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Chromium(II)-Mediated Nickel(II)-Catalysed Cyclisations of (Iodoaryl)-Substituted Alkynes and Alkynals

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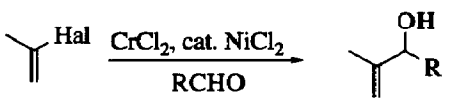
Abstract: *The Chromium(II)-mediated Nickel(II)-catalysed cyclisations of (iodoaryl)-substituted alkynes* ***1****,* ***2*** *and* ***7*** *and (iodoaryl)-substituted alkynals* ***9*** *and* ***10*** *to give the products* ***5****,* ***6****,* ***8****,* ***11*** *and* ***12*** *respectively is described.*

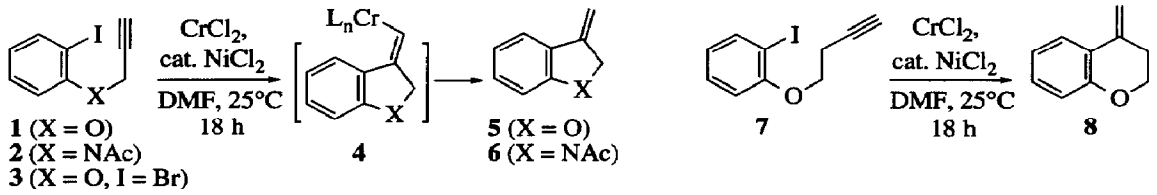
The $CrCl_2$-mediated $NiCl_2$-catalysed reaction of alkenyl and aryl halides with aldehydes (Eq. 1) has established itself as one of the most useful reactions for forming a C-C bond under extremely mild conditions.[1,2] Functional groups known to be tolerated on either the halide or aldehyde partner include ester, amide, nitrile, ketone, alcohol, and various alcohol protecting groups, as well as centres susceptible to epimerisation or elimination.[3] The reaction has found extensive application towards important natural product targets; particularly noteworthy are Kishi's landmark syntheses of palytoxin[1] and the halichondrins (in which *five* of the key C-C bonds were constructed using this chemistry).[4] More recently, the reaction has been used towards the histrionicotoxins,[5] and the taxanes.[6] The mild method of C-Hal activation has made the reaction ideally suited to intramolecular ring closures, as exemplified in the elegant syntheses of brefeldin C[7] and ophiobolin C.[8] In view of the major impact this reaction has made in organic synthesis, we have initiated a project to determine the propensity of the reaction to effect a *carbometallation* step,[9] for example across an alkyne, rather than aldehyde addition. This paper discloses our initial investigations in this area.



(1)

The basis for this research arose after consideration of the unique method of (sp^2)C-Hal bond activation (Eq. 1), which is believed to occur *via* oxidative addition of an *in situ* generated Ni(0) or Ni(I) species to the halide followed by transmetallation to Cr(III) or Cr(II), prior to coupling with an aldehyde.[3] Whilst alkyne insertion into an organonickel (or organopalladium) is a well precedented process,[10] to the best of our knowledge there are no reported examples of alkyne insertion into an organochromium species formed *in situ* under the mild $CrCl_2$-cat. $NiCl_2$ conditions.[11] Therefore, we first chose to examine whether an intramolecular carbometallation of an aryl iodide could occur onto a pendant alkyne using this chemistry.

The (iodoaryl)-substituted alkynes **1** and **2** (Scheme 1), designed to answer this question, were readily prepared from commercial 2-iodophenol and 2-iodoaniline.[12] The initial studies indicated that the carbometallation step has scope for the synthesis of five-membered rings as in **5**[13] (57% yield) and **6**[14] (73%).[15] The mild nature of the current process is shown by formation of the exocyclic methylene compounds. **5** can be easily isomerised to 3-methylbenzofuran using catalytic acid,[13] whereas *N*-acyl-3-methylindole[16] was isolated if the $CrCl_2$-cat.$NiCl_2$ reaction with **2** was left for 60 h at 25°C prior to work-up. The process thus provides alternative methodology to free-radical and Heck-based cyclisation strategies for five-membered ring synthesis under mild conditions.[14] Notably, alkyl halides are known to be unaffected under the present $CrCl_2$ conditions.[17] Aryl bromide functionality should also survive as the analogous (bromoaryl)-substituted alkyne **3** proved inert to the reaction conditions.

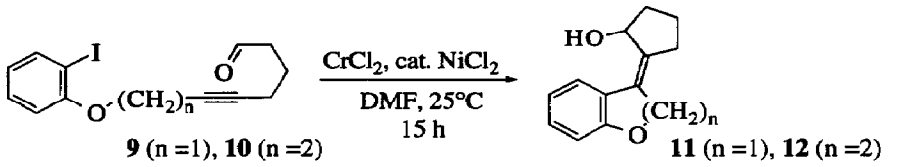


Scheme 1

The reaction could also be extended to six-membered ring synthesis,[18] where the benzopyran **8**[13] was isolated (52%).[15] Radical cyclisations to form these rings can suffer from competing 1,5-H-atom abstraction.[13]

The utility of this chemistry would be enhanced if the putative C-Cr bond of **4** could be used to trap electrophiles other than a proton on work-up. However, we were unable to trap the putative alkenyl chromium species when benzaldehyde was also present with **1** *in situ*. Nevertheless, this experiment served to indicate that the intramolecular carbometallation step was not diverted to aldehyde addition when an aldehyde was present. Since there was also no deuterium incorporation when working up the reactions with D_2O, it seems likely that Cr-C bond homolysis was occurring followed by H-atom abstraction from the solvent.[19] Similar results were obtained with **1** using DMSO as solvent.[6]

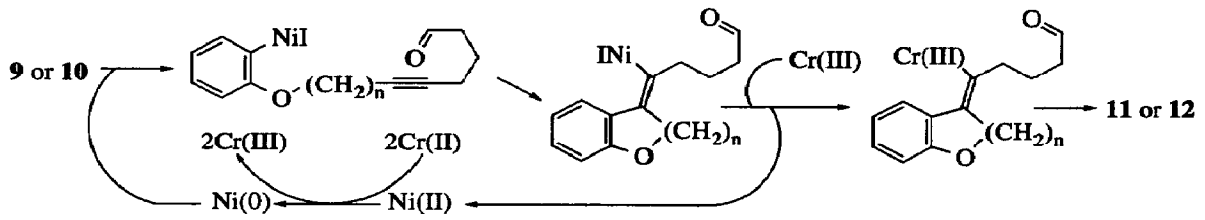
On the basis that the lack of aldehyde trapping reflected the lifetime of the transient C-Cr bond and/or steric hindrance to the incoming electrophile, we prepared substrates **9** and **10** containing an aldehyde tether.[20] We were delighted to find that trapping occurred to give the alcohols **11** (11%) and **12** (25%) (Eq. 2),[15] although the reaction was clearly less facile than cyclisation onto an unsubstituted alkyne.[21]



(2)

Whilst the yields are disappointing for the tandem reactions they do imply that an alkenyl chromium species is forming. Moreover, only the products of *syn*-vicinal difunctionalisation of the triple bond were observed, as determined by nOe studies.[22] Mechanistically, our current working hypothesis for the tandem cyclisation (Scheme 2) involves oxidative addition into the C-I bond by a Ni(0) [or Ni(I)] species followed by intramolecular *syn* arylnickelation of the triple bond prior to transmetallation to Cr(III) [or Cr(II)] with retention of geometry and then attack on the pendant electrophilic aldehyde. Conceptually, the metal 'switch', which allows a carbometallation followed by an intramolecular reaction with an aldehyde, complements Heck-style chemistry where the reaction can be terminated by an organic 'anion' (or hydride) *via* transmetallation from, for

example, an organostannane.[23]



Scheme 2

In summary, we have demonstrated that the $CrCl_2$-mediated $NiCl_2$-catalysed reaction of (sp^2)C-Hal bonds can also be directed towards a carbometallation process, which provides mild methodology for ring synthesis. Based on our present results we are currently examining the scope of the reaction with other substrates.

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12. **1** was prepared by a modification (2-iodophenol, propargyl bromide, K_2CO_3, DMF, 90%) of the literature procedure (Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1990**, *55*, 6171-6176). **2** was prepared by a modification (2-iodoaniline, Ac_2O, AcOH, 85%) of the literature *N*-acylation procedure (Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119-10128), then as for **1** (91%).

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15. Isolated total yields, not optimised, of chromatographically homogeneous, spectroscopically pure products are reported. All new compounds were characterised by a full range of spectroscopic data, including ^{1}H and ^{13}C NMR and high resolution mass spectrometry.
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18. The (iodoaryl)-substituted alkyne **7** was prepared by Mitsunobu reaction (Hughes, D. L. *Org. React.* **1992**, *42*, 335-656) between 2-iodophenol and 3-butyn-1-ol (DEAD, PPh_3, CH_2Cl_2, 56%).
19. There is precedent for this type of decomposition pathway. See Ref. 11, pp. 243-248.
20. The (iodoaryl)-substituted alkynals **9** and **10** were prepared from the appropriate mono-THP protected alkyndiol (Heitz, M.-P.; Wagner, A.; Mioskowski, C.; Noël, J.-P.; Beaucourt, J.-P. *J. Org. Chem.* **1989**, *54*, 500-503 and Paquette, L. A.; Begland, R. W. *J. Am. Chem. Soc.* **1968**, *90*, 5159-5164 respectively):

(a) 2-iodophenol, DEAD, PPh_3, CH_2Cl_2, 84% (n = 1), 63% (n = 2); (b) MeOH, cat. *p*-TSA, 75% (n = 1), 90% (n = 2); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 77% (n = 1), 63% (n = 2).
21. Reaction of **1** (≡C-H = ≡C-Bu) in DMF, in the absence of an aldehyde, gave the cyclised product in 15% yield after 15 h.
22. The following procedure is representative: A solution of the aldehyde **10** (515 mg, 1.5 mmol) in dry deoxygenated DMF (2 ml) was added to a stirred solution of $CrCl_2$ (589mg, Aldrich 95% w/w pure, 4.5 mmol) and anhydrous $NiCl_2$ [7.3 mg , 0.06 mmol, obtained from $NiCl_2.6H_2O$ (Fluka, 98% w/w pure) by heating at *ca.* 80 °C for 10 min at 1 mmHg and allowing to cool under argon] in dry deoxygenated DMF (3 ml) under argon at 25 °C. After 15 h the reaction mixture was diluted with water (5 ml) and extracted with ether (4 x 5 ml). The combined organic layers were washed with water (5 ml), brine (5 ml), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography [35% ether-light petroleum (b.p. 40-60 °C)] gave a colourless oil, the *alcohol* **12** (81 mg, 25%); R_f 0.30 [50% ether/light petroleum (b.p. 40-60 °C)]; found: M^+, 216.1150, $C_{14}H_{16}O_2$ requires 216.11502; ν_{max} (neat)/cm^{-1} 3601m, 2960s, 1699s, 1482s, 1451s, 1302s and 1218s; δ_H(400 MHz; $CDCl_3$; $SiMe_4$; *J*/Hz) 7.93 (1H, dd, *J*8 and 1.5, Ar. CH), 7.16 (1H, ddd, *J*8, 7 and 1.5, Ar. CH), 6.93 (1H, ddd, *J*8, 7 and 1.5, Ar. CH), 6.84 (1H, dd, *J*8 and 1.5, Ar. CH), 4.84 (1H, br d, *J*4, C*H*OH), 4.28 (1H, ddd, *J*10.5, 6 and 4.5, H of OCH_2), 4.14 (1H, ddd, *J*10.5, 9.5 and 4, H of OCH_2), 2.72-2.53 (3H, m), 2.39-2.30 (1H, m), 2.06-1.90 (2H, m) and 1.86-1.65 (2H, m); *nOe experiments*: irradiation at 4.84 saw enhancement (5.8%) at 7.93, irradiation at 7.93 saw enhancement (5.2%) at 4.82, (similar enhancements were obtained for alcohol **11**); δ_C(100 MHz; $CDCl_3$) 154.0 (quat. C), 138.5 (quat. C), 135.5 (quat. C), 128.6 (Ar. CH), 128.4 (Ar. CH), 126.1 (quat. C), 120.6 (Ar. CH), 116.8 (Ar. CH), 73.0 (CHOH), 66.5 (OCH_2), 37.2 (CH_2), 30.5 (CH_2), 29.2 (CH_2) and 22.0 (CH_2); *m/z* (EI) 216 (20%), 198 (35), 170 (30) and 133 (100).
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