OL Organic Letters

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Enantioselective Ir-Catalyzed Hydrogenation of Terminal Homoallyl Sulfones: Total Synthesis of (−)-Curcumene

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Cite This: *Org. Lett.* 2023, 25, 1453−1457 Read Online

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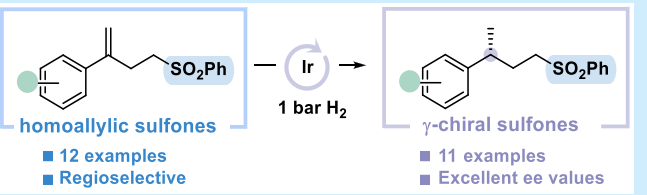
ABSTRACT: A novel methodology for the preparation of chiral methyl benzylic compounds is reported. Terminal homoallyl sulfones were prepared from homoallyl alcohols, which are easily accessible through the recently reported Lewis acid isomerization of oxetanes. The iridium-catalyzed asymmetric hydrogenation of homoallylic sulfones afforded γ-chiral sulfones with excellent enantioselectivities (up to 98% ee). The synthetic potential of this novel methodology was demonstrated by the total synthesis of (*R*)-(−)-curcumene.



The stereogenic α-methyl aromatic fragment is found in many drugs and natural products (Figure 1). Among

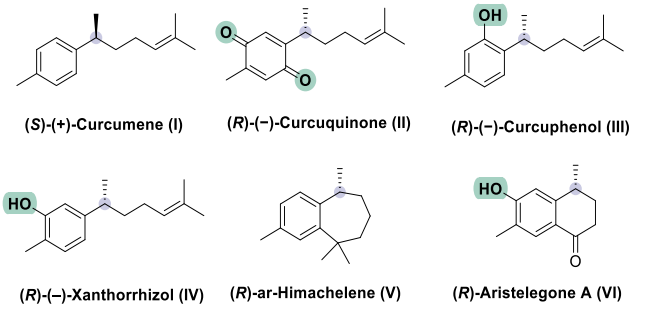


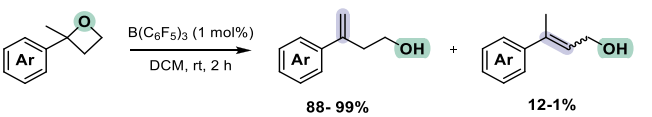
Figure 1. Examples of biologically active compounds containing a chiral methyl benzylic fragment.

them, the bisabolane family of sesquiterpenes[1] (**I**−**VI**) displays a wide range of biological activities that have been used in traditional medicine.[2] In fact, quite often, the two enantiomers of these terpenes have been isolated from natural sources and show distinct but key biological properties. (*S*)-α-Curcumene (**I**) has been described as an insecticide, whereas its enantiomer shows notable antimicrobial and antitumoral properties.[3,4] (−)-Curcuquinone (**II**) was isolated from a Caribbean gorgonian sea plume and is responsible for its antibacterial properties.[5] (*R*)-Curcuphenol (**III**) shows antibiotic activity, whereas its enantiomer exerts cytotoxicity against human tumors and inhibits HK-ATPase.[6] Xanthorrhizol (**IV**) is a wide-spectrum natural bioactive compound.[7] (*R*)-*ar*-Himachalene (**V**) is a male-specific pheromone, whereas its enantiomer is a key component in cedar wood essential oils.[8] In addition, these sesquiterpenes have proven to be functional chiral building blocks for the construction of natural products of biological relevance, such as heliannuols[9] or aristelegone A (**VI**).[10]

Asymmetric catalysis[11] is among the most useful methodologies in drug syntheses, since the two enantiomers usually display distinct biological activity. Iridium complexes bearing chiral *P*,*N* ligands have been successfully applied to the asymmetric hydrogenation of a wide range of C═C and C═N bonds.[11,12] In regents years, we used this approach for the synthesis of chiral amines through the asymmetric hydrogenation of cyclic enamides,[13] *N*-aryl and *N*-alkyl imines,[14] nonfunctionalized olefins,[15] and 2,3-diarylallyl amines.[16] With the aim to expand the substrate scope to terminal olefins, the group developed a new methodology to synthesize homoallylic alcohols through a highly selective Lewis acid catalyzed isomerization of 2,2-oxetanes (Scheme 1).[17]

Although the reaction was highly diastereoselective, some homoallylic alcohols were difficult to purify from their corresponding *E*/*Z*-allylic isomer, whose presence resulted in a substantial decrease of the enantioselectivity of the

Scheme 1. Isomerization of 2,2-Oxetanes to Homoallylic Alcohols



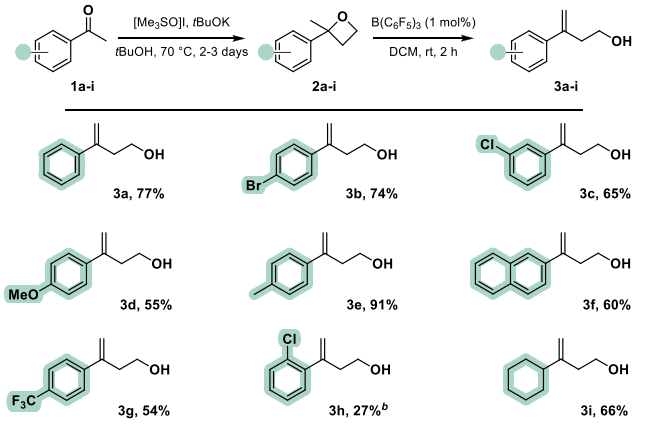
Received: January 18, 2023
Published: March 1, 2023

hydrogenated products. To overcome this, we envisioned a new strategy on the basis of the replacement of the OH group by a sulfonyl group, as this approach might increase the enantioselectivity, ease the separation of the regioisomers, and facilitate a wide range of reactivity. In this regard, chiral sulfones have become useful functional groups in synthetic chemistry because of not only their presence in biologically active drugs[18] but also the acidity of their α-position.[19] The latter enables their transformation into other functional groups and further derivatization. Several strategies involving asymmetric hydrogenation have been used to construct chiral sulfones.[20] Outstanding enantioselectivities were achieved in the iridium-based asymmetric hydrogenation of sulfones reported by Andersson and co-workers.[21] More recently, additional examples using rhodium have been described by the Hou and Zhang groups.[22] Nevertheless, all of the aforementioned cases were internal, trisubstituted olefins, which often encounter *E*/*Z*-selectivity issues, and whose hydrogenation requires high-pressure conditions. In contrast, terminal olefins have the advantages of being more reactive and do not show *E*/*Z*-isomerism.[23] We used this strategy in the asymmetric hydrogenation of 1,1-disubstituted *N*-sulfonyl allyl amines[24] and 2-aryl allyl phthalimides.[25]

Here, we describe the efficient synthesis of homoallylic sulfones on the basis of the regioselective isomerization of oxetanes and their highly enantioselective Ir-catalyzed hydrogenation. The potential and versatility of this approach was successfully demonstrated in the total asymmetric synthesis of (−)-curcumene.

The synthesis of homoallylic sulfones was envisaged from the corresponding homoallylic alcohols. Commercially available aryl methyl ketones **1a**−**i** were transformed into the corresponding oxetanes **2a**−**i** by a double Corey−Chaykovsky reaction without further purification.[26] The resulting oils were regioselectively isomerized using a catalytic amount of $B(C_6F_5)_3$ to afford homoallylic alcohols **3a**−**i** in excellent regioselectivities and good to excellent yields (Scheme 2).[17] The lower yield observed in the case of homoallylic alcohol **3d** (with a *p*-methoxyphenyl group) was mainly because of the formation of a dimer that resulted from the ring opening of the oxetane by the reaction product. The *orto*-chloroacetophenone

Scheme 2. Regioselective Synthesis of Homoallylic Alcohols[a]



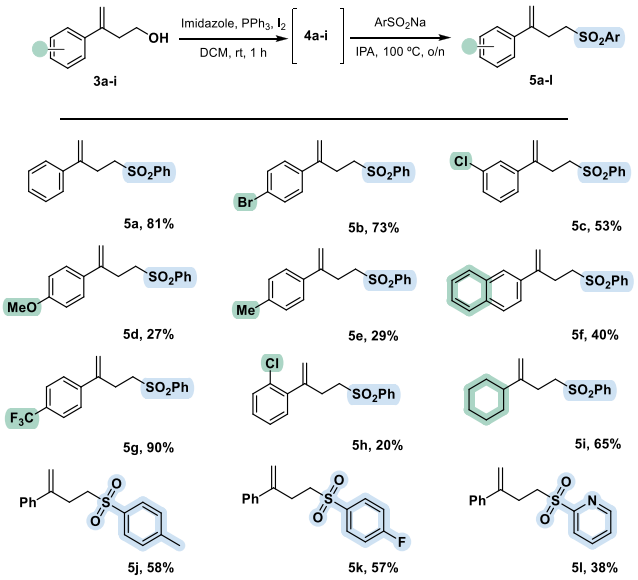
[a]Overall yields for both reactions. [b]The first reaction was performed at 100 °C for 4 days, and the second was run for 17 h.

1h was very unreactive because of steric hindrance. Both reactions had to be performed at higher temperatures and longer reaction times.

The homoallylic alcohols **3a**−**i** were converted into the corresponding iodides **4a**−**i** by the Appel reaction and used without further purification in the subsequent substitution step. Among the several conditions to transform the alcohol into a good leaving group, those reported by Gibbs and co-workers afforded the highest yield.[27]

The substrate scope was expanded from the model substrate **5a** to a wide range of compounds. Homoallylic sulfones **5a**−**l** were prepared by heating iodides **4a**−**i** with aryl sulfinates at 100 °C in a pressure tube (Scheme 3). At first, we evaluated

Scheme 3. Scope of the Conversion of Homoallylic Alcohols 3a−i to Sulfones 5a−l[a]



[a]Yields are given for overall two-step reaction.

the incorporation of electron-withdrawing groups, such as **5b**−**c** and **5g**, and observed that they were well tolerated, thereby giving good yields in both steps. However, substrates with an electron-donating group, such as **5d**−**e** and bicyclic **5f**, showed lower yields. The *ortho*-substituted **5h** was also obtained in low yield. Additionally, we expanded the substrate scope to aliphatic **5i** and other aromatic sulfinate groups, such as *p*-tolyl (**5j**) or *p*-F-phenyl (**5k**), to achieve good yields for both steps. Furthermore, we also prepared the heteroaromatic sulfone **5l** by using sodium pyridine-2-sulfinate as the nucleophile.

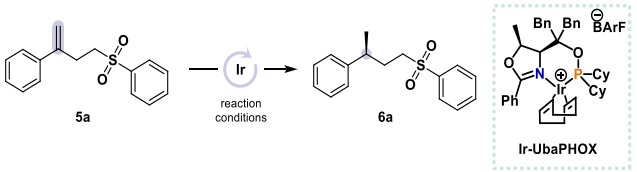
As expected, sulfones **5a**−**l** were easily purified by column chromatography. The small amounts of undesired regioisomers were completely removed. Moreover, the presence of triphenylphosphine oxide in the crude product of the Appel reaction did not affect the following reaction.

The Ir-catalyzed asymmetric hydrogenation of the novel family of homoallylic sulfones was next explored. We used **5a** as a model substrate and commercially available Ir-Ubaphox, {[(4*S*,5*S*)-Cy_2-Ubaphox]Ir(COD)}BAr_F (**C1**),[28] as the catalyst to screen the reaction conditions (Table 1).

Gratifyingly, the reaction took place at low hydrogen pressure and afforded 93% ee at 1 bar of hydrogen at room temperature (for the sake of comparison, the trisubstituted

https://doi.org/10.1021/acs.orglett.3c00181
Org. Lett. 2023, 25, 1453−1457

Table 1. Iridium-Catalyzed Asymmetric Hydrogenation of 5a[a]

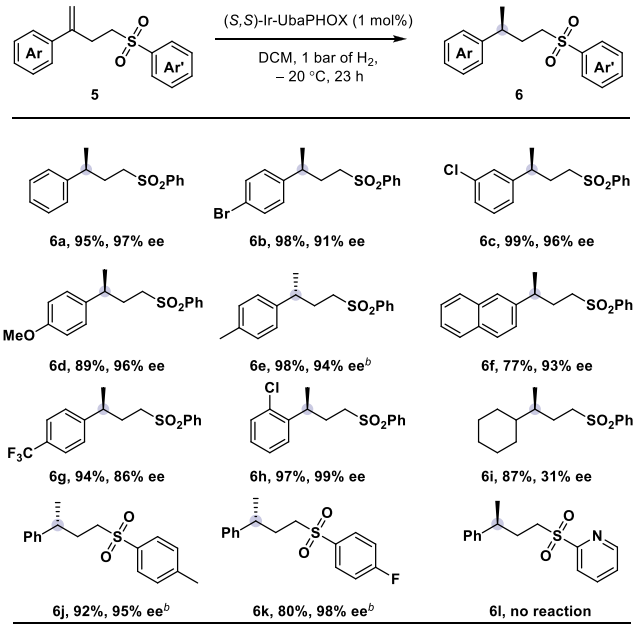


	solvent	T (°C)	H_2 (bar)	conv. (%)[b]	ee (%)[c]
1	DCM	25	50	>99	88 (*S*)
2	DCM	25	15	>99	89 (*S*)
3	DCM	25	1	>99	93 (*S*)
4	DCM	−20	1	>99	97 (*S*)
5	TFE	−20	1	85	94 (*S*)

[a]The reaction was performed in a pressure reactor using 1 mol % of catalyst loading and left stirring for 17 h. [b]Determined by ^{1}H NMR spectroscopy of the crude product. [c]Measured by chiral HPLC.

allylic sulfones[21b] were hydrogenated at 50 bar of H_2 by Andersson's group). An increase in the pressure to 15 or 50 bar led to a reduction in enantioselectivity, probably because of isomerization into the internal isomers (Table 1, entries 1 and 2).[23b] When the temperature was lowered to −20 °C, the enantioselectivity was increased up to 97% ee (Table 1, entry 4). The use of TFE as solvent under the same conditions resulted in a reduction of both enantioselectivity and conversion (Table 1, entry 5). The optimized conditions were applied to the whole set of sulfones **5a**−**l** (Scheme 4). Excellent yields and enantioselectivities were obtained in all cases, with pyridyl sulfone **5l** as the only exception. In that case, deactivation of the catalyst by coordination of the pyridine to iridium prevented the reaction. Substrates bearing either electron-withdrawing substituents, such as *p*-Br (**6b**), *m*-Cl (**6c**), *p*-CF_3 (**6g**), and *o*-Cl (**6h**), or electron-donating groups, such as *p*-Me (**6d**), *p*-OMe (**6e**), and naphthyl (**6f**), gave full conversions and excellent enantioselectivities (up to 99% ee). The enantioselectivity was not significantly affected when the aryl sulfone was changed to *p*-tolyl (**6j**) and *p*-F-phenyl (**6k**) and achieved up to 98% ee. As could be anticipated, replacement of the aryl ring by a cyclohexyl afforded sulfone **6i** in very low enantiomeric excess, probably because of the loss of the π-stacking capability.

Scheme 4. Iridium-Catalyzed Asymmetric Hydrogenations of Homoallylic Sulfones



[a]Yields correspond to isolated material; ee values were measured by chiral-phase HPLC. [b](*R*,*R*)-Ir-UbaPHOX was used as the catalyst.

The absolute configurations of compound **6a** and analogues had been assigned by Andersson's group using chemical correlation.[21b] We confirmed this assignment by the anomalous scattering X-ray diffraction of **6b** (Figure 2 and Supporting Information).

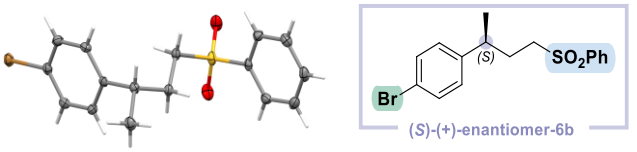


Figure 2. X-ray analysis of enantioenriched sulfone **6b**. Ortep drawing with ellipsoids at 50% probability.

The hydrogenation of trisubstituted allylic sulfones described by Andersson and co-workers gave the opposite sign of the specific rotation compared with our case.[21b] For compound **6a**, they applied the quadrant model to predict the stereochemical outcome in their chemical transformation (see the Supporting Information).[29] We can also explain our observed enantioselectivity by applying Andersson's quadrant model to our catalyst-substrate system with the assumption that the aromatic ring is the bulkiest group (see the Supporting Information). The possibility of isomerization to the internal olefin prior to hydrogenation was ruled out by hydrogenation of **5a** with deuterium under the optimized conditions. The expected deuterated product was obtained in >90% by ^{1}H NMR (see the Supporting Information).

To highlight the applicability of the developed methodology, the total synthesis of the natural terpene (−)-curcumene was performed. Taking advantage of the chemical versatility of sulfones in the construction of carbon−carbon bonds,[18−20] we designed a straightforward route starting from the γ-chiral sulfone **6e** (Scheme 5). α-Deprotonation of **6e** with LDA/TMEDA in Et_2O at −78 °C and subsequent treatment with 2,2-dimethyloxirane[30] afforded **7e** as a 2:1 mixture of diastereomers. Alcohol **7e** was afterward treated with *p*-toluenesulfonic acid in toluene at reflux to furnish olefin **8e**.

Although reduction with metal amalgams is a common strategy for the removal of the sulfone group, we used a greener and safer alternative. Allylic sulfones undergo Pd-catalyzed oxidative addition to form π-allylpalladium complexes, which can be attacked by superhydride ($LiHBEt_3$) under mild conditions.[31] The use of this methodology efficiently removed the sulfonyl group to afford the corresponding desired product **9e** (Scheme 5).

This route allowed us to isolate enantiomerically enriched (*R*)-(−)-curcumene (**9e**) in 72% overall yield starting from **5e**.[32] As the two enantiomers of curcumene could not be separated by chiral HPLC or GC chromatography, the enantiomeric excess was measured after derivatization to **10e** by reductive ozonolysis.[33] The enantiomeric purity was found

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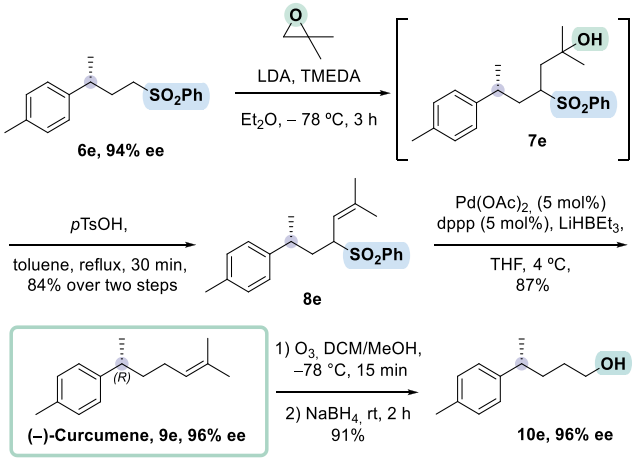
Org. Lett. 2023, 25, 1453−1457

Scheme 5. Enantioselective Total Synthesis of (−)-Curcumene 9e



to be 96% ee by chiral HPLC. Gratifyingly, we observed a slight increase of enantioselectivity during the synthesis.[34]

In conclusion, the described transformation of the homoallylic alcohol to a sulfone served as a scaffold for the installation of the benzylic stereogenic center with high enantioselectivity for a wide range of substrates. In addition, the further derivatization of the sulfone because of the acidity of its α-proton allowed the efficient asymmetric preparation of the natural product (*R*)-(−)-curcumene.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00181.

Experimental procedures and spectroscopic data; ^{1}H NMR and ^{13}C NMR of all new compounds; HPLC of racemic and enantioenriched sulfones and compound **10e**; and origin of the stereoselectivity and isotopic labeling experiment of **6a** (PDF)

Accession Codes

CCDC 2210833 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

Conceptualization: A.R. and M.B. Synthesis of compounds: M.B., C.R.-M., and A.D.-M. Funding and experimental supervision: A.R. and X.V. Writing: M.B., A.R., and X.V.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a grant to A.R. and X.V. from FEDER/*Ministerio de Ciencia, e Innovación* (MICINN) (PID2020-115074GB-I00). M.B. thanks Generalitat de Catalunya for a predoctoral fellowship. IRB Barcelona is the recipient of institutional funding from MICINN through the Centres of Excellence Severo Ochoa award and from the CERCA Program of the Catalan Government.

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https://doi.org/10.1021/acs.orglett.3c00181
Org. Lett. 2023, 25, 1453−1457