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Exploration of Nicholas methodology using chiral heterobimetallic cobalt–molybdenum propargylium complexes

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Abstract—Nicholas methodology has been used successfully with chiral heterobimetallic cobalt–molybdenum propargylium complexes in the formation of enyne complexes, new stereocentres and heteroatom ring systems, in high yield and moderate diastereoselectivity.

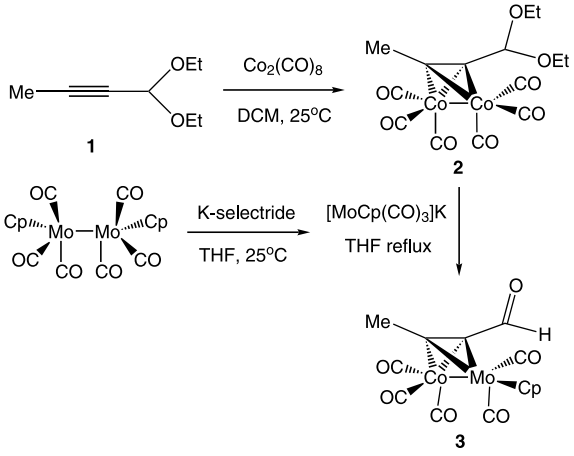
The use of dicobalt hexacarbonyl propargylium complexes in the Nicholas reaction,[1] which involves addition of nucleophiles to complexed propargylic cations, is a widely known and explored method of C–C and C–heteroatom bond formation.[2] This chemistry has been developed with the use of dimolybdenum dicyclopentadienyl tetracarbonyl and diastereomeric dicobalt pentacarbonyl arylphosphite complexes,[3,4] the latter establishing a route to enantiomerically enriched diastereomeric product complexes.[5] Application to the synthesis of ether ring systems has been recognised as a key step in natural product synthesis.[6–10]

Although a great deal of research has been carried out with homobimetallic systems, limited chemistry has been carried out with heterobimetallic propargylium complexes. Examples of interest are the inherently chiral complexes of cobaltmolybdenum cyclopentadienyl pentacarbonyl propargylium complex alkyne[CoMoCp(CO)$_5$], where synthesis and characterisation are known in the literature, but only limited reactivity studies have been reported.[11–17]

With these precedents in mind, we report herein our exploration of the chiral directing capability of the heterobimetallic Co–Mo–alkyne core in nucleophilic attack via the Nicholas approach using propargylic salt complexes both preformed, and formed in situ after protonation of the corresponding enyne. We have also used this methodology in intramolecular nucleophilic additions to form heterocycles. Yields are high, and moderate stereoselectivity is observed.

The Co–Mo alkyne aldehyde complex **3** was first prepared by complexation of but-2-ynal diethyl acetal **1** ($Co_2(CO)_8$, DCM, 25°C) to afford **2** (Scheme 1). Isolobal displacement of $Co(CO)_3$ with $MoCp(CO)_2$ using the molybdenum anion $[Mo(CO)_3]K$ (THF reflux, 2 h) and hydrolysis of the diethyl acetal on chromatographic purification led to **3** (86% from uncomplexed acetal **1**).

Grignard reagent addition to the heterobimetallic aldehyde complex **3** at −78°C in THF, as we have previously reported, led to the propargylic alcohols **4a–e** in 93–96% yield and 5:1 to 10:1 d.r.[18] Slow addition of HBF_4 to these alcohols (Et_2O, 25°C) gave the orange, air stable propargylic salt complexes **5a–e**, respectively, in 81–93% yield (Scheme 2).[19]



Scheme 1.

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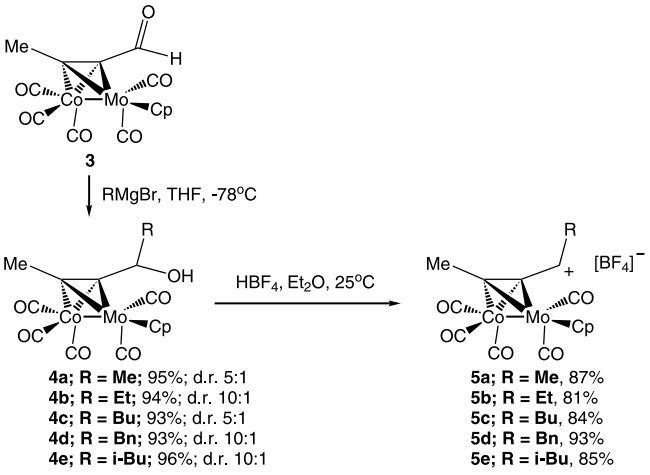
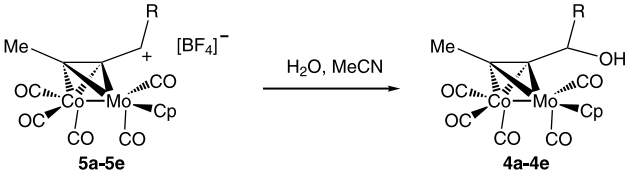


Scheme 2.

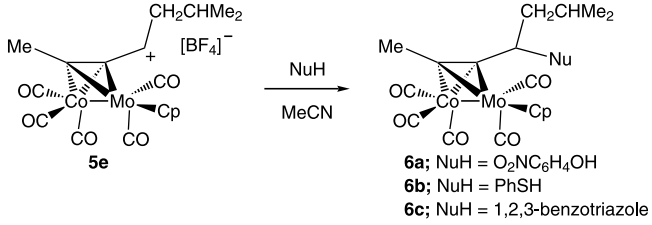
Nucleophilic addition to the propargylic salts **5** was examined using water over a range of solvents and temperatures. Optimum conditions were found to be in MeCN at –40°C (Scheme 3). Interestingly, the relative d.r. of the returned alcohol complexes **4a**–**e** (Table 1, entries 1–5) was reversed compared to those isolated from the Grignard addition reaction (Scheme 2), thus enabling access to both alcohol diastereoisomers, which are separable by column chromatography. In the case of benzyl substituted cation **5d**, the corresponding alkene **7d** (see below) was isolated.



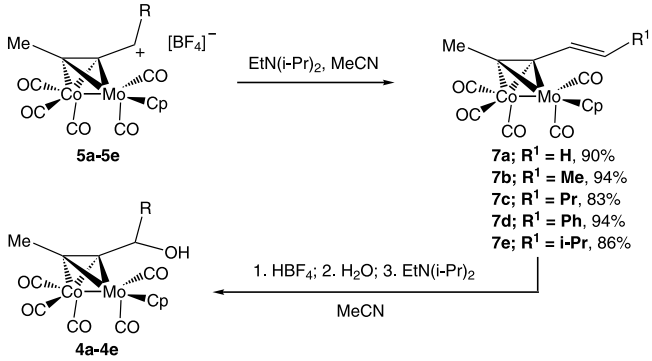
Scheme 3.

As the highest diastereoselectivity was found with the isobutyl substrate **5e**, additions with different heteroatom nucleophiles were carried out using this salt (Scheme 4). Excellent yields of **6a**–**c** were achieved; diastereoselectivity was moderate but improved at –40°C relative to room temperature (Table 1, entries 6–11).[20] The diastereoisomers were not separable by standard column chromatography, and all products formed were oils, hence diastereoselectivities were confirmed using 250 MHz ^{1}H NMR spectroscopy.

When the propargylic salt complexes **5a**–**e** were treated with the mild base *N*-ethyldiisopropylamine (Hünig's base) (MeCN, 25°C), the corresponding *trans* enynes **7a**–**e** were obtained in 83–94% yield (Scheme 5).[22,23]



Scheme 4.



Scheme 5.

Table 1. Nucleophilic capture of propargylic salt complexes **5** and alkene complexes **7**

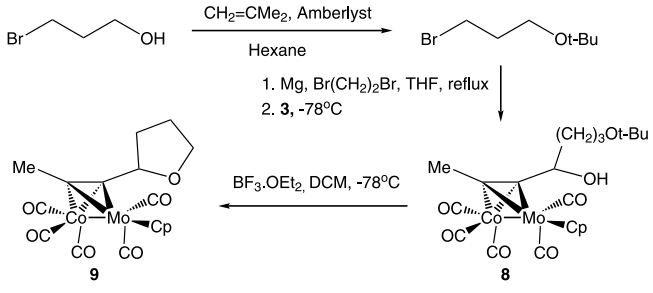
Entry	Complex	Product	Nucleophile	*T* (°C)	Yield (%)	D.r.
1	**5a**	**4a**	H_2O	−40	68	1:3
2	**5b**	**4b**	H_2O	−40	62	1:5
3	**5c**	**4c**	H_2O	−40	64	1:4.5
4	**5d**	**(4d)**	H_2O	−40	78	(Alkene **7d** isolated)
5	**5e**	**4e**	H_2O	−40	70	1:6
6	**5e**	**6a**	4-Nitrophenol	25	58	1:1.5
7				−40	89	1:2
8	**5e**	**6b**	PhSH	25	90	1:2
9				−40	93	1:4
10	**5e**	**6c**	1,2,3-Benzotriazole	25	91	1:1
11				−40	95	1:3
12	**7a**	**4a**	H_2O	25	59	1:2
13	**7b**	**4b**	H_2O	25	61	1:3
14	**7c**	**4c**	H_2O	25	66	1:5
15	**7d**	**4d**	H_2O	25	30	1:1
16	**7e**	**4e**	H_2O	25	65	1:5

As only **7b** showed any sign of a *cis* enyne by ^{1}H NMR spectroscopy, this indicated that more highly substituted R-groups favour *trans* enyne formation. This useful preparation of the enyne complexes bypasses the enynes themselves, and may be valuable in synthesis.[21]

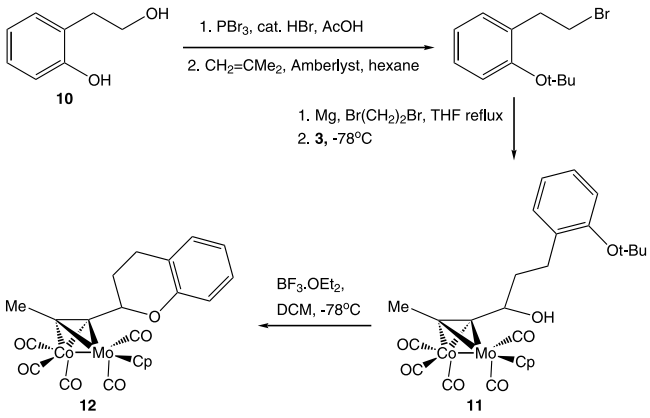
We wished to determine whether addition of a nucleophile to the propargylic carbon atom of the alkenes **7** would be possible and would give results matching direct addition to the salt complexes **5**. Complexes **7a**–**e** were thus treated successively with HBF_4 (MeCN, 25°C), water and Hünig's base (Scheme 5). Alcohol complexes **4a**–**e** were indeed recovered (Table 1, entries 12–16); yields were lower than direct addition of water to the salt complexes **5**, with recovery of 10–40% of alkene. The alcohol complexes **4** had equivalent or lower d.r. than from direct addition to the salt complexes and in the same direction (Table 1). It is thus likely that the reactions proceed via the same transition state. Benzyl substituted alcohol **4d** was retrieved in only 30% yield from a mixture; non-regiospecific protonation and stability (conjugation) of alkene **7d** may be factors here.

We wished to demonstrate the scope of this methodology for assembly of diastereomerically enriched heterocyclic rings of varying size via intramolecular nucleophile capture. Thus, we first prepared simple substrate **8** from 3-bromo-1-propanol by protection as the *tert*-butyl ether (2-methylpropene, Amberlyst, hexane),[24] generation of the Grignard reagent (Mg, cat. 1,2-bromoethane, THF reflux) and addition to the aldehyde complex **3** in good yield and d.r. (89%, 7:1) (Scheme 6). Initial trials with THP and *tert*-butyldimethylsilyl protecting groups were unsuccessful. A series of Lewis acids was examined for deprotection–ring closure. TFA, $TiCl_4$ and HBF_4 all formed the corresponding alkene by water loss, but on reaction with $BF_3{\cdot}OEt_2$ (DCM, −78°C) the tetrahydrofuran **9** was isolated (79%) with reduced d.r. (2:1), as observed by ^{1}H NMR spectroscopy.[25]

As a pilot study of six-ring formation, we decided to make the unsubstituted dihydrobenzopyran **12** (Scheme 7). Bromination of the primary alcohol of **10** (PBr_3, cat. HBr, AcOH; 49%) was followed by protection of the phenol as its *tert*-butyl ether as above (54%), generation of the Grignard reagent and subsequent addition to **3** to furnish complex **11** in 75% yield and d.r. 7:1. The cyclisation product **12** was formed on treatment



Scheme 6.



Scheme 7.

with $BF_3{\cdot}OEt_2$ (DCM, −78°C) in 20% yield (unoptimised) and d.r 1:2.

To conclude, preliminary studies using Nicholas methodology with inherently chiral heterobimetallic Co–Mo propargylium complexes have demonstrated the generation of new propargylic centres by nucleophilic addition in high yields with moderate to good stereoselectivity, and of enyne complexes. Intramolecular nucleophilic capture to form heterocycles shows promise and development is continuing in this area, including extension to nitrogen heterocycles.

Acknowledgements

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18. Christie, S. D. R.; Fletcher, A. J.; Fryatt, R.; Rutherford, D. T.; Elsegood, M. R. J. *Synlett* **2001**, 1711–1714.
19. **Typical procedure**: **salt complex 5e**. To cobalt molybdenum alcohol complex **4e** (1.50 g, 3.10 mmol) in dry diethyl ether (40 mL) stirred under nitrogen was added dropwise tetrafluoroboric acid (54 wt.%; 0.60 mL, 4.30 mmol). The reaction mixture was stirred for a further 10 min before the precipitated orange solid was filtered, washed with dry diethyl ether (60 mL) and dried under reduced pressure to yield the salt **5e** as an orange solid (1.59 g, 93%). IR (KBr)/cm^{-1} 2045, 1974, 1932. mp = 87–88°C (dec.). Found: C, 38.43; H, 3.21%. $C_{18}H_{18}O_5$–$BCoF_4Mo$ requires C, 38.88; H, 3.26%.
20. **Typical procedure**: **complex 6b**. To Co–Mo salt complex **5e** (435 mg, 0.78 mmol) in dry acetonitrile (20 mL) stirred under nitrogen at −40°C was added thiophenol (0.12 mL, 1.17 mmol). The reaction mixture was stirred for 30 min at −40°C, before addition of Hünigs base (0.20 mL, 1.56 mmol). The reaction mixture was allowed to warm to 25°C before filtration through a pad of Celite and silica. The solvent was removed in vacuo to leave a red oil, purified by flash silica chromatography eluting with light petroleum:diethyl ether (10:1 v/v) to yield the complex **6b** as a red oil (420 mg, 93%, 1:4 mixture of diastereoisomers). IR (film)/cm^{-1} 2044, 1970, 1933. Major diastereoisomer: ^{1}H NMR (250 MHz, $CDCl_3$) 7.41–7.20 (5H, m), 5.20 (5H, s), 4.50–4.40 (1H, m), 2.69 (3H, s), 2.09–1.92 (1H, m), 1.72–1.56 (2H, m), 0.92 (6H, dd, J = 2, 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 226.9, 225.1, 204.8, 138.1, 130.4, 129.4, 126.7, 100.8, 92.6, 90.9, 55.2, 48.5, 26.5, 23.6, 22.1, 21.5. Minor diastereoisomer: ^{1}H NMR (250 MHz, $CDCl_3$) 7.41–7.20 (5H, m), 5.40 (5H, s), 4.50–4.40 (1H, m), 2.56 (3H, s), 2.09–1.92 (1H, m), 1.72–1.56 (2H, m), 0.89 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$) 227.1, 225.0, 204.8, 137.8, 130.8, 129.5, 126.8, 101.7, 93.7, 90.9, 54.6, 48.9, 26.2, 23.8, 21.9, 21.4. Found: M^+–3CO, 495.98165. $C_{21}H_{23}O_2CoMoS$ requires 495.98070.
21. See, for example: Caddick, S.; Delisser, V. M. *Tetrahedron Lett.* **1997**, *38*, 2355–2358; Melikyan, G. G.; Khan, M. A.; Nicholas, K. M. *Organometallics* **1995**, *14*, 2170–2172.
22. Cf in Co–Co system: Nicholas, R. M.; Pettit, R. *J. Organomet. Chem.* **1972**, *44*, C21–C24.
23. **Enyne complex 7e**. To Co–Mo salt complex **5e** (100 mg, 0.18 mmol) in dry acetonitrile (10 mL) stirred under nitrogen at 25°C was added Hünigs base (0.05 mL, 0.36 mmol). The reaction mixture was stirred for 30 min before filtration through a pad of Celite and silica. The solvent was removed in vacuo to leave a red oil, purified by flash silica chromatography eluting with light petroleum:diethyl ether (15:1 v/v) to yield the enyne complex **7e** as a red oil (72 mg, 86%). IR (film)/cm^{-1} 2959, 2045, 1968, 1885. ^{1}H NMR (250 MHz, $CDCl_3$) 6.34 (1H, d, J = 15 Hz), 5.67 (1H, dd, J = 7, 22 Hz), 5.33 (5H, s), 2.65 (3H, s), 2.47–2.34 (1H, m), 1.03 (6H, d, J = 6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 226.3, 225.5, 203.9, 141.8, 126.2, 91.1, 90.0, 31.5, 22.7, 22.6, 21.4. Found: M^+, 469.9462. $C_{18}H_{17}O_5CoMo$ requires 469.9462.
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25. **Tetrahydrofuran complex 9**. To Co–Mo complex **8** (200 mg, 0.37 mmol) in dry DCM (15 mL) stirred under nitrogen at −78°C was added $BF_3{\cdot}OEt_2$ (0.14 mL, 1.11 mmol). The reaction mixture was stirred for 30 min and H_2O (0.2 mL) was added before filtration through a pad of Celite and silica, washing with DCM and EtOH. The solvents were removed in vacuo to leave a red oil, purified by flash silica chromatography eluting with light petroleum:diethyl ether (10:1 v/v) to yield the tetrahydrofuran **9** as a red oil (136 mg, 79%, 2:1 mixture of diastereoisomers). IR (film)/cm^{-1} 2044, 1969, 1926. Major diastereoisomer: ^{1}H NMR (250 MHz, $CDCl_3$) 5.44 (5H, s), 4.82 (1H, t, J = 7 Hz), 3.94–3.75 (2H, m), 2.68 (3H, s), 2.24–2.11 (1H, m), 2.02–1.87 (2H, m), 1.71–1.57 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) 226.6, 224.9, 204.4, 98.4, 91.2, 90.2, 83.0, 67.9, 34.0, 26.7, 20.1. Minor diastereoisomer: ^{1}H NMR (250 MHz, $CDCl_3$) 5.41 (5H, s), 4.98 (1H, t, 7 Hz), 3.94–3.75 (2H, m), 2.70 (3H, s), 2.24–2.11 (1H, m), 2.02–1.87 (2H, m), 1.71–1.57 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) 226.0, 225.2, 204.4, 98.5, 91.8, 90.2, 83.1, 68.0, 33.2, 26.6, 20.6. Found: M^+–CO, 443.93075. $C_{16}H_{15}O_5CoMo$ requires 443.93055.