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Stereoselective Alkylidenation of Ketones with 2-(*p*-Toluenesulfinyl)benzyl Iodide: Synthesis of Enantiomerically Pure Trisubstituted Epoxides

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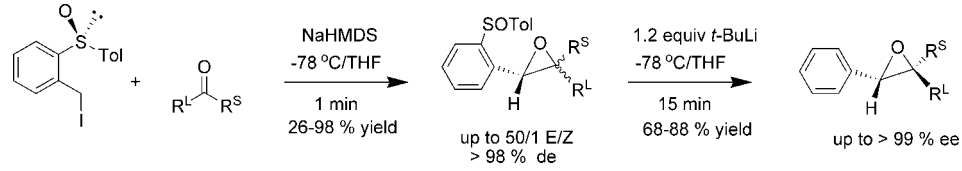
ABSTRACT



Alkylidenation of arylmethyl, dialkyl, and cyclic ketones with 2-(*p*-toluenesulfinyl)benzyl iodide in the presence of $NaN(SiMe_3)_2$ takes place with a high or complete control of the facial selectivity at the carbonyl group (up to 98% de) and the carbanion (>98% de), respectively, yielding mixtures of only two optically pure trisubstituted epoxides (*E*/*Z* ratio ranges between 2:1 and >50:1). Removal of the *p*-tolylsulfinyl group with *t*-BuLi provides the corresponding (*E*)-3-phenyl-2,2-disubstituted epoxides without affecting their optical purity.

Enantiomerically pure trisubstituted epoxides with two stereocenters are versatile and powerful intermediates for synthesizing a wide range of chiral molecules bearing connected tertiary and quaternary stereocenters, via nucleophilic opening of the oxiranic ring. Trisubstituted epoxides can be obtained by asymmetric epoxidation of trisubstituted double bonds,[1] but despite recent advances in the development of effective asymmetric epoxidation catalysts, these have not proven generally useful in the context of trisubsubstituted alkenes. An alternative method for preparing these compounds involves alkylidenation of ketones using ylides, carbenoids or Darzens reagents as the nucleophilic species.[2] Once again, low or moderate success had been achieved for trisubstituted epoxides till Aggarwal reported the reactions between a chiral benzyl sulfonium ylide and carbonyl compounds.[3] The results were extraordinary with aldehydes, but the only four studied ketones provided poorer results. Cyclohexanone and 4-*tert*-butyl cyclohexanone evolved in high ee's but acetophenone and *p*-nitro acetophenone afforded epoxides with modest *E*/*Z* or enantio- selectivities, the (*Z*)-epoxides being the major isomers. This indicates that non symmetric

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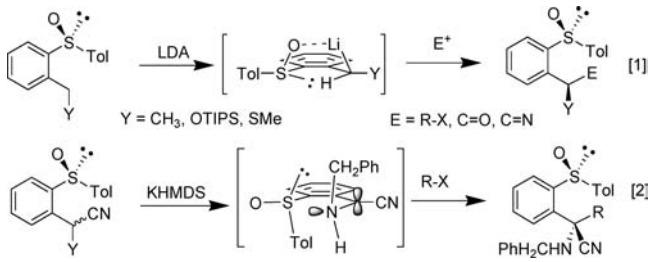
ketones are still challenging substrates for direct transformation into epoxides.

We have recently reported the almost completely stereoselective transference of chiral benzyl groups to different electrophiles starting from α-trimethylsilyloxy,[4] α-alkyl,[5] and α-methylthiolithium[6] benzylcarbanions. Anionic intermediates with the lithium chelated by the sulfinyl oxygen and the benzyl carbon[7] (Scheme 1, eq 1) seem to be involved in

Scheme 1. Reactions of the 2-(*p*-Tolylsulfinyl)carbanions with *N*-Sulfinylimines



these tranformations. Highly stereoselective quaternization at benzylic position on α-alkyl α-oxygenated (or nitrogenated) benzylcarbanions has been possible with KHMDS, presumably through non chelated carbanions (Scheme 1, eq 2).[8] Bearing in mind these antecedents, we thought that the reactions of 2-*p*-tolylsulfinylbenzyl iodide (*S*)-**1** with ketones could provide a new strategy for synthesizing trisubstituted epoxides. In this paper, we report the results of this study.

Optically pure iodo derivative (*S*)-**1** was prepared starting from (*S*)-2-(*p*-tolylsulfinyl)-α-(tributyltin)toluene[9] by treatment with iodine in CCl_4. We then studied the reaction of (*S*)-**1** with different ketones **2**. After exhaustive experimental work, we found that optimal conditions involve the addition of $NaN(SiMe_3)_2$ to a THF solution containing (*S*)-**1** and the electrophile at −78 °C (Barbier conditions). As summarized in Table 1, this process evolved in a highly stereoselective manner with a wide range of diaryl-, alkylaryl-, and dialkyl-(cyclic and acyclic) ketones. Alkylidenation competes with the homocoupling reaction yielding (*E*)-1,2-di(2-*p*-tolylsulfinylphenyl) ethylene **4**.[10] After 1 min, starting products had disappeared in all the cases, and epoxides **3** were obtained in a high yield except for the sterically hindered and therefore less reactive ketones **2e** and **2j** (Table 1, entries 5 and 10). In these reactions, a significant amount of byproduct **4** was recovered. In reactions with **2f**, **2k**, and **2l**, a small amount of **4** was also detected (entries 6, 11, and 12). All attempts to minimize the extent of this side reaction by using an excess of ketone were unsuccesful.

Reaction starting from benzophenone **2a** (entry 1) gave the desired epoxide **3a** in a high yield and complete diastereoselectivity (>98% de), which proved that the sulfinyl group completely controls the configuration at its benzylic carbon. The reactions with alkyl aryl ketones **2b**−**g**, where two stereogenic centers were simultaneously formed, evolved into a mixture of only two (*E*)-**3** and (*Z*)-**3** epoxides, with high (*E*)-selectivity. *E*/*Z* ratio ranges from 6/1 to >49/1 except for isobutyrophenone **2g**, which yielded a 2/1 mixture of (*E*)-**3g** and (*Z*)-**3g** (entry 7). For ketones **2b**−**d**, bearing neutral or electron-donating groups, the *E*/*Z* ratio increases when the electron-donating ability of the substituent became stronger (entries 2−4). Complete *E*-selectivity was achieved in reactions with ketones **2e** and **2f** bearing the bulkier 2-bromophenyl and naphthyl groups, although only **2f** evolved in good yield (Table 1, entries 5 and 6). Reactions with aryl ketones containing electron-withdrawing groups, such as *p*-trifluoromethyl, were less successful, and mixtures of the four possible epoxides were formed with low diastereoselectivities. The method was also found to be successful for acyclic dialkylketones **2 h-k**, furnishing the corresponding epoxides (*E*)-**3** as the major or exclusive diastereoisomers (entries 8−11). Once again, the *E*/*Z* ratio increases (from 86/14 up to >98/2) when the differences in size of the R groups become higher. The low yield obtained for **2j** could be due to its lower reactivity (see above).

Cyclic ketones also proved the effectiveness of the process (entries 12−14). Starting from symmetrical **2l** and **2m** ketones the corresponding spiroepoxides **3l** and **3m** were obtained as single diatereoisomers in 46% and 98% yields respectively. Reaction with 5-methoxy-1-tetralone **2n** evolved with high de (*E*/*Z* = 93:7) affording the major spiroepoxide **3n** in 79% isolated yield.

Spiroepoxides **3l**−**n** in Cl_3CD underwent spontaneous ring-opening reaction (presumably catalyzed by the acidic traces contained in the solvent) to afford the corresponding allylic alcohols **5** in quantitatively yield and total stereoselectivity. Reaction was complete in 1 h starting from **3l** and **3n**, whereas 48 h was needed to get the complete evolution of **3m** (Figure 1). These differences can be rationalized on the basis of the relative stability of the resulting cycloalkenes or the relative easiness of the formation the carbocations from compounds **3l**, **3m** and **3n**.

Taking into account the *S* configuration exhibited by all compounds of Table 1 at the benzylic carbon (the opposite one to that observed in reactions of the benzylcarbanions shown in Scheme 1, eq 1), the stereochemical results for

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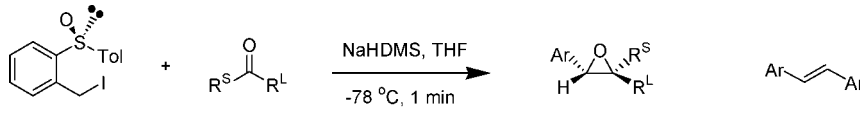
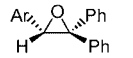
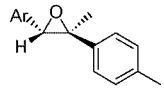
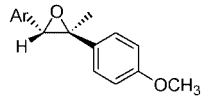
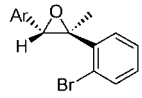
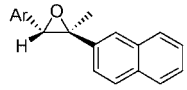
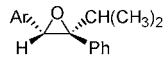
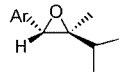
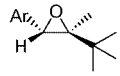
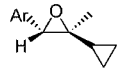
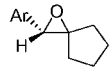
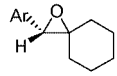
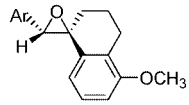
Table 1. Stereoselective Alkylidenation of Ketones with (*S*)-**1** Using a Single Asymmetric Induction Process



(*S*)-**1** **2a-n** (*E*)-**3** and (*Z*)-**3** **4**

entry	ketone, **2a-n**	major epoxide (2S,3S)-**3a-n**	yield (%) (*E*)-**3**[a]	yield (%) **4**[a]	(*E*)-**3** : (*Z*)-**3**[b]	de (%)[b] (*E*)-**3**
1	Benzophenone, **2a**		90	-	-	>98
2	Acetophenone, **2b**		73	-	86:14	>98
3	4'-Methylacetophenone, **2c**		78	-	90:10	>98
4	4'-Methoxyacetophenone, **2d**		80	-	92:8	>98
5	2'-Bromoacetophenone, **2e**		35	29	>98:<2	>98
6	2-Acetonaphthone, **2f**		74	10	>98:<2	>98
7	Isobutyrophenone, **2g**		57	-	66:34	>98
8	2-Butanone, **2h**		72	-	86:14	>98
9	3-Methyl-2-butanone, **2i**		87	-	98:2	>98
10	3,3-Dimethyl-2-butanone, **2j**		26	33	>98:<2	>98
11	Cyclopropylmethylketone, **2k**		65	12	93:7	>98
12	Cyclopentanone, **2l**		46	18	-	>98
13	Cyclohexanone, **2m**		98	-	-	>98
14	5-Metoxy-1-tetralone, **2n**		79	-	93:7	>98

[a] Yield of isolated product. [b] Determined by ^{1}H NMR from the crude reaction product.

(*S*)-**1** could be explained by assuming the formation of the structure **I**, stabilized by steric and electrostatic factors, with the *p*-tolyl group oriented toward the lower face in Figure 2, and therefore only allowing the access of the electrophile to the upper face. It would explain the complete control of the configuration at the benzyl carbon (only compounds with *S* configuration at this center are formed). The relative stability of the two possible aproaches of the ketones to species **I** determines the *E*/*Z* selectivity. Steric effects favor the approach **A** (the larger R^L group does not interact with Ar) evolving into *E*-epoxides and explain the de changes observed for aliphatic ketones. The increase in the *E*-selectivity with the electron-donating power of the substituent in aromatic ketones could be explained as the result of the electronic repulsion (Ar/R^L) between two electron-riched rings (R^L is also aromatic) in the approach **B** (Figure 2).

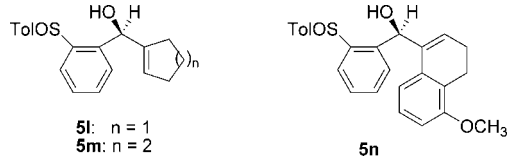


Figure 1. Allylic alcohols resulting from the ring opening of spiroepoxides **3l**−**n**.

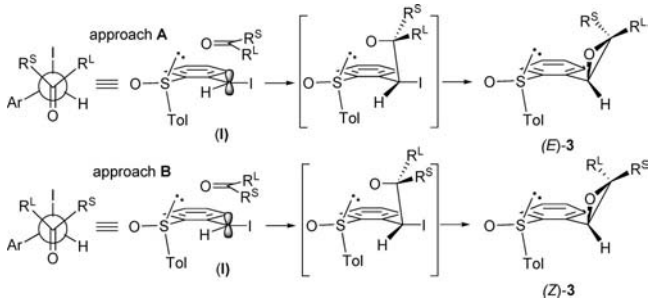
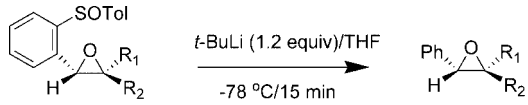


Figure 2. Rationalization of the stereochemical results.

Desulfinylation of epoxides **3** can be easily achieved in very mild conditions by treatment with 1.2 equiv of *t*-BuLi at −78 °C. Thus, as summarized in Table 2, compounds **3a**, **3b**, **3f**, and **3i** were transformed into the corresponding 3-phenyl-2,2-disubstituted epoxides **6a**, **6b**, **6f**, and **6i** in good yields. The optical purity of **6a**, **6b**, and **6f**, determined by chiral HPLC with a Chiralcel OD column, indicates that starting epoxides **3** are not significantly epimerized under the reaction conditions.

Table 2. Desulfinylation of Epoxides **3**



entry	substrate	product	yield[a] (%)	ee[b] (%)
1	(3*S*)-**3a**	(3*S*)-**6a**	75	95.6
2	(2*S*,3*S*)-**3b**	(2*S*,3*S*)-**6b**	68	>99
3	(2*S*,3*S*)-**3f**	(2*S*,3*S*)-**6f**	88	96.6
4	(2*S*,3*S*)-**3i**	(2*S*,3*S*)-**6i**	75	-[c]
5	(2*R*,3*S*)-**3b**	(2*R*,3*S*)-**6b**	69	-[c]

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Not determined.

The absolute configurations of compounds (*E*)-**3b** and **5n** were unequivocally established by X-ray diffraction studies. They allowed us to assign the *S* configuration to both oxiranic carbons at (*E*)-**3b** and the *R* configuration to the benzylic carbon at **5n** (which means that configuration at C3 in the starting epoxide **3n** is *S*). Additionally, the absolute configuration of **6a** was assigned as *S* by comparison of optical rotation and HPLC retention times with those reported in the literature.[11] The similar behavior observed in all the epoxidation reactions summarized in Table 1, all of them evolving with complete control of the configuration at the benzyl carbon and high *E*/*Z* diastereoselectivities, suggests that the absolute configuration for the epoxides **3c**−**k** is also 2*S*,3*S*. For the same reasons, **3l** and **3m** must be assigned as 3*S*. Additionally, the (*E*)-stereochemistry of epoxides **3h**−**3k**, synthesized from alkyl alkyl ketones, was based on the NOE experiments performed on pure sample of the major isomer of 3i (see the experimental methods, Supporting Information).

The absolute configuration of the minor (*Z*)-**3b** isomer was established as (2*R*,3*S*) by desulfinylation with 1.2 equiv of *tert*-BuLi at −78 °C, and comparison of the HPLC retention time of the resulting 2-methyl-2,3-diphenyldioxirane with that reported in the literature for the (2*R*,3*S*)-isomer.[3]

In summary, we have described the highly enantio- and diastereoselective reaction of ketones with chiral α-iodo-2-(*p*-tolylsulfinyl)toluene (*S*)-**1** to generate trisubstituted epoxides.

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Supporting Information Available: General experimental methods, chromatograms for the determination of ee values, X-ray sturcture data (CIF) for (*E*)-**3b** and **5n**, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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