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Reversing the Stereoselectivity of the Intermolecular Pauson–Khand Reaction: Formation of *endo*-Fused Norbornadiene Adducts

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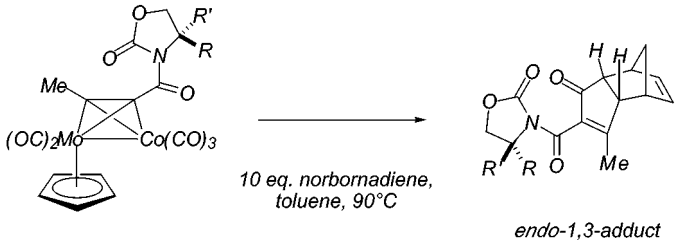
ABSTRACT

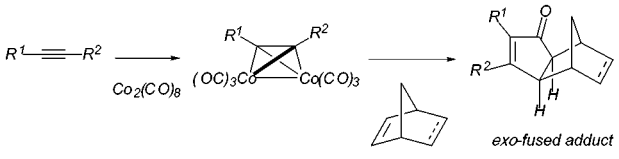


An unprecedented *endo*-selective and regioselective intermolecular Pauson–Khand reaction takes place when heterobimetallic (Mo–Co) complexes derived from *N*-(2-alkynoyl)oxazolidinones or sultams are heated in the presence of norbornadiene.

One important factor that has contributed to the widespread use of the Pauson−Khand reaction for the synthesis of 2-cyclopentenone derivatives[1] is the high degree of predictability of the regio- and stereochemical outcome of this process, both in the intermolecular[2] and intramolecular[3] versions.

In particular, intermolecular Pauson−Khand reactions of bridged or fused cycloalkenes such as norbornadiene, norbornene, or bicyclo[3.2.0]heptene invariably take place at the least hindered face of the reacting olefin, leading to the formation of *exo*-fused cyclopentenone adducts[1a] (Scheme 1). We disclose here that the heterobimetallic (Mo−Co) complexes of *N*-(2-alkynoyl) derivatives of chiral oxazolidinones or sultams show an unprecedented reversal of stereoselectivity in their reaction with norbornadiene, pre-

Scheme 1. Steric Course of Intermolecular Pauson−Khand Reactions of Bicyclo[2.2.1]heptenes



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[‡] Universidade da Coruña.

(1) Recent reviews on the Pauson-Khand reaction: (a) Schore, N. E. *Org. React.* **1991**, *40*, 1−90. (b) Geis, O.; Schmalz, H. G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 911−914. (c) Buchwald, S. L.; Hicks, F. A. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. II, pp 491−510. (d) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263−3283. (e) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Chem. Eur. J.* **2001**, *7*, 1589−1595.

(2) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977−981.

(3) Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436−5438.

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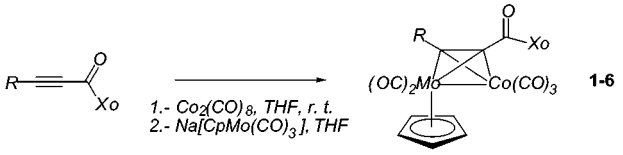
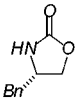
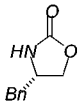
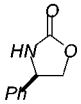
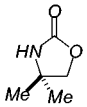
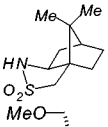
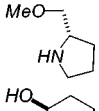
dominantly giving rise to *endo*-fused cyclopentenone adducts in a totally regioselective fashion.

Recently, Christie et al.[4] have reported that, upon replacing one of the $Co(CO)_3$ groups of an alkyne−dicobalt(hexacarbonyl) complex by an isoelectronic $MoCp(CO)_2$ moiety, the resulting heterobimetallic complexes still are active partners in intermolecular Pauson−Khand cycloadditions with norbornadiene, giving rise to the expected *exo*-fused adducts. Moreover, the chirality of the metal−alkyne tetrahedral core introduced by this substitution can be used to induce high levels of stereocontrol in the reaction. Inspired by these findings, we decided to explore the reactivity of the heterobimetallic (Mo−Co) complexes of 2-alkynoate derivatives. Our initial aim was to shed some light on the relationship between the stereochemistry of the heterobimetallic complexes and that of the corresponding Pauson−Khand adducts, whose absolute configurations had previously been established by us.[5] Heterobimetallic complexes **1**−**6** were prepared from the starting 2-alkynoates by a one-pot procedure involving the in situ generation of the dicobalt(hexacarbonyl) complex in THF and treatment with 1.5 molar equiv of $Na[MoCp(CO)_3]$ (Table 1).

Table 1. Preparation of Heterobimetallic (Mo−Co) Complexes of 2-Alkynoates



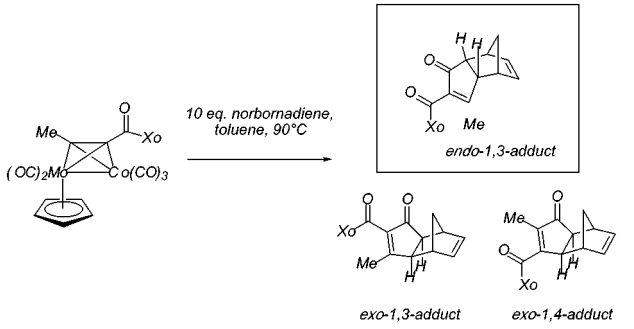
HX_0	R	complex (%yield,[a] d.r.[b])	time [min], temperature
	Me	**1a,b** (49, 1.8:1[c])	80, reflux
	Ph	–	60, reflux
	Me	**2a,b** (43, 2.3:1[c])	90, reflux
	Me	**3** (49, –)	90, reflux
	Me	**4a,b** (64, 1.2:1)	90, reflux
	Me	**5a,b** (55, 1.5:1)	90, reflux
	Me	**6a,b** (35, 1:1)	90, reflux

[a] After chromatographic purification on silica gel. [b] By ^{13}C NMR. [c] The two diastereomers were isolated in pure state after chromatography.

After chromatographic purification, orange-colored complexes **1**−**6** were isolated in yields comparable to those reported in the literature for other alkynes.[4a,6] For *N*-(phenylpropionyl)-4-benzyloxazolidinone (second entry of Table 1) only, the formation of the heterobimetallic complex could not be observed, probably because of the increased steric hindrance of the substrate.[7] The diastereoselectivities of the complexation reactions of the two chiral oxazolidinone derivatives (first and third entries of Table 1) were very similar, and the diastereomeric complexes (**1a**/**1b** and **2a**/**2b**, respectively) were easily separated by column chromatography in both cases. The heterobimetallic complexes derived from 2,10-camphorsultam (**4a,b**), 2-methoxymethylpyrrolidine (**5a,b**), and *trans*-2-phenylcyclohexanol (**6a,b**) were obtained as nonseparable diastereomer mixtures.[8]

We nex turned our attention to the Pauson−Khand reactions of these complexes. Much to our surprise, the reaction of either **1a** or **1b** with norbornadiene led to a completely new product **7**, whose spectroscopic data were however coincident with those expected for a Pauson−Khand adduct. Examination of the reactivity of other complexes revealed that this anomalous behavior was general, since the major product was in each case a compound different from the *exo*-fused 1,3- and 1,4-dicarbonyl adducts arising from the corresponding dicobalt complexes. Interestingly enough, these new adducts (for which we postulated an *endo*-ring fusion stereochemistry) appeared to be obtained in a totally regioselective fashion (Table 2).

Table 2. Intermolecular Pauson-Khand Reactions of Heterobimetallic (Mo−Co) Complexes **1**−**5** with Norbornadiene



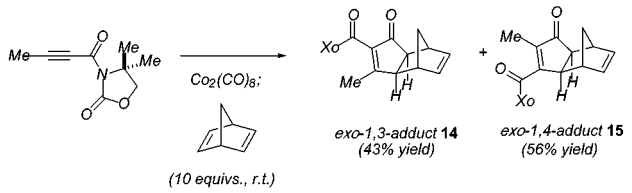
starting complex	*endo*−1,3-adduct (% yield,[a] dr)	*exo*−1,3-adduct (% yield,[a] dr)	*exo*−1,4-adduct (% yield,[a] dr)
1a	**7** (56, 4:1[b])	− (0, −)	− (0, −)
1b	**7** (75, 1:7.3[b])	− (0, −)	− (0, −)
2a	**8** (24, 4:1[c])	**12** (12, >10:1[b])	**13** (6, 5:1[b])
2b	**8** (92, 1:9[c])	**12** (4, n.d.)	**13** (3, n. d.)
3	**9** (80, −)	**14** (7, −)	**15** (10, −)
4a,b	**10** (36, >10:1[b])	**16** (18, > 10:1[b])	− (0, −)
5a,b	**11** (9,[d] nd)	**17** (8,[d] nd)	**18** (34, 7:1[c])

[a] After chromatographic purification on silica gel. [b] By ^{13}C NMR. [c] By HPLC. [d] Yield estimated by NMR analysis of a mixture of the two compounds.

An unambiguous proof of the *endo*-stereochemistry and of the regiochemistry of these anomalous cyclopentenone

adducts was provided by using the 4,4-dimethyloxazolidinone-derived complex **3** (fifth entry of Table 2), whose thermally induced reaction with norbornadiene led to the formation of three products, **9** (80% yield), **14** (7% yield) and **15** (10% yield). The minor compounds **14** and **15** were identical with those obtained in the standard Pauson-Khand reaction of *N*-(2-butynoyl)-4,4-dimethyl-1,3-oxazolidin-2-one (Scheme 2).

Scheme 2. Pauson−Khand Cyclization of Norbornadiene with the Dicobalt(hexacarbonyl) Complex of *N*-(2-Butynoyl)-4,4-dimethyl-1,3-oxazolidin-2-one



We were able to grow crystals of **9** suitable for X-ray diffraction analysis. The resolved structure (Figure 1)[9] confirmed our hypotheses about the regio- and the stereochemistry of this new Pauson−Khand product. Careful examination of spectral data led us to conclude that compounds **7**−**11** in Table 2 are in all instances *endo*-fused, 1,3-dicarbonyl cyclopentenone adducts. In particular, the 1,3-dicarbonyl regiochemistry of these compounds was inferred from the fact that the cyclopentenone methyls appear at ca. 17 ppm in the ^{13}C NMR, while those of the 1,4-dicarbonyl regioisomers appear at ca. 9 ppm. The *endo* stereochemistry

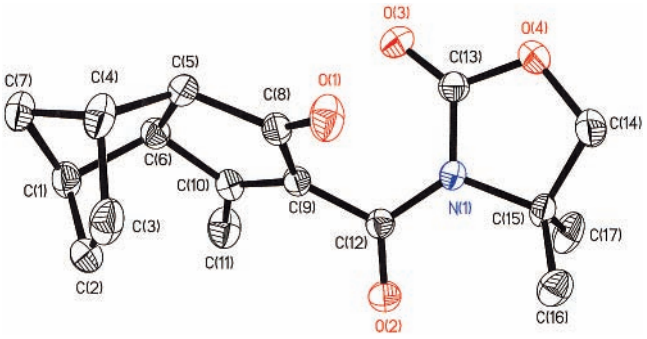


Figure 1. ORTEP drawing of **9** with thermal ellipsoids drawn at the 50% probability level. For clarity, the hydrogen atoms are omitted.

of adducts **7**−**11** was deduced by comparison with the authentic *exo* compounds[5] and is also consistent with the observation that in the *endo* adducts the olefin carbons show two signals at ca. 131 and 134 ppm in the ^{13}C NMR, while in the *exo* adducts these same carbons show two signals at ca. 138 ppm (see Supporting Information).

Not unexpectedly,[4] the two diastereomers of a given heterobimetallic complex lead to different diastereomer ratios of the adduct. Thus, while complex **1a** (first entry of Table 2) affords a 4:1 mixture of diastereomers, complex **1b** (second entry of Table 2) gives rise to a 1:7.3 diastereomer mixture, in which the minor isomer obtained with **1a** now largely predominates. A completely parallel behavior is exhibited by complexes **2a** and **2b** (third and fourth entries of Table 2, respectively). *The chirality of the tetrahedral C_2CoMo core appears therefore to control the diastereoselectivity of the formation of these endo-fused adducts.* It is also worth noting that the minor, less polar diastereomers of the heterobimetallic complexes (**1b**, **2b**) lead to higher yields of *endo*-adducts and with higher stereoselectivities than the major, more polar isomers (**1a**, **2a**). The mixture of heterobimetallic complexes **4a**,**b** derived from *N*-(2-butynoyl)-2,10-camphorsultam reacted with norbornadiene to give a 36% yield of the *endo*-1,3-dicarbonyl adduct **10**, together with an 18% yield of the *exo*-1,3-dicarbonyl adduct **16**. Both compounds were obtained essentially as single stereoisomers, which tends to indicate that only one isomer of the heterobimetallic complex had reacted. Again, this behavior is totally at variance with the standard Pauson−Khand reaction of the same alkyne precursor, which affords as the only products **16** (with very low stereoselectivity, 1.7:1 dr) in admixture with the *exo*-1,4-dicarbonyl regioisomer.[5a] The reaction of the mixture of pyrrolidine-derived complexes **5a**,**b** gave the *endo*-1,3-dicarbonyl adduct **11** only in minor amounts. Attempted reaction of complexes **6a**,**b** led only to decomposition of the starting material. Thus, the presence of an acyloxazolidinone or acylsultam moiety appears to be necessary for this process.

Although at this point any attempt to rationalize the present results would be premature, the following points should be noted: (i) The $[MoCp(CO)_2]_2$ complex of *N*-(2-butynoyl)-

(4) (a) Rutherford, D. T.; Christie, S. D. R. *Tetrahedron Lett.* **1998**, *39*, 9805−9808. (b) Fletcher, A. J.; Rutherford, D. T.; Christie, S. D. R. *Synlett* **2000**, 1040−1042.

(5) (a) Fonquerna, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Am. Chem. Soc.* **1997**, *119*, 10225−10226. (b) Fonquerna, S.; Rios, R.; Moyano, A.; Pericàs, M. A.; Riera, A. *Eur. J. Org. Chem.* **1999**, 3459−3478.

(6) Albiez, T.; Bantel, H.; Vahrenkamp, H. *Chem. Ber.* **1990**, *123*, 1805−1810.

(7) Further experiments indicate that alkyl substituents other than methyl can be used in this reaction. Thus, 4,4-dimethyl-3-(non-8-ene-2-ynoyl)-1,3-oxazolidin-2-one affords the corresponding heterobimetallic (Mo−Co) complex in 83% yield.

(8) Pure isolated heterobimetallic complexes were dark-orange or red crystalline solids. Although their limited stability in solution prevented the isolation of crystals suitable for X-ray diffraction analysis, they could be characterized by spectroscopical means. Spectral data for **3**: IR (NaCl) ν_{max} = 2925, 2054, 1998, 1946, 1881, 1779, 1647, 1460, 1312, 1180 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6, 25 °C, TMS) δ 4.8 (s, 5H, Cp), 3.2 (m, 2H), 2.8 (s, 3H), 1.15 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6, 25 °C, TMS) δ 227.6 (br C, 3CO), 225.7 (br C, 2CO), 201.0 (C), 169.5 (C), 151.8 (C), 92.5 (5CH + C), 75.0 (CH_2), 61.6 (C), 24.3 (CH_3), 24.0 (CH_3), 23.5 (CH_3); MS (posit. electrospray, MeOH) *m*/*z* 544.2 [M + 1].

(9) Crystallographic data for this structure (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-167246. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, U.K. (Fax: (+44) 1223-336-033. E-mail: deposit@ccdc.cam.ac.uk) Spectral data for **9**: IR (NaCl) ν_{max} = 2975, 1782, 1705, 1680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 5.98 (m, 1H), 5.82 (m, 1H), 4.0 (m, 2H), 3.30−2.85 (m, 4H), 2.07 (s, 3H), 1.52 (s, 6H), 1.30−1.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS) δ 203.2 (C), 168.0 (C), 163.5 (C), 153.3 (C), 139.0 (C), 134.4 (CH), 131.4 (CH), 75.5 (CH_2), 60.5 (C), 52.5 (CH_2), 51.4 (CH), 50.8 (CH), 44.3 (CH), 43.8 (CH), 24.8 (CH_3), 24.5 (CH_3), 17.1 (CH_3); HRMS (CI) calcd for $C_{17}H_{20}NO_4$ [M + H] 302.1379, found 302.1392.

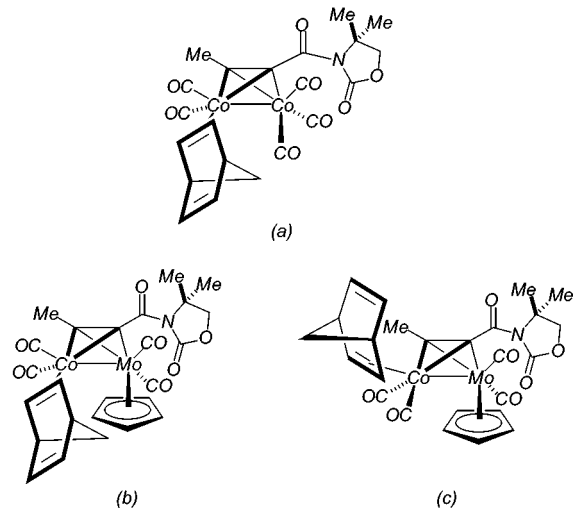


Figure 2. (a) Preferred coordination mode of norbornadiene (equatorial site, *exo* face) in the dicobalt complex of *N*-(2-butynoyl)-4,4-dimethyl-1,3-oxazolidin-2-one (according to PM3 calculations, see ref 5b). (b) This coordination mode of the olefin in the heterobimetallic complex is disfavored by steric repulsions between the methylene bridge of norbornadiene and the Cp moiety. (c) Coordination of the olefin from the *endo* face alleviates these steric interactions.

4,4-dimethyl-1,3-oxazolidin-2-one failed to react with norbornadiene. This strongly suggests that the "active" atom in these heterobimetallic complexes is the Co one. (ii) Examination of molecular models shows that the presence of an oxazolidinone or sultam moiety could force the bulky Cp substituent to occupy an equatorial (i.e., *cis* to the Mo−Co bond) coordination site. This would in turn distort the geometry of the ligands around the Co and affect the coordination mode of the olefin in the complex (Figure 2).

In summary, we have found that the heterobimetallic (Mo−Co) complexes of several 2-butynoate derivatives undergo an intermolecular Pauson−Khand cycloaddition with norbornadiene that for the first time affords *endo*-fused tricyclo[5.2.1.$0^{2,6}$]deca-3,8-dien-5-ones as the predominant or exclusive products. Previous access to these types of systems involved the multistep transformation of cyclopentadiene-derived *endo* Diels−Alder adducts.[10] Through the use of chiral oxazolidinones or sultams, the Pauson−Khand adducts can be obtained with good to excellent diastereoselectivities, which paves the way to the preparation of optically active derivatives. Further studies on the scope and the mechanism of this stereocomplementary intermolecular Pauson−Khand reaction[11] are underway in our laboratory.

Acknowledgment. Financial support of this work by the Ministerio de Ciencia y Tecnología (DGI, project BQU2000-0648) and by the Ministerio de Educación y Cultura (DGES, project PB98-1246) is gratefully acknowledged. R.R. thanks the Ministerio de Educación y Cultura for a predoctoral fellowship.

Supporting Information Available: Crystal data for compound **9** and experimental procedures and characterization data for compounds **1**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Only a few *endo*-4-acyltricyclo[5.2.1.$0^{2,6}$]deca-3,8-dien-5-ones have been described in the literature. See: (a) Verlaak, J. M. J.; Klunder, A. J. M.; Zwanenburg, B. *Tetrahedron Lett*. **1982**, *23*, 5463−5466. (b) Mal, D.; N. Hazra, N. K. *J. Chem. Soc,. Chem. Commun.* **1996**, 1181−1182. (c) Lee, B. H.; Clothier, M. F.; Dutton, F. E.; Clonder, G. A.; Johnson, S. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3317−3320.

(11) Recently, an stereocomplementary intramolecular Pauson−Khand reaction that primarily affords *endo*-6-alkoxybicyclo[3.3.0]oct-1-en-3-ones instead of the 6-*exo* ones has been disclosed: (a) Adrio, J.; Rivero, M. R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2000**, *39*, 2906−2909. (b) Adrio, J.; Rivero, M. R.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 2435−2448.