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Asymmetric Intermolecular Pauson−Khand Reactions of Unstrained Olefins: The (*o*-Dimethylamino)phenylsulfinyl Group as an Efficient Chiral Auxiliary

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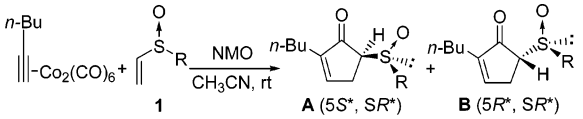
Since its discovery three decades ago, the $Co_2(CO)_8$-mediated cocyclization of an alkene, an alkyne, and carbon monoxide, known as the Pauson−Khand reaction (PKR), has become one of the most efficient methods for the synthesis of cyclopentanoid systems.[1] However, despite impressive recent advances in this field, such as the development of the first versions of both catalytic and asymmetric intramolecular PKR,[2] some important limitations still remain. One of these is the lack of asymmetric intermolecular versions of PKR for unstrained olefins, which would open a synthetically quite general access to the enantioselective synthesis of substituted nonfused cyclopentenones from simple alkenes and alkynes. Up to now, to the best of our knowledge, all the reported examples of asymmetric intermolecular PKR are limited to the use of highly reactive strained cyclic alkenes, such as norbornene, norbornadiene, and bicyclo[3.2.0]hept-6-ene.[1,3]

Herein we report that vinyl sulfoxides, in particular the potentially cobalt-coordinating[4,5] 2-(*N*,*N*-dimethylamino)phenyl vinyl sulfoxide, react with a wide variety of alkyne dicobalt complexes under mild conditions and with exceptionally high levels of regio- and stereocontrol. In addition, the chemical versatility of the resulting 5-sulfinyl-2-cyclopentenones makes this type of PK adducts very appealing intermediates in organic synthesis, as illustrated here by a highly efficient four-step enantioselective synthesis of (−)-pentenomycin I antibiotic.[6]

Having demonstrated previously that 1-*tert*-butylsulfinyl-1,6-enynes were suitable substrates for stereoselective intramolecular PKR,[7,8] we decided to explore the ability of sulfoxide-based chiral auxiliaries in the much less thermodynamically favorable intermolecular processes. First, to check the viability of this hypothesis a series of racemic vinyl sulfoxides (**1a**−**f**), displaying different steric and electronic environments around the sulfur atom, were prepared by straightforward methods and treated with the dicobalt complex of 1-hexyne under a variety of reaction conditions. In accordance with the usual low reactivity of unstrained alkenes in intermolecular PKR,[1] we only found metal decomplexation and formation of side products under thermal conditions (toluene or CH_3CN at 80 °C), while a sluggish reaction was observed at room temperature using amine *N*-oxides as promoters in low polar solvents (e.g., toluene or CH_2Cl_2). Pleasingly, a faster and cleaner reaction was observed using *N*-methylmorpholine *N*-oxide (NMO) in acetonitrile (Table 1).

Some important conclusions are drawn from the data of Table 1. Unlike the low regioselectivity usually observed in the PKR of simple monosubstituted alkenes with terminal alkynes,[9] the PKR of all vinyl sulfoxides **1** was completely regioselective, leading exclusively to the 2,5-disubstituted cyclopentenones **2**. In contrast, both the reactivity and the stereoselectivity proved to be strongly dependent on the substitution at sulfur. Thus, a low conversion (although very high stereoselectivity) was observed in the case of the bulky sulfoxides **1d**,**e** (entries 4 and 5), even in the presence of a large excess of the alkyne dicobalt complex (3-fold excess) and under prolonged reaction times. On the opposite end, the PKR of the less hindered *p*-tolylsulfoxide **1a** was complete in 2 h, although with poor stereocontrol (entry 1). An intermediate result with regard to reactivity and stereoselectivity was obtained in the case of the o-substituted arylsulfoxides **1b**,**c** (entries 2 and 3). *However, the ortho-amino-substituted sulfoxide **1f** afforded by far the most synthetically interesting result: not only was **1f** the most reactive alkene, but the reaction was also highly diastereoselective[10] (entry 6).* This remarkable reactivity, which may be tentatively ascribed to the prior coordination of the Me_2N moiety to the cobalt complex,[4,5] allowed it to carry out the process at 0 °C (entry 7), affording **2f** as a 93:7 mixture of **A**/**B** epimers[11] in 74% yield.

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



entry[a]	R	alkene	*t* (h)	adduct	**A**/**B** ratio[b]	yield (%)[c]
1	*p*-Tol	**1a**	2	**2a**	74:26	68
2[d]	*o*-Tol	**1b**	24	**2b**	90:10	28
3[d]	*o*-BrC_6H_4	**1c**	24	**2c**	86:14	30
4[d]	2,4,6-(*i*-Pr)$_3C_6H_2$	**1d**	24	**2d**	94:6	24
5[d]	*t*-Bu	**1e**	24	**2e**	>98:<2	20
6	*o*-$(Me_2N)C_6H_4$	**1f**	1	**2f**	92:8	63
7[e]	*o*-$(Me_2N)C_6H_4$	**1f**	4	**2f**	93:7	74

[a] Reaction conditions: dicobalt complex (1.5 equiv), alkene **1** (1.0 equiv), NMO (6.0 equiv), CH_3CN, rt. [b] By ^1H NMR on the crude mixtures after filtration of the cobalt byproducts. [c] In pure adducts after chromatography. [d] Dicobalt complex (3 equiv) was used. [e] Reaction run at 0 °C.

Next, to explore the structural scope of the PKR of the optimal vinyl sulfoxide **1f**, a variety of alkyne dicobalt complexes were subjected to the same reaction conditions (NMO, CH_3CN, 0 °C). The results are collected in Table 2.

Gratifyingly, reasonable yields of isolated adducts (49−74%), complete regioselectivities, and very high diastereoselectivities[11] (de = 86 to >96%) were obtained from all terminal alkynes, including primary-, benzyl-, and tertiary alkyl-substituted ones (entries 1−3), aryl acetylenes (entry 4), and functionalized alkynes (entries 5−7). It is worth noting that the reaction conditions are so mild that even alkynes having a primary bromoalkyl chain can be successfully used (entry 7). However, no reaction at all occurred in the case of internal alkynes, as 2-butyne (entry 8). This drawback was partially solved by performing the reaction at high pressure (10 Kbar) at room temperature, affording the adducts **9** in 33% yield and high stereoselectivity (entry 9).[12]

To apply these highly diastereoselective PKR in asymmetric synthesis, enantiopure vinyl sulfoxide **1f** was required. The preparation of (*R*)-**1f** was readily achieved in two steps from the sulfinyl

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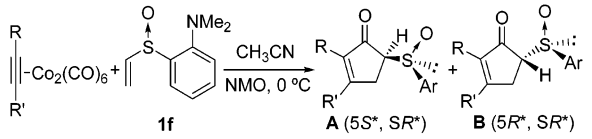
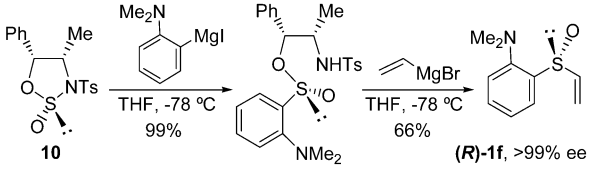
Table 2. PKR of Vinyl Sulfoxide **1f** with Differently Substituted Alkynes



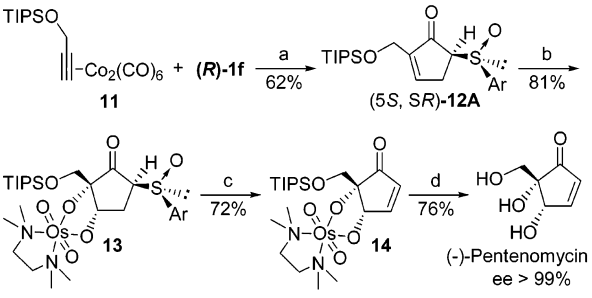
entry[a]	R	R′	*t* (h)	adduct	**A**/**B** ratio[b]	yield (%)[c]
1	*n*-Bu	H	4	**2f**	93:7	74
2[d,e]	*t*-Bu	H	26	**3**	>98:<2	55
3[d]	Bn	H	14	**4**	93:7	58
4	*p*-Tol	H	12	**5**	93:7	49
5[e]	TMS	H	16	**6**	>98:<2	59
6	CH_2CH_2OTIPS	H	7	**7**	>98:<2	66
7	$CH_2CH_2CH_2Br$	H	6	**8**	>98:<2	68
8	Me	Me	24	**9**		nr
9[f]	Me	Me	48	**9**	92:8	33

[a] Reaction conditions: dicobalt complex (1.5 equiv), alkene **1** (1.0 equiv), NMO (6.0 equiv), CH_3CN, 0 °C. [b,c,d] As in Table 1. [e] Reaction run at room temperature. [f] Reaction run at 10 Kbar.

Scheme 1



Scheme 2



(a) NMO, CH_3CN, 0 °C. (b) OsO_4, TMEDA, CH_2Cl_2, −78 °C. (c) Toluene, reflux. (d) HCl 2M, rt.

derivative of norephedrine **10** following the recently reported Senanayake's procedure.[13] Reaction of **10** with *o*-(dimethylamino)-phenylmagnesium iodide (THF, −78 °C) and further treatment with vinylmagnesium bromide afforded (*R*)-**1f** in 66% overall yield and in very high optical purity (ee > 99%, HPLC), showing that both displacement reactions at sulfur occur with complete inversion of configuration (Scheme 1).

Finally, to highlight the synthetic potential of these sulfinylated PK products, we accomplished the shortest reported synthesis of the antibiotic (−)-pentenomycin I[14] (Scheme 2). Treatment of cobalt complex **11** with (*R*)-**1f** under the optimized PKR conditions afforded the adduct **12** (62% yield) in a 93:7 isomer ratio. Simple precipitation with cold hexane gave pure **12A**, whose excellent optical purity (ee > 99%, HPLC) proved that, as expected, the PKR took place without racemization at sulfur.[15,16] The stereoselective dihydroxylation of **12A** with OsO_4/TMEDA furnished the remarkably stable osmate diester **13** (81% yield). Sulfoxide pyrolysis in refluxing toluene gave the hydroxyl-protected enone **14** (72%), which after acidic hydrolysis afforded the natural (−)-(2*S*,3*S*)-pentenomycin I (ee > 99%, determined by HPLC on its triacetate derivative).[14]

In conclusion, the first asymmetric version of intermolecular PKR of acyclic alkenes, relying on the use of sulfoxides as chiral auxiliaries, has been developed. *o*-(Dimethylamino)phenyl vinyl sulfoxide (**1f**), readily available in both racemic and enantiopure forms, reacts under very mild conditions with terminal alkynes in a completely regioselective and highly stereoselective manner. The resulting enantiopure 5-sulfinyl-2-cyclopentenones are versatile intermediates in asymmetric synthesis since the five positions at the ring can be easily functionalized by straightforward carbonyl- or sulfoxide-based reactions. Further studies on the mechanistic behavior of **1f**, as well as the application of the PK adducts in enantioselective synthesis of cyclopentanoids are underway.

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Supporting Information Available: Experimental procedures, characterization data of all new compounds, X-ray diffraction data of **3A**, and NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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