Stereoselective Hydrocyanation of Alkenyl Sulfoxides as a Method to Highly Enantiomerically Enriched Compounds with Tertiary and Quaternary Chiral Carbon Atoms[**]

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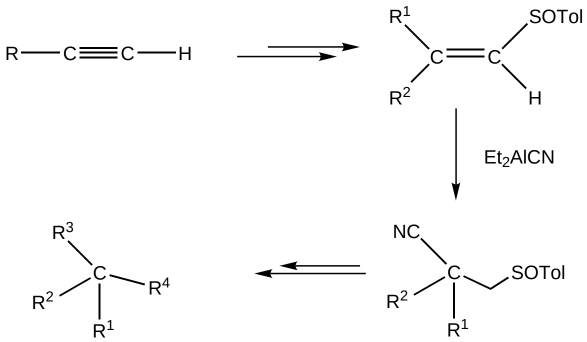
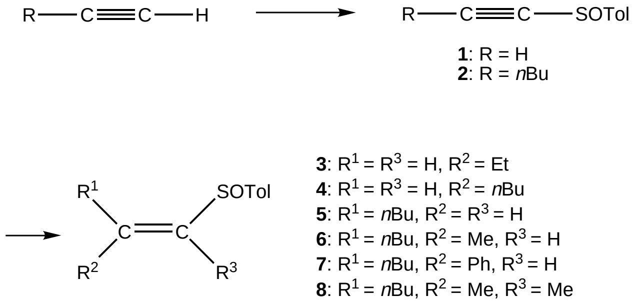
Hydrocyanation of double bonds is an important synthetic task because it allows the direct transformation of alkenes into carboxylic acid derivatives.[1] With regard to catalytic asymmetric hydrocyanation, the results obtained so far can be considered as rather modest.[2] Thus, in the case of norbornene and norbornadiene—some of the most well studied substrates because of the rigidity conferred by the bicyclic structure[3, 4]—palladium complexes bearing the phosphane–phosphite ligand (*R*)-2-(diphenylphosphino)-1,1′-binaphthalen-2′-yl (*S*)-1,1′-binaphthalen-2,2′-diylphosphite ((*R*,*S*)-BINAPHOS) were claimed to be the most efficient chiral catalysts, although only 48% *ee* was obtained.[5] The highest enantiomeric excess ever reported for an enantioselective hydrocyanation corresponds to reactions of arylethenes catalyzed by glucose-derived bisphosphinite–Niquel complexes (the *ee* value ranged from 40 to 70%, but in the case of the 6-methoxy-2-vinylnaphthalene it increased to 91%).[6] This result was not improved by the use of chiral aryl diphosphite ligands derived from binaphthol.[7] Diastereoselective hydrocyanations of double bonds, involving the nucleophilic addition of cyanide to deactivated alkenes,[8, 9] have been occasionally carried out on chiral substrates[10] to obtain difunctionalized substrates in diastereoselective processes. The low efficiency of the above-mentioned methods indicates that finding a general method to achieve the asymmetric hydrocyanation of alkenes, and thus allow the synthesis of nitriles bearing a chiral center at α-C, still remains a challenge.

The use of the sulfinyl group as a chiral inductor in asymmetric synthesis has been widely exploited.[11] The ability of the sulfinyl oxygen atom to associate with different metals is the key for controlling the stereoselectivity of many reactions. For reactions of α-sulfinyl ketones with aluminum reagents $YAlR_2$ (Y = H,[12] alkyl,[13] CN[14]), it could be established that formation of the Al–OS bond as a preliminary step in the intramolecular transfer of the Y^- group was responsible for the high stereoselectivity. We envisioned that unsaturated sulfinyl derivatives could react with Et_2AlCN in the manner of a highly stereocontrolled intramolecular cyanide transfer. This assumption was verified for alkynyl sulfoxides.[15] Here we report that hydrocyanation of alkenyl sulfoxides with Et_2AlCN is completely stereoselective. This reaction allows the transformation of terminal alkynes into nitriles bearing tertiary or quaternary chiral centers at α-C (Scheme 1). The chemical versatility of the cyano and sulfinyl groups suggests that this is a general method for preparing any kind of chiral carbon atom that is not bonded to a heteroatom.



Scheme 1. General scheme for the hydrocyanation of alkenyl sulfoxides with Et_2AlCN, and further reaction of the nitriles obtained to provide compounds containing chiral centers. Tol = 4-tolyl.

The starting compounds for the asymmetric hydrocyanation were obtained from alkynyl sulfoxides **1**[15] and **2** (Scheme 2). A sequence involving sulfinylation of terminal alkynes followed by stereoselective reduction or alkylation of the alkynyl sulfoxide[16] provided vinyl sulfoxides **3** (from **1**) and **4**–**8** (from **2**). Capture of the intermediates from the reaction of lithium dimethyl cuprate with **2**, yielding **6**, with MeI as an electrophile allows the preparation of tetrasubstituted ethylene **8**.



Scheme 2. Synthesis of vinyl sulfoxides **3**–**8**.

The reaction of alkenyl sulfoxides **3**–**5** with Et_2AlCN in refluxing THF (15 min) solely afforded β-sulfinyl nitriles **9**–**11** in very good yields (Table 1, entries 1–5). The (*E*)-sulfoxide **4** was more reactive than the *Z* isomer **5**. The β,β'-disubstituted compound **6** exhibited lower reactivity than the monoalkylated vinylsulfoxides **3**–**5**, and required heating for two hours at reflux to afford a 96:4 mixture of **12a** and **12b**, epimers at carbon, which could not be separated (entry 6). Fortunately, the reaction was completely stereoselective at room temperature, although it required 48 h (entry 7). The

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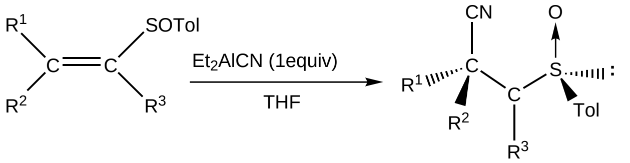
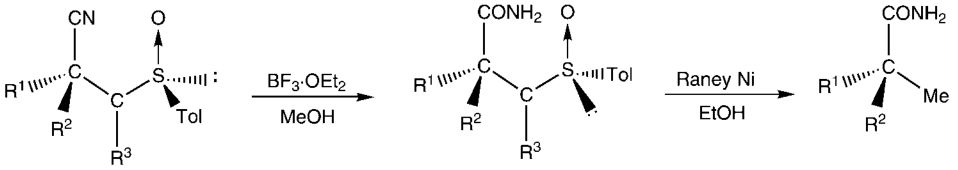
Table 1. Results from the hydrocyanation of alkenyl sulfoxides with Et_2AlCN.



Entry	R^1	R^2	R^3	Substrate	*t*	*T* [°C][a]	Product	Yield [%]	de [%]
1	H	Et	H	**3**	15 min	65	**9**	80	> 98
2	H	*n*Bu	H	**4**	15 min	65	**10**	90	> 98
3	*n*Bu	H	H	**5**	15 min	65	**11**	75	> 98
4	H	*n*Bu	H	**4**	4 h	25	**10**	90	> 98
5	*n*Bu	H	H	**5**	24 h	25	**11**	75	> 98
6	*n*Bu	Me	H	**6**	2 h	65	**12a**/**12b**[b]	72	92
7	*n*Bu	Me	H	**6**	48 h	25	**12a**[c]	72	> 98
8	*n*Bu	Ph	H	**7**	24 h	65	**13**	82[d]	> 98
9	*n*Bu	Me	Me	**8**	48 h	65	**14**	–[e]	–

[a] The reactions were carried out at room temperature (25 °C) or in refluxing THF (66 °C). [b] Epimers **12a** and **12b** were obtained in a 96:4 mixture. [c] 10 % of vinyl sulfone was also isolated. [d] Conversion 58 % (42 % of the starting material **7** was recovered). [e] Product **14** was not formed.



9: R^1 = H, R^2 = Et	**15** (75%)	**21** (82%)
10: R^1 = H, R^2 = *n*Bu	**16** (78%)	**22** (84%)
11: R^1 = *n*Bu, R^2 = H	**17** (70%)	**23** (80%)
12: R^1 = *n*Bu, R^2 = Me	**18** (70%)	
13: R^1 = *n*Bu, R^2 = Ph	**19** (76%)	**24** (84%)

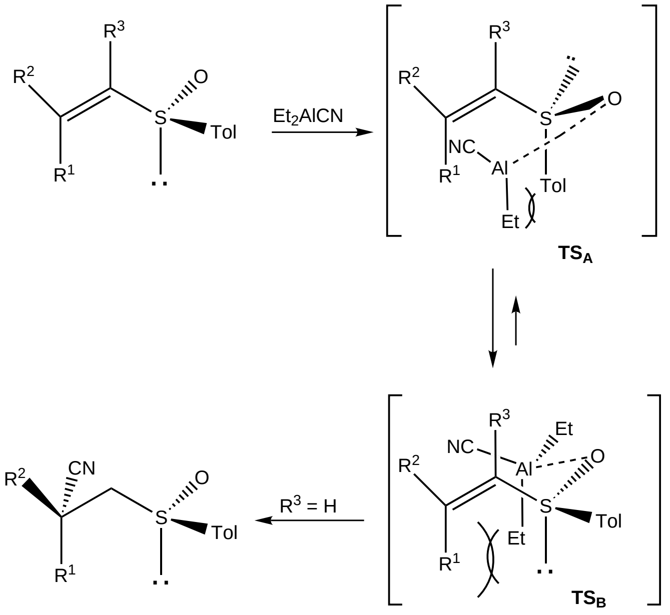
Scheme 3. Hydrolysis and subsequent reduction of nitriles **9**–**13**.

presence of a phenyl group at the double bond decreased the reactivity of the alkenyl sulfoxide even more. Therefore, the transformation of **7** into **13** (isolated in 48 % yield) was not complete after heating for 24 h at reflux (42 % of unaltered **7** was recovered, entry 8). An increase in the reaction time and in the amount of reagent did not improve these results, but caused decomposition of **7**. In all these reactions the order of addition was critical for obtaining the nitriles in good yields: The alkene must be added to Et_2AlCN. Compound **8** did not evolve into sulfinyl nitrile **14**[17] after heating for 48 h at reflux (entry 9).

The most relevant result of all these hydrocyanation reactions is the almost complete stereoselectivity. Starting from enantiopure alkenyl sulfoxides, only one diastereoisomer of the corresponding nitrile could be detected in the crude products by 300-MHz ^1H NMR analysis. The desired configuration at α-C of the resulting sulfinyl nitriles could be achieved by choosing either the configuration at the sulfinylic sulfur atom or that of the double bond in the starting compound.

Hydrolysis of these nitriles with $BF_3 \cdot OEt_2$ and methanol[18] afforded sulfinyl amides **15**–**19** (Scheme 3). Product **16** gave suitable crystals that could be analyzed by X-ray diffraction,[19] thus allowing unequivocal assignment of the configuration as (2*S*,(S)*S*).[20] Accordingly, we can state that the *S* configuration induced at the chiral carbon atom in the hydrocyanation step is opposite to that of the sulfur atom in (*E*)-vinyl sulfoxide (*R*)-**4**.

The stereochemical results could be rationalized by assuming association of the aluminum atom with the sulfinyl oxygen atom prior to the intramolecular transfer of the cyanide group. In Scheme 4 are depicted the two possible chairlike transition states for such a transfer, TS_B being clearly more stable than TS_A from the point of view of sterics. This stereochemical model also explains the lower reactivity of the (*Z*)-sulfoxides with respect to the *E* isomers as a consequence



Scheme 4. Possible mechanism for the hydrocyanation of alkenyl sulfoxides.

of the $(R^1/Et)_{1,3\text{-p}}$ interaction. The lower reactivity of dialkyl and alkyl aryl acrylonitriles compared to monosubstituted substrates is not unexpected considering the influence of the substituents on the electronic density at the double bond. This could also be responsible for the low reactivity of trisubstituted vinyl sulfoxide **8**, but the $(O/R^3)_{gauche}$ and $(Tol/R^3)_{gauche}$ interactions present when $R^3 \neq H$ can also be involved in the destabilization of both $\mathbf{TS_A}$ and $\mathbf{TS_B}$.

Desulfinylation of the amides **15**–**17** and **19** with Raney nickel afforded the corresponding enantiopure amides **21**–**24**, which were isolated in good yields (>70%, Scheme 3).[21]

In summary we have shown that the hydrocyanation of alkenyl sulfoxides with Et_2AlCN takes place in a completely stereoselective manner. Taking into account the chemical versatility of the cyano and sulfinyl groups, this reaction can be considered as the key step in a short sequence that allows the creation of optically pure molecules containing tertiary or quaternary chiral centers from terminal alkynes, as illustrated with the preparation of amides **21**–**24**.

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[17] After the reaction mixture was heated for 24 h at reflux, we isolated an unexpected compound (30% yield) which has not been identified yet.

[18] These conditions promote the conversion of sulfinyl nitriles into sulfinyl amides with inversion of the configuration at sulfur (see refs. [14c, 15]) The hydrolysis of nitrile **12** with KOH in refluxing *t*BuOH (J. H. Hall, M. Gisler, *J. Org. Chem.* **1976**, *41*, 3769) afforded diastereomer **18′**, an epimer at sulfur of **18**, because under these conditions neither the configuration at carbon or at sulfur is affected.

[19] Proper crystals of compunds **9**–**13** could not be obtained.

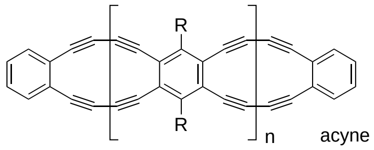
[20] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-154583 (**16**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[21] As the optical purity of the amides could not be established by chiral shift reagents or chiral HPLC, the chemical correlation of **21** with commercially availale (*S*)-2-methylbutanoic acid was neccesary. The amides derived from (*S*)-2-methylbutanoic acid and from **21** by desulfurization exhibited a specific rotation of the same value and sign. Therefore, we can conclude that the configuration at C2 of **21** must be *S*, in complete agreement with the X-ray structure analysis.

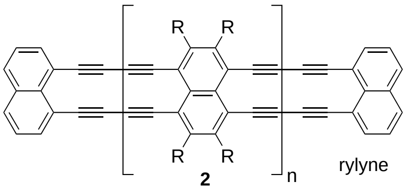
Synthesis of a Remarkably Stable Dehydro[14]annulene[**]

Grant J. Palmer, Sean R. Parkin, and John E. Anthony[*]

Dehydroannulenes are a fascinating class of carbon-rich molecules which have been studied intensively.[1] With the development of improved synthetic methodologies, these macrocycles are now being exploited for their potential material properties. Recent applications employ such annulenes as conjugated scaffolds for nonlinear optical applications[2] and as precursors for carbon nanotube synthesis.[3] We are currently exploring the use of fused dehydroannulenes as components in conjugated ladder polymers (e.g. acynes **1** and rylynes **2**).



1



2

While the phenyldiacetylene macrocycles that comprise **1** are well-known compounds,[4] the class of dehydroannulenes that make up the backbone of **2** is poorly understood. The parent compound **3** was prepared in 1968 by Mitchell and Sondheimer, who were unable to fully characterize this new

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