The *tert*-Butylsulfinyl Group as a Highly Efficient Chiral Auxiliary in Asymmetric Pauson−Khand Reactions

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The stoichiometric reaction of an alkene and an alkyne−dicobalt hexacarbonyl complex, known as the Pauson−Khand (PK) reaction, has become one of the most powerful methods for cyclopentenone synthesis.[1] Furthermore, the recent developments of new reaction conditions and catalytic versions of this reaction are even increasing its synthetic utility.[2] Regarding the synthesis of optically active cyclopentenones by asymmetric PK reactions, three different approaches have been envisaged: (a) the use of a chiral auxiliary covalently attached either to the alkyne[3] or to the alkene component,[4] (b) the generation of a chiral C_2Co_2 core,[5] and (c) the addition of a chiral promoter (a chiral amine oxide).[6] Up till now, the first approach, mainly developed by Pericàs et al.,[3,4] has led to the best results, especially when the chiral auxiliary is bound to the alkyne.[3] Although the sulfinyl group has been widely used as a chiral auxiliary in important reactions such as Diels−Alder reactions or nucleophile additions,[7] it has been scarcely applied in transition-metal-catalyzed reactions.[8] In particular, we have recently reported the first examples of vinyl sulfoxides in asymmetric Heck reactions.[9] Extending its use to other cornerstone metal-mediated reactions, here we report that appropriately substituted sulfinylated enynes undergo intramolecular PK reactions with exceptionally high stereoselectivities.[10]

First, to check the viability of the intramolecular PK reaction of α,β-unsaturated sulfoxides, a series of differently substituted racemic trans 1-sulfinylhept-1-en-6-ynes was prepared[11] (substrates **1**−**3**). It is well-documented that alkenes substituted with electron-withdrawing groups are unsuitable substrates in PK reactions, because after the olefin insertion step the mechanism evolves by β-H elimination rather than by carbonyl insertion, leading to conjugated dienes instead of cyclopentenones.[12] Against these precedents, the enyne dicobalt complexes of **1**−**3**, readily formed by treatment of **1**−**3** with $Co_2(CO)_8$ in CH_2Cl_2 at room temperature, reacted under the usual thermal (CH_3CN, 80 °C) or amine *N*-oxide promoted conditions [6 equiv of *N*-methylmorpholine *N*-oxide (NMO), CH_2Cl_2, room temperature] to give the PK diastereomeric aducts **A** and **B**[13] in reasonable yields (46−55%, Table 1) as the only isolated products after flash chromatography. However, the most interesting outcome concerns the dependence of the stereoselectivity with the substitution at sulfur: although the cyclizations of both the *p*-tolylsulfoxide **1** and the potentially chelating *o*-dimethylaminophenylsulfoxide[9,14] **2** were moderately stereoselective, leading to a 3:1 mixture of **A** and **B** isomers (compounds **4** and **5**, entries 1−3), *the PK reaction of the tert*-butyl sulfoxide ***3*** *occurred with very high stereocontrol affording a crude mixture in which the* ***B*** *isomer could not be detected by* ^{1}*H NMR (A:B ratio >98:<2, entries 4−5).*

To apply this procedure in asymmetric synthesis, a variety of (*S*)-*tert*-butylsulfinylated enynes (ee ≥96% by NMR)[15] were prepared by olefination of the corresponding alkynyl aldehyde with *(R)*-diethyl *tert*-butylsulfinylmethylphosphonate (**7**, ee 98.5% by HPLC).[15] In Table 2 are summarized the results of the thermal PK reactions of the major trans enynes *(S)*-**8**−**13**.

Remarkably, with all the terminal alkynes (entries 1−5) the reactions took place again with complete stereoselectivity, providing the corresponding **A** adduct (**6A** and **14A**−**17A**)[13] as the only isolated isomer (**A:B** ratio >98:<2). Furthermore, the optical purity of the adducts (ee ≥96% by NMR)[16] was as high as the starting enynes, proving that the PK reactions occurred without racemization at sulfur.[10] Concerning the synthetic scope of the method, the yields were somewhat higher in the case of the 4,4-disubstituted 1,6-enynes **8** and **9** (65% and 60%, entries 2 and 3, respectively) than in the unsubstituted case **3** (50%, entry 1) likely due to the beneficial *gem*-dialkyl effect. Interestingly, the procedure can also be applied to the synthesis of azabicyclo[3.3.0]-octenones as is shown by the reaction of the aza-enyne **10** (60%,

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(2) See, for instance: (a) Belanger, D. B.; O'Mahony, D. J. R.; Livinghouse *Tetrahedron Lett.* **1998**, *39*, 7637 (and 7641). (b) Sugihara, T.; Yamaguchi, M. *Synlett* **1998**, 1384. (c) Sugihara, T.; Yamaguchi, M. *J. Am. Chem. Soc.* **1998,** *120,* 10782 and references therein.

(3) Complete asymmetric inductions have been reported in the PK reaction of alkynoyl derivatives of Oppolzer's sultam with norbornadiene, see: Fonquerna, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Am. Chem. Soc.* **1997**, *119*, 10225. See, also: Verdaguer, X.; Vázquez, J.; Fuster, G.; Bernardes-Génisson, V.; Greene, A. E.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1998**, *63*, 7037 and references therein.

(4) (a) The best diastereoselectivities (up to 10:1 isomer ratio) have been reported from alkenyl ethers derived from optically pure *trans*-2-phenylcyclohexanol, see: Castro, J.; Sörensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388. See, also: (b) Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A.; Greene, A. E.; Piniella, J. F.; Alvarez-Larena, A. *J. Organomet. Chem.* **1992**, *433*, 305. (c) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A.; Greene, A. E.; Alvarez-Larena, A.; Piniella, J. *F J. Org. Chem.* **1996**, *61*, 9016.

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(7) For a review, see: Carreño, C. *Chem. Rev.* **1995**, *95*, 1717.

(8) For sulfoxides as chiral auxiliaries in transition-metal-catalyzed reactions, see: (a) Paley, R. S.; Rubio, M. B.; Fernández de la Pradilla, R.; Dorado, R.; Hundal, G.; Martínez-Ripoll, M. *Organometallics* **1996**, *15*, 4672. (b) Villar, J. M.; Delgado, A.; Llebaria, A.; Moretó, J. M. *Tetrahedron*: *Asymmetry* **1995**, *6*, 665. (c) Hiroi, K.; Arinaga, Y. *Tetrahedron Lett.* **1994**, *35*, 153. (d) Chaigne, F.; Gotteland, J.-P.; Malacria, M. *Tetrahedron Lett.* **1989**, *30*, 1989. For a recent report on the use of sulfoxides as chiral ligands, see: Hiroi, K.; Suzuki, Y.; Kawagishi, R. *Tetrahedron Lett.* **1999**, *40*, 715 and references therein.

(9) Díaz Buezo, N.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc*. **1998**, *120*, 7129.

(10) During the editorial review process several examples of intermolecular PK reactions of optically pure alkynyl *p*-tolyl sulfoxides have been published: Montenegro, E.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J.-F. *Tetrahedron: Asymmetry* **1999**, *10*, 457.

(11) Racemic trans enynes **1**−**3** were readily prepared from 5-hexynal by either Wadsworth−Emmons olefination with a (±)-sulfinylmethyl phosphonate or by condensation with the anion of a (±)-aryl methyl sulfoxide and further dehydratation (MsCl, Et_3N; then DBU). Both methods afforded cis + trans mixtures of olefins (the trans α,β-sulfoxide as the major one) which were easily separated by flash chromatography. Similarly, *(R)*-**1** was prepared from the readily available *(R)*-methyl *p*-tolyl sulfoxide (Solladié, G.; Hunt, J.; Girardin, A. *Synthesis* **1987**, 13).

(12) (a) Smit, W. A.; Gybin, A. S.; Shashkov, A. S.; Strychkov, Y. T.; Kizmina, L. G.; Mikaelian, G. S.; Caple, R.; Swanson, E. D. *Tetrahedron Lett.* **1986**, *27*, 1241. (b) Khand, I. U.; Pauson, P. L. *Heterocycles* **1978**, *11*, 59. To the best of our knowledge, only some specific alkynyl enones have led to successful results in cobalt-catalyzed PK reactions, see: (c) Veretenov, A. L.; Smit, W. A.; Vorontsova, L. G.; Kurella, M. G.; Caple, R.; Gybin, A. S. *Tetrahedron Lett.* **1991**, *32*, 2109. See, also: (d) Costa, M.; Mor, A. *Tetrahedron Lett.* **1995**, *36*, 2867.

(13) The configuration of **A** and **B** isomers was established first by X-ray difraction of enantiopure **6A** (see Supporting Information) and confirmed afterwards by chemical correlations: (a) The oxidation of either **4A** or **4B** with MCPBA led to the same sulfone. (b) The desulfinylation (Zn, NH_4Cl, THF) of the enantiopure major isomer **4A** obtained from the PK reaction of *(R)*-**1**, and that of **6A** obtained from *(S)*-**3**, led to opposite enantiomers of enone **21a** (Table 3). (c) The desulfinylation of enantiopure **14A** [from *(S)*-**8**] afforded the *(R)* enantiomer of the known enantiopure enone **21b**[19] (Table 3).

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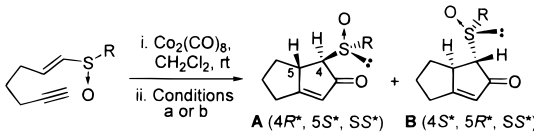
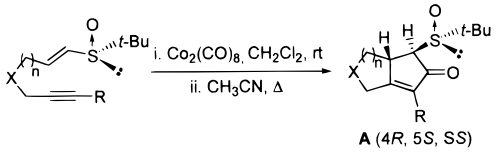
Table 1. PK Reactions of (±) Trans Enynes **1**−**3**



entry	R	enyne	conditions[a,b]	adduct	A:B ratio[c]	yield[d] (%)
1	*p*-Tol	**1**	*a*	**4**	75:25	52
2	*p*-Tol	**1**	*b*	**4**	73:27	49
3	*o*-$Me_2NC_6H_4$	**2**	*a*	**5**	71:29	55
4	*t*-Bu	**3**	*a*	**6**	>98:<2	50
5	*t*-Bu	**3**	*b*	**6**	>98:<2	46

[a] CH_3CN, 80 °C. [b] NMO·H_2O (6 equiv), CH_2Cl_2, room temperature. [c] By ^1H NMR on the crude mixtures after filtration of the cobalt byproducts. [d] In pure adducts **A** and **B**. Isomers **A** and **B** were separated by flash chromatography.

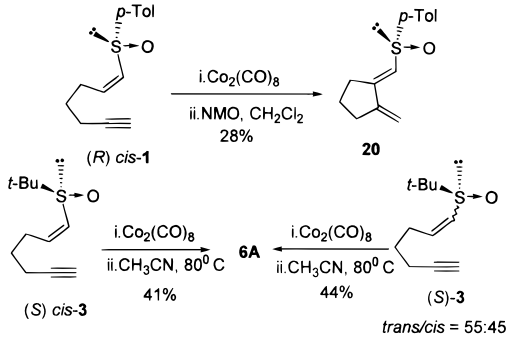
Table 2. Thermal PK Reactions of (*S*) Trans Enynes **3** and **8**−**13**



entry	enyne	X	*n*	R	*T* (°C)	adduct	yield[a] (%)
1	**3**	CH_2	1	H	80	**6A**	50
2	**8**	CMe_2	1	H	60	**14A**	65
3	**9**	$C(CO_2Et)_2$	1	H	60	**15A**	60
4	**10**	NBOC	1	H	80	**16A**	60
5	**11**	$C(CO_2Et)_2$	2	H	80	**17A**	30
6	**12**	CH_2	1	TMS	80	**18A**	*b*
7	**13**	CMe_2	1	Ph	80	**19A**	*b*

[a] In pure product after flash chromatography. [b] The starting enyne was recovered unchanged.

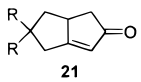
Scheme 1



entry 4). In contrast, a poor yield was obtained in the reaction of the 1,7-enyne **11** (30%, entry 5), and disappointingly, no reaction at all was observed from substituted alkynes (entries 6 and 7).

Unexpected results were observed in the cobalt-meditated reactions of the sulfinylated enynes of cis configuration (Scheme 1). Thus, whereas the aromatic sulfoxide *(R)-cis*-**1** gave the exocyclic diene **20** as the only characterized product (28% yield), in fact the expected product from an electron poor alkene under PK reaction conditions, the *tert*-butyl sulfoxides *(S)-cis*-**3** and *(S)-cis*-**9** evolved by a very highly stereoselective PK reaction to give, respectively, the same cyclopentenones **6A** (41% yield) and **15A** (56% yield) obtained from the diastereomeric enynes *(S)-trans*-**3** and *(S)-trans*-**9**.[17] From a synthetic point of view this result is particularly interesting because it allows the PK reaction to be carried out with the cis + trans mixtures of enynes directly obtained after the olefination step:[15] thus, a 55:45 mixture of trans + cis olefins *(S)*-**3** afforded **6A** as the only isomer in 44% yield.

Table 3. Optically Active Enones **21** Obtained by Desulfinylation of **A** Adducts



21

ee ≥ 96%

enyne	R	adduct	enone	$[\alpha]_D$[a] **21**
(*R*)-**1**	H	**4A**	(*S*)-**21a**	−40 (*c* 0.6)
(*S*)-**3**	H	**6A**	(*R*)-**21a**	+41 (*c* 0.6)
(*S*)-**8**	Me	**14A**	(*R*)-**21b**	+139 (*c* 0.6)[b]
(*S*)-**9**	CO_2Et	**15A**	(*R*)-**21c**[c]	+88 (*c* 0.4)

[a] In $CHCl_3$. [b] $[\alpha]_D$ (ref 19) (*S*)-**21b** = −141 (*c* 0.2, $CHCl_3$). [c] ee 96.5% by HPLC (Chiralpak AS column).

As the final step of this sulfinyl-mediated asymmetric PK reaction, the reductive cleavage of the chiral auxiliary was simply performed by desulfinylation of the **A** adducts with activated zinc[18] (sat NH_4Cl, THF, room temperature) leading in very high yields (92−96%) to the corresponding optically active bicyclo[3.3.0]oct-1-en-3-ones **21** (Table 3). In particular, the (*R*) enantiomer of the known enantiomerically pure enone **21b**[19] was obtained by desulfinylation of **14A**, confirming otherwise the configurational assignment of the PK adducts previously established by X-ray difraction.[13] Finally, the very high optical purity of enones **21** [ee 96.5% by HPLC for (*R*)-**21c**] was confirmed, proving that, as expected, the desulfinylation step occurs without racemization at C-5.

In summary, it has been demonstrated that the sulfinyl group can be used as a novel and efficient chiral auxiliary in intramolecular asymmetric PK reactions. Especially, the PK reactions of the readily available *(S)*-1-*tert*-butylsulfinylhept-1-en-6-ynes afforded a single isomer (dr >96%). This exceptionally high stereoselectivity, coupled with the efficient final chiral auxiliary elimination step, makes this procedure very appealing for the synthesis of enantiopure bicyclo[3.3.0]oct-1-en-3-ones.

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Supporting Information Available: Experimental procedures and characterization data of the new compounds and X-ray diffraction data of **6A** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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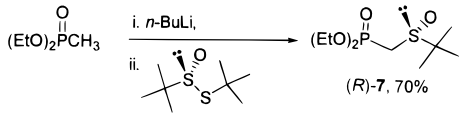
(14) (a) Krafft, M. E.; Juliano, C. A. *J. Org. Chem.* **1992**, *57*, 5106. (b) Krafft, M. E.; Juliano, C. A.; Scott, I. L.; Wright, C.; McEachin, M. D. *J. Am. Chem. Soc.* **1991**, *113*, 1693.

(15) The sulfinylation of the lithium carbanion of diethyl methylphosphonate with the known *(R)-tert*-butyl *tert*-butanethiosulfinate (Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011) in THF at −100 °C provided *(R)*-**7** in 70% yield ($[\alpha]_D$ = −106, *c* 1, $CHCl_3$; ee 98.5%, HPLC, Chiralpak AS).



Deprotonation of *(R)*-**7** (*n*-BuLi, THF, −78 °C) and addition of the corresponding alkynyl aldehyde (−78 °C) led to the enynes *(S)*-**3** and *(S)*-**8**−**13** in high yields (77−89%) as cis + trans mixtures of olefins, which were readily separated by flash chromatography. On the other hand, we checked that the optical purity of the enynes was very high as proved by ^1H NMR [Yt(hfc)$_3$] in the case of *(S)*-**3** and *(S)*-**8** (ee ≥96%).

(16) A single enantiomer was observed by ^1H NMR analysis of **6A** and **14A** in the presence of Eu(hfc)$_3$ (ee ≥96%).

(17) A possible explanation justifying the same stereochemical outcome of the PK reaction from trans and cis enynes might be that both vinyl sulfoxides exhibit the same π-facial selectivity in the key olefin insertion step, and that the initial cis substituted adduct obtained from the cis enyne epimerizes under the reaction conditions to the most stable trans substituted cyclopentenone. For previous cis to trans epimerizations of disubstituted cyclopentenones adducts in PK reactions, see: Krafft, M. E. *J. Am. Chem. Soc.* **1988**, *110*, 968.

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