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Intramolecular transition-metal catalyzed cyclizations of electron rich chloroarenes

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Abstract

Electron rich chromium tricarbonylchloroarene complexes bearing an allyl ether moiety were cyclized under palladium catalysis with concomitant loss of the metal carbonyl fragment to give heterocyclic systems in moderate to good yields. Bimetallic catalysis with palladium and chromium compounds gave rise to cyclization of the parent chloroarenes in moderate yields and with low turnover numbers. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: chloroarenes; heterocycles; bimetallic catalysis; Heck reaction.

The activation of chloroarenes by metal-catalysis towards the synthesis of both simple and more complex molecules has attracted increasing attention as a cheaper alternative to the analogous bromo or iodo compounds.[1] Hence, various approaches have been investigated in the past,[2] such as tuning of ligand and catalyst systems, reaction conditions and use of additives. By employing thermally stable complexes such as palladacycles,[3] metal–carbene complexes[4], palladium-cluster[5] or electron–donor ligand containing complexes,[6] high turnover numbers at elevated temperatures (over 120°C) have been achieved. Unusual reaction conditions (e.g. high-pressure[7]) or additives[8] have also led to an increased reactivity of the chloroarenes.[9,10] In addition, the activation of chloroarenes by chromium tricarbonyl fragments has been used for the intermolecular Heck[11] and Stille[12] reaction as well as palladium-catalyzed carbonylations[13] amongst others. During these investigations concerning the intramolecular palladium-catalyzed reactions of chloroarenes, Kündig et al.[14] showed that Heck reactions of chromium tricarbonyl chloroarene complexes can proceed smoothly. This paper reports the intramolecular Heck reaction of electron-rich chromium tricarbonyl complexes.

Oxygen substituted chloroarenes were chosen as starting materials. Accessible from commercially available 3,5-dimethoxybenzoic acid (**1**), esterfication to yield the methylester and subsequent reduction gave the corresponding alcohol in nearly quantitative yield (Scheme 1).[15] The chlorination was effected with *N*-chlorosuccinimide in DMF to give the dichlorobenzylic alcohol **2** in good yields (89%). The alkenyl group was attached via alkylation with allyl bromide. The complexation was effected with

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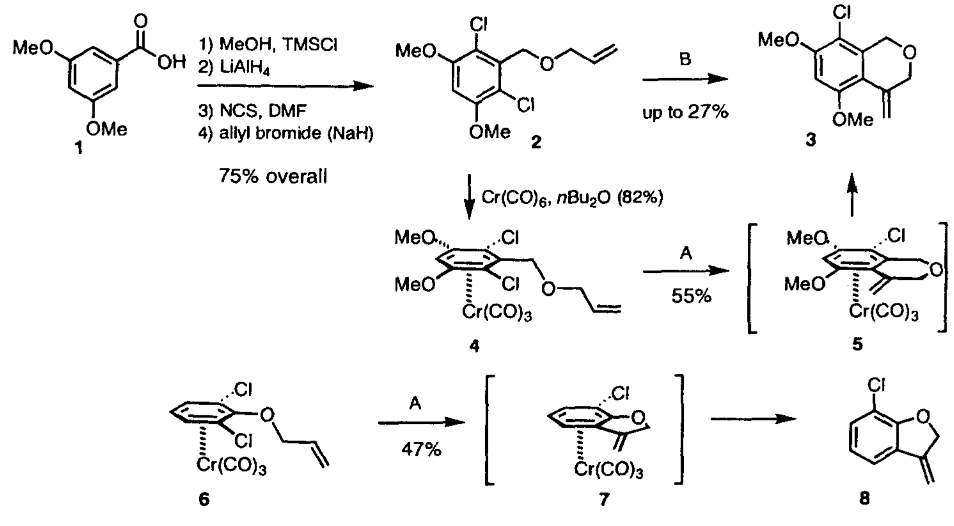
chromium hexacarbonyl in dibutyl ether to give the complex **4** in up to 82% yield. Similarly, the aryl ether complex **6** was synthesized from commercially available 2,6-dichlorophenol. The intramolecular cyclization of complex **4** was effected under standard Heck conditions [$Pd(OAc)_2$, PPh_3, NEt_3, DMF, 80°C, 24 h]. Aqueous workup gave the heterocycle **3** in up to 55%.[16] Switching to acetonitrile as solvent produced the complex **5** in 37–48% yield in addition to decomplexed product **3**. The same product pattern was observed with the aryl ether complex **6** to give the benzofuran **8** in up to 47% yield. These results show that even electron rich chloroarene complexes are excellent precursors for the intramolecular Heck reaction.



Scheme 1. (A) $Pd(OAc)_2$, PPh_3, NEt_3, DMF, 80°C, 24 h. (B) Cat. $Pd(OAc)_2$, cat. Cr^0 (see text)

Apparently, in DMF the arene complex **5** is less stable than the starting complex **4**, since the dihalide **2** is inert under pure palladium catalysis. Therefore, a bimetallic catalytic version was tested. Hence, a chromium(0) source [5 mol% $Cr(CO)_6$ or ($Cr(CO)_3$·naphthalene] was used in the presence of the palladium catalyst system. Under these conditions, the cyclized compound **3** was isolated in up to 27% yield, which corresponds to a turn-over number of about five. As an intermediate, the chromium complex **5** could be detected in trace amounts.

In conclusion, a novel bimetallic catalysis for the synthesis of highly donor-substituted heterocycles starting from chloroarenes has been achieved. Optimization of the catalyst protocol and application for the synthesis of biologically active compounds is in progress.

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15. All new compounds were fully characterized (^{1}H and ^{13}C NMR, IR, MS, elemental analysis and/or HRMS). Typical ^{1}H NMR data: **3**: δ=3.74 (s, 3H, MeO), 3.80 (s, 3H, MeO), 4.80 (s, 2H, CH$_2$O), 6.22 (d, ^{3}J=2.3 Hz, 1H), 6.35 (s, 1H, Ar-H), 6.38 (d, ^{3}J=2.3 Hz, 1H). **8**: δ=4.92 (s, 2H, CH$_2$O), 6.04 (d, ^{3}J=2.5 Hz, 1H), 6.42 (d, ^{3}J=2.5 Hz, 1H), 6.96–7.23 (m, 4H, Ar-H).
16. Various amounts of double bond isomerized compounds (3–15% based on cyclized material) were detected in all cases.