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Stereoselectivity in the intermolecular Pauson–Khand reaction of electron-deficient terminal alkynes

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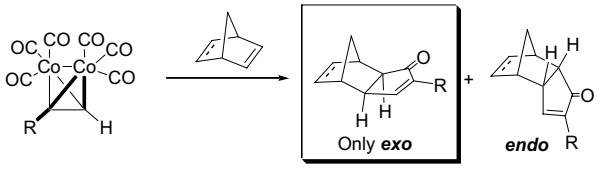
Abstract—A family of terminal alkyne dicobalthexacarbonyl complexes bearing groups with a range of electron-withdrawing abilities has been synthesized. After submitting these complexes to the intermolecular Pauson–Khand reaction with norbornadiene, electron-deficient substrates afforded up to 26% of the unexpected *endo*-cyclopentenone.

Since its discovery in 1971 the Pauson–Khand reaction (PKR) has become one of the most powerful tools for the synthesis of cyclopentenoid systems, both in its intra and intermolecular versions.[1] A wide array of biologically significant natural products has been prepared by means of the PKR.[2] Our group and others have contributed to the development of highly efficient asymmetric versions of this process.[3]

One of the key features that has led to the widespread use of the PKR is its high degree of regio and stereoselectivity. Early on, for the intermolecular version of the PKR, it was demonstrated that the cycloaddition reaction took place invariably at the less hindered face of the olefin. Reaction with norbornene, norbornadiene and bicyclo[3.2.0]heptene *yields exclusively the exo-fused cyclopentenone adducts* (Scheme 1).[1a]



Scheme 1.

There a several examples of *endo*-selectivity in the intramolecular version of the PKR.[4] However, to our knowledge, there are only two reports in the literature of intermolecular PKRs that yield *endo*-adducts. Moyano and co-workers observed the reversal of cyclization stereoselectivity in the reaction of heterobimetallic (Mo–Co, W–Co) complexes of *N*-(2-alkynoyl) oxazolidinones.[5,6] Shen and Hsung has recently reported that $Co_2(CO)_6$ complexes of *N*-(1-alkynyl) oxazolidinones lead, in some instances, to the corresponding *endo*-product.[7] In both studies this behaviour was observed exclusively for disubstituted alkyne complexes, and was attributed to the preference of norbornadiene to coordinate in an *endo*-fashion, because of distinct steric requirements. Although the alkyne complexes reported in these studies are electron deficient, an electronic effect has not been taken into account.

Here we examined whether stereoselectivity in the intermolecular PKR is dependent on electronic factors. With this aim, we synthezized terminal alkyne complexes bearing groups with gradual electron-withdrawing abilities, to react with norbornadiene and norbornene. We undertook the synthesis of sulfur- and amido-substituted alkyne complexes (Scheme 2). Varying the oxidation state of sulfur and the substitution on nitrogen, we modulated the electron-withdrawing power

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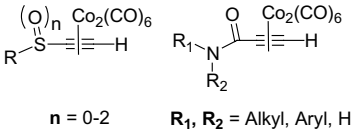
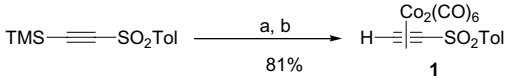


Scheme 2.



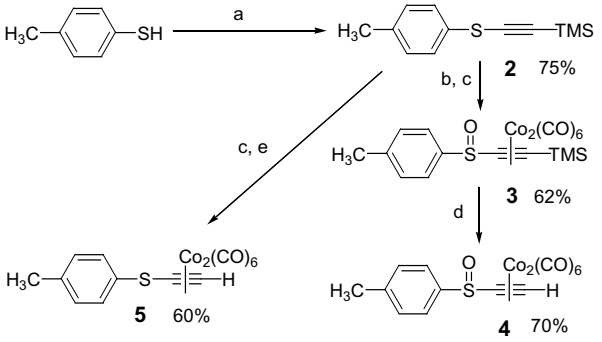
Scheme 3. Reagents: (a) $Co_2(CO)_8$, Et_2O, rt; (b) $KHCO_3/K_2CO_3$ aq, MeOH, 40 °C.

of groups directly attached to the dicobalt–alkyne cluster.

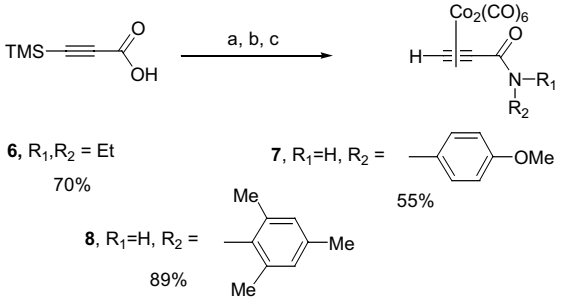
For this purpose, a series of *p*-tolylsulfonyl, *p*-tolylsulfinyl and *p*-tolylsulfanyl ethyne complexes were synthesized. The hexacarbonyl complex of *p*-tolylsulfonyl acetylene (**1**) was prepared following the procedure described in (Scheme 3). Reaction of trimethylsilyl(tosyl)acetylene[8] with $Co_2(CO)_8$, followed by removal of the corresponding terminal-TMS group with a $KHCO_3/K_2CO_3$ buffer in methanol provided the desired orange complex **1** in 81% yield. Alternatively, *p*-tolylsulfinylacetylene–$Co_2(CO)_6$ (**4**) and *p*-tolylsulfanylacetylene–$Co_2(CO)_6$ (**5**) were prepared following the synthetic pathway displayed in Scheme 4. Using *p*-tolylsulfanyl(trimethylsilyl)ethyne (**2**) as a common intermediate, **3** and **4** were conveniently prepared in two and three steps, respectively.

Dicobalt hexacarbonyl complexes of three amides derived from the propynoic acid were also synthesized (Scheme 5). Starting from commercially available 3-trimethylsilylpropynoic acid, amide formation, complexation with $Co_2(CO)_8$ and deprotection, with potassium hydrogen carbonate buffer, led to amido complexes **6**, **7** and **8** in good to excellent overall yields.

Subsequently, the resulting complexes were submitted to the intermolecular PKR with norbornadiene in two sets of conditions: (A) thermal activation and (B) *N*-oxide-promoted[9] reaction (Table 1). Thermal reaction of



Scheme 4. Reagents: (a) (i) KH, THF, (ii) trichloroethylene, (iii) BuLi, (iv) ClTMS; (b) MCPBA; (c) $Co_2(CO)_8$; (d) $KHCO_3/K_2CO_3$ aq, MeOH; (e) K_2CO_3, MeOH.



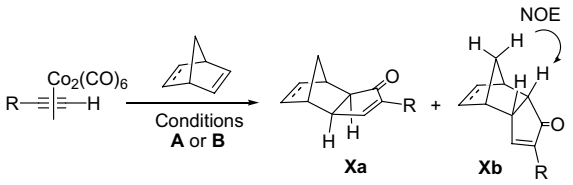
Scheme 5. Reagents: (a) HOBt, DCC, HNR_1R_2; (b) $Co_2(CO)_8$, hexane; (c) $KHCO_3/K_2CO_3$ aq, MeOH.

tosylacetylene complex **1** with norbornadiene provided a 84:16 mixture of two cyclopentenone adducts in 52% yield (Table 1, entry 1). Upon separation of the two isomers, NOESY experiments revealed that the minor compound corresponded to the *endo*-cyclopentenone. A positive NOE interaction between the methylene bridge and the hydrogens on the ring fusion allowed us to ascertain the *endo*-configuration. In general, *intermolecular PKR of electron-deficient dicobalthexacarbonyl complexes with norbornadiene was not stereoselective and provided exo:endo ratios between 84:16 and 74:26* (Table 1). PKR of sulfoxide complex **4** (Table 1, entry 3) and sulfone complex **1** provided a similar proportion of *endo*-cyclopentenone (16%). Conversely, sulfide complex **5** provided the *exo*-adduct as a sole product (Table 1, entries 5 and 6). Amido-substituted complexes showed a similar trend, while amido-compound **6** yielded exclusively the standard *exo*-cyclopentenone. The more electron-withdrawing *N*-aryl amides **7** and **8** provided a significant amount of the *endo*-product (Table 1, entries 9–12, 20–26%).[10] The *endo*-stereochemistry of adduct **14b** was ascertained by X-ray crystallography (Fig. 1).

Data in Table 1 also illustrate that the activation method used in the PKR does not significantly affect the stereochemical outcome of the reaction. Cyclization reactions run under either thermal or *N*-oxide-promoted activation provided similar *exo endo*-ratios. *N*-Methyl morpholine *N*-oxide (NMO) in CH_2Cl_2, however, provided higher yields for electron-deficient substrates (Table 1, entries 10 and 12). Alternatively, the anomalous behaviour observed in the intermolecular PKR of norbornadiene with electron-deficient dicobalt complexes was not observed for its equivalent norbornene. For complex **8**, cyclization with norbornene provided only the standard *exo*-fused adduct (Table 1, entry 13).

In summary, here we report for the first time that *terminal* electron-deficient alkyne complexes yield a mixture of *exo*- and *endo*-fused cyclopentenones in the intermolecular PKR with norbornadiene. In the present study, structurally analogous dicobalt hexacarbonyl complexes exhibited an entirely different stereoselectivity pattern to that normally observed in this cyclization process. This fact suggests that electronic differences within the dicobalt clusters are responsible for the observation of the anomalous *endo*-adduct. To properly explain the electronic effects observed on the intermo-

Table 1. Intermolecular PKR of sulfur- and amido-substituted acetylene $Co_2(CO)_6$ complexes with norbornadiene and norbornene



Entry	$Co_2(CO)_6$ complex	Conditions[a]	Time (h)	Yield (%)	Adduct	Xa:Xb ratio
1	**1**	A	10	52	**9a/9b**	84:16
2	**1**	B	1	66	**9a/9b**	84:16
3	**4**	A	8	50	**10a/10b**	84:16[b]
4	**4**	B	1	63	**10a/10b**	75:25[b]
5	**5**	A	4	90	**11a/11b**	100:0
6	**5**	B	12	89	**11a/11b**	100:0
7	**6**	A	16	33	**12a/12b**	100:0
8	**6**	B	1	81	**12a/12b**	100:0
9	**7**	A	16	32	**13a/13b**	80:20
10	**7**	B	1	85	**13a/13b**	78:22
11	**8**	A[c]	16	44	**14a/14b**	77:23
12	**8**	B	1	92	**14a/14b**	74:26
13	**8**	B[d]	1	94	**15a/15b**	100:0

[a] Conditions A: 10 equiv norbonadiene, 60–70 °C, N_2, Toluene. Conditions B: 10 equiv norbornadiene, NMO, rt, CH_2Cl_2.
[b] *exo*-Adduct was isolated as a 2/1 mixture of diastereomers.
[c] Reaction was carried out at 50 °C.
[d] Reaction was performed with 10 equiv of norbornene.

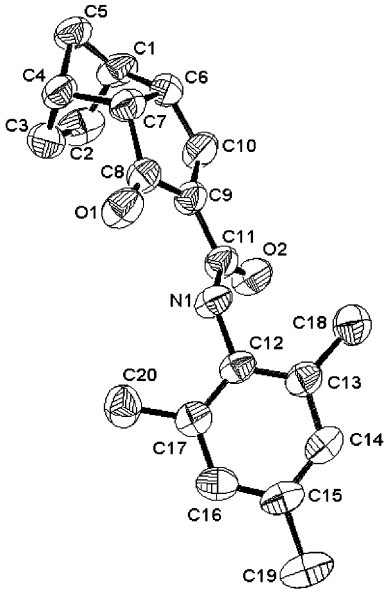


Figure 1. X-ray structure of the PKR *endo*-adduct **14b**, resulting from the reaction of **8** and norbornadiene. ORTEP drawing at 50% probability ellipsoids.

lecular PKR, a detailed theoretical analysis of the stereochemical outcome of the reaction is currently underway in our laboratories.

Acknowledgements

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10. Resonance delocalization of the lone pair of nitrogen onto the aromatic ring dictate that *N*-Aryl amides are more electron withdrawing with respect to their *N*,*N*-dialkyl counterparts. Thus, the methyl group (CH_3CO–) in acetanilide is shifted downfield in the ^{13}C NMR spectra with respect to diethylacetamide.