Pauson−Khand Reactions of Electron-Deficient Alkenes

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Despite the common perception that alkenes possessing electron-withdrawing groups are not adequate substrates for Pauson–Khand (PK) reactions, a number of successful examples of this reaction involving electron-deficient alkenes, such as α,β-unsaturated ketones, esters, nitriles, sulfoxides and sulfones, have been reported in recent years. In the case of the intramolecular PK reaction of 1-sulfinyl-1,6-enynes and 1-sulfonyl-3-oxygenated-1,6-enynes these processes have been applied in asymmetric synthesis.

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Introduction

Since its discovery in the early 70s,[1] the cobalt-mediated carbonylative cocyclization of an alkyne and an alkene, known as the Pauson−Khand (PK) reaction,[2] has become nowadays one of the most convergent and versatile methods for the synthesis of cyclopentenones. Although the classical PK reaction was originally carried out by heating a mixture of stoichiometric amounts of dicobalt octacarbonyl, alkyne and alkene, in the last ten years the synthetic interest of this process has been greatly improved in several ways. First, the discovery of very effective and simple promoters,[3] for instance tertiary amine oxides or cyclohexylamine, that allow the reaction to be performed at much lower temperatures (usually 0−25 °C) and often in high yields. Second, the development of efficient versions of asymmetric PK reactions[4] and catalytic PK reactions[5] makes possible the synthesis of enantiopure substituted cyclopentenones and fulfills the principle of atom economy. Third, this metal-mediated cyclopentenone annelation of alkynes and alkenes is not limited to the case of cobalt: complexes of other

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Javier Adrio (left) was born in Madrid, Spain, in 1968. He studied chemistry at the UAM, where he received his B.S. and M.S. degrees in 1992 and 1994, respectively. From 1995 to 2000 he carried out his PhD thesis at the Department of Organic Chemistry, under the supervision of Prof. Juan Carlos Carretero, working in new synthetic applications of functionalized α,β-unsaturated sulfoxides and sulfones in intramolecular radical cyclizations and Pauson−Khand reactions. He is currently working as a senior scientist at the pharmaceutical company PharmaMar.

Juan Carlos Carretero (centre) was born in Madrid, Spain, in 1960. He studied chemistry at the UAM (B.S. degree in 1982) and received his PhD in Organic Chemistry in 1985, under the supervision of Prof. José L. García Ruano. He spent almost 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. He has been involved in the development of highly stereoselective methods from sulfur compounds, mainly sulfoxides and sulfones, and their application to the synthesis of natural products and pharmacologically active compounds. One of his current research interests deals with the use of enantiomerically sulfur compounds as stereochemical controllers in transition metal-catalyzed reactions.

Marta Rodríguez Rivero (right) was born in Segovia, Spain, in 1976. She studied chemistry at the Universidad Autónoma de Madrid (UAM), where she received her B.S. and M.S. degrees in 1999 and 2001, respectively. Currently she is a graduate student at the Department of Organic Chemistry under the supervision of Prof. Juan Carlos Carretero. In 2001 she enjoyed a three months stay in the group of Prof. Gary A. Molander (University of Pennsylvania). She is working on metal-mediated stereoselective cyclization of enynes.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

metals, especially Ti,[6] Cr,[7] Fe,[8] Ni,[9] Zr,[10] Mo,[11] Ru,[12] Rh[13] and W,[14] have also proved to be effective in this kind of formal [2+2+1] cycloaddition.

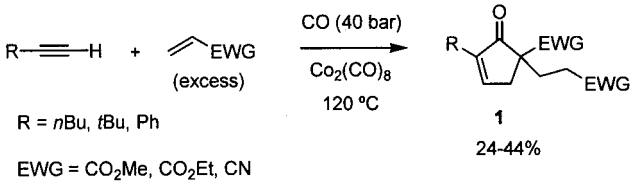
Concerning the structural scope of the PK reaction, although its tolerance for a wide variety of substituents at the alkyne moiety is well-known,[15] this seemed not to be the case for the alkene partner. Since the seminal work of Pauson and Khand, it has been widely accepted that electron-deficient alkenes, such as α,β-unsaturated aldehydes, ketones, esters and nitriles, are not suitable substrates for PK reactions. In these cases it has been postulated that the key cobaltacyclic intermediate preferentially undergoes a β-hydride elimination process, to furnish the conjugated 1,3-diene,[2a−2e][5a,16] rather than the carbonyl insertion step required for the formation of the cyclopentenone product (Scheme 1).

This result is in sharp contrast to the case of the PK reactions of alkenes possessing electron-donating substituents (like alkyl[17] or ether groups[18]) or strained C-C double bonds (like allenes[19] or cyclopropylmethylene and cyclopropene groups[20]), which afford the expected cyclopentenone products.

However, several studies, most of them reported recently, show that under certain circumstances a relatively broad variety of electron-deficient alkenes can also be appropriate substrates in PK reactions, and this is a major improvement of the structural versatility of this reaction.

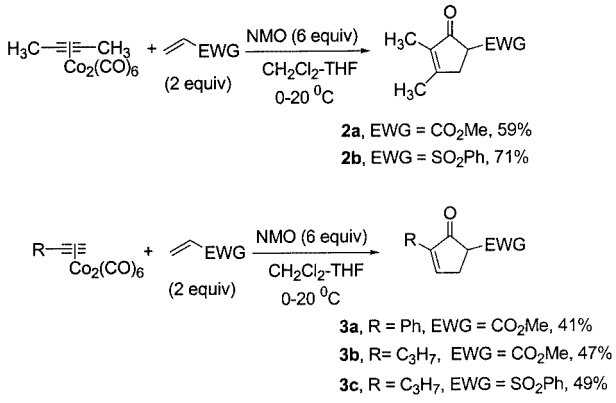
Intermolecular Processes

To the best of our knowledge, there are only two papers regarding successful intermolecular PK reactions of electron-deficient alkenes. The reaction of alkyl acrylates and acrylonitrile with terminal alkynes (like 1-hexyne or phenylacetylene), reported by Costa et al. in 1995,[21] can be driven towards the formation of PK cyclopentenone products, 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 cyclopentenones **1**, resulting from a regioselective domino Pauson−Khand/Michael addition reaction, were obtained in moderate yields (24−44%, Scheme 2).



Scheme 2

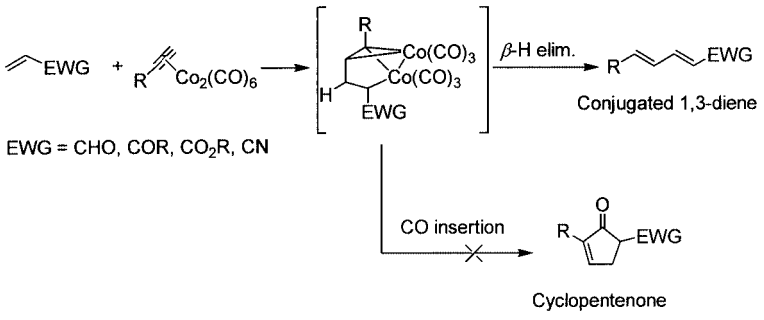
More recently, Cazes et al. have reported that dicobalt hexacarbonyl complexes of terminal and internal alkynes react with methyl acrylate and phenyl vinyl sulfone at 0−20 °C when *N*-methylmorpholine oxide (NMO) is used as promoter.[22] Under these mild conditions the cyclopentenones **2**−**3** were obtained in moderate to acceptable yields (41−71%; Scheme 3). Disappointingly, no reaction was observed in the case of other types of conjugated alkenes such as substituted α,β-unsaturated esters and α,β-unsaturated ketones.



Scheme 3

Intramolecular Processes

From a synthetic point of view, because of its complete regiocontrol and broad structural scope, the intramolecular PK reaction of 1,6- and 1,7-enynes has been by far the most studied version of this process.[2] Thus, it is not surprising

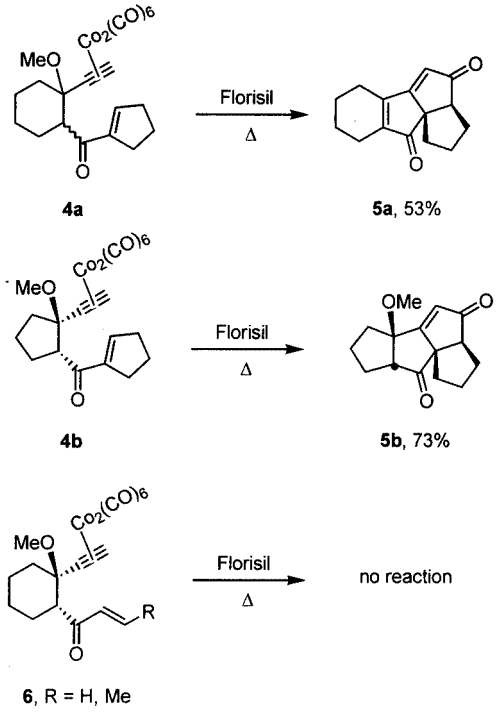


Scheme 1

that almost all the precedents regarding the use of electron-deficient alkenes in PK reactions fit into this category.

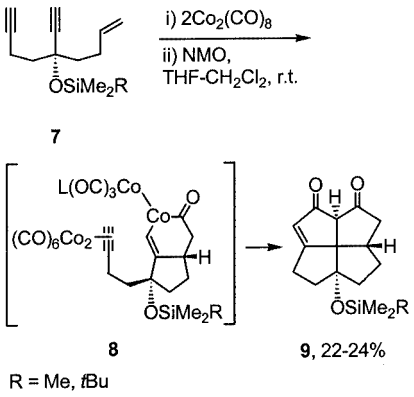
a) α,β-Unsaturated Enones

The first successful intramolecular PK reactions of electron-deficient alkenes were described in 1991 with certain conformationally restricted 1-en-6-yn-3-ones.[23] In particular, the dicobalt hexacarbonyl complex of the 1,6-enynes **4**, bearing a carbonyl group at position C-3 of the enyne framework, underwent an intramolecular PK reaction in the presence of Florisil as promoter of the process, affording the corresponding cyclopentenones in acceptable to good yields (Scheme 4). Interestingly, the tetracyclic adducts **5a** and **5b** possess the structural core of the natural products retigeranic acid[24] and crinipellin B,[25] respectively. However, the structurally related enones **6**, which in comparison with **4** are not disubstituted at C-2, failed to react under the same conditions. The authors ascribed this different outcome to the presumably more restricted conformational mobility of enones **4**, which would facilitate the coordination of the alkene to the cobalt atom. On the other hand, the absence of hydrogens at C-2 in enynes **4** makes the evolution of their dicobalt hexacarbonyl complexes by a β-hydrogen elimination pathway impossible.



Scheme 4

On the other hand, Keese et al. reported in their synthesis of [5.5.5.5]fenestranes some quite outstanding examples of intramolecular tandem PK reactions.[26] The readily available acyclic ene-diynes **7** reacted with two equivalents of dicobalt octacarbonyl in the presence of NMO to give the fenestrane products **9** in 22−24% yield. According to the authors,[26a] the second PK reaction takes place at the intermediate metallacycle **8** rather than on the fully decomplexed enone (Scheme 5).

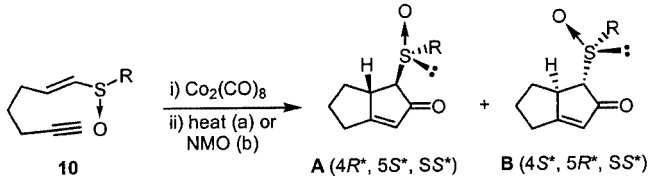


Scheme 5

b) α,β-Unsaturated Sulfoxides

Unlike the previous cases of intramolecular PK reactions, which involve substrates with constrained conformational mobility, our group has reported that simple 1,6-enynes bearing a sulfoxide group at C-1 are suitable substrates for PK cyclizations.[27] Thus, the dicobalt hexacarbonyl complexes of the readily available 1-sulfinyl-1-hepten-6-ynes **10** react under both thermal (CH_3CN, 80 °C) and *N*-oxide-promoted conditions (NMO, CH_2Cl_2, room temp.) to give the PK bicyclo[3.3.0]octenones **11** as the only characterizable products (Table 1). Although the yields after silica gel chromatography were moderate (46−55%), the presumed competitive 1,3-diene product could not be detected in any case.

Table 1. PK reaction of (±)-1-sulfinyl-1,6-enynes **10**



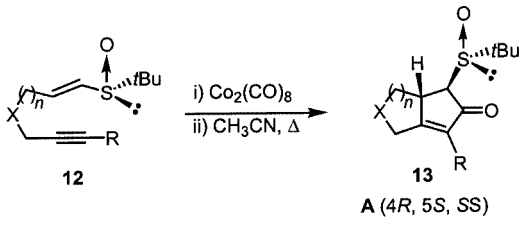
Entry	R	Enyne	Cond.[a]	Product	**A**:**B** ratio	Yield [%]
1	*p*Tol	**10a**	a	**11a**	75:25	52
2	*p*Tol	**10a**	b	**11a**	73:27	49
3	$pMe_2NC_6H_4$	**10b**	a	**11b**	71:29	55
4	*t*Bu	**10c**	a	**11c**	>98:<2	50
5	*t*Bu	**10c**	b	**11c**	>98:<2	46

[a] a: CH_3CN, 80 °C; b: NMO·H_2O (6 equiv.), CH_2Cl_2, room temp.

As our main goal was the development of an efficient version of the asymmetric PK reaction by using sulfoxides as chiral auxiliaries, the formation of a single diastereomer (isomer **A**) from the *tert*-butyl sulfoxide **10c** was quite promising (entries 4 and 5). The configurational assignment of the **A** adduct (4*R**,5*S**,S*S**) was unequivocally established by NMR spectroscopy and X-ray diffraction studies.[27] To establish the stereochemical generality of this pro-

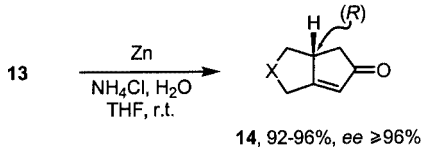
cess and its potential in asymmetric synthesis a variety of enantiopure (*S*)-*tert*-butylsulfinylated enynes **12** (*ee* > 96%), readily prepared by Wadsworth−Emmons olefination of the corresponding alkynyl aldehyde with (*R*)-diethyl *tert*-butylsulfinylmethylphosphonate,[27a] were treated under thermal PK reaction conditions (Table 2). Pleasingly, with all terminal alkynes the PK reaction (CH_3CN, 60−80 °C) took place again with complete diastereocontrol [exclusive formation of the (4*R*,5*S*,S*S*) adduct, entries 1−4]. Compared to the case of the unsubstituted 1,6-enyne **10c** (Table 1), the yields were somewhat higher in the case of the 4-substituted 1,6-enynes **12a−c** (60−65% yield), probably due to the entropically beneficial *gem*-dialkyl effect. The cyclization of the 1,7-enyne **12d** was also completely diastereoselective, but much less efficient (30% yield). Disappointingly, no reaction at all was observed in the case of the internal alkynes **12e,f** (entries 5 and 6). This lack of reactivity might be caused by the great steric hindrance resulting from the bulky substitution at both ends of the enyne.

Table 2. PK reaction of (*S*)-1-*tert*-butylsulfinylenynes **12**



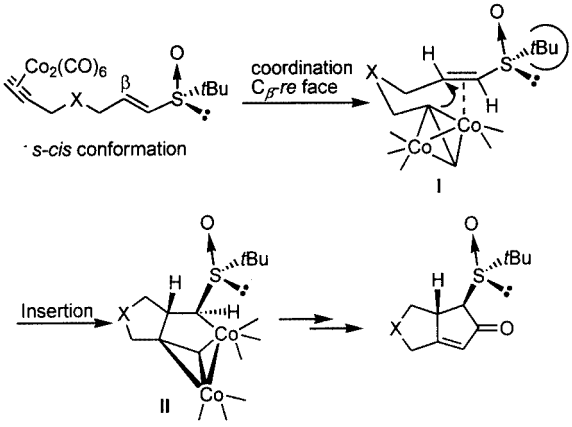
Entry	Enyne	X	n	R	Product	Yield [%]
1	**12a**	CMe_2	1	H	**13a**	65
2	**12b**	$C(CO_2Et)_2$	1	H	**13b**	60
3	**12c**	NBOC	1	H	**13c**	60
4	**12d**	$C(CO_2Et)_2$	2	H	**13d**	30
5	**12e**	CH_2	1	TMS	**13e**	–
6	**12f**	CMe_2	1	Ph	**13f**	–

As the final step of this sulfinyl-mediated asymmetric PK reaction, the reductive cleavage of the sulfoxide was accomplished in very high yields by treatment with activated zinc, affording the corresponding enantiopure (*R*)-bicyclo-[3.3.0]oct-1-en-3-ones **14**[28] (Scheme 6).



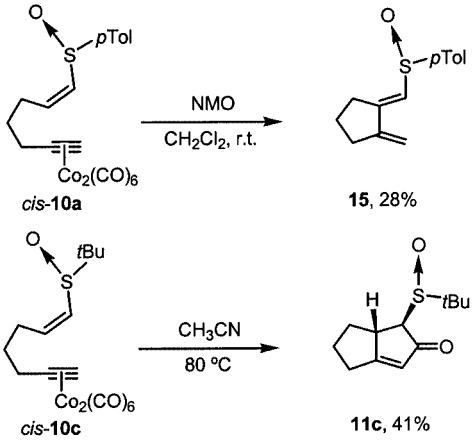
Scheme 6

A plausible explanation of the high diastereoselectivity observed in the PK reactions of 1-*tert*-butylsulfinyl enynes could rely on the conformational preferences around the C−S bond in the starting α,β-unsaturated sulfoxide,[29] as shown in Scheme 7. Thus, assuming that, as in other *trans* α,β-unsaturated sulfoxides, the *s-cis* conformation is the most stable (dihedral angle C=C−S−O of approximately 0°), complexation of the cobalt atom to the less-hindered side of the double bond (that opposite to the bulky *tert*-butyl group) would lead to the complex **I** which, by further *syn* C−Co insertion, would afford the key cobaltacycle intermediate **II**, in which the stereogenic carbons at positions C-4 and C-5 have been formed.



Scheme 7

A more striking result was observed in the case of the PK reactions of 1-sulfinyl-1,6-enynes of *cis* configuration. Unexpectedly, depending on the substitution at the sulfur atom, either the PK cyclopentenone **11c** (from the *tert*-butyl sulfoxide *cis*-**10c**) or the exocyclic 1,3-diene **15** (from the *p*-tolyl sulfoxide *cis*-**10a**) were obtained as the main products, albeit in low yields[27] (Scheme 8).

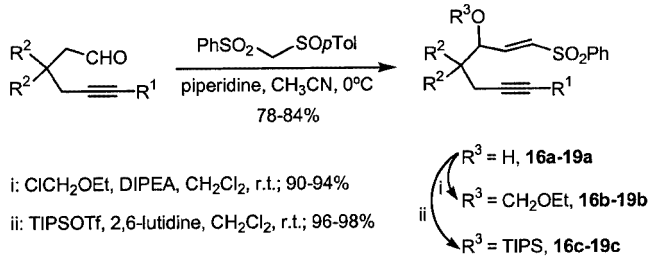


Scheme 8

c) α,β-Unsaturated Sulfones

In addition to the case of α,β-unsaturated sulfoxides, our group has reported that other types of sulfur-substituted electron-deficient alkenes are also excellent substrates in intramolecular PK reactions. 1-Phenylsulfonyl-3-oxygenated enynes provided particularly interesting results.[30] These compounds were prepared in one step by condensation of the corresponding alkynyl aldehyde with phenylsulfinyl phenylsulfonyl methane in the presence of piperidine[31] and

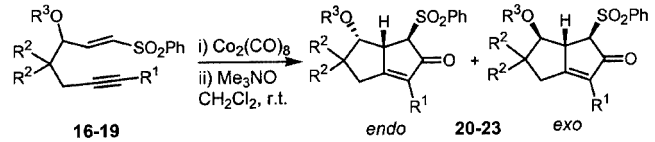
further protection of the hydroxyl group (compounds **16**−**19**, Scheme 9). Although the free alcohols (substrates **a**) proved to be in most cases hardly reactive under typical PK reaction conditions, the hydroxyl-protected derivatives such as the ethoxymethyl ketal (substrates **b**) and the TIPS derivative (substrates **c**) underwent a clean intramolecular PK reaction under both thermal and *N*-oxide-promoted conditions (Me_3NO as promoter), affording the corresponding bicyclo[3.3.0]octenones **20**−**23** in good yields (usually 70−80% yield after flash chromatography, Table 3). In no case was the competitive 1,3-diene product, resulting from an elimination process on the cobaltacyclic intermediate, detected in the crude reaction mixtures.



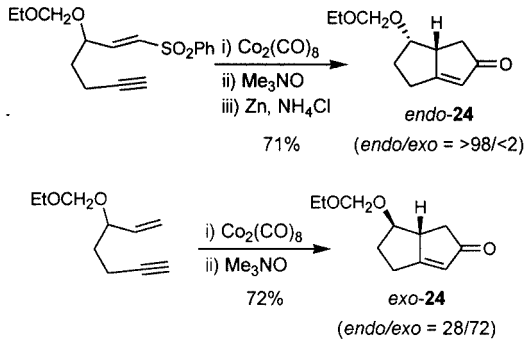
Scheme 9

Besides the high reactivity displayed by these 1-sulfonylated enynes in PK reactions, the most outstanding result was the stereochemical outcome of the cyclization. Unlike the usual selectivity of allylically substituted enynes in PK cyclizations, in which the allylic substituent ends up on the unhindered *exo* face of the bicyclic product,[32] the PK reactions of the 1-sulfonylated enynes **16**−**19** were *endo* selective in most cases (Table 3). Particularly high *endo* selectivities were observed in the case of enynes **16b**, **17b** and **19c** (entries 2, 4 and 9). As the sulfonyl group can subsequently be removed in quantitative yield by reductive cleavage of the C−S bond with zinc, this two-step sequence — intramolecular PK reaction and desulfonylation — constitutes an interesting stereocomplementary approach to the diastereoselective synthesis of C-6 substituted bicyclo[3.3.0]octenones. An example of the independent stereoselective access to each diastereoisomer of a C-6 substituted bicyclo[3.3.0]octenone (compound **24**) by PK reaction of either a 1,6-enyne or its 1-phenylsulfonyl derivative is depicted in Scheme 10.

Table 3. PK reaction of 3-oxygenated-1-phenylsulfonyl-1,6-enynes **16**−**19**

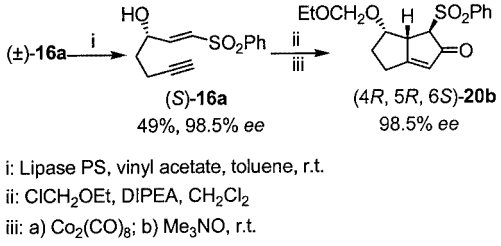


Entry	Enyne	R^1	R^2	R^3	Product	Yield [%]	*endo*/*exo*
1	**16a**	H	H	H	**20a**	–	–
2	**16b**	H	H	CH_2OEt	**20b**	76	>98/<2
3	**16c**	H	H	TIPS	**20c**	74	92/8
4	**17b**	Me	H	CH_2OEt	**21b**	77	93/7
5	**17c**	Me	H	TIPS	**21c**	73	91/9
6	**18b**	H	Me	CH_2OEt	**22b**	74	67/33
7	**18c**	H	Me	TIPS	**22c**	71	39/61
8	**19b**	Ph	Me	CH_2OEt	**23b**	79	87/13
9	**19c**	Ph	Me	TIPS	**23c**	78	94/6



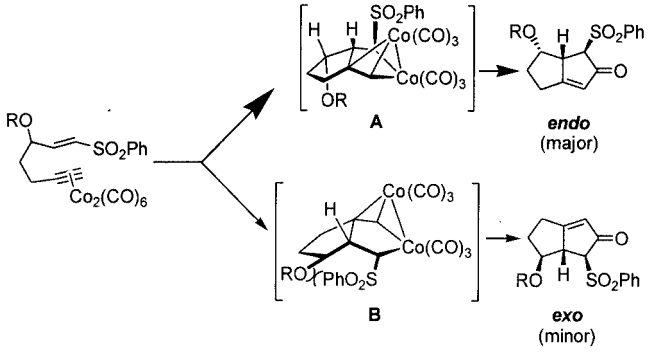
Scheme 10

Given its potential in asymmetric synthesis, it is also interesting to note that the starting 1-sulfonylenynes can readily be prepared in high enantiopurity by enantioselective lipase-mediated acetylation of the racemic starting alcohol.[33] An example is shown in Scheme 11.



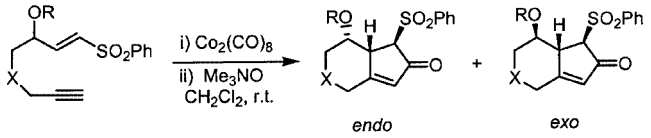
Scheme 11

In diastereoselective intramolecular PK reactions, the relative thermodynamic stability of the key diastereomeric *cis*-cobaltacyclic intermediates is usually considered to be the main factor controlling the stereochemical course of the reaction.[2,34] Thus, the major formation of the *endo* adduct in the case of the 1-sulfonylated-1,6-enynes can be rationalized by assuming that the *cis*-cobaltacycle **A** is more stable than its diastereomer **B**, probably because in **A** the allylic OR group and the bulky sulfone moiety are located on opposite faces of the cobaltacycle, whereas in **B** 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 **16**−**19** could also reinforce the *endo* selectivity of the cyclization.[30b]



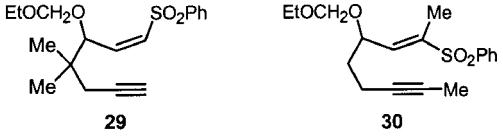
Scheme 12

Table 4. PK reaction of 3-oxygenated-1-phenylsulfonyl-1,7-enynes



Entry	Enyne	X	R	Product	Yield [%]	*endo*/*exo*
1	**25a**	CH_2	H	**27a**	49	59/41
2	**25b**	CH_2	CH_2OEt	**27b**	49	52/48
3	**25c**	CH_2	TIPS	**27c**	62	34/66
4[a]	**26a**	O	H	**28a**	14	79/21
5[a]	**26b**	O	CH_2OEt	**28b**	50	66/34
6	**26c**	O	TIPS	**28c**	50	58/42

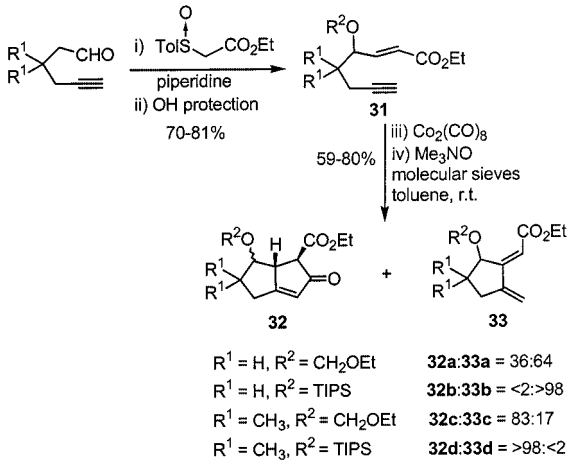
[a] $Me_3NO{\cdot}2H_2O$ + molecular sieves as promoter of the reaction.



In the exploration of the structural scope of the intramolecular PK reaction of α,β-unsaturated sulfones, the homologous 1-sulfonylated-1,7-enynes **25**−**26** were also studied (Table 4). These substrates afforded the corresponding bicyclo[4.3.0]nonenones **27**−**28**, although both the yield and the *endo*-selectivity of the cyclization were lower than in the case of the 1,6-enynes. Disappointingly, neither the sulfone of *cis*-configuration **29** nor the α-substituted vinylsulfone **30** were able to react under either thermal or *N*-oxide-promoted PK reaction conditions.

d) α,β-Unsaturated Esters and α,β-Unsaturated Nitriles

Taking into account the high reactivity exhibited by 1-sulfonyl-3-oxygenated-1,6-enynes in PK cyclizations, we extended the same study to the related α,β-unsaturated esters **31**. These compounds were readily prepared by piperidine-mediated condensation of 5-hexynal with ethyl *p*-tolylsulfinyl acetate (SPAC condensation[35]) and further OH protection. The cyclization of the dicobalt hexacarbonyl complexes of these substrates, under the same conditions previously employed in the case of the α,β-unsaturated sulfones and sulfoxides, furnished in good yields (59−80%) a mixture of the PK bicyclic product **32** and the exocyclic 1,3-diene **33** resulting from the competitive elimination pathway of the cobaltacyclic intermediate.[16] Interestingly, depending on the particular substitution at the enyne chain either the PK adduct (**32d**) or the 1,3-diene (**33b**) could be selectively obtained[36] (Scheme 13). The different behavior of enynes having an α,β-unsaturated ester (**31**), compared to the case of α,β-unsaturated sulfones (**16**−**19**) and sulfoxides (**10** and **12**), suggests that the thermodynamically very favorable π-conjugation between the C-C double bond and the ester moiety (but not so favorable in α,β-unsaturated sulfoxides or sulfones[37]) is a key factor in the formation of the conjugated 1,3-diene vs. the formation of the PK cyclopentenone.



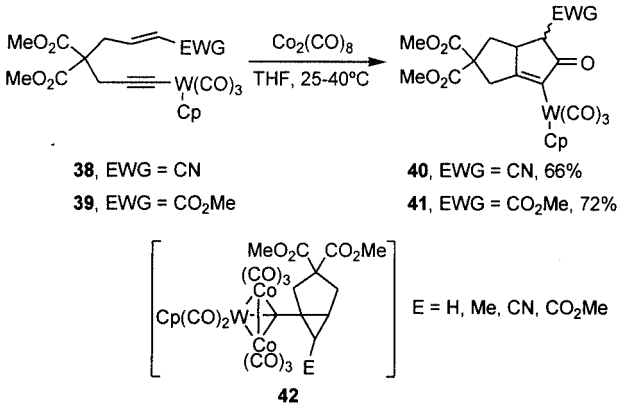
Scheme 13

Remarkable results have been reported with this kind of substrates by Hoye et al.[38] in the tungsten-mediated PK cyclizations of 1,6-enynes. In the presence of a stoichiometric amount of tungsten pentacarbonyl [$W(CO)_5{\cdot}THF$] a variety of 1,6-enynes, including substrates possessing a cyano or an ester function at the alkene terminus (compounds **34** and **35**), underwent the PK cyclization in THF at 65−110 °C to give the corresponding bicyclo[3.3.0]octenones as mixture of epimers at C-4 (compounds **36** and **37**, Scheme 14).

Scheme 14

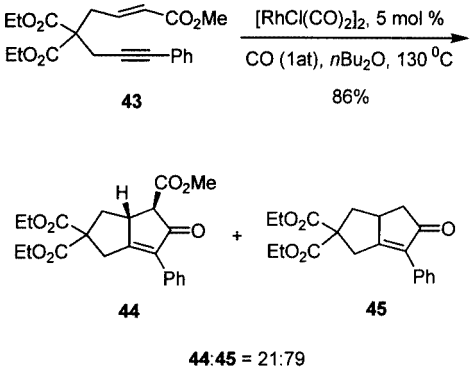
It has also been reported that the alkynyltungsten complexes of the α,β-unsaturated nitrile **38** and α,β-unsaturated ester **39** react with a stoichiometric amount of $Co_2(CO)_8$ under very mild conditions (THF, 25−40 °C) to afford the bicyclo[3.3.0]octenones **40** and **41** in satisfactory yields (66−72%) as mixtures of epimers at C-4.[14] According to the authors, the mechanistic course of this tungsten/cobalt-

mediated Pauson−Khand reaction would take place through the formation of the key bicyclic cyclopropane intermediate **42**, bearing a pendant mixed W−Co carbonyl complex as a substituent of the cyclopropane ring (Scheme 15). This intermediate has been isolated in certain cases (for instance E = H, Me) and it has been proved that it yields the bicyclo[3.3.0]octenone after heating in benzene at 60−80 °C.



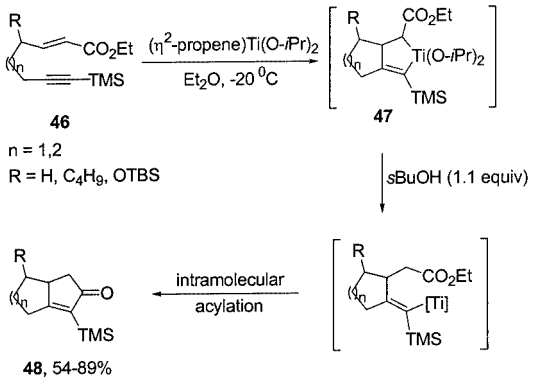
Scheme 15

Instead of cobalt-based complexes Narasaka et al. have recently reported that $[RhCl(CO)_2]_2$ is a suitable catalyst for the rhodium-mediated PK cyclization of a variety of alkyne substituted 1,6- and 1,7-enynes.[39] Among the tested substrates, the α,β-unsaturated ester **43** reacted in the presence of a catalytic amount of the rhodium catalyst under a CO atmosphere at 130 °C to afford a mixture of the cyclopentenone **44** and its demethoxycarbonylated derivative **45** in 86% overall yield (Scheme 16).



Scheme 16

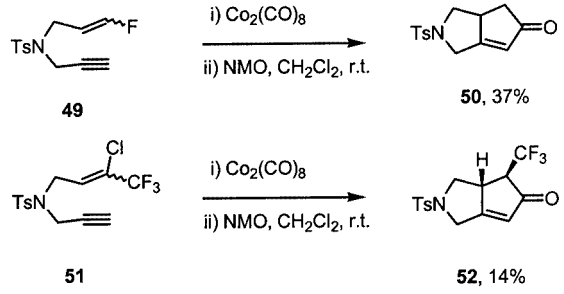
Through a different mechanistic pathway, 1,6- and 1,7-enynes with an ester group at the alkene terminus have also been used in low-valent titanium-promoted cyclizations. Sato et al. have reported that the cyclization of enynes **46** in the presence of a stoichiometric amount of $[Ti(OiPr)_2(\eta^2$-propene)] gives the intermediate titanacycle **47** which, by an in situ selective protonation (1.1 equiv. of *s*BuOH) and intramolecular acylation of the resulting alkenyltitanium intermediate, furnishes the cyclopentenones **48** in satisfactory yields[40] (54−89%, Scheme 17).



Scheme 17

e) Other Electron-Deficient Alkenes in PK Reactions

Considering electron-deficient alkenes that contain atoms with strong inductive effects, it has been reported that fluorine-containing 1,6-enynes are able to undergo the PK reaction in low to moderate yields.[41] For instance, the dicobalt hexacarbonyl complex of the fluoroalkene **49** reacted in the presence of NMO (CH_2Cl_2, room temp.) to afford the defluorinated cyclopentenone **50** in 37% yield. Under the same conditions the trifluoromethyl-substituted alkene **51** gave the cyclopentenone **52** in 14% yield (Scheme 18).



Scheme 18

Summary and Outlook

Since the pioneering work of Pauson and Khand it was widely accepted that alkenes substituted with electron-withdrawing groups were not suitable substrates in PK reactions due to their presumed low reactivity and high tendency to evolve by a competitive elimination process, which leads to 1,3-dienes instead of cyclopentenones. However, in recent years several reports show that this general assumption is far from being exact. To date a number of examples of intermolecular and, especially, intramolecular PK reactions of alkenes bearing an electron-withdrawing substituent, such as carbonyl, ester, nitrile, sulfoxide and sulfone, have been reported. In particular, the wide structural scope of the intramolecular PK reaction of the enantiopure sulfur-based substituted enynes 1-*tert*-butylsulfinyl-1,6-enynes and 1-phenylsulfonyl-3-oxygenated-1,6-enynes makes this pro-

cedure very interesting in asymmetric synthesis. In addition, compared to the cobalt-mediated PK reaction, several results suggest that tungsten and rhodium carbonyl complexes are less sensitive to the electronic properties of the alkene partner in intramolecular PK-like reactions.

The extension of this study to other types of electron-deficient olefins, as well as the clarification of the electronic and structural factors involved in the competition between 1,3-diene formation and the PK reaction, is under research in our group.

Acknowledgments

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[1] [1a] I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, *J. Chem. Soc., Chem. Commun.* **1971**, 36. [1b] I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, M. I. Foreman, *J. Chem. Soc., Perkin Trans. 1* **1973**, 977−981.

[2] For reviews on the Pauson−Khand reaction, see: [2a] P. L. Pauson, *Tetrahedron* **1985**, *41*, 5855−5860. [2b] N. E. Schore, *Chem. Rev.* **1988**, *88*, 1081−1119. [2c] N. E. Schore, *Org. React.* **1991**, *40*, 1−90. [2d] N. E. Schore, in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, Vol. 5, p. 1037−1064.[2e] N. E. Schore, in *Comprehensive Organometallic Chemistry II* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson, L. Hegedus), Pergamon Press, Oxford, **1995**, Vol. 12, p. 703−739.[2f]S. T. Ingate, J. Marco-Contelles, *Org. Prep. Proc. Int.* **1998**, *30*, 121−143. [2g] O. Geis, H.-G. Schmalz, *Angew. Chem.* **1998**, *110*, 955−958; *Angew. Chem. Int. Ed.* **1998**, *37*, 911−914. [2h] N. Jeong, in *Transition Metals for Organic Synthesis* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, p. 560−577.[2i]Y. K. Chung, *Coord. Chem. Rev.* **1999**, *188*, 297−341. [2j] A. J. Fletcher, S. D. R. Christie, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1657−1668. [2k] K. M. Brummond, J. L. Kent, *Tetrahedron* **2000**, *56*, 3263−3283. [2l] T. Sugihara, M. Yamaguchi, M. Nishizawa, *Chem. Eur. J.* **2001**, *7*, 3315−3318.

[3] Silica gel and zeolites: [3a] W. A. Smit, A. S. Gybin, A. S. Shaskov, Y. T. Strychkov, L. G. Kyzmina, R. Caple, E. D. Swanson, *Tetrahedron Lett.* **1986**, *27*, 1241−1245. [3b] W. A. Smit, S. L. Kireev, O. M. Nefedov, V. A. Tarasov, *Tetrahedron Lett.* **1989**, *30*, 4021−4024. Amine *N*-oxides: [3c] S. Shambayati, W. E. Crowe, S. L. Schreiber, *Tetrahedron Lett.* **1990**, *31*, 5289−5292. [3d] N. Jeong, Y. K. Chung, B. Y. Lee, S. E. Yoo, *Synlett* **1991**, 204−207. Molecular sieves and amine *N*-oxides: [3e] L. Pérez-Serrano, L. Casarrubios, G. Domínguez, J. Pérez-Castells, *Org. Lett.* **1999**, *1*, 1187−1188. [3f] L. Pérez-Serrano, J. Blanco-Urgoiti, L. Casarrubios, G. Domínguez, J. Pérez-Castells, *J. Org. Chem.* **2000**, *65*, 3513−3519. Sulfoxides and sulfides: [3g] A. Stumpf, N. Jeong, H. Sunghee, *Synlett* **1997**, 205−207. [3h] Y. K. Chung, B. Y. Lee, N. Jeong, M. Hudecek, P. L. Pauson, *Organometallics* **1993**, *12*, 220−223. [3i] T. Sugihara, M. Yamada, M. Yamaguchi, M. Nishizawa, *Synlett* **1999**, 771−773. Amines: [3j] T. Sugihara, M. Yamada, H. Ban, M. Yamaguchi, C. Kaneko, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2801−2804. [3k] T. Rajesh, M. Periasamy, *Tetrahedron Lett.* **1998**, *39*, 117−118. [3l] M. E. Krafft, L. V. R. Boñaga, C. Hirosawa, *J. Org. Chem.* **2001**, *66*, 3004−3020. Ethers and water: [3m] T. Sugihara, M. Yamaguchi, *Synlett* **1998**, 1384−1386.

[4] For recent references on asymmetric PK reactions see: [4a] K. Hiroi, T. Watanabe, R. Kabagishi, I. Abe, *Tetrahedron Lett.* **2000**, *41*, 891−895. [4b] K. Hiroi, T. Watanabe, R. Kabagishi, I. Abe, *Tetrahedron: Asymmetry* **2000**, *11*, 797−808. [4c] A. J. Fletcher, D. T. Rutherford, S. D. R. Christie, *Synlett* **2000**, 1040−1042. [4d] W. J. Kerr, D. M. Lindsay, E. M. Rankin, J. S. Scott, S. P. Watson, *Tetrahedron Lett.* **2000**, *41*, 3229−3233. [4e] J. Castro, A. Moyano, M. A. Pericàs, A. Riera, A. Álvarez-Larena, J. F. Piniella, *J. Am. Chem. Soc.* **2000**, *122*, 7944−7952. [4f] I. Marchueta, E. Montenegro, D. Panov, M. Poch, X. Verdaguer, A. Moyano, M. A. Pericàs, A. Riera, *J. Org. Chem.* **2001**, *66*, 6400−6409. [4g] S. J. Sturla, S. L. Buchwald, *J. Org. Chem.* **2000**, *67*, 3398−3403.

[5] For recent references on catalytic PK reactions see: [5a] S.-W. Kim, S. U. Son, S. I. Lee, T. Hyeon, Y. K. Chung, *J. Am. Chem. Soc.* **2000**, *122*, 1550−1551. [5b] M. Hayashi, Y. Hashimoto, Y. Yamamoto, J. Usuki, K. Saigo, *Angew. Chem. Int. Ed.* **2000**, *39*, 631−633. [5c] N. Jeong, S. H. Hwang, *Angew. Chem. Int. Ed.* **2000**, *39*, 636−638. [5d] S.-W. Kim, S. U. Son, S. S. Lee, T. Hyeon, Y. K. Chung, *Chem. Commun.* **2001**, 2212−2213. [5e] A. C. Comely, S. E. Gibson, A. Stevenazzi, N. J. Hales, *Tetrahedron Lett.* **2001**, *42*, 1183−1185. [5f] S. U. Son, S. I. Lee, T. Hyeon, Y. K. Chung, S.-W. Kim, T. Hyeon, *Org. Lett.* **2002**, *4*, 277−279. [5g] T. Shibata, N. Toshida, K. Takagi, *Org. Lett.* **2002**, *4*, 1619−1621. [5h] T. Morimoto, K. Fuji, K. Tsutsumi, K. Kakiuchi, *J. Am. Chem. Soc.* **2002**, *124*, 3806−3807.

[6] See for instance: [6a] S. C. Berk, R. B. Grossman, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 8593−8601. [6b] F. A. Hicks, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 7026−7033.

[7] See for instance: L. Jordi, A. Segundo, F. Camps, S. Ricart, J. M. Moretó, *Organometallics* **1993**, *12*, 3795−3797.

[8] See for instance: [8a] A. J. Pearson, R. A. Dubbert, *J. Chem. Soc., Chem. Commun.* **1991**, 202−203. [8b] A. J. Pearson, R. A. Dubbert, *Organometallics* **1994**, *13*, 1656−1661.

[9] See for instance: [9a] K. Tamao, K. Kobayashi, Y. Ito, *Synlett* **1992**, 539−546. [9b] L. Pages, A. Llebaria, F. Camps, E. Molins, C. Miravitlles, J. M. Moretó, *J. Am. Chem. Soc.* **1992**, *114*, 10449−10461. [9c] M. Zhang, S. L. Buchwald, *J. Org. Chem.* **1996**, *61*, 4498−4499.

[10] See for instance: [10a] E. Negishi, S. J. Holmes, J. M. Tour, J. A. Miller, F. E. Cederbaum, D. R. Swanson, T. Takahashi, *J. Am. Chem. Soc.* **1989**, *111*, 3336−3346. [10b] E.-I. Negishi, in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, Vol. 5, p. 1163−1188.

[11] See for instance: [11a] C. Mukai, M. Uchiyama, M. Hanaoka, *J. Chem. Soc., Chem. Commun.* **1992**, 1014−1015. [11b] N. Jeong, S. J. Lee, B. Y. Lee, Y. K. Chung, *Tetrahedron Lett.* **1993**, *34*, 4027−4030.

[12] See for instance: [12a] T. Kondo, N. Suzuki, T. Okada, T.-A. Mitsudo, *J. Am. Chem. Soc.* **1997**, *119*, 6187−6188. [12b] T. Morimoto, N. Chatani, Y. Fukumoto, S. Murai, *J. Org. Chem.* **1997**, *62*, 3762−3765.

[13] See for instance: [13a] Y. Koga, T. Kobayashi, K. Narasaka, *Chem. Lett.* **1998**, 249−250. N. Jeong, S. Lee, B. K. Sung, *Organometallics* **1998**, *17*, 3642−3644.[13b] N. Jeong, B. K. Sung, Y. K. Choi, *J. Am. Chem. Soc.* **2000**, *122*, 6771−6772. [13c] P. A. Evans, J. E. Robinson, *J. Am. Chem. Soc.* **2001**, *123*, 4609−4610.

[14] See for instance: Y.-T. Shiu, R. J. Madhushaw, W.-T. Li, Y.-C. Lin, G.-H. Lee, S.-M. Peng, F. L. Liao, S.-L. Wang, R. S. Liu, *J. Am. Chem. Soc.* **1999**, *121*, 4066−4067. See also ref.[38].

[15] Relevant examples of functionalized alkynes in PK reactions. Alkynyl sulfoxides: [15a] E. Montenegro, A. Moyano, M. A. Pericàs, A. Riera, A. Álvarez-Larena, J.-F. Piniella, *Tetrahedron: Asymmetry* **1999**, *10*, 457−471. Alkynyl metalcarbenes: [15b] L. Jordi, S. Ricart, J. M. Viñas, J. M. Moretó, *Organometallics* **1997**, *16*, 2808−2818. [15c] J. Pares, J. M. Moretó, S. Ricart, J. Barluenga, F. J. Fañanás, *J. Organomet. Chem.* **1999**, *586*, 247−253. Alkynyl ethers: [15d] M. Poch, E. Valentí, A. Moyano, M. A. Pericàs, J. Castro, A. De Nicola, A. E. Greene, *Tetrahedron Lett.* **1990**, *31*, 7505−7508. [15e] X. Verdaguer, A. Moyano, M. A. Pericàs, A. Riera, V. Bernardes, A. E. Greene, A. Álvarez-Larena, J. F. Piniella, *J. Am. Chem. Soc.* **1994**, *116*, 2153−2154. [15f] X. Verdaguer, J. Vázquez, G. Fuster, V. Bernardes-Génisson, A. E. Greene, A. Moyano, M. A. Pericàs, A. Riera, *J. Org. Chem.* **1998**, *63*, 7037−7052. Nitrogen substituted alkynes: [15g] B. Witulski, M. Gößmann, *Chem. Commun.* **1999**, 1879−1880. Alkynyl thioethers: [15h] E. Montenegro, M. Poch, A. Moyano, M. A. Pericàs,

A. Riera, *Tetrahedron Lett.* **1998**, *39*, 335−338. [15i] B. L. Pagenkopf, D. B. Belanger, D. R. R. O'Mahony, T. Livinghouse, *Synthesis* **2000**, 1009−1019. [15j] See also ref. 4f. Propargylic acid derivatives: [15k]M. E. Krafft, R. H. Romero, I. L. Scott, *J. Org. Chem.* **1992**, *57*, 5277−5278. [15l] S. Fonquerna, A. Moyano, M. A. Pericàs, A. Riera, *J. Am. Chem. Soc.* **1997**, *119*, 10225−10226. [15m] S. Fonquerna, R. Rios, A. Moyano, M. A. Pericàs, A. Riera, *Eur. J. Org. Chem.* **1999**, 3459−3478. [15n] K. Hiroi, T. Watanabe, *Tetrahedron Lett.* **2000**, *41*, 3935−3939. [15o] R. Rios, A. Moyano, M. A. Pericàs, *Tetrahedron Lett.* **2002**, *43*, 1023−1026. Alkynyl ketals: [15p] A. Stolle, H. Becker, J. Salaün, A. de Meijere, *Tetrahedron Lett.* **1994**, *35*, 3521−3524.

[16] [16a] I. U. Khand, P. L. Pauson, *J. Chem. Soc., Chem. Commun.* **1974**, 379. [16b] I. U. Khand, P. L. Pauson, *Heterocycles* **1978**, *11*, 59−67. For an alternative mechanism to the formation of the 1,3-diene product, see: [16c] M. E. Krafft, A. M. Wilson, O. A. Dasse, L. V. R. Bonaga, Y. Y. Cheung, Z. Fu, B. Shao, I. L. Scott, *Tetrahedron Lett.* **1998**, *39*, 5911−5914.

[17] See for instance: [17a] M. E. Krafft, C. A. Juliano, I. L. Scott, C. Wright, M. D. McEachin, *J. Am. Chem. Soc.* **1991**, *113*, 1693−1703. [17b] N. Jeong, S. Yoo, S. J. Lee, S. H. Lee, Y. K. Chung, *Tetrahedron Lett.* **1991**, *32*, 2137−2140. [17c] M. Ishizaki, K. Iwahara, Y. Niimi, H. Satoh, O. Hoshino, *Tetrahedron* **2001**, *57*, 2729−2738.

[18] [18a] J. Castro, H. Sörensen, A. Riera, C. Morin, A. Moyano, M. A. Pericàs, A. E. Greene, *J. Am. Chem. Soc.* **1990**, *112*, 9388−9389. [18b] J. Castro, A. Moyano, M. A. Pericàs, A. Riera, A. E. Greene, *Tetrahedron: Asymmetry* **1994**, *5*, 307−310. [18c] W. J. Kerr, M. McLaughlin, P. L. Pauson, S. M. Robertson, *J. Organomet. Chem.* **2001**, *630*, 104−117.

[19] See for instance: [19a] M. Ahmar, O. Chabanis, J. Gauthier, B. Cazes, *Tetrahedron Lett.* **1997**, *38*, 5277−5280. [19b] M. Ahmar, C. Locatelli, D. Colombier, B. Cazes, *Tetrahedron Lett.* **1997**, *38*, 5281−5284. [19c] K. M. Brummond, H. Wan, J. L. Kent, *J. Org. Chem.* **1998**, *63*, 6535−6545.

[20] Recent references: [20a] H. Corlay, E. Fouquet, E. Magnier, W. B. Motherwell, *Chem. Commun.* **1999**, 183−184. [20b] H. Nüske, S. Bräse, A. de Meijere, *Synlett* **2000**, 1467−1469. [20c] B. Witulski, M. Gossmann, *Synlett* **2000**, 1793−1797. [20d] I. Marchueta, X. Verdaguer, A. Moyano, M. A. Pericàs, A. Riera, *Org. Lett.* **2001**, *3*, 3193−3196.

[21] M. Costa, A. Mor, *Tetrahedron Lett.* **1995**, *36*, 2867−2870.

[22] M. Ahmar, F. Antras, B. Cazes, *Tetrahedron Lett.* **1999**, *40*, 5503−5506.

[23] [23a] A. L. Veretenov, W. A. Smit, L. G. Vorontsova, M. G. Kurella, R. Caple, A. S. Gybin, *Tetrahedron Lett.* **1991**, *32*, 2109−2112. [23b] A. S. Gybin, W. A. Smit, R. Caple, A. L. Veretenov, A. S. Shashkov, L. G. Vorontsova, M. G. Kurella, V. S. Chertkov, A. A. Carapetyan, A. Y. Kosnikov, M. S. Alexanyan, S. V. Lindeman, V. N. Panov, A. V. Maleev, Y. T. Struchkov, S. M. Sharpe, *J. Am. Chem. Soc.* **1992**, *114*, 5555−5566.

[24] E. J. Corey, M. C. Desai, T. A. Engler, *J. Am. Chem. Soc.* **1985**, *107*, 4339−4341.

[25] G. Mehta, K. S. Rao, M. S. Reddy, *J. Chem. Soc., Perkin Trans. 1* **1991**, 693−700.

[26] [26a] M. Thommen, A. L. Veretenov, R. Guidetti-Grept, R. Keese, *Helv. Chim. Acta* **1996**, *79*, 461−476. [26b] M. Thommen, R. Keese, *Synlett* **1997**, 231−240. See also: [26c] S. U. Son, A.-J. Paik, S. I. Lee, Y. K. Chung, *J. Chem. Soc., Perkin Trans. 1* **2000**, 141−143. [26d] S. U. Son, Y. A. Yoon, D. S. Choi, J. K. Park, B. M. Kim, Y. K. Chung, *Org. Lett.* **2001**, *3*, 1065−1067.

[27] [27a] J. C. Carretero, J. Adrio, *J. Am. Chem. Soc.* **1999**, *121*, 7411−7412. [27b] J. C. Carretero, J. Adrio, *Synthesis* **2001**, 1888−1896.

[28] D. H. Hua, *J. Am. Chem. Soc.* **1986**, *108*, 3836−3837.

[29] For conformational aspects in α,β-unsaturated sulfoxides, see: [29a] S. D. Kahn, W. J. Hehre, *J. Am. Chem. Soc.* **1986**, *108*, 7399−7400. [29b] Y. Arai, H. Takayama, T. Koizumi, *Tetrahedron Lett.* **1987**, *28*, 3689−3692. [29c] L. F. Tietze, A. Schuffenhauer, P. R. Schreiner, *J. Am. Chem. Soc.* **1998**, *120*, 7952−7958.

[30] [30a] J. Adrio, M. Rodríguez Rivero, J. C. Carretero, *Angew. Chem. Int. Ed.* **2000**, *39*, 2906−2909. [30b] J. Adrio, M. Rodríguez Rivero, J. C. Carretero, *Chem. Eur. J.* **2001**, *7*, 2435−2448.

[31] [31a] E. Domínguez, J. C. Carretero, *Tetrahedron* **1990**, *46*, 7197−7206. [31b] B. M. Trost, T. A. Grese, *J. Org. Chem.* **1991**, *56*, 3189−3192.

[32] For examples of *exo* selectivity in PK reactions of enynes substituted at allylic or propargylic positions, see: [32a] P. Magnus, L. M. Principe, M. J. Slater, *J. Org. Chem.* **1987**, *52*, 1483−1486. [32b] P. Magnus, D. P. Becker, *J. Am. Chem. Soc.* **1987**, *109*, 7495−7498. [32c] W. R. Roush, J. C. Park, *Tetrahedron Lett.* **1991**, *32*, 6285−6288. [32d] S. Yoo, S. H. Lee, N. Jeong, I. Cho, *Tetrahedron Lett.* **1993**, *34*, 3435−3438. [32e] N. Jeong, B. Y. Lee, S. M. Lee, Y. K. Chung, S.-G. Lee, *Tetrahedron Lett.* **1993**, *34*, 4023−4026. [32f] N. Jeong, S. H. Hwang, Y. Lee, Y. K. Chung, *J. Am. Chem. Soc.* **1994**, *116*, 3159−3160. [32g] C. Mukai, M. Uchiyama, S. Sakamoto, M. Hanaoka, *Tetrahedron Lett.* **1995**, *36*, 5761−5764. [32h] C. Mukai, J. S. Kim, M. Uchiyama, S. Sakamoto, M. Hanaoka, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2903−2916. [32i] C. Mukai, H. Sonobe, J. S. Kim, M. Hanaoka, *J. Org. Chem.* **2000**, *65*, 6654−6659. [32j] See also ref. 3 h and 17b.

[33] For lipase-mediated resolution of γ-hydroxy-α,β-unsaturated sulfones, see: E. Domínguez, J. C. Carretero, *J. Org. Chem.* **1992**, *57*, 3867−3873.

[34] For discussions on cobaltacycles stability, see for instance: [34a] P. Magnus, L. M. Principe, *Tetrahedron Lett.* **1985**, *26*, 4851−4854. [34b] J. Castro, A. Moyano, M. A. Pericàs, A. Riera, *Tetrahedron* **1995**, *51*, 6541−6556. [34c] P. M. Breczinski, A. Stumpf, H. Hope, M. E. Krafft, J. A. Casalnuovo, N. E. Schore, *Tetrahedron* **1999**, *55*, 6797−6812. [34d] See also ref. 32a and 32b. For recent theoretical studies on Pauson−Khand reactions, see: [34e]M. Yamanaka, E. Nakamura, *J. Am. Chem. Soc.* **2001**, *123*, 1703−1708. [34f] T. J. M. de Bruin, A. Milet, F. Robert, Y. Gimbert, A. E. Greene, *J. Am. Chem. Soc.* **2001**, *123*, 7184−7185.

[35] J. Nokami, A. Nishimura, M. Sunami, S. Wakabayashi, *Tetrahedron Lett.* **1987**, *28*, 649−650 (and references therein).

[36] M. Rodríguez Rivero, J. C. Carretero, unpublished results.

[37] α,β-Unsaturated sulfones tend to be thermodynamically less stable than β,γ-unsaturated sulfones. See for example: [37a] J. Hine, M. J. Skoglund, *J. Org. Chem.* **1982**, *47*, 4766−4770. [37b] N. S. Simpkins, in *Sulphones in Organic Synthesis* (Eds.: J. E. Baldwin, P. D. Magnus), Pergamon, Oxford, **1993**, p. 39 (and references therein).

[38] T. R. Hoye, J. A. Suriano, *J. Am. Chem. Soc.* **1993**, *115*, 1154−1156.

[39] T. Kobayashi, Y. Koga, K. Narasaka, *J. Organomet. Chem.* **2001**, *624*, 73−87.

[40] H. Urabe, K. Suzuki, F. Sato, *J. Am. Chem. Soc.* **1997**, *119*, 10014−10027.

[41] M. Ishizaki, D. Suzuki, O. Hoshino, *J. Fluorine Chem.* **2001**, *111*, 81−90.

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