A Short Three-Component Synthesis of Tricyclic Compounds

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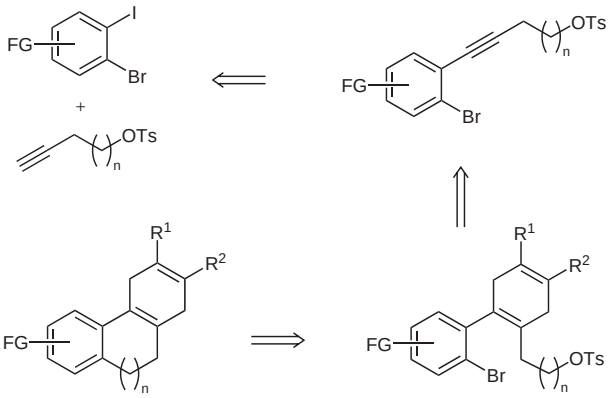
Abstract: A facile reaction sequence, consisting of a palladium-catalyzed Sonogashira coupling, a cobalt-catalyzed Diels–Alder reaction and a subsequent cyclization initiated by a bromine-lithium exchange reaction, allows a three-component synthesis of tricyclic compounds. Thereby, structurally different functionalized compounds can be generated when functionalized dihalo-arenes, tosylated alkynols and substituted 1,3-dienes are used as starting materials.

Key words: alkynes, catalysis, cobalt, cyclization, Diels–Alder reactions

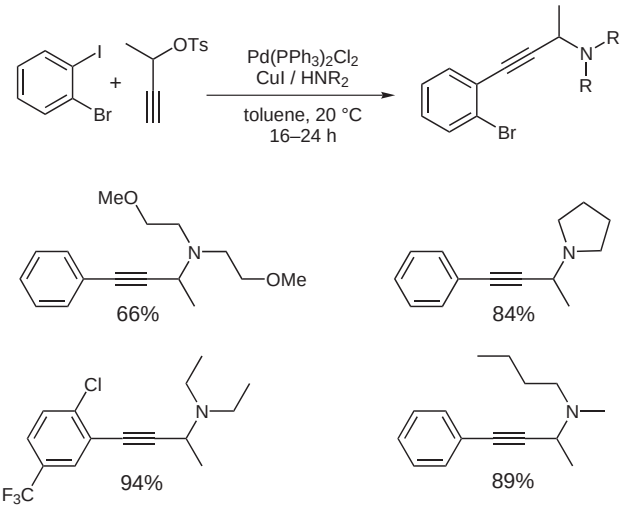
Short reaction sequences with a high degree of variability allow the preparation of a large number of complex molecules from commercially available or easily prepared starting materials in a very efficient way in a short period of time. When transition metal-catalyzed reactions are involved, many functional groups can be tolerated in each step to avoid lengthy and tedious protection-deprotection steps. Herein, we wish to report a short reaction sequence involving two transition metal-catalyzed reactions followed by a stoichiometric bromine-lithium exchange reaction for the synthesis of tricyclic ring systems. The general design for the reaction sequence is outlined below (Scheme 1). The chemoselective Sonogashira coupling reaction of bromo-iodo arenes or dibromo-heteroarenes generates the key alkyne intermediates, bearing a sterically bulky (hetero)aryl substituent and a sterically less-demanding alkyl substituent. A regioselective cobalt-catalyzed neutral Diels–Alder reaction with symmetrical and unsymmetrical 1,3-dienes was envisioned in order to generate ring C of the tricyclic compounds and to bring the aryl bromide and the tosylate group into proximity. A fast bromine-lithium exchange reaction generates the aryllithium nucleophile, which displaces the tosylate to complete the intramolecular ring closure reaction and forms ring B.

The Sonogashira coupling reaction of bromo-iodobenzene derivatives with different alkynols and their subsequent reaction with tosyl chloride gave the corresponding products in excellent yields and with complete chemoselectivity, following standard procedures.[1] However, when the coupling reaction was performed with the tosylated alkynols (especially propynol derivatives, Scheme 2), the secondary amine bases displaced the tosylates to give the



Scheme 1

corresponding propargylic amines in moderate to good yields.[2] Besides diethylamine (R = Et 92%), other secondary amines can also be used, as shown in Scheme 2.



Scheme 2

When tertiary amine bases such as triethylamine were used as a substitute for diethylamine, the amount of the desired tosylated alkynol did not overcome the yields for the reversed synthetic protocol (see Scheme 3). Therefore, the Sonogashira coupling reactions were performed with the free alcohols, which were subsequently tosylated.[3]

The key step of the reaction sequence, our recently described cobalt-catalyzed neutral Diels–Alder reaction of internal alkynes with 1,3-dienes was initiated by zinc re-

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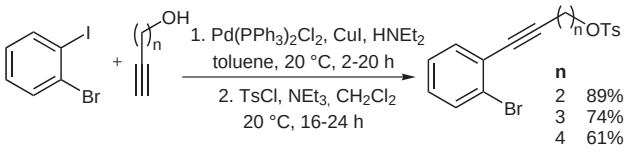
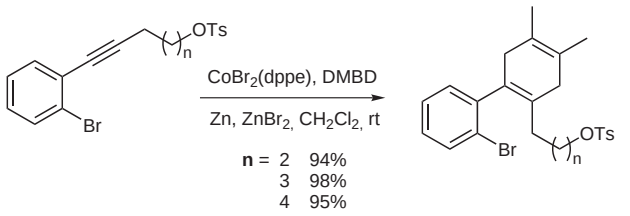


Scheme 3

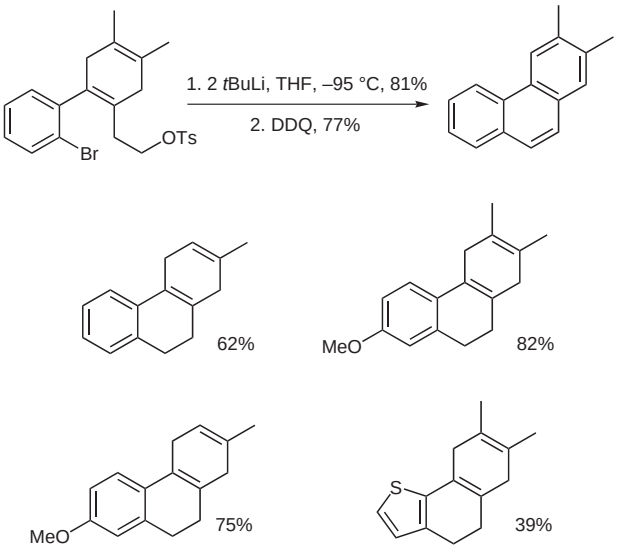
duction of the cobalt(II)-dppe complex. In these cases, the usual reductant of choice, tetrabutylammonium borohydride, gave some triple bond reduction as a side reaction, but this was avoided when zinc powder was used as the reducing agent.[4] The reaction of 2,3-dimethyl-1,3-butadiene (DMBD) and isoprene as simple 1,3-diene test systems gave the desired dihydroaromatic products in good yields (Scheme 4) after 14–20 h reaction time at room temperature.[5] In the case of isoprene, the products were generally formed as an 80:20 mixture of regioisomers where the major product has the methyl group of the isoprene and the aromatic ring substituent in a 1,4-relationship.



Scheme 4

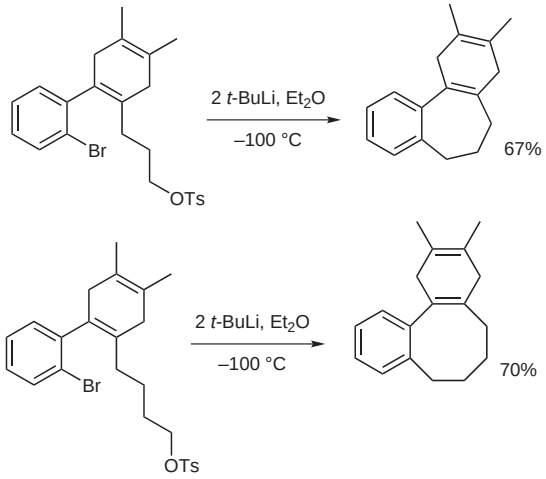
At this point the stage was set for the formation of ring B. The final reaction, a bromine-lithium exchange reaction in the presence of a tosylate, has no precedent in the literature. However, similar Parham-type cyclization reactions are described with several functional groups such as epoxides or halides as electrophiles.[6] Under these circumstances, we were delighted to see that the exchange reaction proceeded smoothly in THF at –95 °C to produce the tricyclic phenanthrene derivatives. The products, which can be isolated as the dihydroaromatic compounds in good yield, accompanied by some air-oxidized aromatic side products, can be oxidized with various oxidizing agents, such as DDQ, to the aromatic compound in good overall yield.[7] Following this protocol, several functionalized and specifically substituted phenanthrene derivatives, as well as heterocyclic tricyclic compounds, could be generated (Scheme 5, yields are given for the cyclization step) in good overall yields.

An even higher degree of flexibility could be realized when the reaction sequence was performed with higher homologues of the alkynols leading to tricyclic compounds where ring B consists of a seven- or eight-membered ring as shown in Scheme 6. In these cases, the bromine-lithium exchange reaction worked only sluggishly in THF. However, in diethyl ether the desired products were formed rapidly upon bromine-lithium exchange at



Scheme 5

low temperature (–100 °C) and subsequent warming to room temperature.[8] Although the formation of larger ring systems with a simple S_N2 reaction should be more and more disfavored. Nonetheless, to the best of our knowledge, for the first time seven and eight membered ring systems were generated using the Parham cyclization methodology and the tetrahydro-dibenzo[*a*,*c*]cycloheptene and the hexahydro-dibenzo-[*a*,*c*]cyclooctene[9] derivatives were isolated in good yields.



Scheme 6

In summary, we have developed a new protocol for the generation of various tricyclic ring systems in a short reaction sequence. Further variations with more highly functionalized iodo arene derivatives, substituted alkynols of different chain lengths, and functionalized 1,3-dienes can be envisioned for the synthesis of a wide range of compounds. Such investigations are currently underway in our laboratory.

Acknowledgment

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References

(1) (a) Sonogashira, K. In *Comprehensive Organic Synthesis*, Vol. 3; Trost, B.; Flemming, I.; Pattenden, G., Eds.; Pergamon Press: New York, **1991**, 521. (b) Sonogashira, K. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, **1998**, 203.

(2) Besides secondary amines, primary amines such as *tert*-butylamine, also gave the propargylic amine product in this three component reaction, albeit in lower yields (46%).

(3) (a) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447. (b) The tosylation of propargylic alcohols (n = 1) under these conditions gave the desired products only in moderate yields (up to 25%) accompanied with the corresponding propargylic chloride in up to 35% yield and recovered starting material.

(4) For recent cobalt(I)-catalyzed Diels–Alder reactions see: (a) Hilt, G.; Lüers, S.; Polborn, K. *Isr. J. Chem.* **2001**, *41*, 317. (b) Hilt, G.; Smolko, K. I. *Synthesis* **2002**, 686. (c) Hilt, G.; Smolko, K. I. *Synlett* **2002**, 1081.

(5) Typical procedure: Preparation of 3-[2-(2-bromophenyl)-4,5-dimethyl-1,4-cyclohexadien-1-yl]propyl 4-methylbenzenesulfonate (Scheme 4, n = 3): To 5-(2-bromophenyl)-4-pentynyl-4-methylbenzenesulfonate (321 mg, 0.82 mmol) in dry CH_2Cl_2 (2.0 mL) were added $CoBr_2$(dppe) (40 mg, 0.07 mmol, 9 mol%), 2,3-dimethyl-1,3-butadiene (145 mg, 1.77 mmol, 2.0 equiv), zinc (300 mg, 4.69 mmol, 5.7 equiv) and $ZnBr_2$ (100 mg, 0.45 mmol, 55 mol%) under nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight. The crude product was purified by column chromatography (SiO_2, pentane:diethyl ether = 2:1) affording the desired product (381 mg, 0.80 mmol, 98%) as a colorless oil.
^{1}H NMR (300 MHz, C_6D_6): δ = 7.70–7.64 (m, 2 H), 7.39 (dd, *J* = 8.4, 1.1 Hz, 1 H), 7.00–6.85 (m, 2 H), 6.74–6.64 (m, 3 H), 4.77–3.63 (m, 2 H), 3.02–2.84 (m, 1 H), 2.56–2.34 (m, 3 H), 1.82 (s, 3 H), 1.80–1.35 (m, 10 H); ^{13}C NMR (75 MHz, C_6D_6): δ = 143.9, 143.6, 134.6, 133.0, 131.8, 130.6, 130.4, 129.7, 128.4, 128.1, 127.8, 123.6, 123.0, 122.8, 70.1, 39.4, 36.6, 29.4, 27.2, 21.1, 18.2, 17.9; MS *m*/*z* (%) = 474 (M^+, 2), 208(15), 194(24), 179(12), 91(11), 74(100); HRMS calcd for $C_{24}H_{27}BrO_3S$: *m*/*z* = 474.0864, found: *m*/*z* = 474.0811.

(6) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300.

(7) (a) Typical procedure: Preparation of 7-methoxy-2,3-dimethyl-1,4,9,10-tetrahydrophenanthrene (Scheme 5): To 2-[2-(2-bromo-4-methoxyphenyl)-4,5-dimethyl-1,4-cyclohexadien-1-yl]ethyl 4-methylbenzenesulfonate (134 mg, 0.27 mmol) in anhyd THF (5.0 mL) at –90 °C was added *tert*-butyllithium (0.4 mL, 1.7 M in THF, 0.56 mmol, 2.1 equiv) in one portion under nitrogen atmosphere. The reaction mixture was allowed to warm up to room temperature. After water addition (1.0 mL), the reaction mixture was extracted with diethyl ether (4 × 50 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed and the crude product was purified by column chromatography (SiO_2, pentane) affording the desired product (54 mg, 0.23 mmol, 82%) as a colorless crystalline solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 8.0 Hz, 1 H), 6.75–6.65 (m, 2 H), 3.81 (s, 3 H), 2.94 (t, *J* = 7.1 Hz, 2 H), 2.84–2.70 (m, 4 H), 2.20 (t, *J* = 8.3 Hz, 2 H), 1.77 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9, 137.2, 128.8, 128.5, 123.9, 123.5, 122.7, 122.6, 113.6, 110.7, 55.2, 39.0, 33.3, 28.5, 28.1, 18.5, 18.1; MS *m*/*z* (%) = 240 (M^+, 91), 238(75), 225(100), 210(26), 165(20); HRMS calcd for $C_{17}H_{20}O$: *m*/*z* = 240.1514, found: *m*/*z* = 240.1522. (b) For a recent flexible synthesis of phenanthrene derivatives see: Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264; and references cited therein.

(8) Schlosser, M. In *Organometallics in Synthesis*; Wiley: Chichester, **1994**, 129–133.

(9) Typical procedure: Preparation of 1,4,5,6,7,8-hexahydro-2,3-dimethyl-dibenzo[*a*,*c*]cyclooctene (Scheme 6, structure at the bottom): To 4-[2-(2-bromophenyl)-4,5-dimethyl-1,4-cyclohexadien-1-yl]butyl 4-methylbenzenesulfonate (1.282 g, 2.62 mmol) in dry diethyl ether (5.0 mL) at –100 °C *tert*-butyllithium (3.74 mL, 1.4 M in THF, 5.24 mmol, 2.0 equiv) was added slowly, such that the reaction temperature did not exceed –80 °C. Then, the reaction mixture was allowed to warm up to room temperature. After water (2.0 mL) was added, the reaction mixture was extracted with diethyl ether (4 × 50 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed and the crude product was purified by column chromatography (SiO_2, pentane) affording the desired product (437 mg, 1.84 mmol, 70%) as a colorless oil.
^{1}H NMR (300 MHz, C_6D_6): δ = 7.22–7.08 (m, 4 H), 3.16–3.00 (m, 1 H), 2.90–2.75 (m, 1 H), 2.70–2.40 (m, 4 H), 1.98–1.80 (m, 2 H), 1.77 –1.49 (m, 8 H), 1.44–1.11 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6): δ = 142.2 (C_q), 141.5(C_q), 132.2(C_q), 129.7 (CH), 128.5 (C_q), 127.4 (CH), 127.1 (CH), 125.8 (CH), 123.7 (C_q), 123.3 (C_q), 38.8 (CH_2), 38.6 (CH_2), 33.5 (CH_2), 32.1 (CH_2), 30.4 (CH_2), 24.2 (CH_2), 18.2 (CH_3), 18.1 (CH_3); MS *m*/*z* (%) = 238 (M^+, 100), 223(18), 195(50), 181(57), 165(22); HRMS calcd for $C_{18}H_{22}$: *m*/*z* = 238.1721, found: *m*/*z* = 238.1714.
Analytical data for 1,4,6,7-tetrahydro-2,3-dimethyl-dibenzo[*a*,*c*]cycloheptene (Scheme 6, structure at the top): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.02 (m, 4 H), 2.96–2.87 (m, 2 H), 2.83–2.74 (m, 2 H), 2.48 (t, *J* = 7.1 Hz, 2 H), 2.10–1.98 (m, 2 H), 1.77 (t, *J* = 6.7 Hz, 2 H), 1.64 (s, 6 H); ^{13}C NMR (75 MHz, C_6D_6): δ = 142.2 (C_q), 140.3 (C_q), 132.4 (C_q), 128.6 (CH), 128.2 (C_q), 126.1 (CH), 125.9 (CH), 125.4 (CH), 123.8 (C_q), 123.2 (C_q), 39.3 (CH_2), 36.9 (CH_2), 33.6 (CH_2), 32.3 (CH_2), 29.8 (CH_2), 18.3 (CH_3), 18.1 (CH_3); MS *m*/*z* (%) = 224 (M^+, 100), 209(51), 195(24), 181(38), 165(22), 121(27); HRMS calcd for $C_{17}H_{20}$: *m*/*z* = 224.1565, found: *m*/*z* = 224.1572.