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The Isopropylsulfinyl Group: A Useful Chiral Controller for the Asymmetric Aziridination of Sulfinylimines and the Organocatalytic Allylation of Hydrazones

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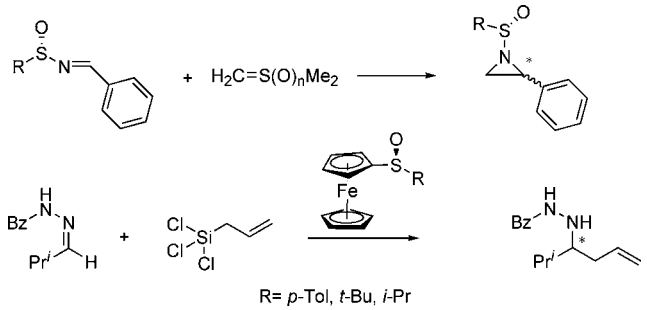
ABSTRACT



A comparative study shows that the isopropylsulfinyl group for which an enantiodivergent and highly diastereoselective approach is reported behaves better than the *tert*-butylsulfinyl and *p*-tolylsulfinyl groups, both in terms of reactivity and stereoselectivity in the Corey–Chaykovsky reaction of chiral sulfinylimines and the organocatalytic allylation of acyl hydrazones.

The past decades have witnessed an increased interest in the preparation of chiral sulfinyl derivatives in relation to their application in asymmetric synthesis.[1] This interest was mainly directed toward the preparation of enantiomerically pure sulfoxides as a consequence of their high efficiency, as well as their wide applicability as chiral controllers in asymmetric carbon−carbon and carbon−heteroatom bond formation.[2] Recent interesting applications of enantiomerically pure sulfoxides include inter alia their utilization as chiral ligands or ligand precursors in metal-catalyzed asymmetric reactions,[1] in coordination chemistry,[1,3] and as Lewis bases in organocatalysis.[4] On the other hand, the exceptional behavior of the chiral sulfinyl group in sulfinylimine, as an activator, a chiral controller, and finally as a useful protective group makes the sulfinylimines a universal intermediate for the asymmetric synthesis of chiral amines.[5,6] Due mainly to

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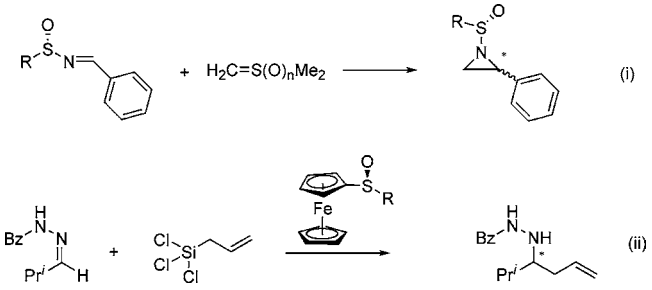
a lack of synthetic methodologies, the main chemistry with chiral sulfinyl derivatives has been carried out using a *p*-tolylsulfinyl group.[2,7] Nevertheless, recent studies have demonstrated that hindered alkyl substituents on the sulfur do confer better stereochemical control in different processes compared to their aryl counterparts. Pioneering work from Casey's group has shown the superiority of *tert*-butyl sulfoxide over the *p*-tolyl sulfoxide in Michael addition.[8] The same trend was recently reported by Ellmann in the synthesis of chiral amines[5] and in metal-catalyzed asymmetric synthesis,[9] by Ruano and Fernández in the aziridination of sulfinylimine,[10] and by Carretero in the Pauson−Khand reaction.[11]

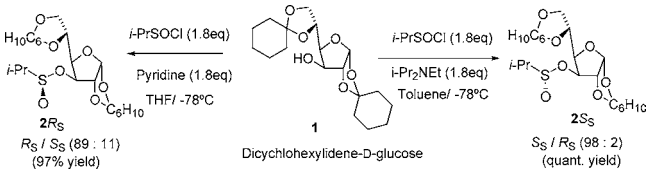
These results promoted an active search of new and more hindered sulfinylating agents.[12] Surprisingly, the synthesis of sulfinyl auxiliaries with an intermediate size between the *p*-tolylsulfinyl and the *tert*-butylsulfinyl group did not attract much interest. Significantly, while the effect of the steric hindrance on the stereoselectivity is always beneficial, there are cases where the reaction becomes exceedingly slow if not inhibited (vide infra).[10] With these premises in mind, we thought that the development of less sterically demanding sulfinyl substituents such as the isopropyl derivatives might present the advantages of lower molecular weight and higher reactivity and could thus be a good alternative to the popular *tert*-butyl sulfinyl group, provided that the enantioselectivity achieved is equally high. In this communication, we have found that this is indeed true for two important reactions, the Corey−Chaykovsky reaction of chiral sulfinylimine (eq 1) and the organocatalytic allylation of acyl hydrazones with ferrocenylsulfinyl derivatives (eq 2). In both processes, the isopropylsulfinyl group behaves better than the *tert*-butylsulfinyl and *p*-tolylsulfinyl groups, both in terms of reactivity and stereoselectivity.



Our first comparative study was the Corey−Chakovsky reaction of chiral sulfinylimine for the synthesis of chiral aziridine. The synthetic importance of this reaction has attracted the attention of different research groups, who showed that the diastereomeric ratio of the final aziridines is highly dependent on the nature of the chiral auxiliary. The Ruano[10] and Davis[14] groups were the first to report on the modest diastereocontrol exerted by aromatic sulfinyl auxiliaries. A subsequent study by Ruano and Fernández showed that the *tert*-butylsulfinyl group was the best chiral auxiliary for this transformation, affording the final products with high de.[10]

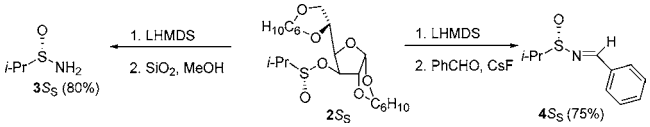
The syntheses of both isomers of the isopropanesulfinate esters, **2(*R*$_S$)** and **2(*S*$_S$)**, have been carried out in high yield and diastereoslectivity applying our DAG methodology (Scheme 1).[13] It is noteworthy that, in this case, we have found that the glucose-derived dicyclohexylidene-D-glucose (DCG) **1** gives better chemical yields and diastereoselectivities than diacetone-D-glucose. Additionally, the DCG isopropylsulfinate esters **2** were stable, as no decomposition of these sulfinates was detected after months at 4 °C.

Scheme 1



Treatment of **2(*S*$_S$)** with LHMDS at −78 °C followed by suspending the crude reaction mixture in silica gel afforded, after filtration and crystallization, the sufinamide **3(*S*$_S$)** with a good 80% isolated yield. Using Davis' conditions for the synthesis of chiral sulfinyl aldimine afforded in a one-pot manner phenyl isopropylsulfinylimine **4(*S*$_S$)** in 75% yield and in only 2 h.[14] The absolute configuration of the obtained sulfinylimine was *S* as shown by X-ray analysis (see Supporting Information), confirming the *S* configuration at sulfur in the starting sulfinate ester (Scheme 2).

Scheme 2



A comparative study on the asymmetric aziridination of *N*-sulfinylaldimines **4**, **5**, and **6** employing either dimethylsulfonium methylide (**A**) or dimethyloxosulfonium methylide (**B**) as methylene transfer is presented in Table 1.

As it can be seen from Table 1, both the *tert*-butyl and isopropylsulfinyl groups are better chiral auxiliaries than the

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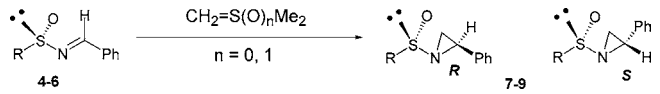
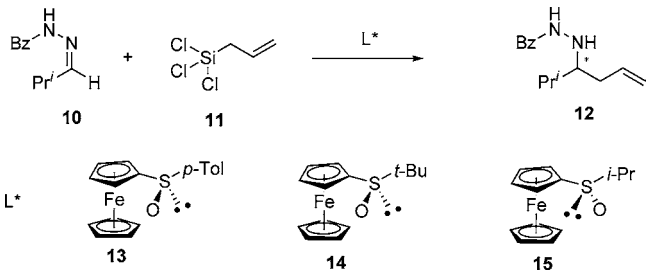
Table 1. Reaction of *N*-Sulfinylimines with Dimethylsulfonium Ylide ($n = 0$, Reagent A) and with Dimethyloxosulfonium Ylide ($n = 1$, Reagent B)[10]



entry	R	*N*-sulfinylimine	reagent[a]	time (h)	aziridine	2*S*:2*R*[b] ratio	de[c]
1	*p*-Tol	**6**	A	2	**9**	40:60	20
2	*p*-Tol	**6**	B	48	**9**	73:27	46
3	*t*-Bu	**5**	A	48	**8**	15:85	70
4	*t*-Bu	**5**	B	168	**8**	95:5	90
5	*i*-Pr	**4**	A	1	**7**	15:85	70
6	*i*-Pr	**4**	B	48	**7**	91:9	86

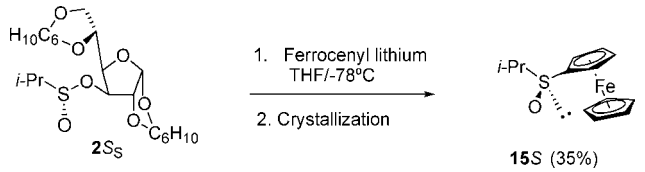
[a] Reagent generated in situ, ($n = 0$ for **A** and $n = 1$ for **B**). [b] C-2 configuration of the aziridine. [c] Determined by ^{1}H NMR of the crude.

p-tolylsulfinyl group. When dimethylsulfonium methylide was used for methylene transfer (reagent A), the isopropyl sulfinyl and *tert*-butyl sulfinyl groups gave the (2*R*)-aziridine with the same diastereomeric excess (entries 3 and 5), higher than that obtained with the *p*-tolyl derivative **6** (entry 1). Nevertheless, while 48 h was needed to complete the reaction in the case of the *tert*-butyl group (entry 3), the reaction with the isopropyl sulfinyl group was complete after only 1 h (entry 5). The same trend is observed when dimethyloxosulfonium methylide was used for methylene transfer (reagent B). In this case, the isopropylsulfinyl group maintains the same reactivity as the *p*-tolyl group (compare times of reaction in entries 2 and 6), but with only a slightly lower diastereomeric excess than the *tert*-butylsulfinyl group, for which not less than 168 h was needed to complete the reaction. A close look at the results in Table 1 allows us to conclude that the isopropyl group combines the advantages of both chiral auxilaries, the higher reactivity of the *p*-tolylsulfinyl group with the better chiral discrimination of the *tert*-butylsulfinyl group.



One of the most appealing recent applications of enantiomerically pure sulfoxides is their utilization as a chiral Lewis base in the allylation of aldehydes and hydrazones with allyl trichlorosilane.[4,15] Even though the reason for the ee observed is unknown, the apparent relation of enantioselectivity and the size difference between the substituents on the sulfinyl sulfur prompted us to carry out a study of the allylation of *N*-(benzoyl)isobutylhydrazone **10** with trichloroallyl silane **11** using the electronically rich ferrocenyl sulfoxides **13**, **14**, and **15** as chiral Lewis bases. For the synthesis of the unknown *i*-Pr-ferrocenylsulfoxide **15** in optically pure form, we used the approximation pioneered by Kagan for the synthesis of **13** and **14**.[16] Condensation of 1.5 equiv of ferrocenyllithium on **2(*S*$_S$)** at −78 °C, followed by a rapid quench, afforded the desired sulfoxide **15** in 55% yield and 90% ee.[16] A simple recrystallization from hexanes afforded optically pure **15(*S*$_S$)** in a 35% isolated yield (Scheme 3).

Scheme 3



Using the best conditions reported by Kobayashi for the allylation of hydrazones with trichloroallyl silane,[4a] we underwent a comparative study of the effect of the substituent at the sulfinyl sulfur on the stereoselectivity, and the results are reported in Table 2.

As it can be seen from Table 2, the sulfinylferrocenes are good ligands for the allylation of hydrazone, as they all give the product in high chemical yield and short reaction time. With regard to the enantioselectivity, the *p*-tolylsulfinylferrocene **13(*R*)** gave the product in quantitative yield but with quasiracemization (4% ee, Table 2, entry 1). The *tert*-butylsulfinylferrocene **14(*R*)**, which has recently been successfully used as a ligand precursor for asymmetric catalysis,[16b] gave the product in longer reaction time and 72% yield, with a deceiving 26% ee (Table 2, entry 2). Remarkably enough, the isopropylsulfinylferrocene **15(*S*)** gave the (*S*)-allyl hydrazone in quantitative yield and 82% ee.

The results presented in this work show that besides the advantage of lower molecular weight, the isopropylsulfinyl

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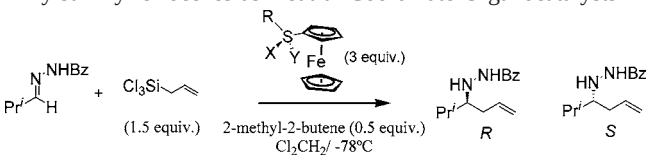
Table 2. Asymmetric Allylation Using Various Alkylsulfinylferrocenes as Neutral Coordinate Organocatalysts



entry	R	X	Y	time (h)	enantiomeric ratio (%)[a] *S*:*R*	yield (%)[b]
1	*p*-Tol		O	1.5	48:52	≥95
2	*t*-Bu		O	1.0	37:63	72
3	*i*-Pr	O		1.0	91:9	≥95

[a] Determined by chiral HPLC. [b] Isolated yield.

group also confers higher chemical reactivity and better enantiomeric discrimination than the *p*-tolylsulfinyl group and similar or even much better reactivity and enantiomeric discrimination than the most popular *tert*-butylsulfinyl group. These results make us optimistic about the behavior of the isopropylsulfinyl group in other chiral transformations, especially those using chiral sulfinyl derivatives as ligands or ligand precursors in metal-catalyzed asymmetric transformation. Work in this area is under active investigation in our group.

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Supporting Information Available: Representative experimental procedures for the synthesis of compounds **2(*S*)**, **2(*R*)**, **3(*S*)**, **4(*S*)**, and **15(*S*)**; general methods for aziridination and allylation; and listings of positional and thermal parameters for **4(*S*)** and **15(*S*)** with bond distances and angles for the non-hydrogen atoms (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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