Pauson–Khand Reactions of Alkenyl Sulfones and Alkenyl Sulfoxides: Applications in Asymmetric Synthesis

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Abstract: Unlike other types of electron-deficient alkenes, alkenyl sulfones and alkenyl sulfoxides are excellent alkene partners in Pauson–Khand reactions (PKR). In the case of the intramolecular PKR of appropriately substituted 1-sulfinyl-1,6-enynes and 1-sulfonyl-3-oxygenated-1,6-enynes novel stereoselective processes and applications in asymmetric synthesis have been developed. Furthermore, using the cobalt-chelating dimethylaminophenyl vinyl sulfoxide as substrate, their intermolecular PKR with terminal alkynes provide the first intermolecular asymmetric version of PKR with non-strained alkenes. The resulting 5-sulfinyl-2-cyclopentenones are versatile intermediates in the enantioselective synthesis of natural cyclopentanoids.

Key words: Pauson–Khand reaction, alkenyl sulfones, alkenyl sulfoxides, asymmetric synthesis, chiral auxiliary, cyclopentanoid synthesis

1 Introduction

The cobalt-mediated [2+2+1] cycloaddition of an alkyne, an alkene and CO, the Pauson–Khand reaction (PKR), is nowadays a fundamental tool in organic synthesis.[1] This reaction represents an extremely convergent method for the synthesis of cyclopentenones, allowing the formation of three C-C bonds in a single step. Due to its great synthetic potential, since the first publications reported in the early 70s a huge effort has been devoted to the improvement of all the synthetic features of this fascinating reaction.

The classical PKR was originally carried out by heating a mixture of hexacarbonyldicobalt alkyne complex and alkene.[2] To avoid these relatively severe conditions amine *N*-oxides,[3] amines[4] and thioethers,[5] as well as heterogeneous inorganic polymers like silica gel[6] or molecular sieves[7] have been employed as effective promoters in PKR. These additives allow the use of very mild conditions (usually 0–25 ºC) and shorter reaction times, affording usually higher chemical yields than those of the thermally activated reaction.

Although until recently most applications of PKR employed stoichiometric approaches, in the last decade a wide variety of reaction conditions employing catalytic amounts of cobalt species have been reported.[8] Interestingly, the discovery of catalytic PKR has been extended to other transition metals different from cobalt; particularly effective among these are Pauson–Khand-type reactions catalyzed by titanium,[9] rhodium,[10] ruthenium[11] and iridium[12] species. Although most of these procedures require CO atmosphere, some safer and environmentally friendly catalytic versions involving the use of a simple aldehyde as carbonyl source have been reported.[13]

In parallel to the currently increasing demand of methods of enantioselective synthesis, a good number of reliable versions of asymmetric PKR have been developed.[14] These methodologies mainly rely on either the use of chiral auxiliaries[15] or chiral ligands coordinated to the cobalt cluster.[16] Quite outstandingly, some very promising asymmetric PKR involving catalytic amounts of both metal and chiral ligand have been reported in the last few years, especially using Ti,[9a,c] Rh[17] and Ir[12a] catalysts.

The mechanistic complexity of this metal-mediated reaction has been another important and appealing topic of research. Recent theoretical calculations[18] on the cobalt-mediated PKR strongly support the original basic pathway proposed by Magnus,[19] based on the sequence CO decomplexation, coordination of the alkene, olefin insertion with formation of a five-membered cobaltacycle intermediate, CO insertion into the cobaltacycle, reductive elimination and cyclopentenone decomplexation (Scheme 1).

Both theoretical and experimental data strongly suggest that the olefin insertion step is irreversible and determines the regio- and stereochemistry of the process, while the initial CO decomplexation/alkene complexation is the rate limiting step, which justifies the well-known difficulty in isolating any kind of PKR intermediate.

These remarkable improvements in the scope and reaction conditions have led to the application of PKR as key steps in a variety of total syntheses of complex natural and non-natural molecules.[20]

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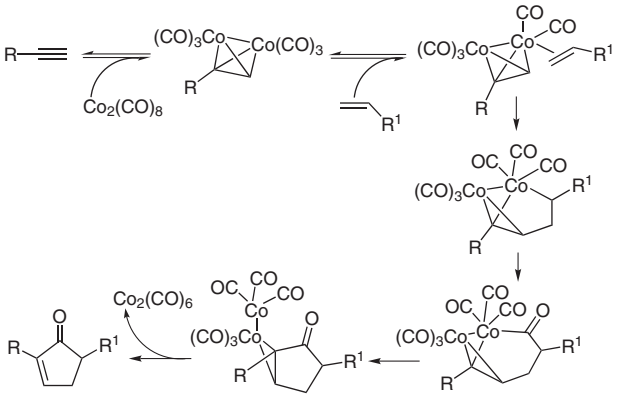
Despite all these impressive progresses that have converted the PKR into a fundamental tool in current organic chemistry, some important limitations still remain, providing enough room for significant new improvements. One of the main drawbacks is the insufficient structural generality of this reaction. Most of the reported studies on intramolecular PKR have been restricted to the thermodynamically very favorable construction of bicyclic [4.3.0]nonenones and [3.3.0]octenones. By contrast there are a few precedents of synthesis of medium-sized rings by cyclization of 1,n-enynes (n > 7), requiring always a constrained substitution at the enyne backbone.[21] On the other hand, the intermolecular PKR is far to be a general process. The reaction is highly sensitive to steric effects at both the alkene and alkyne moieties. Furthermore, due to the low or moderate regioselectivitity with regard to the alkene substitution, most precedents on intermolecular PKR involve the use of highly reactive alkenes such as

Biographical Sketches

Marta Rodríguez Rivero (left) was born in Segovia, Spain, in 1976. She received her B.Sc. in chemistry at the Universidad Autónoma de Madrid (UAM) in 1999 and stayed to study for her M.Sc. and Ph.D. degrees in organic chemistry (2004) with Professor Juan Carlos Carretero, working on stereoselective Pauson–Khand reactions. In 2001 she enjoyed a three months stay in the group of Prof. Gary A. Molander (University of Pennsylvania). She is currently a postdoctoral researcher in the laboratory of Professor Stephen L. Buchwald at the Massachusetts Institute of Technology.

Javier Adrio (center) was born in Madrid, Spain, in 1968. He studied chemistry at the UAM, where he received his B.Sc. and M.Sc. degrees in 1992 and 1994, respectively. From 1995 to 2000 he carried out his Ph.D. thesis at the Department of Organic Chemistry, under the supervision of Prof. Juan Carlos Carretero, working on new synthetic applications of functionalized α,β-unsaturated sulfoxides and sulfones in Pauson–Khand reactions. Up to 2003 he worked on PharmaMar S. A. as a senior scientist. During this period he spent one year in the laboratories of Professor Madeleine M. Joullié at the University of Pennsylvania as a postdoctoral researcher and worked on the synthesis of marine origin peptides. In 2003 he accepted a Ramon y Cajal position at the Department of Organic Chemistry of the UAM.

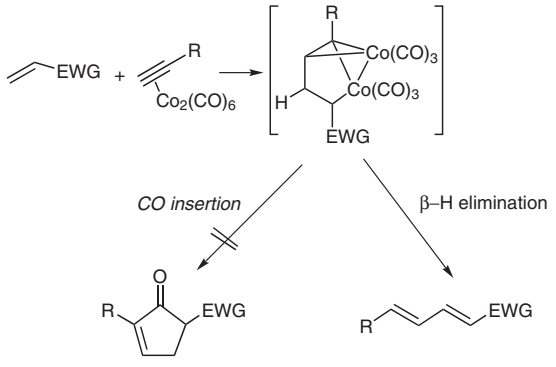
Juan Carlos Carretero (right) was born in Madrid, Spain, in 1960. He studied chemistry at the UAM (B.Sc. degree in 1982) and received his Ph.D. in organic chemistry in 1985, under the supervision of Prof. José L. García Ruano. He spent nearly three years (1985–1988) at the Université Catholique de Louvain, Belgium, as a postdoctoral fellow with Prof. Léon Ghosez. He subsequently joined the Department of Organic Chemistry of the UAM, where he became Associate Professor in 1988 and Professor of Organic Chemistry in 2000. His current research efforts are on developing highly stereoselective methods using functionalized sulfur compounds, and their application to the synthesis of natural products and novel chiral ligands for enantioselective catalysis. One of these projects deals with the use of enantiomerically pure sulfur compounds as stereochemical controllers in transition metal-catalyzed reactions.



Scheme 1

ethylene or symmetrical strained bicyclic alkenes, specifically norbornene and norbornadiene. This limitation is particularly severe in the asymmetric version of the intermolecular PKR.[22,12a]

Regarding the current scope of the PKR, the functional group compatibility is very high for the substitution at the alkyne, in which both electron-donating and electron-withdrawing functional groups are well tolerated. However, a very different picture appears in the case of functionalized alkenes. Thus, it was widely accepted since the seminal work of Pauson and Khand, that electron-deficient alkenes, such as α,β-unsaturated aldehydes, ketones, esters and nitriles, were not suitable substrates in PKR.[23] In these cases, it was assumed that the key cobaltacycle intermediate preferentially underwent a β-H elimination process, leading to the observed conjugated 1,3-diene, rather than the carbonyl insertion step required for the formation of the cyclopentenone product[24] (Scheme 2). This result is in sharp contrast with the PKR of alkenes with electron-donating substituents (like alkyl[25] or ether groups[26]) or strained C–C double bonds (like allenes[27] or cyclopropene groups[28]), which afford the expected cyclopentenone products.

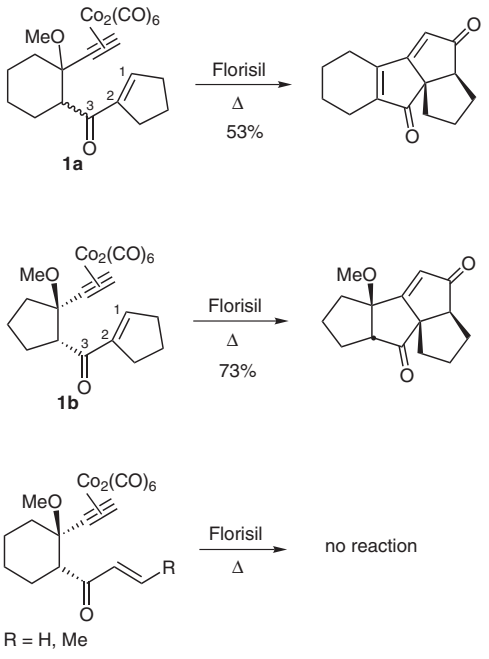


Scheme 2

In contrast to this general believe, in this account we summarize our recent work on the PKR of alkenyl sulfoxides and alkenyl sulfones, showing that under appropriate conditions these electronically poor sulfur-substituted alkenes can be excellent partners in both intramolecular and intermolecular PKR. Additionally, the well-known chemical versatility of sulfoxides and sulfones, along with the chirality of the sulfinyl group, makes these electron-deficient alkenes very appealing substrates for the development of new diastereoselective and asymmetric versions of PKR.

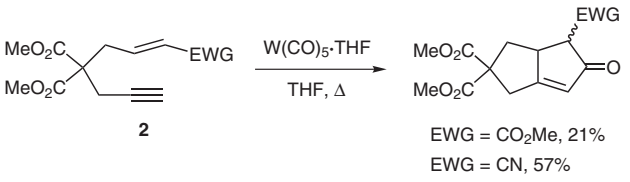
2 Background: PKR of Electron-Deficient Alkenes

As previously stated, only a few examples of PKR of electron-deficient alkenes had been reported.[29] The first successful intramolecular PKR of electron-deficient alkenes was achieved by Caple et al.[30] in 1991 using some conformationally restricted 1-en-6-yn-3-ones. In particular, the dicobalt hexacarbonyl complex of the 1,6-enynes **1a**,**b**, bearing a carbonyl group at position C-3 of the enyne framework, underwent an intramolecular PKR in the presence of Florisil as promoter, affording the corresponding tetracyclic adducts in acceptable to good yields (Scheme 3). It is worth noting that in these cases the absence of hydrogens at C-2 prevents the participation of the β-hydrogen elimination pathway.



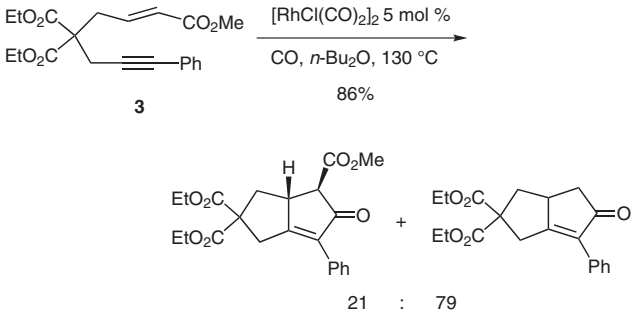
Scheme 3

Using conformationally less rigid substrates, Hoye et al. reported some interesting results in the tungsten-mediated Pauson–Khand-type cyclization of 1,6-enynes.[31] In the presence of a stoichiometric amount of tungsten pentacarbonyl [$W(CO)_5$·THF] a variety of 1,6-enynes, including substrates having a cyano or an ester function at the alkene terminus (compounds **2**), underwent the PK cyclization in THF at 65–110 °C to give the corresponding bicyclo[3.3.0]octenones as a mixture of epimers at C-4 in low to moderate yield (Scheme 4).



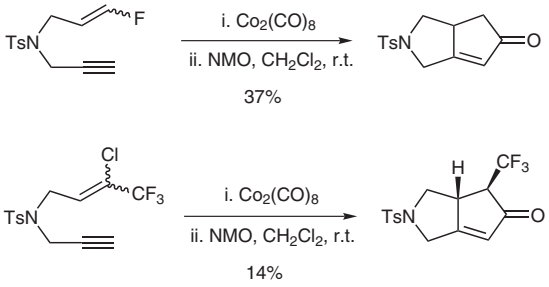
Scheme 4

Similarly, Narasaka et al. have recently reported the rhodium-mediated PKR of a variety of alkyne-substituted 1,6- and 1,7-enynes.[32] Among the tested substrates, the α,β-unsaturated ester **3** reacted in the presence of a catalytic amount of $[RhCl(CO)_2]_2$ under CO atmosphere at 130 °C, affording a mixture of the cyclopentenone adduct and its demethoxycarbonylated derivative (Scheme 5).



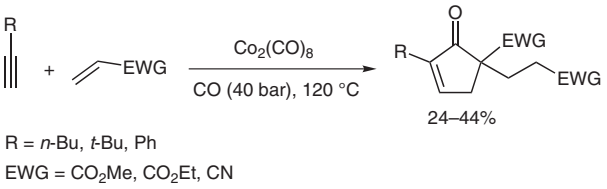
Scheme 5

The intramolecular PKR of 1,6-enynes substituted at the alkene moiety with halogens (F or Cl) has also been reported, leading to the dehalogenated PK products in low yield[33] (Scheme 6).



Scheme 6

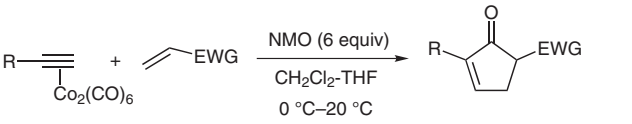
With regard to the intermolecular PKR, Costa et al. reported in 1995[34] the reaction of alkyl acrylates and acrylonitrile with terminal alkynes. PK cyclopentenone products were isolated, instead of the expected 1,3-dienes, by performing the reaction in the presence of a catalytic amount of $Co_2(CO)_8$ and a large excess of the olefin (preferably used as solvent), under CO pressure (40 bar) at high temperatures (120 °C in an autoclave). Under these conditions the products resulting from a regioselective domino Pauson–Khand/Michael addition reaction were obtained in moderate yields (Scheme 7).



R = *n*-Bu, *t*-Bu, Ph
EWG = CO_2Me, CO_2Et, CN

Scheme 7

Simultaneously with our work on intramolecular PKR of α,β-unsaturated sulfoxides and sulfones, Cazes et al. reported[35] some very interesting results in the intermolecular PKR of typical conjugated alkenes. Thus, the dicobalt hexacarbonyl complexes of terminal and internal alkynes react with certain unhindered electron-deficient alkenes, such as methyl acrylate and phenyl vinyl sulfone, under very mild conditions (0–20 °C) in the presence of *N*-methylmorpholine *N*-oxide (NMO) as promoter. As in the previous case the reactions were completely regioselective, providing the 2,5-disubstituted cyclopentenone in acceptable yields (Scheme 8). Finally, as other examples of conjugated alkenes in PKR, Wender et al.[36] have recently reported excellent results using dienes as alkene partners.



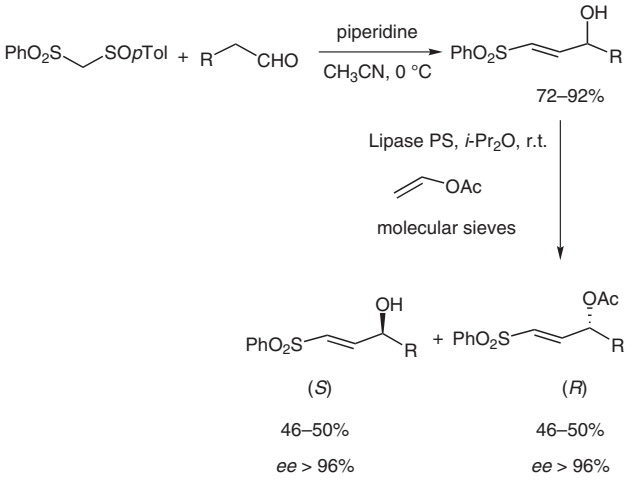
R = C_3H_7, EWG = SO_2Ph, 49%
R = C_3H_7, EWG = CO_2Me, 47%
R = Ph, EWG = CO_2Me, 41%

Scheme 8

3 Intramolecular PKR of γ-Oxygenated α,β-Unsaturated Sulfones and Related Enynes

In 1990 we reported[37] a convergent and very practical synthesis of γ-hydroxy-α,β-unsaturated sulfones based on the direct condensation of phenylsulfonyl arylsulfinyl methanes with enolizable aldehydes in the presence of piperidine in MeCN at 0 °C. This SPAC type condensation (Sulfoxide Piperidine Aldehyde Condensation)[38] presumably takes place according to the sequence Knoevenagel condensation, vinyl to allyl sulfoxide isomerization and [2,3] sigmatropic rearrangement, providing in excellent yield the hydroxyvinyl sulfones of *E* stereochemistry. We also found that enantiomerically pure alcohols were readily available by a further lipase-mediated (*Pseudomonas cepacia*) enantioselective acetylation[39] (Scheme 9).

Taking advantage of the great functional group tolerance of this synthesis of chiral alkenyl sulfones, in the 90s we developed a variety of applications to the stereoselective and enantioselective synthesis of highly functionalized cyclic compounds (including pyrrolizidine,[40] indolizidine[41] and quinolizidine alkaloids[42]) based on the initial stereoselective conjugate or radical addition to the



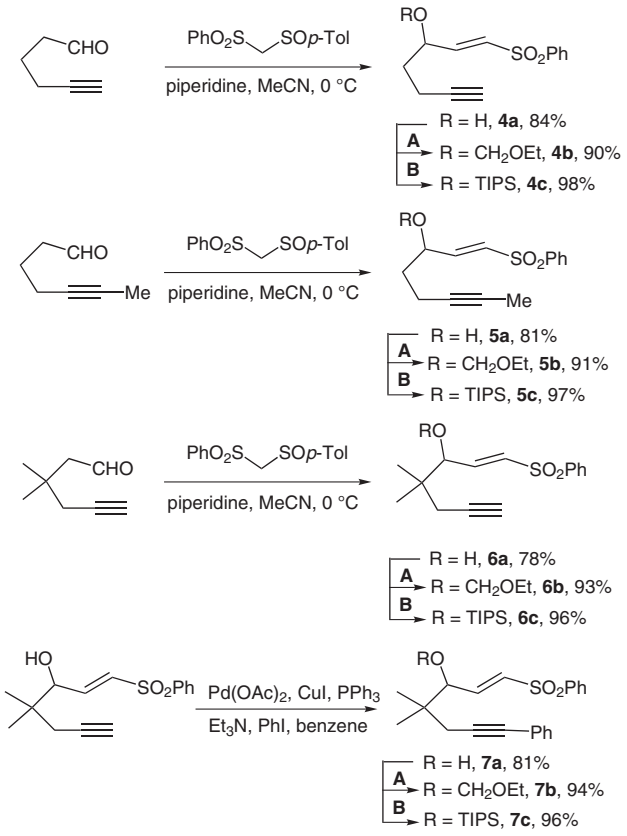
Scheme 9

vinyl sulfone moiety. At this point, the availability and appealing chemical versatility of this little explored type of compounds prompted us to investigate their synthetic interest in key metal-mediated C-C bond forming reactions, particularly the palladium-catalyzed allylic substitution,[43] the Heck reaction[44] and the PKR.[45]

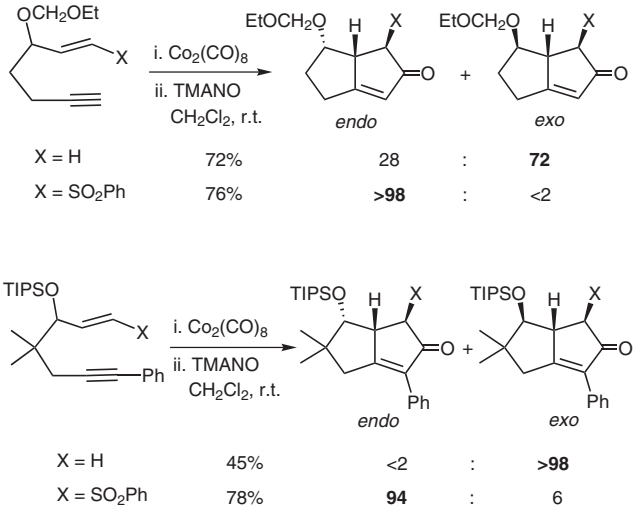
With respect to the topic of this Account, differently substituted 1-sulfonyl-3-hydroxy-1,6-enynes **4a**–**7a** were readily prepared, as expected, by the piperidine-mediated condensation of the corresponding alkynyl aldehyde with phenylsulfonyl *p*-tolylsulfinyl methane and, eventually, further functionalization of the terminal alkyne (Scheme 10).

Disappointingly, the first experiments, performed with alcohols **4a** and **5a**, showed that these substrates were hardly reactive under typical PKR conditions. However, to our delight, their hydroxyl protected derivatives, such as the ethoxymethyl ketal (substrates **b**) and the TIPS derivative (substrates **c**) underwent a clean intramolecular PK reaction under both thermal (MeCN, 80 °C) and *N*-oxide promoted conditions (Me_3NO, CH_2Cl_2, r.t.), affording cleanly the corresponding bicyclo[3.3.0]octenones **8**–**11** in good yields (usually 70–80% yield after flash chromatography, Table 1). In no case the competitive 1,3-diene product, resulting from a elimination process on the cobaltacycle intermediate, could be detected in the crude reaction mixture. It must be pointed out that the chemical yields of these PKR proved to be even higher than those of the corresponding enynes lacking the sulfonyl group (a couple of examples are shown in Scheme 11). In contrast with the enduring claim about the unsuitability of electronically deficient olefins in PKR, these results prove that the phenylsulfonyl group has a positive effect compared to the parent unsubstituted enyne.

Besides the high reactivity displayed by these 1-sulfonylated enynes in PKR, a second outstanding result is the stereochemical outcome of the reaction. It is well known that the PK cyclization of allyl-substituted enynes gives rise to the bicyclic product in which the allylic substituent



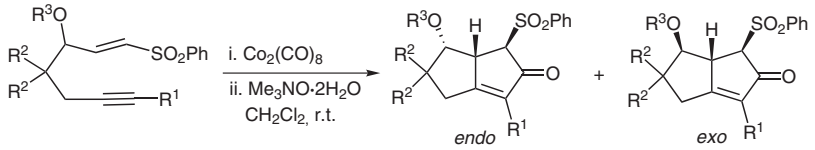
Scheme 10 Conditions **A**: $ClCH_2OEt$, *i*-Pr_2EtN, CH_2Cl_2, r.t. Conditions **B**: TIPSOTf, 2,6-lutidine, CH_2Cl_2, r.t.



Scheme 11

ends up in the unhindered *exo* face.[46] On the contrary, the PK reactions of the four series of 1-sulfonylated enynes **4**–**7** were highly *endo* selective in most cases (Table 1), revealing the strong capability of the phenylsulfonyl group to reverse the 'natural' *exo* selectivity of the process. Particularly high *endo* selectivities were observed in the case of enynes **4b**,**c** (entries 1 and 2), **5b**,**c** (entries 3

Table 1 Pauson–Khand Reaction of 1,6-Enynes **4**–**7**



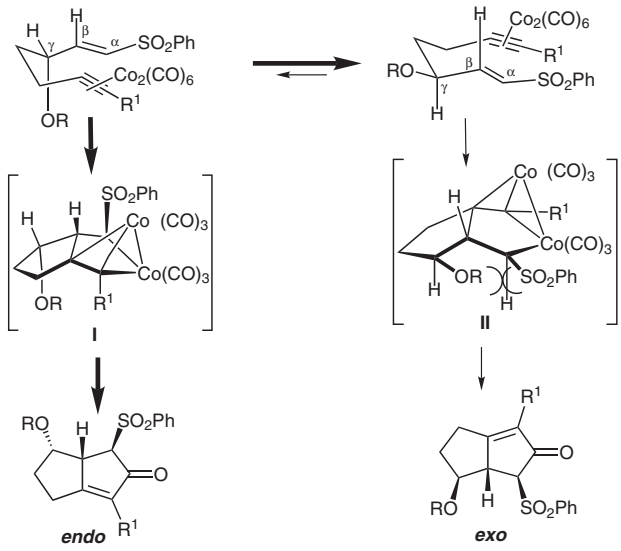
Entry	Enyne	R^1	R^2	R^3	Product	*endo*/*exo*[a]	Yield (%)[b]
1	**4b**	H	H	CH_2OEt	**8b**	>98:<2	76
2	**4c**	H	H	TIPS	**8c**	92:8	74
3	**5b**	Me	H	CH_2OEt	**9b**	93:7	77
4	**5c**	Me	H	TIPS	**9c**	91:9	73
5	**6a**	H	Me	H	**10a**	80:20	60[c]
6	**6b**	H	Me	CH_2OEt	**10b**	67:33	74
7	**6c**	H	Me	TIPS	**10c**	39:61	71
8	**7a**	Ph	Me	H	**11a**	76:24	75[c]
9	**7b**	Ph	Me	CH_2OEt	**11b**	87:13	79[c]
10	**7c**	Ph	Me	TIPS	**11c**	94:6	78[c]

[a] Determined by ^1H NMR after filtration of the cobalt by-products.
[b] Overall yield (*endo* + *exo*) after flash chromatographic separation.
[c] The *endo*- and *exo*-adducts could not be separated.

and 4), and **7c** (entry 10). The sulfonyl group was further removed in nearly quantitative yield by reductive cleavage of the C–S bond by reaction with zinc. Consequently, this two-step sequence intramolecular PK reaction and desulfonylation constitutes a very interesting stereocomplementary approach to the diastereoselective synthesis of C-6-substituted bicyclo[3.3.0]octenones. Some examples of the stereoselective access to each diastereoisomer of a C-6-substituted bicyclo[3.3.0]octenone by PKR of either a 1,6-enyne or its 1-phenylsulfonyl derivative are depicted in Scheme 11.

Considering the stereochemically determining cobaltacycle formation step, the major formation of the *endo*-adduct in the 1-sulfonylated-1,6-enynes might be rationalized assuming that the *cis*-cobaltacycle **I** is more stable than its diastereomer **II**. In **I** the allylic OR group and the bulky sulfone moiety are located on opposite faces of the cobaltacycle structure, whereas in **II** both groups could suffer an important steric interaction due to their nearly 1,3-parallel arrangement (Scheme 12). In addition, the conformational preferences around C2–C3 in the starting enynes **4**–**7** could also reinforce the *endo* selectivity of the cyclization.[47]

Exploring the structural scope of the intramolecular PK reaction of α,β-unsaturated sulfones, the homologous 1-sulfonylated-1,7-enynes **12** and **13** were also studied (Table 2). Under the same reaction conditions these substrates also afforded the corresponding PK adducts, the bicyclo[4.3.0]nonenones **14** and **15**, albeit both the yield

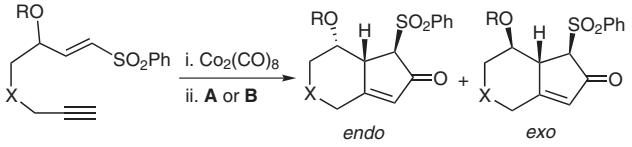


Scheme 12

and the *endo* selectivity of the cyclization were significantly lower.

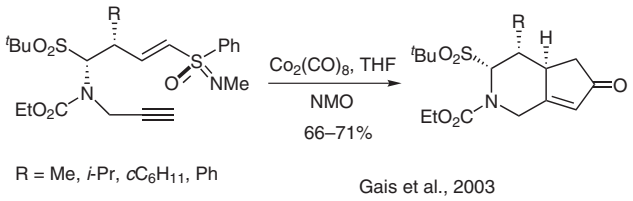
In parallel to the behavior of alkenyl sulfones, Gais et al. have recently reported the intramolecular reaction of related 1,7-enynes having a sulfoximine moiety at C-1, showing again the efficiency of electronically deficient sulfur-substituted alkenes in PKR[48] (Scheme 13).

Table 2 Pauson–Khand Reaction of 1,7-Enynes **12**, **13**



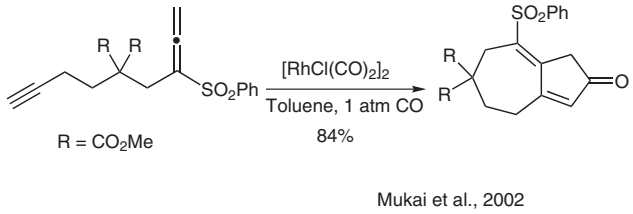
Enyne	X	R	Conditions	Product	*endo*/*exo*[b]	Yield (%)[c]
12a	CH_2	H	**A**	**14a**	59.41	49
12a	CH_2	H	**B**	**14a**	59:41	48
12b	CH_2	CH_2OEt	**A**	**14b**	52:48	49
12c	CH_2	TIPS	**A**	**14c**	34:66	62
13a	O	H	**B**	**15a**	79:21	14
13b	O	CH_2OEt	**B**	**15b**	66:34	50
13c	O	TIPS	**A**	**15c**	58:42	50[c]

[a] Conditions **A**: $Me_3NO{\cdot}2H_2O$ (7 equiv), CH_2Cl_2, r.t. Conditions **B**: $Me_3NO{\cdot}2H_2O$ (7 equiv)/molecular sieves, toluene, r.t.
[b] Determined by ^1H NMR after filtration of the cobalt by-products.
[c] Overall yield (*endo* + *exo*) after flash chromatography.
[d] The *endo*- and *exo*-products could not be separated by chromatography.



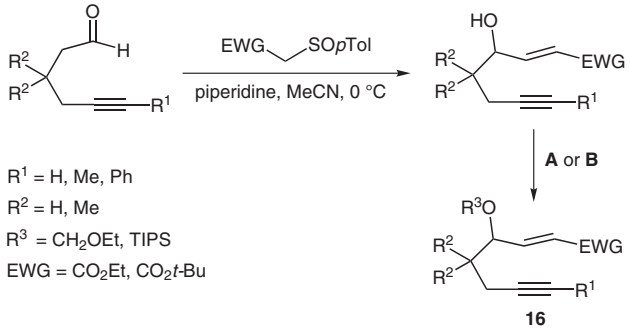
Scheme 13

On the other hand, Mukai et al. have recently described that phenylsulfonyl allenes undergo intramolecular PKR in the presence of a catalytic amount of rhodium(I) under carbon monoxide atmosphere.[21f,i] In this case the reaction takes place selectively with the non-sulfonylated terminal C–C double bond, providing bicyclo[5.3.0]decane products. A significant example is shown in Scheme 14.



Scheme 14

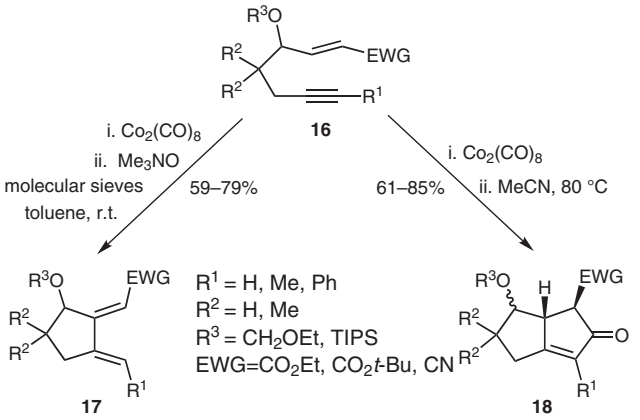
After having proved the effectiveness of γ-oxygenated α,β-unsaturated sulfones as olefinic partners in intramolecular PKR, we wondered if this kind of chemistry could be extended to typical π-conjugated electronically deficient alkenes, such as α,β-unsaturated esters and nitriles.[49] The model γ-oxygenated α,β-unsaturated esters **16** were readily prepared in excellent yields by SPAC reaction of α-sulfinylacetates with enolizable aldehydes (Scheme 15).



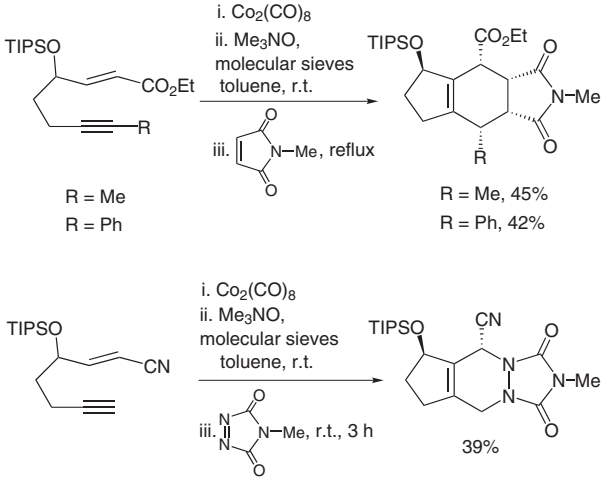
Scheme 15 Conditions **A**: $ClCH_2OEt$, *i*-Pr_2EtN, CH_2Cl_2. Conditions **B**: TIPSOTf, 2,6-lutidine, CH_2Cl_2.

From the very beginning we observed that, unlike the previously studied alkenyl sulfones, the chemoselectivity of the cobalt-mediated cyclization was deeply dependent on the reaction conditions, especially the nature of the solvent and the promoter used. After systematic experimentation, we found that the 1,3-exocyclic dienes **17**, resulting of an interrupted PKR, were the major products under *N*-oxide/molecular sieves promoted conditions in toluene as solvent (at r.t.). The bicyclic PK adducts **18** were selectively obtained (61–85% yield) in acetonitrile at 80 °C, usually with low *endo* selectivity (Scheme 16). Other experimental conditions generally provided mixtures of both types of products.

Interestingly, the same kind of chemoselectivity could be reproduced in the case of the γ-oxygenated α,β-unsaturated nitrile **19** (Scheme 17): the 1,3-exocyclic diene **20** was

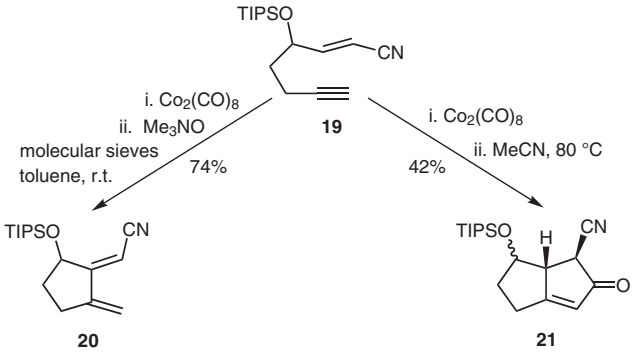


Scheme 16



Scheme 18

obtained under TMANO/molecular sieves promoted conditions while the PK adduct **21** was selectively formed under thermal conditions (MeCN, 80 °C). These results in intramolecular PKR clearly evidence a very different behavior between typical π-conjugated olefins and α,β-unsaturated sulfones, partially justifying the extended believe on the unsuitability of electron-deficient alkenes in PKR.



Scheme 17

The non-carbonylative cyclization of α,β-unsaturated esters and nitriles was applied to the development of one-pot cobalt cyclization/Diels–Alder cycloaddition sequences (Scheme 18). In all cases the Diels–Alder reaction with highly reactive dienophiles was completely stereoselective, affording a single *endo*-isomer.

4 PKR of α,β-Unsaturated Sulfoxides

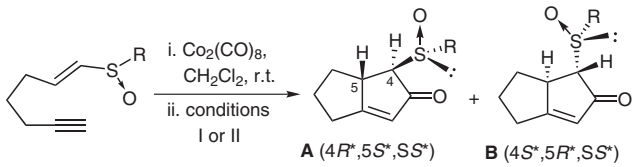
4.1 Intramolecular Processes

In connection with our previous work on the use of sulfoxides as chiral auxiliaries in Heck reactions,[50] and simultaneously with the study on alkenyl sulfones in PKR, we started a similar project focused on the potential synthetic interest of alkenyl sulfoxides in PKR,[51] and especially on the development of new versions of asymmetric PKR. As model substrates for the intramolecular process, we first prepared several racemic (*E*)-1-sulfinylhept-1-en-6-ynes **22a–c** from 5-hexynal by either Wadsworth–Emmons olefination with sulfinylmethyl phosphonate or by condensation of the anion of aryl methyl sulfoxides and further dehydration (MsCl, Et_3N; then DBU).

The alkyne dicobalt complexes of enynes **22** reacted under both thermal (MeCN, 80 °C; conditions **I**) and amine *N*-oxide promoted conditions (NMO, CH_2Cl_2, r.t.; conditions **II**) giving rise to the bicyclic PK adducts in yields around 50% after chromatographic purification. As in the case of the intramolecular PKR of related alkenyl sulfones, we did not observe the formation of exocyclic 1,3-dienes resulting from the competitive β-hydrogen elimination process on the cobaltacycle intermediate. However, the most interesting outcome was the stereoselectivity of the process: while both the reaction of the *p*-tolylsulfoxide **22a** and the potentially cobalt-chelating *o*-dimethylamino phenylsulfoxide **22b** were moderately stereoselective, leading to a ca. 3:1 mixture of **A** and **B** diastereomers (entries 1–4), the cyclization of the bulky *tert*-butylsulfinyl derivative **22c** was completely stereoselective, affording exclusively the **A** isomer (entries 5 and 6). The stereochemical assignment of the **A** (4*R**,5*S**,S*S**) and **B** (4*S**,5*R**,S*S**) isomers was first established by a combination of NMR studies (mainly values of $J_{4,5}$ and δ_5) and chemical correlations (*m*-CPBA oxidation of the **A** + **B** mixtures to the same sulfone). This assignment was unequivocally confirmed in the case of **23cA** by X-ray diffraction.

To establish the scope and applicability in asymmetric synthesis of the *tert*-butyl sulfinyl group as chiral auxiliary in intramolecular PKR, we next prepared a variety of enantiomerically pure 1-*tert*-butylsulfinyl enynes **25–28** by Wadsworth–Emmons olefination of the corresponding aldehyde with the enantiopure sulfinyl phosphonate (*R*)-**24**.[51] As it is shown in Table 4 the olefination was generally low *E* stereoselective, although the *E* + *Z* mixtures of isomers could be easily separated by standard silica gel chromatography.

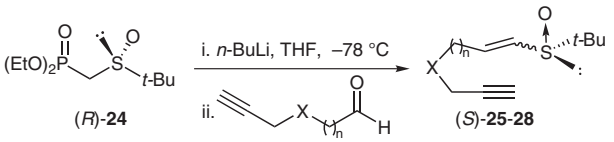
Table 3 Pauson–Khand Reaction of (±)-*trans* **22**



Entry	R	Enyne	Conditions[a]	Adduct	**A**:**B** ratio[b]	Yield (%)[c]
1	*p*-Tol	**22a**	**I**	**23a**	75:25	52
2	*p*-Tol	**22a**	**II**	**23a**	73:27	49
3	*o*-$Me_2NC_6H_4$	**22b**	**I**	**23b**	71:29	55
4	*o*-$Me_2NC_6H_4$	**22b**	**II**	**23b**	70:30	46
5	*t*-Bu	**22c**	**I**	**23c**	>98:<2	50
6	*t*-Bu	**22c**	**II**	**23c**	>98:<2	46

[a] Conditions **I**: MeCN, 80 °C. Conditions **II**: NMO·H_2O (6 equiv), CH_2Cl_2, r.t.
[b] By ^{1}H NMR on the crude mixtures after filtration of the cobalt by-products.
[c] Combined yield of **A**/**B** PK products after chromatographic purification (isomers **A** and **B** were separated by flash chromatography).

Table 4 Synthesis of Enantiomerically Pure (*S*)-1-*tert*-Butylsulfinylenynes

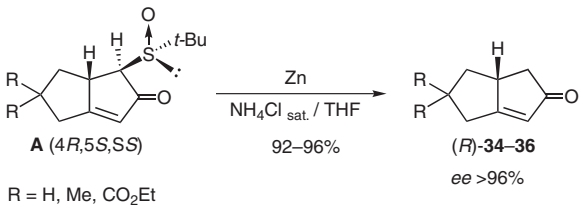


X	n	Enyne	*trans*/*cis*[a]	Yield (%)[b] [*trans*][c]
CH_2	1	**22c**	56:44	81 [45]
CMe_2	1	**25**	>98:<2	89 [89]
$C(CO_2Et)_2$	1	**26**	75:25	85 [64]
$C(CO_2Et)_2$	2	**27**	65:35	84 [55]
NBOC	1	**28**	60:40	77 [46]

[a] Determined by ^{1}H NMR on the crude mixture.
[b] Combined yield of *trans* and *cis* olefins after flash chromatography.
[c] In brackets yield of pure isolated *trans* isomer.

Table 5 summarizes the results obtained in the PKR of the dicobalt complexes of (*E*)-enynes **22c**, **25**–**29** under thermal conditions (MeCN, 80 °C). Remarkably, with all the terminal alkynes (entries 1–5) the reactions took place with complete stereoselectivity in favor of the **A** adduct (**A**:**B** ratio >98:<2), showing the powerful and general stereochemical control exerted by the *tert*-butylsulfinyl group. It is also worth noting that the yields were somewhat higher for the 4,4-disubstituted-1,6-enynes **25** and **26** (65% and 60%, entries 2 and 3, respectively) than for the unsubstituted substrate **22c** (50%, entry 1) likely due to the entropically favorable *gem*-dialkyl effect. The procedure can also be applied to the synthesis of enantiomerically pure azabicyclo[3.3.0]octenones as it is shown by the reaction of the aza-enyne **28** (60%, entry 5). Disappointingly, the cyclization of the 1,7-enyne **27** was much less efficient (entry 4, 30% yield) and no reaction was observed with non-terminal alkynes, such as **29** (entry 6). Taking into account the sensitivity of the PKR to steric effects, the lack of reactivity of **29** might be ascribed to the great steric hindrance resulting from the bulky substitution at both ends of the enyne.

As the final step of this chiral auxiliary based asymmetric PKR, the elimination of the sulfinyl group was cleanly achieved, without affecting the enone moiety, by treatment of the sulfinylated cyclopentenones with activated zinc (Zn, NH_4Cl, THF–H_2O, r.t.). The resulting (*R*)-bicyclo[3.3.0]octenones **34**–**36** were obtained in almost quantitative yield and very high optical purity (Scheme 19).

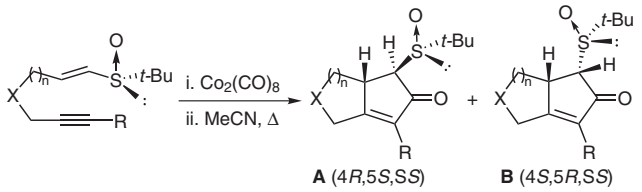


Scheme 19

4.2 Intermolecular Processes

As mentioned in the introduction, one of the current limitations in PKR is the lack of asymmetric intermolecular versions for simple non-strained alkenes. Thus, all reported precedents require the use of highly reactive bicyclic olefins, especially norbornene and norbornadiene. Our previous results on the intramolecular PKR of 1-sulfinyl-1,6-enynes led us to the question if simple vinyl sulfoxides could be suitable substrates in intermolecular PKR.[52]

Table 5 Thermal Pauson–Khand Reaction of (*S*)-*trans*-Enynes **22c** and **25–29**



Entry	Enyne	X	n	R	Product	**A**:**B** ratio[a]	Yield (%)[b]
1	**22c**	CH_2	1	H	**23c**	>98:<2	50
2	**25**	CMe_2	1	H	**30**	>98:<2	65
3	**26**	$C(CO_2Et)_2$	1	H	**31**	>98:<2	60
4	**27**	$C(CO_2Et)_2$	2	H	**32**	>98:<2	30
5	**28**	NBOC	1	H	**33**	>98:<2	60
6	**29**	CMe_2	1	Ph	**–**	–	–

[a] Determined by ^{1}H NMR on the crude mixtures.
[b] In pure **A** adduct after flash chromatography.

In addition, the expected products, the chiral 5-sulfinyl-2-cyclopentenones, could be versatile intermediates in enantioselective synthesis of substituted cyclopentanoids.

To test the reactivity of vinyl sulfoxides in PKR, a variety of substrates having different steric and electronic environments around the sulfur atom (substrates **37a–i**) were prepared. We first explored the thermal reaction with the cobalt complex of 1-hexyne. However, regardless of the substrate (**37a** or **37i**) and solvent used (toluene or acetonitrile at 80 °C), we obtained a complex mixture of products. A similar result was also observed when the reaction was carried out in the presence of cyclohexylamine as promoter[4] in toluene at 90 °C. As these disappointing results could be due, at least partially, to the low thermal stability of the sulfinyl group, we turned to the PKR promoted by amine *N*-oxides at room temperature. Under the conditions reported by Cazes (excess of NMO, CH_2Cl_2–THF at r.t.)[35] a sluggish reaction was observed. Gratifyingly, a much faster reaction was observed using acetonitrile as solvent. The reaction of **37a** with the dicobalt complex of 1-hexyne under these conditions (6 equiv of NMO·H_2O, MeCN, r.t.) was over within two hours, occurring with complete chemoselectivity (the possible competitive formation of the 1,3-diene product was not detected) and regioselectivity (only the 2,5-disubstituted cyclopentenone was formed), providing the cyclopentenone **38a** in 68% yield as a 74:26 mixture of diastereomers.

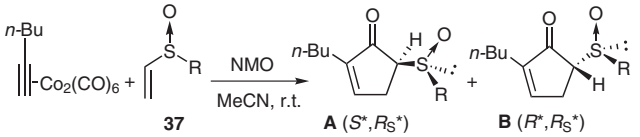
In Table 6 are summarized the most relevant results obtained in the PKR of the set of vinyl sulfoxides **37a–i** with 1-hexyne, using these optimized conditions.

All the reactions were completely regioselective with regard to both alkyne and alkene components, affording exclusively the 2,5-disubstituted cyclopentenones. The same type of PK regioisomers had been previously reported for ethyl acrylate, acrylonitrile and phenyl vinyl sulfone,[35] suggesting that this 2,5-regioselectivity is a general trend for electron-deficient alkenes.[53]

On the other hand, both the reactivity and the stereoselectivity proved to be highly dependent on the substitution at sulfur. In the series of non-coordinating sulfoxides (**37a–e**) a correlation between steric bulk and reactivity was observed. Thus, the *ortho*-substituted sulfoxides **37b** and **37c** (entries 2 and 3) and, particularly, the very bulky triisopropylphenylsulfoxide **37d** (entry 4) and *tert*-butylsulfoxide **37e** (entry 5) gave incomplete conversions and unpractical chemical yields even when a large excess of the cobalt complex and long reaction times were used. Regarding the stereoselectivity of the reaction, a qualitative correlation with the bulkiness of the sulfoxide was also observed: the greater the steric bulk of the sulfoxide, the higher the stereoselectivity, reaching a complete stereocontrol for the *tert*-butylsulfoxide **37e** (**A**:**B** ratio: >98:<2, entry 5). As previously discussed, the *tert*-butylsulfinyl group was also found to be the most stereodiscriminating chiral auxiliary in the intramolecular PKR (see Table 3).

A different outcome was observed for the potentially cobalt coordinating sulfoxides **37f–i**. The *ortho*-aminophenyl derivative **37h** (entry 8) evolved completely, albeit with formation of complex mixtures of products, and the pyridyl sulfoxide **37g** (entry 7) provided the expected Pauson–Khand product in only 19% yield. In this study, the best result was obtained from the *ortho*-dimethylaminophenyl sulfoxide **37i**, which was not only the most reactive alkene but the reaction was also highly diastereoselective (entry 9, 93:7 **A**:**B** ratio). This remarkable reactivity, which might be ascribed to the prior coordination of the Me_2N moiety to the cobalt complex, allowed us to perform the reaction at 0 °C, affording the corresponding cyclopentenone in 74% yield as a 93:7 mixture of diastereomers (entry 10).

Table 6 *N*-Oxide Promoted Intermolecular PKR of 1-Hexyne Dicobalt Complex with Racemic Vinyl Sulfoxides **37**



Entry[a]	R	37	Time (h)	Conversion	Adduct	**A**:**B** ratio[b]	Yield (%)[c]
1	*p*-Tol	**37a**	2	>99	**38a**	74:26	68
2[d]	*o*-Tol	**37b**	24	70	**38b**	90:10	28
3[d]	*o*-BrC_6H_4	**37c**	24	73	**38c**	86:14	30
4[d]	2,4,6-(*i*-Pr)$_3C_6H_2$	**37d**	24	60	**38d**	94:6	24
5[d]	*t*-Bu	**37e**	24	65	**38e**	>98:<2	20
6[d]	*o*-$MeSC_6H_4$	**37f**	24	<1	**38f**	–	–
7	*o*-Py	**37g**	1	>99	**38g**	73:27	19
8[d]	*o*-$(H_2N)C_6H_4$	**37h**	24	>99	**38h**	–	–
9	*o*-$(Me_2N)C_6H_4$	**37i**	1	>99	**38i**	92:8	63
10[e]	*o*-$(Me_2N)C_6H_4$	**37i**	4	>99	**38i**	93:7	74

[a] Reaction conditions: cobalt complex (1.5 equiv), alkene **37** (1.0 equiv), NMO·H_2O (6.0 equiv), MeCN, r.t.
[b] By ^1H NMR on the crude mixtures after filtration of the cobalt by-products.
[c] Yield of pure **A**+**B** isomers after chromatography.
[d] 3 Equiv of dicobalt complex were used.
[e] Reaction run at 0 °C.

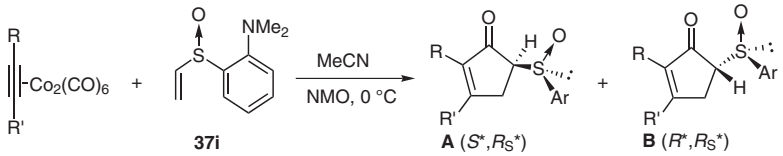
Once we found the best balance between reactivity and stereoselectivity by using the vinyl sulfoxide **37i**, we next explored the structural scope of the PKR with differently substituted alkynes (Table 7). Reasonable yields in isolated adducts (49–74%), complete regioselectivities, and very high diastereoselectivities (de 86–96%) were obtained for all terminal alkynes, including primary, benzyl and tertiary alkyl-substituted ones (entries 1–3), aryl acetylenes (entry 4) and functionalized alkynes (entries 5–8). It is worth noting that the reaction conditions are so mild that even alkynes having a primary bromoalkyl chain can be successfully used (entry 8). Disappointingly, no reaction occurred in the case of internal alkynes as 2-butyne (entry 9). This drawback was partially solved by performing the reaction at high pressure (10 kbar), which afforded the adducts **46** in 33% yield and high stereoselectivity (entry 10). The S^*,R_S^* configuration of the major isomer **A** was first assigned by NMR studies and unequivocally confirmed by X-ray crystal analysis of **39A**.[52]

Both theoretical and experimental studies unequivocally proved that the observed stereoselectivity, at least in the case of the optimal sulfoxide **37i**, was in fact the result of the easy thermodynamic epimerization at the C-5 acid position in the **A**/**B** adducts.[52b] For instance, a NMR sample of pure **43A** isomerized again to the 93:7 isomeric **A**:**B** reaction ratio in 16 hours in acetone-d_6, in three hours in CD_3CN and instantaneously in DMSO-d_6 or CD_3OD. On the other hand, the high reactivity displayed by the dimethylaminophenyl sulfoxide **37i** in PKR seems to be due to the previous chelation of the amine moiety to the cobalt cluster, facilitating the further coordination of the alkene to cobalt, which is supposed to be the rate determining step. As a kinetic data of this accelerating effect, the reaction of equimolecular amounts of *o*-tolylsulfoxide **37b**, *o*-(dimethylamino)phenyl sulfoxide **37i** and dicobaltcarbonyl complex of 1 hexyne (NMO, MeCN, 0 °C, 60 min) led to a 11:89 mixture of the corresponding Pauson–Khand products **38b** and **38i**. This result clearly shows that substrate **37i**, despite the higher steric bulk of the Me_2N group with regard to the methyl group, is nearly one order of magnitude more reactive than **37b**. Taking into account other precedents on heteroatom directed PKR[54] and some of our theoretical calculations,[52b] we speculate that the coordination of both nitrogen atom and the alkene moiety occur on the same cobalt atom (homonuclear complex). A brief mechanistic proposal is summarized in Scheme 20.

4.3 Applications to the Enantioselective Synthesis of Natural Cyclopentanoids

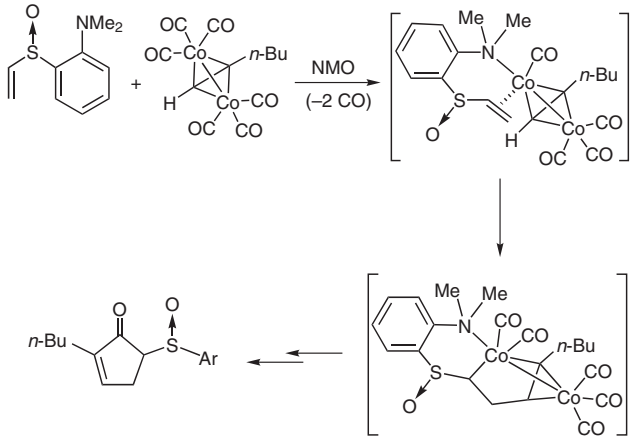
In order to apply this intermolecular Pauson–Khand methodology in asymmetric synthesis the preparation of enantiomerically pure vinyl sulfoxide **37i** was required. (*R*)-**37i** was efficiently prepared from norephedrine following the recently reported Senanayake's procedure.[55] Reaction of **47** with *o*-(dimethylamino)phenyl magnesium iodide (THF, –78 °C) and further treatment with vinyl magne-

Table 7 Pauson–Khand Reaction of Vinyl Sulfoxide **37i** with Substituted Alkynes

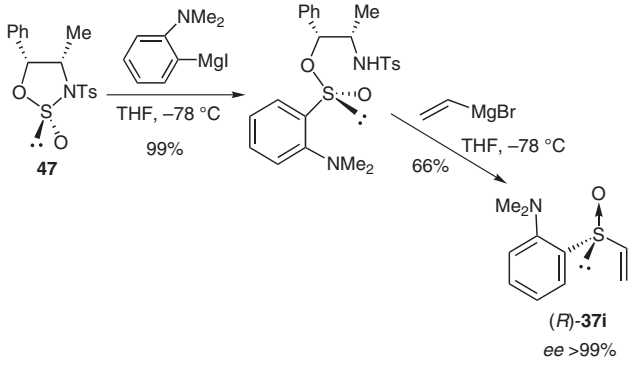


Entry[a]	R	R′	Time (h)	Adduct	**A**:**B** ratio[b]	Yield (%)[c]
1	*n*-Bu	H	4	**38i**	93:7	74
2[d,e]	*t*-Bu	H	26	**39**	>98:<2	55
3[d]	Bn	H	14	**40**	93:7	58
4	*p*-Tol	H	12	**41**	93:7	49
5[e]	TMS	H	16	**42**	>98:<2	59
6	CH_2OTIPS	H	2	**43**	93:7	62
7	CH_2CH_2OTIPS	H	7	**44**	>98:<2	66
8	$CH_2CH_2CH_2Br$	H	6	**45**	>98:<2	68
9	Me	Me	24	**46**	–	–
10[f]	Me	Me	48	**46**	92:8	33

[a] Reaction conditions: dicobalt complex (1.5 equiv), alkene **37i** (1.0 equiv), NMO·H_2O (6.0 equiv), MeCN, 0 °C.
[b] By ^1H NMR on the crude mixtures after filtration of the cobalt by-products.
[c] Yield of pure **A**+**B** isomers after chromatography.
[d] 3 Equiv of dicobalt complex were used.
[e] Reaction run at r.t.
[f] Reaction run at 10 kbar.



Scheme 20



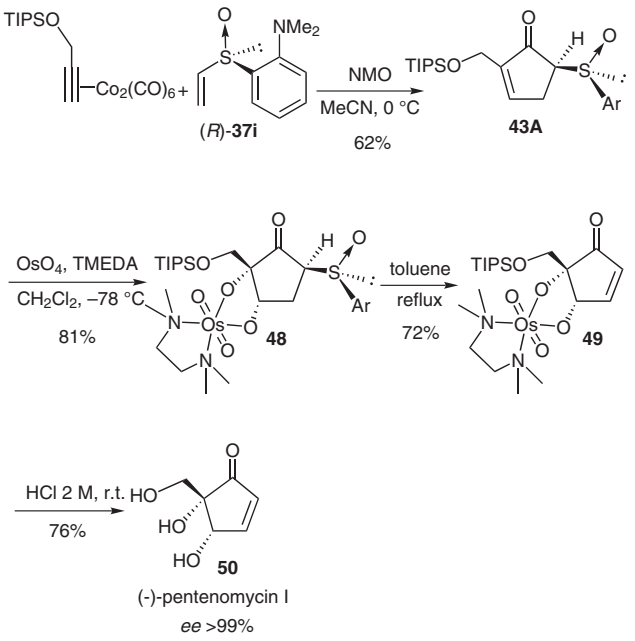
Scheme 21

sium bromide afforded (*R*)-**37i** in 66% overall yield and very high optical purity (ee >99%, HPLC), showing that both displacement reactions at sulfur occur with complete inversion of configuration (Scheme 21).

To highlight the versatility of this convergent asymmetric synthesis of cyclopentenones, we selected two natural cyclopentanoids as synthetic objectives: the antibiotic (–)-pentenomycin I, having a 4,5,5-trisubstituted cyclopentenone structure, and the aminocyclopentitol moiety of the hopanoid of *Zymomonas mobilis*, which displays a stereochemically complex 1,1,2,3,4,5-hexasubstituted cyclopentane framework (Figure 1).

(–)-Pentenomycin I was isolated in 1973 from the culture broths of *Streptomyces eurythermus*[56] and has proved to be moderately active against Gram-positive and Gram-negative bacteria.[57] Of the five asymmetric syntheses of this compound reported to date[58] four involve the use of carbohydrates as starting materials, which imply the use of long synthetic sequences. A very efficient enantioselective four-step synthesis of (–)-pentenomycin I from the vinyl sulfoxide (*R*)-**37i** is shown in Scheme 22. Treatment

of the cobalt complex of the TIPS derivative of propargylic alcohol with enantiopure (*R*)-**37i** (NMO, MeCN, 0 °C) afforded the adduct **43** in a 93:7 isomer ratio (62% yield). Trituration of this mixture with cold hexane provided the major diastereomer (*S*,R_S)-**43A** (ee >99%, HPLC, Chiralcel OD column). Since the dihydroxylation of (*S*,R_S)-**43A** with OsO_4 under usual catalytic conditions (OsO_4 3 mol%, NMO, CH_2Cl_2, 0 °C) gave a mixture of stereoisomers, we alternatively used the Donohoe's procedure of dihydroxylation of alkenes with the stoichiometric pair OsO_4/TMEDA under extremely mild reaction conditions.[59] In CH_2Cl_2 at –78 °C the reaction was highly stereoselective in favor of the dihydroxylation on the expectedly less hindered face of the double bond, that opposite to the sulfinyl group at C-5, providing the stable osmate diester **48** in 81% yield. Compound **48** suffered a clean sulfoxide pyrolysis in refluxing toluene, affording the enone-osmate diester **49** in 72% yield. Final acid hydrolysis of the hydroxyl protected groups provided the natural (–)-(2*S*,3*S*)-pentenomycin I (**50**), whose very high optical purity was unequivocally confirmed by HPLC analysis of its triacetate derivative (ee >99%, Chiralpak AD column).



Scheme 22

The bacteriohopanetetrol ether shown in Figure 1 is an abundant triterpenoid of the hopane family, found in the membrane of several bacteria, such as *Methylobacterium organophylum*, *Rhodopseudomonas acidophila* and *Zymomonas mobilis*.[60] To our best knowledge, only a previous total synthesis of its aminocyclopentitol unit had been reported, using D-glucosamine as commercially available starting material.[61]

In Scheme 23 is shown the eight-step stereodirected synthesis of the (–)-enantiomer of this aminocyclopentitol starting from the PK adduct (*S*,R_S)-**43A**. The stereo-

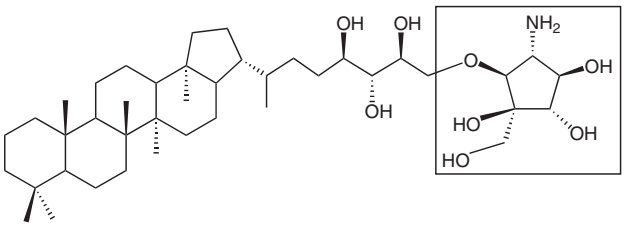
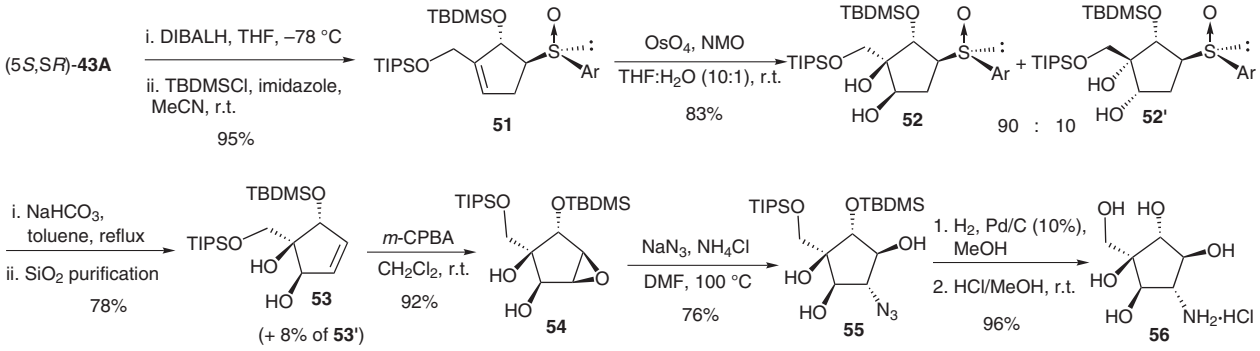


Figure 1

selective carbonyl reduction of **43A** with DIBALH in THF at –78 °C provided a single alcohol, which was protected as its TBDMS derivative **51**. The *trans* stereochemistry of **51** was inferred from the well known stereochemical behavior of β-ketosulfoxides with reducing hydride reagents.[62] The dihydroxylation of **51** under standard OsO_4 catalytic conditions (OsO_4 3 mol%, NMO, THF–H_2O, r.t.) occurred mainly on the alkene face opposite to the bulky allylic substituent, providing an inseparable 90:10 mixture of both *cis* diols **52** and **52′** (83% yield). Sulfoxide pyrolysis of this mixture by heating in toluene at 110 °C and further silica gel chromatographic separation afforded the cyclopentenediol **53** in 78% yield. As expected, the epoxidation of **53** with *m*-CPBA (CH_2Cl_2, r.t.) was completely stereoselective, occurring on the same side of the allylic hydroxyl group to give a single epoxide **54**. Due to the very different steric environment of both epoxidic carbons, the *trans* opening of **54** with NaN_3 in DMF at 100 °C was completely regioselective in favor of the attack at the least hindered position, giving rise to the azide **55** (76% yield). Finally, hydrogenation of the azide moiety (H_2, Pd/C), followed by hydroxyl deprotection in acid media (HCl, MeOH), afforded the (–)-aminocyclopentitol (**56**) in excellent yield (96%).

5 Summary

This account summarizes our work on the reactivity and synthetic relevance of alkenyl sulfones and alkenyl sulfoxides as alkene partners in PKR. Contrary to the extended belief on the unsuitability of electron-deficient alkenes for the PKR, we have proved that this is not certainly the case for this type of sulfur-substituted alkenes. Both 1-sulfinyl and 1-sulfonyl-1,6-enynes underwent a clean intramolecular PKR under either thermal activation or *N*-oxide amine promoted conditions. Yields in the range 50–80% were obtained for a wide variety of substituted enynes, showing the generality of this process. These electron-deficient alkenes also provided some very interesting stereochemical results. For instance, the PKR of 3-oxygenated 1-phenylsulfonyl-1,6-enynes occurred with high *endo* selectivity, which complements the usual *exo* selectivity obtained for allylically substituted 1,6-enynes. On the other hand, it was found that the *tert*-butylsulfinyl group is an excellent chiral auxiliary for the intramolecular PKR of 1-sulfinyl-1,6-enynes, providing in all cases a single diastereomer. Although the intermolecular PKR is



Scheme 23

known to have a more limited scope than the intramolecular version, we have demonstrated that vinyl sulfoxides can be used as substrates in intermolecular PKR. Interestingly, the use of the cobalt-chelating dimethylaminophenyl vinyl sulfoxide as highly reactive alkene has led to the first version of intermolecular asymmetric PKR with non-strained alkenes. The resulting 5-sulfinyl-2-cyclopentenones are versatile intermediates in the enantioselective synthesis of natural cyclopentanoids, as demonstrated by the development of short syntheses of (–)-pentenomycin I and a complex aminocyclopentitol.

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