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# The brucine *N*-oxide-promoted asymmetric Pauson–Khand reaction

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**Abstract**

The brucine *N*-oxide-mediated asymmetric Pauson–Khand reaction has been further investigated. It was found that the best levels of enantioselection were obtained with substituted propargylic alcohol complexes. The studies also revealed that when acetone or 1,2-dimethoxyethane is used as the reaction solvent, enhanced levels of enantioselectivity, up to an enantiomeric ratio of 11:89, are achieved. 

*Keywords:* amine *N*-oxides; asymmetric synthesis; cobalt and compounds; cyclopentenones; Pauson–Khand reactions.

One of the most striking examples of the use of organometallic complexes in organic synthesis is the Pauson–Khand (P–K) reaction, which allows the single step formation of cyclopentenones from alkynes, via their hexacarbonyldicobalt complexes, and alkenes.[1] Although the thermal conditions used in first generation P–K reactions often led to low yields and formation of by-products, the last decade has seen vast improvements in P–K methodology. Foremost amongst these methods is the use of amine *N*-oxide promoters,[2] which allow these cyclisations to proceed cleanly at room temperature and in good to excellent yields. As such, the widespread use of the P–K reaction in total synthesis now attests to the versatility and efficiency of this transformation.[1a,3] Nonetheless, there is still potential for the formulation of asymmetric variants of the P–K reaction.[4] Departing from the previous methods employing diastereomerically pure complexes,[5] chiral auxiliaries,[6] or a combination of both,[7] we previously demonstrated the use of a chiral amine *N*-oxide to mediate the first direct enantioselective P–K reaction (Scheme 1).[8]

We proposed that the enantioselectivity observed in the reaction was due to a selective decarbonylation (or activation) of the prochiral hexacarbonyl complex (Scheme 2), i.e. the chiral *N*-oxide discriminates between the two enantiotopic cobalt units of the starting complex, leading to a preference of, say, path **a** and, hence, enantiomer **a** in the product.

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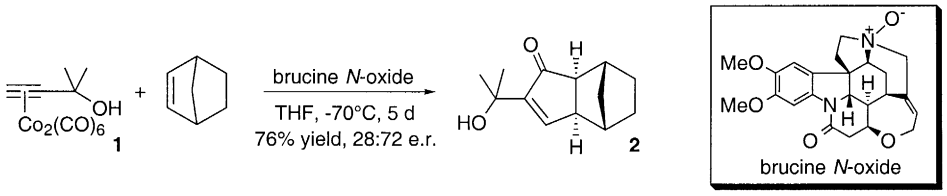
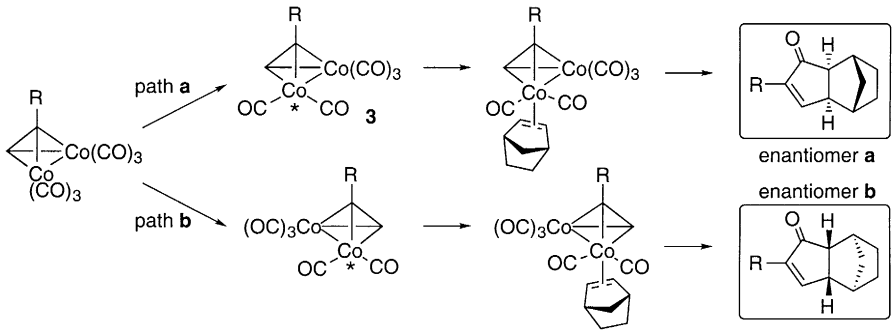



Scheme 1.




Scheme 2.

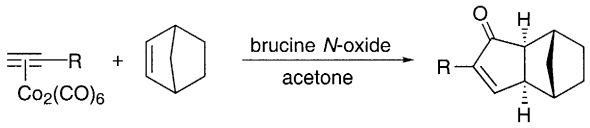
Following on from this initial communication, we now wish to report wider studies on the scope of this methodology.[9] Since our preliminary paper, the reaction has been studied in great detail with respect to both solvent and alkyne substrate. In the course of these studies, acetone was found to be superior to THF as solvent, in terms of enantioselection. A range of alkyne substrates were then examined in the brucine *N*-oxide (BNO) promoted P–K reaction with norbornene in acetone. The reactions consistently proceeded in acceptable yields (Table 1),[10] at the temperatures required (−49 to −70°C) to achieve the enantioselection shown. Using our model system, i.e. the reaction of dimethylpropargyl alcohol complex **1** with norbornene to give cyclopentenone **2** (Table 1, Entry 1), the highest enantiomeric ratio (22:78) was obtained, an improvement on the previous best of 28:72 using THF as solvent.[8]

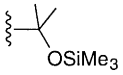
Having now studied a range of cobalt alkyne complexes, some trends have become apparent. As can be seen from Table 1, substituted propargylic alcohols give the best enantioselectivities (Entries 1–5) and this seems to be a general requirement when BNO is used as promoter.[11] Thus, removal of propargylic substituents (Entry 6) or protection of the hydroxyl group in complex **1** as its TMS ether (Entry 7) both led to a complete loss of enantioselectivity. Replacing the OH group in complex **1** with the sterically similar, but electronically neutral, methyl group (Entry 8) also produced a significant decrease in enantioselection.

As stated earlier, we proposed that the enantioselection observed in this reaction was due to a selective decarbonylation of the prochiral dicobalt alkyne cluster by the chiral *N*-oxide. The selectivities obtained in this study may, indeed, arise from such a selective decarbonylation. However, the necessity for substituted propargylic alcohols may also indicate the requirement of a hydrogen bonded interaction (between the hydroxyl group of the complex and some polar functional group on brucine *N*-oxide) which, in turn, may serve to align the approach of the *N*-oxide to the complex in such a way as to enhance discrimination between the two enantiotopic cobalt centres in the key decarbonylation process. Furthermore, the required additional substitution in the propargylic position: (i) is believed to enhance the asymmetric interactions of the *N*-oxide following an H-bonding interaction, due to more restricted conformational movement of the 'tethered' oxidant; and (ii) would be expected to enhance discrimination between the two enantiotopic faces of the complex on more simple steric grounds.

Returning to the study in hand, and having established appreciable levels of enantioselection for a

Table 1
Brucine *N*-oxide promoted P–K reactions of a range of alkyne cobalt complexes in acetone




| Entry | R | Temp. (°C) | Reaction Time (h) | Yield (%) | Enantiomeric Ratio (e.r.)[a] |
|---|---|---|---|---|---|
| 1 |  | -67 | 120 | 75 | 22:78 |
| 2 |  | -60 | 72 | 68 | 66:34 |
| 3 |  | -50 | 68 | 44 | 34:66 |
| 4 |  | -70 | 42 | 53 | 38:62 |
| 5 |  | -60 | 72 | 54 | 70:30 |
| 6 |  | -49 | 168 | 49 | 48:52 |
| 7 |  | -49 | 120 | 61 | 49:51 |
| 8 |  | -70 | 240 | 67 | 58:42 |

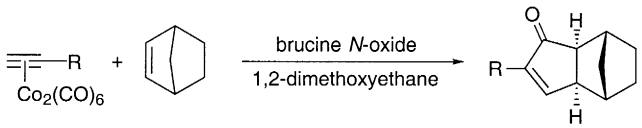
[a]Enantiomeric ratios were determined by chiral HPLC analysis and are presented as the 1st eluting : 2nd eluting enantiomers.

range of substrates, the reaction solvent was once again examined. Having already evaluated monodentate donor solvents of slightly different basicity, a bidentate donor solvent was considered. Recently, 1,2-dimethoxyethane (DME) has been shown to be an excellent solvent for use in a range of catalytic Co-mediated processes;[12] within each individual reported protocol, this solvent is believed to facilitate reactions by stabilising co-ordinatively unsaturated intermediates in the proposed catalytic cycle. In this respect, and in order to investigate the effect of DME in our BNO-promoted asymmetric reactions, a range of complexes were examined with this solvent. The results from this study are displayed in Table 2.

It can be seen that, in every case, the use of DME as solvent further enhances the enantioselection of this asymmetric process, as shown in Table 2. In this respect, it is possible that this improved enantioselectivity is due to enhanced stabilisation of chiral, decarbonylated intermediates (e.g. **3** in Scheme 2), which might otherwise undergo racemisation via intra- or intermolecular carbonyl ligand transfer processes.

In the case of the higher enantiomeric ratios obtained here (e.g. 11:89 with dimethylpropargyl alcohol complex **1**) the selectivities in this direct process, from a prochiral starting complex, are now comparable with the selection previously obtained in our laboratory[5] when utilising the less readily accessible diastereomerically pure (*R*)-(+)-glyphos complexes. Furthermore, the requisite propargyl alcohol complexes

Table 2
Brocine *N*-oxide mediated asymmetric P–K reactions using 1,2-dimethyoxyethane as solvent




| Entry | R | Temp. (°C) | Reaction Time (h) | Yield (%) | Enantiomeric Ratio (e.r.)[a] |
|---|---|---|---|---|---|
| 1 |  | -60 | 120 | 63 | 11:89 |
| 2 |  | -60 | 144 | 48 | 69:31 |
| 3 |  | -60 | 240 | 66 | 24:76 |
| 4 |  | -60 | 240 | 49 | 33:67 |
| 5 |  | -60 | 96 | 48 | 81:19 |

[a]Enantiomeric ratios were determined by chiral HPLC analysis and are presented as the 1st eluting : 2nd eluting enantiomers.

deliver optically enriched functionalised cyclopentenone products for use in asymmetric target synthesis, with the substituted carbinol unit allowing access to a range of alternative functionality.

In conclusion, these investigations have provided significant further details on the scope of the brucine *N*-oxide promoted asymmetric P–K reaction. By careful examination of the reaction parameters, we have obtained enantiomeric ratios of up to 11:89 (78% e.e.) in this the, as yet, only strategy for *direct* asymmetric Pauson–Khand annulation. The screening of alternative chiral *N*-oxides, to find an even more selective and general promoter, and investigations into improving the practical aspects of this process are currently underway in our laboratory and will be reported in due course.

Typical experimental procedure: A solution of hexacarbonyl(2-methylbut-3-yn-2-ol)dicobalt (101.6 mg, 0.275 mmol) and norbornene (130 mg, 1.383 mmol) in dry 1,2-DME (7 ml) was cooled to −60°C in a cryostatically cooled MeOH bath. Brucine *N*-oxide (690 mg, 1.683 mmol) was added and the reaction was stirred under $N_2$ at −60°C for 5 days. The reaction mixture was then filtered through a pad of silica and the residues were washed with ether. The filtrate was concentrated in vacuo and the crude product was purified by flash column chromatography (1:1 petrol:ether) to give 35.9 mg (63% yield) of 3a,4,5,6,7,7a-hexahydro-2-(1-hydroxy-1-methylethyl)-4,7-methano-1*H*-inden-1-one[5] as a white crystalline solid. HPLC analysis (Chiracel OD-H column, 1% *i*-PrOH/heptane, 1 ml $min^{-1}$, UV detector at 230 nm, retention times 14.5 and 17.0 min) indicated an enantiomeric ratio of 11:89 (78% e.e.). IR ($CH_2Cl_2$): 3514 (br w, OH), 1702 $cm^{-1}$ (s, C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.95 (1H, d, $^2$J=10.6 Hz, methano CH), 1.00 (1H, d, $^2$J=10.6 Hz, methano CH), 1.24–1.33 (2H, m, axial $C^5$–H and $C^6$–H), 1.41 (6H, s, 2×$CH_3$), 1.53–1.59 (1H, m, equatorial $C^5$–H), 1.63–1.70 (1H, m, equatorial $C^6$–H), 2.17–2.18 (1H, m, $C^4$–H), 2.20 (1H, d, $^3$J=4.9 Hz, $C^{7a}$–H), 2.38–2.39 (1H, m, $C^7$–H), 2.56 (1H, m, $C^{3a}$–H), 3.83 (1H, br s, OH), 7.18 ppm (1H, d, $^3$J=2.6 Hz, $^3$C–H).

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