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Diastereoselective Uncatalyzed Conjugate Addition of Organoaluminum Reagents: Efficient Desymmetrization of (*R*)-[(*p*-Tolylsulfinyl)methyl]quinols

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The development of efficient enantioselective 1,4-conjugate addition reactions has focused the interest of several research groups in the past two decades. High asymmetric inductions have been achieved by using chiral electrophiles, nucleophiles, and to a lesser extent, chiral catalysts.[1] A number of reports demonstrated that a sulfoxide on either the acceptor[2] or the nucleophile[3] can efficiently control the diastereofacial selectivity of the conjugate addition. To our knowledge, no reports dealing with δ-sulfinyl-α,β-unsaturated carbonyl systems have been published so far.

In the course of our investigations devoted to the use of sulfoxides in asymmetric synthesis,[4] we found that DIBAL[5] or alkylalanes[6] reacted in a highly diastereoselective manner with β-keto sulfoxides. Thus, matching sulfoxides with aluminum derivatives seemed to be highly efficient in asymmetric reactions. Seeking to further exploit this combination, we thought of conjugate additions.

Recently, we synthesized (*R*)-4-hydroxy-4-[(*p*-tolylsulfinyl)methyl]-2,5-cyclohexadienone (**1**)[7] and observed an intriguing diastereotopic C═C group selection for its Diels−Alder cycloadditions. In the present work, we investigate the behavior of *p*-quinols **1** and **2** (prepared from 4,4-dimethoxy-2,6-dimethyl-2,5-cyclohexadien-1-one[8]) showing a prochiral dienone moiety, upon reaction with organoaluminum reagents. We find that exclusive 1,4-addition proceeds without other metal catalysts in good yields and mild conditions. The reaction occurs from the face containing the OH with a total π-facial diastereoselectivity and an effective desymmetrization of the dienone moiety allowing the simultaneous generation of two stereogenic centers.

The results of reactions with a number of organoaluminum reagents are summarized in Table 1. We found that better yields were obtained when **1** or **2** was added over an excess of $AlR^2R^3_2$ (4 equiv). All reactions run in CH_2Cl_2 led to compounds **3** and **4** resulting from the exclusive 1,4-conjugate addition. Both **1** and **2** (a β,β-disubstituted enone) behaved similarly toward trialkyl- (Table 1, entries 1, 2, 6, and 7), alkinyl- (Table 1, entries 3, 4, 8, and 9), or vinylalanes (Table 1, entries 5 and 10), giving rise to only one out of the four possible diastereomers in good yields. The unambiguous stereochemical assignment of **3** and **4** was established on the basis of a detailed ^{1}H-NMR study and confirmed by X-ray diffraction of **4b**.[9]

The high reactivity here reported is surprising because such an easy reaction had only been found in a few cases for simple alanes[10] or in the presence of some transition metals.[11] In the absence of any other metal, the 1,4-transfer was only possible via a free-radical process[12] or by using dialkylaluminum halides.[13] In our case, we could disregard a free-radical process based on a control experiment in the presence of the radical scavenger galvinoxyl with **1** and $AlMe_3$. Even more remarkable are the stereospecificity and the effective diastereotopic C═C bond selection observed. A similar diastereoselective process on *p*-quinols directed by the OH was found in

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[1] Reviews: (a) Schmalz, H. G. in *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I, Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 1.5. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (c) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. For recent references see: (d) Urban, E.; Knühl, G.; Helmchen, G. *Tetrahedron* **1996**, *52*, 971. (e) Enders, D.; Kirchhoff, J.; Mannes, D.; Raabe, G. *Synthesis* **1995**, 659.

[2] Review: Posner, G. H. In *The Chemistry of Sulfones and Sulfoxide*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley & Sons: New York, 1988; Chapter 16.

[3] (a) Review: Hua, H. D. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; JAI Press: London, 1992; Vol. 1, p 249. (b) Haynes, R. K.; Katsifis, A. G.; Vowiller, S. C.; Hambley, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5423. (c) Marco, J. L.; Fernández, I.; Khiar, N.; Fernández, P.; Romero, A. *J. Org. Chem.* **1995**, *60*, 6678.

[4] For an overview of our work see: (a) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717. (b) Solladié, G.; Carreño, M. C. *Organosulphur Chemistry: Synthetic Aspects*; Page, P. C. B.,Ed.; Academic Press: New York, 1995; Chapter 1.

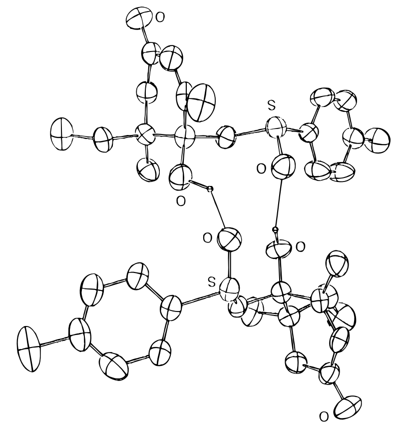
[5] (a) Carreño, M. C.; García Ruano, J. L.; Martín, A. M.; Pedregal, C.; Rodríguez, J. H.; Rubio, A.; Sánchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120. (b) Bueno, A. B.; Carreño, M. C.; García Ruano, J. L.; Peña, B.; Rubio, A.; Hoyos, M. A. *Tetrahedron* **1994**, *50*, 9355.

[6] Carreño, M. C.; García Ruano, J. L.; Maestro, M. C.; Pérez González, M. *Tetrahedron* **1993**, *49*, 11009. Bueno, A. B.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1995**, *36*, 3737. Et$_2$AlCN also produced cyanhidrines diastereoselectively; see: Escribano, A. M.; García Ruano, J. L.; Martín-Castro, A. M.; Rodríguez, J. H. *Tetrahedron* **1994**, *50*, 7567.

[7] Carreño, M. C.; Pérez González, M.; Fischer, J. *Tetrahedron Lett.* **1995**, *36*, 4893.

[8] Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677.

[9] Crystal data for **4b** revealed the associated structure shown:



This hydrogen bonding association should be maintained in solution to account for the low chemical shift observed for the CH_3 of the ethyl substituent (δ = 0.78 ppm) as a consequence of the anisotropic effect exerted by the spatially close aromatic ring. A similar effect could be observed in the proton or methyl group situated on the pro-*R* double bond of *p*-quinols **1** and **2**.

[10] (a) Pappo, R.; Collins, P. W. *Tetrahedron Lett.* **1972**, 2627. (b) Collins, P. W.; Dajani, E. Z.; Bruhn, M. S.; Brown, C. H.; Palmer, J. R.; Pappo, R. *Tetrahedron Lett.* **1975**, 4217. Hooz, J.; Layton, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 7320.

[11] For recent references see: (a) Flemming, S.; Kabbara, J.; Nickisch, K.; Neh, H.; Westermann, J. *Synthesis* **1995**, 317. (b) Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Tetrahedron* **1995**, *51*, 743. (b) Westermann, J.; Nickisch, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1368.

[12] Kabalka, G. W.; Daley, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 4428.

[13] (a) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4792. (b) Rück, K.; Kunz, H. *Synlett* **1992**, 343. (c) Rück, K.; Kunz, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 694.

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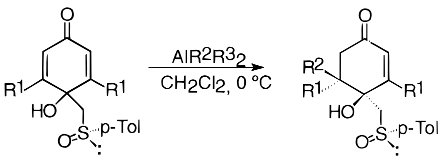
Table 1. Conjugate Additions of $AlR^2R^3_2$ to 1 and 2

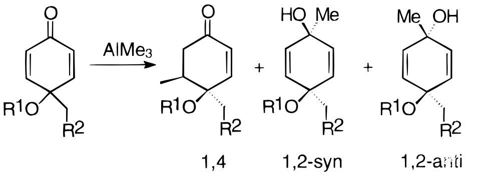


1: R^1 = H
2: R^1 = Me
3: R^1 = H
4: R^1 = Me

	substr	R^2	R^3	prod	t (h)	yield (%)	$[\alpha]^{25}{}_D$ [a]	mp (°C)
1	**1**[b]	Me	Me	**3a**	4	71	+236	120
2	**1**[b]	Et	Et	**3b**	3	89	+229	85
3	**1**	$C_4H_9C{\equiv}C-$	Me	**3c**	3	56[c]	+220	oil
4	**1**	$TMSC{\equiv}C-$	Me	**3d**	2	69[c]	+276	138
5	**1**	(*E*)-$C_4H_9C{=}C-$	Me	**3e**	4	53[c]		oil
6	**2**	Me	Me	**4a**	2	82	+228	150
7	**2**	Et	Et	**4b**	3	71	+204	104.5
8	**2**	$C_4H_9C{\equiv}C-$	Me	**4c**	3	87	+208	oil
9	**2**	$TMSC{\equiv}C-$	Me	**4d**	3	67	+226	145.5
10	**2**	(*E*)-$C_4H_9C{=}C-$	Me	**4e**	3	55	+138	oil

[a] c = 1, $CHCl_3$. [b] $T = -78$ °C. [c] In the crude mixture 5−10% of **3a** and 10−15% of **1** were present.

Table 2. $AlMe_3$ Addition to *p*-Quinols 1, 5, and 6 at −78 °C



1: R^1 = H, R^2 = (*R*)-SOTol
5: R^1 = Me, R^2 = (*R*)-SOTol
6: R^1 = H, R^2 = H

	substr	equiv/*t* (h)	products 1,4	products 1,2-*syn*	products 1,2-*anti*	starting material
1	**5**	4/4		8	2	90
2	**6**	4/4	2	87	11[a]	
3	**1**	1/4				100
4	**1**	2/7	5			95
5	**1**	3/21	66			34

[a] Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678.

Grignard additions to their lithium alkoxides[14] in racemic series, but the dienone desymmetrization of an optically active *p*-quinol had only been achieved in an intramolecular conjugate addition.[15]

The lack of 1,4-addition of the methyl-protected *p*-quinol **5** with $AlMe_3$ (Table 2, entry 1) indicated that the free OH should be present to assist the organoaluminum reagent in the transfer of the R^2 group. Compound **6** produced 1,2- and 1,4-adducts (Table 2, entry 2), the latter being minor. Thus, the sulfoxide seems to be essential to the 1,4-addition. On the other hand, no complete reaction was observed unless 4 equiv of $AlMe_3$ was used (Table 2, entries 3−5).

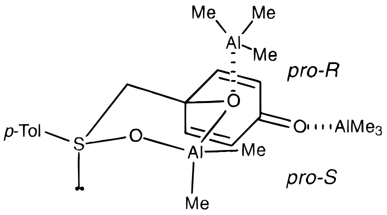


Figure 1. Associated species leading to high site and diastereofacial selective 1,4-conjugate addition.

These results provided a basis for explaining both the high reactivity of these systems and the desymmetrization of the dienone moiety observed. The stoichiometric addition of $AlMe_3$ produced the formation of an unreactive aluminum alkoxide where the metal is associated with the sulfinylic oxygen as shown in Figure 1. This species has a frozen chairlike conformation by the equatorial *p*-Tol. In such an arrangement the axial methyl group linked to the aluminum atom is hindering the pro-*S* double bond to any nucleophile approach from the face containing the alkoxide group and renders only the pro-*R* conjugate position available. This could be the origin of the diastereotopic group selection. The second alane equivalent should associate the carbonyl oxygen. The use of an excess of aluminum reagent warrants the completion, due to the association between the reagent and the sulfinylic oxygen that could retard the intramolecular transfer assisted by the alkoxide.

Further support for our hypothesis was found in experiments carried out by mixing $AlMe_3$ (2 equiv) with **2** and subsequent addition of the resulting species into a solution containing $AlEt_3$ (1 equiv). Under these conditions, the ethyl-substituted compound **4b** was the major component of the reaction mixture (**4a**/**4b**: 30/70).[16]

The mechanism proposed, based on the assisted intramolecular transfer of the organoaluminum reagent, could justify the easy and controlled formation of a stereogenic tertiary center (from **1**) and a quaternary one (from **2**) whatever the nature of the radical to be transferred.

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Supporting Information Available: Experimental details for the synthesis and characterization data of **1**, **2**, **3a**−**e**, **4a**−**e**, and **5** (7 pages).

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(15) Fujioka, H.; Kitagaki, S.; Ohno, N.; Kitagawa, H.; Kita, Y.; Matsumoto, K. *Tetrahedron: Asymmetry* **1994**, *5*, 333.

(16) Once 2 equiv of $AlMe_3$ was added to **2**, an aliquot was extracted. At this stage, only 2% of **4a** was formed. In a parallel experiment, compound **2** was added over a mixture containing 2 equiv of $AlMe_3$ and 1 equiv of $AlEt_3$. In this way, a 45:55 mixture of **4a** and **4b** was obtained. Thus, the result of the experience mentioned in the text suggests the mechanism proposed.