suitable building blocks for annulation reactions with allylic and homoallylic alcohols. Substituted 1H-indenes are obtained by a regioselective domino-Heck-aldol-condensation process using o-bromobenzaldehyde (**6a**; R = H) or o-bromoacetophenone (**6b**; R = CH_3) and allylic alcohol **7a** as coupling components (scheme 2). Applying reaction conditions B the 1H-indene derivative **8b** is isolated in up to 55 % yield[8]. Reaction conditions C appear to be best for the formation of the 1H-indene derivative **8a** (yield: 37 %), whereas reaction conditions A and B lead to less than 5 % yield of **8a** due to various competing reactions. The homoallylic alcohol **9** as coupling partner is giving rise to functionalized 1,2-dihydronaphthalenes as cyclization products with yields in the range of 40 %.



Scheme 2: Domino-Heck-aldol-condensation processes; reaction conditions: 1 mmol bromide, 1 mmol unsaturated alcohol, 5 mol% $Pd(OAc)_2$, 10 ml DMF, N_2; A: 8 equiv. NEt_3, 3 equiv. LiCl, 80 °C, 2-3 d; B: 2.5 equiv. NaOAc, 2 equiv. n-Bu_4NBr, 1 equiv. LiCl, 90 - 100 °C, 24 h; C: 10 mol% PPh_3, 1.2 equiv. $NaHCO_3$, 110 - 120 °C, 24 h.

Model compounds of type **11** with an unsaturated carbonyl group in the side chain are substrates of choice for the domino-Heck-Michael-addition process. Reaction conditions A have proven to be advantageous in this case, leading to annulated products **12** and **13** in up to 60 % yield. In the ^1H NMR spectrum of the crude product of **12c** only one diastereomer has been registered. The analogous condensation of **11b** as well as **11c** with the homoallylic alcohol **9** leads to a mixture of the two diastereomers of the 1,2-disubstituted tetrahydronaphthalenes **13**. In both cases the ratio of the two stereoisomers is determined by ^{1}H NMR to be 85:15 (trans/cis). The assignment has been confirmed by ^{1}H NMR NOE experiments with the two separated isomers of **13b**.



Scheme 3: Domino-Heck-Michael-addition processes; for reaction conditon see scheme 2.

In conclusion, we have shown that with appropriate reaction conditions it is possible to combine Heck reaction with aldol condensation or Michael addition as domino processes in single step operations. Scope, limitations and mechanistic details of these new annulation reactions for the rational and efficient construction of polycyclic ring systems are currently under investigation: of special interest is an approach to the steroid framework as well as using glycals as chiral building blocks.

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8. All new compounds have been fully characterized by spectroscopic means, selected data:

   8a: mp 117 °C; IR (KBr): ν = 1621 (s) cm^{-1}; ^{1}H NMR (400.1 MHz, CDCl$_3$, TMS): δ = 3.95 ppm (d, ^{4}J = 1.6 Hz, 2H), 7.35-7.42 (m, 2H), 7.55-7.62 (m , 5H), 7.91-7.98 (m, 4H), 8.36 ("s", 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$, TMS): δ = 38.71 ppm (t), 124.0 (d), 124.59 (d), 125.30 (d), 126.78 (d), 127.10 (d), 127.87 (d), 128.01 (d), 128.23 (d), 128.39 (d), 129.3 (d), 130.05 (d), 132.44 (s), 135.12 (s), 136.24 (s), 143.07 (s), 143.72 (d), 145.08 (s), 145.41(s), 192.94 (s); MS (70 eV, 25 °C); *m/z* (%): 270 (51) [M^{+}], 155 (100), 127 (45) , 115 (14).

   10a: mp 89 °C; IR (KBr): ν = 1635 (s) cm^{-1}; ^{1}H NMR (400.1 MHz, CDCl$_3$, TMS): δ = 2.87 ppm ("t", "J" = 8.1 Hz, 2H), 2.99 (t, ^{3}J = 8.51 Hz, 2H), 7.00 ("d", "J" = 7.3 Hz, 1H), 7.05 (s, 1H), 7.14 ("t", "J" = 7.4 Hz, 1H), 7.21 ("d", "J" = 7.2 Hz, 1H), 7.26 ("t", "J" = 7.4 Hz, 1H), 7.48-7.54 (m, 3H), 7.56 ("d", "J" = 7.0 Hz, 1H), 7.90-7.92 (m, 1H), 7.97 ("d", "J" = 8.1 Hz, 1H), 7.99-8.01 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$, TMS): δ = 21.68 ppm (t), 27.63 (t), 124.43 (d), 125.62 (d), 126.40 (d), 126.42 (d), 126.80 (d), 127.04 (d), 127.88 (d), 128.36 (d), 129.09 (d), 130.23 (d), 130.39 (d), 130.98 (s), 132.57 (s), 133.77 (s), 137.03 (s), 137.79 (s), 139.03 (s), 142.01 (d), 198.74 (s); MS (70 eV, 25 °C); *m/z* (%): 284 (91) [M^{+}], 155 (100).

   12c: IR (KBr): ν = 1682 (s) cm^{-1}; ^{1}H NMR (400.1 MHz, CDCl$_3$, TMS): δ = 3.19-3.29 ppm (m, 2H), 3.32 (dd, ^{2}J =16.3 Hz, ^{3}J = 9.2 Hz, 1H), 3.53 (dd, ^{2}J =16.5 Hz, ^{3}J = 4.8 Hz, 1H), 4.18 (m, 1H), 4.44 (m, 1H), 7.19-7.24 (m, 4H), 7.38-7.56 (m, 6H), 7.84-7.96 (m, 5H), 8.39-8.41 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$, TMS): δ = 36.01 ppm (t), 43.3 (d), 44.1 (t), 55.89 (d), 123.89 (d), 124.4 (d), 124.5 (d), 125.83 (d), 126.48 (d), 126.95 (d), 127.05 (d), 127.22 (d), 127.79 (d), 128.17 (d), 128.33 (d), 128.61 (d), 130.52 (s), 132.23 (d), 133.16 (d), 133.95 (s), 136.42 (s), 136.83 (s), 140.78 (s), 144.77 (s), 198.91 (s), 204.64 (s). MS (70 eV, 25 °C); *m/z* (%): 390 (12) [M^{+}], 155 (84), 127 (100).

   13 b (trans): mp 129 °C; IR (KBr): ν = 1707 (s) cm^{-1}, 1674 (s); ^{1}H NMR (400.1 MHz, CDCl$_3$, TMS): δ = 1.9-1.98 ppm (m, 1H), 2.02-2.1 (m, 1H), 2.14 (s, 3H), 2.78-2.97 (m, 4H), 3.82-3.87 (m, 1H), 3.96-4.01 (m, 1H), 7.06-7.25 (m, 4H), 7.46-7.53 (m, 3H), 7.84-7.89 (m, 2H), 7.97 ("d", "J" = 8.2 Hz, 1H), 8.13-8.17 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$, TMS): δ = 23.73 ppm (t), 27.57 (t), 30.40 (q), 34.52 (d), 49.18 (d), 50.11 (t), 124.30 (d), 125.36 (d), 125.82 (d), 126.15 (d), 126.19 (d), 126.24 (d), 127.42 (d), 127.93 (d), 128.18 (d), 128.73 (d), 130.41 (s), 131.79 (d), 133.77 (s), 135.96 (s), 136.31 (s), 138.26 (s), 206.14 (s), 207.74 (s); MS (70 eV, 25 °C); *m/z* (%): 342 (14) [M^{+}], 285 (50), 155 (100), 127 (84).

   13b (cis): ^{1}H NMR (400.1 MHz, CDCl$_3$, TMS): δ = 1.96 ppm (s, 3H), 2.12-2.17 (m, 2H), 2.60 (dd, ^{2}J = 18.0 Hz, ^{3}J = 6.2 Hz, 2H), 2.85-2.94 (m, 1H), 3.01 (dt, ^{2}J = 17.0 Hz, ^{3}J = 4.7 Hz, 1H), 3.83-3.87 (m, 1H), 3.99-4.03 (m, 1H), 7.07 -7.14 (m, 4H), 7.49-7.58 (m, 3H), 7.87 ("d", "J" = 8.7 Hz, 1H), 7.92 ("d", "J" = 6 .7 Hz, 1H), 7.99 ("d", "J" = 8.0 Hz, 1H), 8.42 ("d", "J" = 8.3 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$, TMS): δ = 21.35 ppm (t), 28.24 (t), 30.32 (q), 35.40 (d), 47.55 (d), 48.40 (t), 124.54 (d), 125.35 (d), 126.12 (d), 126.40 (d), 126.48 (d), 127.48 (d), 127.86 (d), 128.65 (d), 128.73 (d), 129.16 (d), 130.38 (s), 132.69 (d), 134.07 (s), 135.17 (s), 135.81 (s), 140.27 (s), 206.56 (s), 207.23 (s).

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