Domino Reactions

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# Palladium-Catalyzed Arylative Ring-Opening Reactions of Norbornenols: Entry to Highly Substituted Cyclohexenes, Quinolines, and Tetrahydroquinolines**

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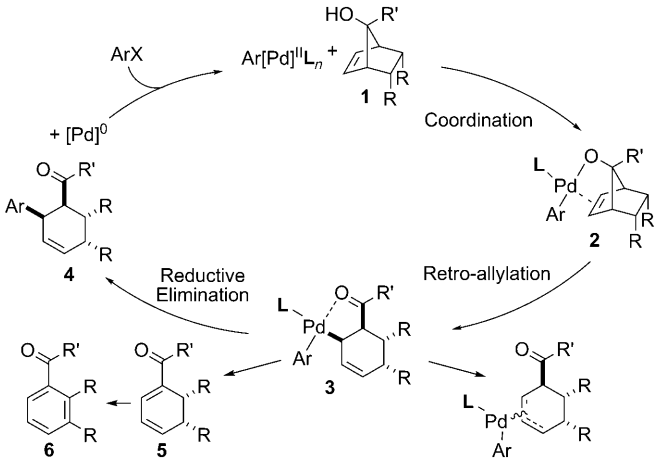
The development of efficient and sustainable procedures towards the synthesis of complex molecules is an important task for modern organic chemistry. Ways to improve efficiency include the use of domino reactions that allow a rapid increase in molecular complexity[1] and the discovery of novel reactivity to address previously inert functionalities. A challenging area of the latter approach are metal-catalyzed activations of C–C bonds.[2] β-Carbon eliminations from tertiary alcohols proceed relatively easily to produce C(sp)–metal[3] and C($sp^2$)–metal species,[4] whereas related formations of C($sp^3$)–metal species usually require ring-strain assistance.[5] In contrast, retro-allylation from bulky tertiary homoallylic alcohols is a known reaction proceeding with a range of transition and main group metals generating allyl metal species that are arguably a highly versatile and valuable reactive group in synthetic organic chemistry.[6] Yorimitsu, Oshima, and co-workers demonstrated in seminal contributions that allyl palladium species arising from such retro-allylations are suitable for coupling reactions with aryl halides.[7] Surprisingly, the concomitantly liberated carbonyl group has never been addressed in subsequent transformations. In this respect, symmetrically substituted bicyclic homoallylic alcohols represent an appealing substrate class. Selective ring-opening by C–C bond cleavage would simultaneously generate arrays of stereogenic centers, an acyl group, and an allylic metal species. Subsequent trapping reactions should allow access to biologically relevant heterocyclic scaffolds with high efficiency.[8]

Herein we report palladium-catalyzed arylative ring-opening reactions of norbornene-derived tertiary alcohols (**1**) to access highly substituted acyl cyclohexenes, quinolines, and tetrahydroquinolines in a stereodefined fashion. The proposed process is initiated by formation of an aryl palladium(II) complex from aryl halides (Scheme 1). A simultaneous coordination of this species to the hydroxy group as well as to the double bond (**2**) is a requirement for the envisioned retro-allylation reactivity.[9] Subsequently, the arising palladium(II) species **3**, could either undergo reductive elimination, β-hydride elimination, or equilibration reactions through σ–π isomerizations. We speculated that reductive elimination would be fast enough to maintain the imprinted stereochemistry and allow access to the thermodynamically less favorable cyclohexene isomer **4** having a *cis* relationship of the two pairs of substituents.




***Scheme 1.*** Palladium-catalyzed arylative ring-opening of norbornenols.

Initially, we explored the viability of the process with norbornenol **1a** and *p*-bromotoluene as a substrate. In the presence of $Pd(OAc)_2$ and tricyclohexylphosphine complete conversion of **1a** was observed and 40% of desired arylated product **4** was formed (Table 1, entry 1). Although no other isomers were detected, arene **6**, arising from β-hydride elimination of **3** into **5** and subsequent aromatization, appeared in 43%. Lowering the temperature mostly suppressed this process and increased the yield of desired product **4** to 72% (entry 2). Replacement of $PCy_3$ by $PtBu_3{\cdot}HBF_4$ slightly increased the yield of **4**, whereas $PPh_3$ gave more aromatized product **6** (entries 3–4). In contrast, the use of S-Phos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl)[10] or X-Phos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl)[11] additionally improved the yield of **4** (entries 5–6). Dioxane or CPME can be used instead of toluene (entries 7–8). Aryl chlorides and aryl iodides work with comparable efficiency, whereas aryl triflates lead to significantly more of the aromatization product **6** (entries 9–11).

We next explored the scope of the reaction. A variety of aryl and vinyl bromides with different electronic and steric

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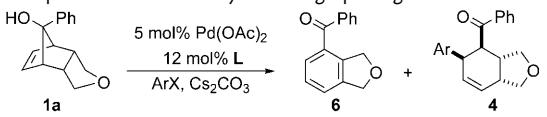
***Table 1:*** Optimization of the arylative ring-opening of **1a**.[a]

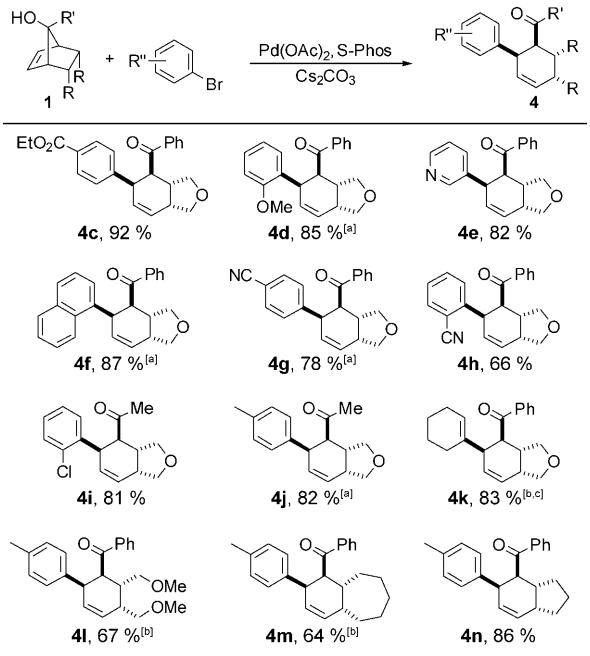



| Entry | L | Solvent | ArX | **6** [%][b] | **4** [%][b] |
|---|---|---|---|---|---|
| 1[c] | $PCy_3$ | xylene | 4-BrTol | 43 | 40 (**4a**) |
| 2 | $PCy_3$ | toluene | 4-BrTol | 11 | 72 (**4a**) |
| 3 | $PtBu_3 \cdot HBF_4$ | toluene | 4-BrTol | 9 | 81 (**4a**) |
| 4 | $PPh_3$ | toluene | 4-BrTol | 41 | 49 (**4a**) |
| 5 | S-Phos | toluene | 4-BrTol | 5 | 87 (**4a**) |
| 6 | X-Phos | toluene | 4-BrTol | 11 | 82 (**4a**) |
| 7 | $PCy_3$ | dioxane | 4-BrTol | 12 | 68 (**4a**) |
| 8 | $PCy_3$ | CPME | 4-BrTol | 16 | 66 (**4a**) |
| 9 | S-Phos | toluene | 4-ClTol | 12 | 77 (**4a**) |
| 10 | $PCy_3$ | toluene | PhI | 17 | 67 (**4b**) |
| 11 | $PCy_3$ | toluene | PhOTf | 53 | 26 (**4b**) |

[a] Reaction conditions: **1a** (0.05 mmol), ArX (4 equiv), $Cs_2CO_3$ (1.5 equiv), $Pd(OAc)_2$ (5 mol%), **L** (12 mol%), 0.15 M in the indicated solvent, 100°C, 3–12 h. [b] Isolated product. [c] Run at 120°C. CPME = cyclopentyl methyl ether, Cy = cyclohexyl, Tf = trifluoromethanesulfonyl.

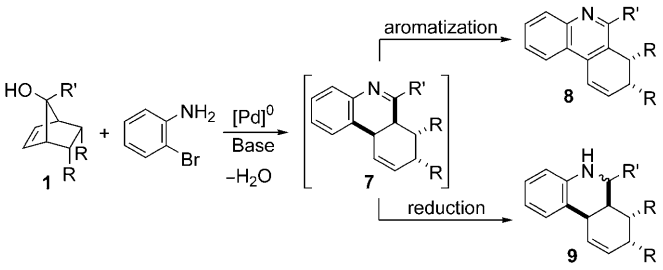
properties can be employed giving **4a–4k** in high yields (Scheme 2). The substitution pattern of norbornenol **1** can be varied from cyclic derivatives with different ring sizes to acyclic substrates (**4l–4n**). Notably, the diastereoselectivity is maintained throughout all substrate combinations leading exclusively to the depicted isomers.[12]

To take advantage of the concomitantly formed carbonyl group, we envisioned using *o*-bromoaniline as the aryl halide



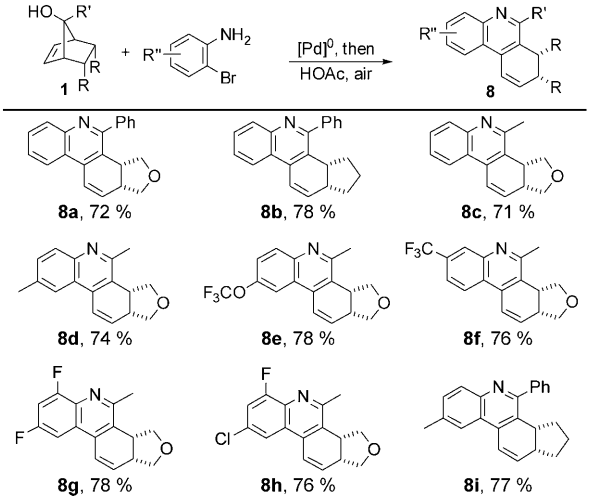

***Scheme 2.*** Scope of norbornenol ring-opening reaction. Reaction conditions: **1** (0.05 mmol), ArBr (4 equiv), $Cs_2CO_3$ (1.5 equiv), $Pd(OAc)_2$ (5 mol%), S-Phos (12 mol%), 0.15 M in toluene, 100°C, 3–12 h. [a] Run with $PCy_3$. [b] Run at 80°C. [c] Used 4 equiv cyclohexenyl triflate.

component to obtain an aniline-bearing cyclohexene **4**. This species could then undergo a dehydrative cyclization giving imine **7** (Scheme 3). Although imine **7** could not be directly




***Scheme 3.*** Domino cyclization of norbornenols **1** with *o*-bromoanilines.

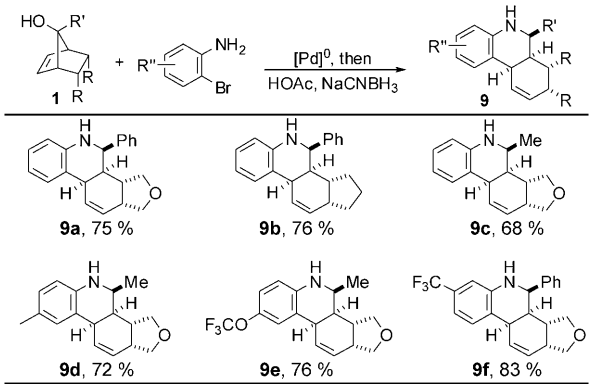
tracked, its aromatization product **8** was isolated in moderate yields.[13] The imine formation as well as the subsequent oxidation is significantly accelerated by addition of acetic acid and exposure of the reaction mixture to air, therefore providing access to quinolines in good yields. This domino sequence proved to be tolerant towards different substituents on the bromoanilines yielding quinolines **8a–8i** with a broad substitution pattern (Scheme 4).




***Scheme 4.*** Scope for quinolines **8**. Reaction conditions: **1** (0.05 mmol), ArBr (2 equiv), $Cs_2CO_3$ (1.5 equiv), $Pd(OAc)_2$ (5 mol%), S-Phos (12 mol%); 0.15 M in toluene, 100°C, 12 h, then AcOH (15 equiv), 23°C, 2 h.

To further capitalize upon intermediate imine **7** for an increase in molecular complexity, we explored the incorporation of a reduction step into the domino process to access tetrahydroquinolines **9** (Scheme 3). Addition of sodium cyanoborohydride and acetic acid prompted a clean reduction and gave tetrahydroquinolines **9a–9f** in good yields and excellent diastereoselectivity for the created N-substituted stereogenic center (Scheme 5). Once again, the process proved to be compatible with a range of substituents. The




***Scheme 5.*** Scope for tetrahydroquinolines **9**. Reaction conditions: **1** (0.05 mmol), ArBr (2 equiv), $Cs_2CO_3$ (1.5 equiv), $Pd(OAc)_2$ (5 mol%), S-Phos (12 mol%); 0.15 M in dioxane, 100 °C, 3 h, then $NaCNBH_3$ (3 equiv), AcOH (5 equiv), 23 °C, 2 h.

stereochemical outcome of the reduction and the relative configuration of the tetrahydroquinolines was established by the X-ray crystallographic analysis of derivative **9f** (Figure 1).[14]

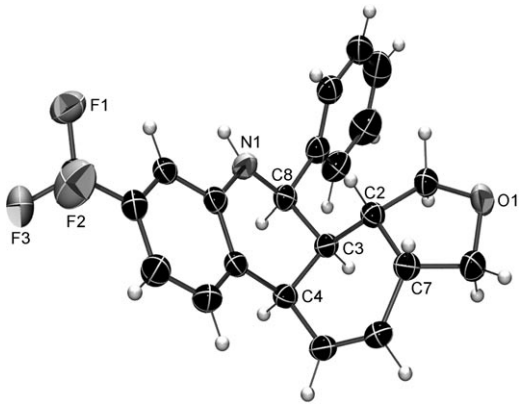
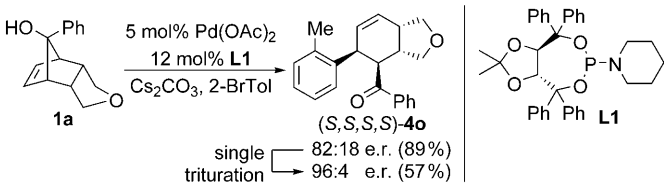



***Figure 1.*** ORTEP representation of **9f**. The thermal ellipsoids are drawn at a 50% probability.

Initial attempts to develop an enantioselective variant[6k] of the retro-allylation process using taddol-based phosphoramidite ligand **L1** gave rise to (*S*,*S*,*S*,*S*)-**4o** in 89% yield and an enantioselectivity of 82:18 e.r. (Scheme 6). The enantiomeric ratio can be enhanced to 96:4 by a single precipitation of the remaining (*rac*)-**4o**.[15]




***Scheme 6.*** Initial result for an enantioselective version of arylative ring-opening.

In summary, we have disclosed palladium-catalyzed ring-opening reactions of norbornene-derived tertiary alcohols. The intermediates arising from this retro-allylative fragmentation are trapped with aryl or vinyl halides in a highly regio- and diastereoselective fashion leading to tetrasubstituted cyclohexenes. This procedure can be extended to domino reactions providing either access to highly functionalized synthetically valuable quinolines or to tetrahydroquinolines. Extension of the methodology to related substrate classes and the development of asymmetric variants are in progress.

## *Experimental Section*

Compound **1a** (11.4 mg, 0.05 mmol), 4-bromotoluene (32.2 mg, 0.20 mmol), $Pd(OAc)_2$ (0.56 mg, 2.50 μmol), S-Phos (2.46 mg, 6.00 μmol), and $Cs_2CO_3$ (24.4 mg, 0.075 mmol) were weighed into an oven dried vial equipped with a magnetic stir bar, sealed with a rubber septum, and flushed with nitrogen. After the addition of 0.25 mL of dry toluene, the reaction mixture was degassed by three freeze-pump-thaw cycles, and immersed into a preheated oil bath (100 °C) for 12 h. After TLC analysis showed the complete conversion, the reaction mixture was cooled to 23 °C and directly purified on silica gel (10% EtOAc in pentane, $R_f = 0.25$) yielding 13.8 mg (87%) of **4a** as a colorless oil.

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[1] a) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; c) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.

[2] a) B. Rybtchinski, D. Milstein, *Angew. Chem.* **1999**, *111*, 918–932; *Angew. Chem. Int. Ed.* **1999**, *38*, 870–883; b) M. Murakami, Y. Ito, *Top. Organomet. Chem.* **1999**, *3*, 97–129; c) M. E. van der Boom, D. Milstein, *Chem. Rev.* **2003**, *103*, 1759–1792; d) C.-H. Jun, *Chem. Soc. Rev.* **2004**, *33*, 610–618; e) T. Satoh, M. Miura, *Top. Organomet. Chem.* **2005**, *14*, 1–20; f) T. Seiser, N. Cramer, *Org. Biomol. Chem.* **2009**, *7*, 2835–2840.

[3] a) H.-F. Chow, C.-W. Wan, K.-H. Low, Y.-Y. Yeung, *J. Org. Chem.* **2001**, *66*, 1910–1913; b) T. Nishimura, H. Araki, Y. Maeda, S. Uemura, *Org. Lett.* **2003**, *5*, 2997–2999.

[4] a) Y. Terao, H. Wakui, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2001**, *123*, 10407–10408; b) Y. Terao, H. Wakui, M. Nomoto, T. Satoh, M. Miura, M. Nomura, *J. Org. Chem.* **2003**, *68*, 5236–5243.

[5] For recent examples see: a) T. Seiser, N. Cramer, *Angew. Chem.* **2008**, *120*, 9435–9438; *Angew. Chem. Int. Ed.* **2008**, *47*, 9294–9297; b) T. Seiser, O. A. Roth, N. Cramer, *Angew. Chem.* **2009**, *121*, 6438–6441; *Angew. Chem. Int. Ed.* **2009**, *48*, 6320–6323; c) T. Seiser, N. Cramer, *Chem. Eur. J.* **2010**, *16*, 3383–3391; d) T. Seiser, N. Cramer, *J. Am. Chem. Soc.* **2010**, *132*, 5340–5341; e) T. Seiser, N. Cramer, *Chimia* **2010**, *64*, 153–156.

[6] For an overview see: a) H. Yorimitsu, K. Oshima, *Bull. Chem. Soc. Jpn.* **2009**, *82*, 778–792; For recent examples see: with zinc: b) P. Jones, N. Millot, P. Knochel, *Chem. Commun.* **1998**, 2405–2406; c) P. Jones, P. Knochel, *Chem. Commun.* **1998**, 2407–2408; d) P. Jones, P. Knochel, *J. Org. Chem.* **1999**, *64*, 186–195; with tin: e) A. Yanagisawa, T. Aoki, T. Arai, *Synlett* **2006**, 2071–2074; with gallium: f) S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima,

  

*Org. Lett.* **2005**, *7*, 3577 – 3579; with ruthenium: g) T. Kondo, K. Kodoi, E. Nishinaga, T. Okada, Y. Morisaki, Y. Watanabe, T. Mitsudo, *J. Am. Chem. Soc.* **1998**, *120*, 5587 – 5588; with nickel: h) D. Nečas, M. Turský, M. Kotora, *J. Am. Chem. Soc.* **2004**, *126*, 10222 – 10223; i) Y. Sumida, S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2008**, *10*, 1629 – 1632; with rhodium: j) Y. Takada, S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2006**, *8*, 2515 – 2517; k) R. Shintani, K. Takatsu, T. Hayashi, *Org. Lett.* **2008**, *10*, 1191 – 1193.

[7] a) S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2006**, *128*, 2210 – 2211; b) S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2007**, *129*, 12650 – 12651; c) M. Iwasaki, S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2007**, *129*, 4463 – 4469; d) M. Iwasaki, S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *Tetrahedron* **2007**, *63*, 5200 – 5203; e) M. Iwasaki, H. Yorimitsu, K. Oshima, *Bull. Chem. Soc. Jpn.* **2009**, *82*, 249 – 253; f) M. Iwasaki, H. Yorimitsu, K. Oshima, *Synlett* **2009**, 2177 – 2179.

[8] J. P. Michael, *Nat. Prod. Rep.* **2007**, *24*, 166 – 187.

[9] Ring-opening reactions of oxa- and aza-bicyclic compounds proceed by a distinctively different mechanism that is initiated by a carbometalation of the strained double bond followed by either β-alkoxide or β-amide elimination, respectively. For leading references see: a) M. Lautens, K. Fagnou, S. Hiebert, *Acc. Chem. Res.* **2003**, *36*, 48 – 58; b) M. Lautens, S. Hiebert, *J. Am. Chem. Soc.* **2004**, *126*, 1437 – 1447.

[10] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685 – 4696.

[11] X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653 – 6655.

[12] Partial epimerization of the stereocenter α to the carbonyl group was observed at higher temperature (130 °C) and prolonged reaction times (> 24 h) or when stronger bases (NaO*t*Bu) were used.

[13] R. C. Larock, S. Babu, *Tetrahedron Lett.* **1987**, *28*, 5291 – 5294.

[14] Crystallographic data for **9 f**: $C_{22}H_{20}F_3NO$, $M = 371.40$, monoclinic, space group $P2_1/c$, $a = 11.7515(4)$, $b = 14.8191(7)$, $c = 10.1800(4)$ Å, $\beta = 90.893(3)°$, $V = 1772.60(12)$ Å$^3$, $Z = 4$, $D_{calc} = 1.392$ Mg m$^{-3}$, $T = 123$ K, reflections collected: 6890, independent reflections: 4014 ($R_{int} = 0.078$), $R$(all) = 0.0806, w$R$(gt) = 0.1411. CCDC 770255 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] See the Supporting Information for determination of the absolute configuration.

  