Synthesis of Enantiomerically Pure Allenes with Central and Axial Chirality Mediated by a Remote Sulfinyl Group

José Luis García Ruano,* Vanessa Marcos, José Alemán*

Departamento de Química Orgánica (C-I), Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain
Fax +34(914)973966; E-mail: joseluis.garcia.ruano@uam.es; E-mail: jose.aleman@uam.es

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Abstract: Enantiomerically pure 2-(p-tolylsulfinyl)benzylcopper reagents react with propargyl bromides and mesylates, affording enantiomerically pure allenes with central and axial chirality. Both regioselectivity ($S_\text{N}2$ processes) and configuration at the chiral axis are completely controlled by the sulfinyl group. The stereoselectivity at the benzylic position is very high. Complete kinetic resolution and moderate dynamic resolution of racemic propargylic mesylates can be achieved. This stereochemical behavior can be explained by assuming the stabilization of the benzylcopper by the sulfinyl oxygen and the association of the triple bond to the metal as a previous step of the intramolecular $S_\text{N}2$ nucleophilic attack.

Key words: allenes, sulfinyl group, axial chirality, central chirality, asymmetric synthesis

In 2000, we reported the first highly stereoselective reactions of lithium 2-(p-tolylsulfinyl)benzyl carbanions with different electrophiles (Scheme 1), which demonstrated the ability of the remote sulfinyl group in controlling the configuration of a benzylic chiral center. Thus, in reactions with prochiral carbonyl groups (two chiral centers are formed in the same step), the control of the sulfinyl group on the new hydroxyl chiral center was also significant and became complete when the electrophile also contained a chiral auxiliary in a double induction process. A similar behavior was observed in reactions of lithium 2-(p-tolylsulfinyl)benzyl carbanions with imines. The reactions of enantiomerically pure $N$-sulfinylimines with benzylic carbanions containing carbon, oxygen, and sulfur as benzylic substituents evolved in a completely stereoselective way, only yielding one diastereomer in a double-induction process (Scheme 1). However, a mixture of epimers at the nitrogenated carbon was obtained in reactions with $N$-arylimines, without a second chiral auxiliary, in a single induction process. However, in the latter reactions the strong influence of electronic factors on the stereoselectivity was evident, which was quite important in the proposal of a stereochemical model. After removal of the sulfinyl group, these reactions provided one of the best reported methods for obtaining enantiomerically pure anti- and syn-1,2-disubstituted propylamines. This methodology has been applied to the synthesis of enantiomerically pure piperidines and pyrrolidines, fluoroindolines, $\beta$-fluoroamino acids, epoxides, and aziridines (Scheme 1).

Despite these good results, all attempts at conjugated addition of the lithium benzyl carbanions to deactivated double bonds were unsuccessful and only 1,2-addition products were usually observed. Similar behavior was found in reactions with propargylic halides, which only afforded the $S_\text{N}2$ products (instead of allenes resulting in a $S_\text{N}2$’ process). Therefore, it prompted us to evaluate the behavior of their corresponding copper reagents. In this paper, we will describe in detail the results obtained by reaction of propargyl derivatives with copper 2-(p-tolylsulfinyl)benzyl carbanions and the mechanistic proposal for explaining these results.

These reactions are interesting because of the importance of allenes, which are a class of unique compounds exhibiting axial chirality and that are present in a large number of medicinal and natural products. Despite the large number of methods for preparing allenes, the number of references allowing their preparation in enantiomerically pure form is rather low. One of the most often used methods for achieving this goal involves the $S_\text{N}2$ reaction of an organocopper reagent with an enantiomerically pure propargylic derivative (Scheme 2, equation 1). As the main limitation of this methodology is the availability of the enantiomerically pure propargylic alcohols, the search for organocopper reagents able to kinetic resolve racemic propargylic derivatives remains a highly desirable challenge.

By assuming that the efficiency of this resolution would be higher when the chiral elements at substrate and reagent, involved in the asymmetric induction, are close in proximity, the use of enantiomerically pure organocopper reagents with a chiral center directly joined to the metal should presumably provide the best results. Thus, we reasoned that organocopper reagents, obtained by transmetalation of our lithium 2-(p-tolylsulfinyl)benzyl carbanions, could be appropriated because they would generate allenes bearing a chiral carbon directly connected to the allenic system and exhibiting axial chirality (Scheme 2, equation 2).

We first performed studies to find the optimal conditions for the transmetalation. Reactions of sulfoxide 1a with propargyl bromide (2a) were used as the control experiment. Lithium carbanion [Li]-1a only gave the terminal alkyne 3a (90% yield) as the result of an $S_{\text{N}}2$ process (Scheme 3). As we presumed that the copper carbanion [Cu]-1a would yield the allene 4a, as the result of a $S_{\text{N}}2$’ process, the observed regioisomeric ratio 3a/4a obtained by treating [Li]-1a with different copper sources before
reacting with 2a could be used as a criterion to gain knowledge of the efficiency of the transmetalation process.

After trying different copper sources (CuTc, CuCl, CuI, CuCN), we found that the best transmetalation conditions were obtained by addition of CuCN–LiCl (2.5 equiv) in tetrahydrofuran at –10 °C to the enantiomerically pure lithium 2-(p-tolylsulfinyl)benzyl carbanion [Li]-1a at –78 °C (Scheme 3). Under these conditions, [Cu]-1a reacts with propargyl bromide (2a) in a completely regioselective manner, only affording the allene 4a in 92% yield. A similar result was obtained by using the propargyl mesylate (2b) instead of the bromide 2a as the starting material.

Reactions of [Cu]-1a with C3-substituted propargylic systems 2c–f under similar conditions also took place with complete regioselectivity and good yields, affording the 1,1-disubstituted allenes 4b–e (Scheme 4). Similar efficiency was observed when this reaction was performed on a larger scale (up to 5.0 mmol). We then studied reactions of the copper benzyl carbanion derived from 1-ethyl-2-(p-tolylsulfinyl)benzene, [Cu]-1b, with propargyl derivatives. The reaction of [Cu]-1b with propargyl bromide (2a) was completely regioselective, but yielded a 94:6 mixture of the S,2’ products 4f and 4f’, epimers at the benzylic position (Scheme 5 and Table 1, entry 1). Identical results were obtained starting from the propargyl mesylate (2b) (Scheme 5 and Table 1, entry 2). This fact reveals the scarce influence of the leaving group on the stereoselectivity control. Moreover, the efficiency of the sulfinyl group in controlling the configuration at the benzylic position of copper benzyl carbanions was similar to that exerted in reactions with lithium carbanions (Scheme 1).1–11 The potential interest in asymmetric synthesis of the allenes such as 4f, with a chiral center directly joined to the π-system, prompted us to check the scope of this reaction (Table 1).

The reaction of [Cu]-1b with 2c afforded a 88:12 mixture of 4g and 4g’ (Table 1, entry 3), epimers at the benzylic carbon. The total observed regioselectivity in this reaction

Biographical Sketches

José Luis García Ruano (right) received his Ph.D. at the Universidad Complutense (Madrid, 1973). He has held appointments as a Visiting Professor at Florida State (1992) and Emory (2003) Universities and received a fellowship with JSPS in 2006. He was appointed Full Professor in Organic Chemistry at Universidad Autónoma de Madrid in 1982 and has served as vice-president of the Spanish Royal Society of Chemistry for four years. His research interests are centered in the chemistry of sulfoxides and related compounds and their applications in asymmetric synthesis. In these fields, he has published more than 300 papers and supervised 35 Ph.D. theses.

Vanessa Marcos (middle) received her B.Sc. in chemistry at the Universidad Autónoma of Madrid (Spain) in 2005. She started her thesis on 2005 on the synthesis and reactivities of sulfinyl-allenes, under the supervision of Professor García Ruano and Dr. Alemán. In 2008 she spent six months in the laboratory of Professor Karl Anker Jørgensen working in the area of organocatalysis.

José Alemán (left) received his B.Sc. in chemistry at the Universidad Autónoma of Madrid (Spain) in 2000. In 2003 he spent six months in the laboratory of Professor Albert Padwa at Emory University (Atlanta, USA) working on Pummerer rearrangements. In 2005 he received the Lilly Research Award for Ph.D. students and presented his Ph.D. thesis, which was focused on remote stereocontrol by sulfinyl groups and supervised by Professor Jose Luis García Ruano. He carried out his postdoctoral research (2006–2008) in the group of Professor Karl Anker Jørgensen (Aarhus, Denmark). He is currently working (2009) in García Ruano’s lab on new asymmetric methods with sulfur compounds. His research interests include asymmetric synthesis, sulfur chemistry, and organocatalysis.
was remarkable despite the fact that the carbon to be at-
tacked was substituted and, therefore, more sterically hin-
dered. Interestingly, the allene 4h is the only epimer
detected by 1H NMR in the reaction of the sulfoxide 1b
with 2e (>96% de, Table 1, entry 4). Complete stereose-
lective control was also achieved in reactions of 1c with
2a and 2c which afforded 4i and 4j, respectively (Table 1,
entries 5 and 6). The reaction of propargylic bromides 2a
and 2c with allylic carbanion [Cu]-1d gave the corre-
sponding 1,2,6-trienes 4k and 4l, respectively, in high
yields and good diastereomeric ratio (Table 1, entries 7
and 8). These results allow us to conclude that the remote
sulfinyl group is quite efficient in controlling the configu-
ration of the benzylic centers in the organocopper re-
agents.
We then investigated the synthesis of allenes with axial chirality. In this sense, we prepared the enantiomerically pure mesylates \((R)-2g\) and \((S)-2g\), derived from 4-phenylbut-3-yn-2-ol, by an enzymatic resolution of the racemic alcohol. Reactions of \([Cu]-1a\) with both enantiomers are completely stereoselective, and respectively afforded enantiomerically pure \((S,S,aS)-4m\) and \((S,S,aR)-4m'\) in 76% and 73% isolated yields (Scheme 6). Configurational assignment of the chiral axis was performed by assuming the predominance of the \(anti\) attack observed in most of the reactions of the copper anions with the propargylic esters. As expected from the similar rate and the complete stereoselectivity observed for these two reactions, \([Cu]-1a\) is not appropriated for getting the kinetic resolution of the racemic mesylate \(2g\).

Much more interesting were the reactions of \([Cu]-1b\) with propargylic derivatives because they would provide allenes with axial and central chirality and mainly because would allow to confirm our initial assumption about the possible kinetic resolution of the propargylic electrophiles. We first studied reaction of \([Cu]-1b\) with \((R)-2g\). Under mild conditions \((-78\,\text{°C})\), a 95:5 mixture of two diastereomers was almost instantaneously formed \((4n\) and \(4n'\)) in 88% isolated yield (Scheme 7). This result evidences that the configurational control of the axis is completed whereas it is very high at the benzylic center. We initially assumed that \(4n\) and \(4n'\) were epimers at the benzylic position, based on the complete \(anti\)-stereoselectivity observed for reactions in Scheme 6 and the high, but incomplete stereoselectivity shown at Table 1. The con-

**Scheme 5** Reaction of \([Cu]-1b\) with \(2a\) and \(2b\) \((\text{LG} = \text{leaving group})\)

**Table 1** The Reaction of \(1b-d\) with Propargylic Derivatives \(2a-c,e^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield(^b) (%)</th>
<th>dr(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>([Cu]-1b)</td>
<td>Me</td>
<td>2a</td>
<td>H</td>
<td>Br</td>
</tr>
<tr>
<td>2</td>
<td>([Cu]-1b)</td>
<td>Me</td>
<td>2b</td>
<td>H</td>
<td>OMs</td>
</tr>
<tr>
<td>3</td>
<td>([Cu]-1b)</td>
<td>Me</td>
<td>2c</td>
<td>Me</td>
<td>Br</td>
</tr>
<tr>
<td>4</td>
<td>([Cu]-1b)</td>
<td>Me</td>
<td>2e</td>
<td>Ph</td>
<td>OMs</td>
</tr>
<tr>
<td>5</td>
<td>([Cu]-1c)</td>
<td>Bn</td>
<td>2a</td>
<td>H</td>
<td>Br</td>
</tr>
<tr>
<td>6</td>
<td>([Cu]-1c)</td>
<td>Bn</td>
<td>2c</td>
<td>Me</td>
<td>Br</td>
</tr>
<tr>
<td>7</td>
<td>([Cu]-1d)</td>
<td>CH(_2)CH=CH(_2)</td>
<td>2a</td>
<td>H</td>
<td>Br</td>
</tr>
<tr>
<td>8</td>
<td>([Cu]-1d)</td>
<td>CH(_2)CH=CH(_2)</td>
<td>2e</td>
<td>Me</td>
<td>Br</td>
</tr>
</tbody>
</table>

\(^a\) All reactions were performed in a 0.2 mmol scale. LG = leaving group.

\(^b\) Combined isolated yield.

\(^c\) Determined by \(^1\)H NMR spectroscopy on the crude mixture.

\(^d\) Conversion measured by \(^1\)H NMR spectroscopy, in which allene 4i was inseparable from sulfoxide 1c.
Diastereomeric ratio was also determined by chiral HPLC.

Determination of diastereomeric ratio determined by 1H NMR on the crude reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rac-2g</td>
<td>Ph</td>
<td>Me</td>
<td>4n</td>
<td>58</td>
<td>95:5&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>rac-2h</td>
<td>H</td>
<td>Me</td>
<td>4o</td>
<td>53</td>
<td>90:10&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>rac-2i</td>
<td>4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Me</td>
<td>4p</td>
<td>56</td>
<td>85:15&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>rac-2j</td>
<td>Bu</td>
<td>Me</td>
<td>4q</td>
<td>53</td>
<td>93:7&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>rac-2k</td>
<td>Ph</td>
<td>Et</td>
<td>4r</td>
<td>56</td>
<td>96:4&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were performed on a 0.2 mmol scale.

<sup>b</sup> Combined isolated yield.

<sup>c</sup> Diastereomeric ratio determined by 1H NMR on the crude reaction.

<sup>d</sup> Diastereomeric ratio was also determined by chiral HPLC.
In order to explain the stereochemical results we propose the initial formation of a benzylcopper intermediate I, stabilized by the ortho-sulfynil oxygen. These species I (Scheme 9) must exhibit the p-tolyl group at the sulfur atom in a pseudoequatorial arrangement in a half-boat conformation of the six-membered ring. The approach of each enantiomer of the propargyl bromine or mesylate could take place by coordination of one of the π-system at the triple bond with the benzylcopper I, respectively forming II-(R) and II-(S). The conformation depicted in Scheme 9 for these intermediates shows the leaving group adopting a pseudo-anti-periplanar arrangement with respect to the remaining π-double bond acting as nucleophile in the subsequent S_N2 reaction. The intermediates III and IV, formed when the leaving group has been shifted by the electrons of the π-system, respectively evolve into allenes V and VI (Scheme 9) by reduction of Cu(III) to Cu(I).

In all the cases, II-(R) will be favored with respect to II-(S) by steric interactions (H/R_1 vs R_1/R_3). In reactions from [Cu]-Ia (R_1 = H), the evolution of both intermediates would be possible. This assumption was confirmed by reacting [Cu]-Ia with rac-2g. The use of one equivalent of both reagents determines the formation of a 1:1 mixture of 4m and 4m’, which is the expected from results depicted in Scheme 6. In this sense, [Cu]-Ib is much more efficient. The spatial arrangement corresponding to II-(S), when [Cu]-Ib (R_1 = Me) is used as reagent, must be strongly destabilized by the R_1/R_3 interactions (Scheme 9), thus precluding this intermediate can be reached it. As a consequence, [Cu]-Ib would only react with the R-enantiomer towards II-(R), determining a complete kinetic resolution.

The fact that in all these reactions we observe dynamic resolution in some extent could be explained by assuming the epimerization of the propargyl mesylate under reaction conditions (the recovered propargylic alcohol in reactions of Table 2 are racemic). In order to confirm this assumption we treated the mesylate (S)-2g with lithium diisopropylamide at –78 °C for five minutes. After work up with saturated aqueous ammonium chloride, we isolated the corresponding propargylic alcohol almost completely racemized. The low dynamic resolution observed in these reactions (ca. 10%) could be due to the formation of species like II-(S) but in a different conformation to that depicted in Scheme 9, which is not able to evolve into the allene or easily transformed into the starting mesylate and it finally will be transformed in the workup of the reaction to the corresponding alcohol.

In summary, we have demonstrated that the reactions of enantiomerically pure 2-(p-tolylsulfinyl)benzylcopper reagents with propargyl bromides and mesylates take place in a completely regioselective S_N2 manner and follow a totally anti-stereoselective pathway when a chiral axis is formed. The sulfinyl group is very efficient in controlling the configuration of the α-alkylbenzyl–copper reagents, providing the first method to obtain enantiomerically pure allenes with a chiral center directly joined to the allenic system, in which the chiral axis can also have a defined...
configuration. Additionally, a complete kinetic resolution of racemic propargylic mesylates can be achieved with sulfonium salts α-alkylbenzyl–copper reagents, which in their turn are moderately efficient for the dynamic kinetic resolution of the propargylic mesylates.

NMR spectra were acquired on a Bruker 200, 300 or a Varian AS 400 spectrometer, running at 200, 300 or 400 and 50, 75, or 100 MHz for 1H and 13C, respectively, referenced to residual solvent signals [CDCl3, δ = 7.26 (1H), CDCl3, δ = 77.0 (13C)]. 1H NMR spectra were acquired on a broad band decoupled mode. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. All reactions were carried out in anhydrous solvents and under an argon atmosphere. THF and Et2O were distilled from Na/benzophenone under argon and CH2Cl2 was distilled from P2O5. Flash column chromatography was performed using silica gel Merck-60 (230–400 mesh).

Commercially available starting materials and solvents were used without further purification. Sulfoxides 1a–d have been previously described in the literature. The racemic or optically enriched propargylic alcohols were prepared following methods described in the literature.

2-(But-3-ynyl)phenyl p-Tolyl (S)-Sulfoxide (3a)

A soln of 2.3 M n-BuLi in hexanes (0.60 mmol) was added to i-Pr2NH (0.89 mmol) in THF (3 mL) at 0 °C and the mixture was stirred for 3 min; it was then cooled to –78 °C. A soln of the sulfoxide 1a (0.50 mmol) in THF (2 mL) was added, the mixture was stirred for 5 min and then propargyl bromide (2a, 2.0 equiv) was added at –78 °C. When the reaction was complete (5 min), the mixture was hydrolyzed with sat. NH4Cl and extracted with Et2O (3 × 10 mL). The combined organic extracts were washed with sat. NH4Cl soln (2 × 10 mL), dried (MgSO4), and the solvent evaporated. The residue was purified by flash column chromatography (n-hexanes–EtOAc, 6:1; yield: 90%.

1H NMR (200 MHz, CDCl3): δ = 2.26 (2H, J = 7.5, 1H), 3.45–3.25 (m, 2 H). 13C NMR (50 MHz, CDCl3): δ = 20.9, 40.4, 122.3, 131.1, 130.3, 128.2, 126.9, 126.2, 125.8, 125.2, 104.3, 77.7, 35.7, 25.0.

HRMS: m/z [M + H+] calcd for C18H17OS: 269.1012; found: 269.0994.


2-(2-(2-Methylbuta-2,3-dienyl)phenyl p-Tolyl) (S)-Sulfoxide (4b)

Following the general procedure starting from sulfoxide 1a and 1-bromobut-2-ynyl (2c) with flash chromatography (toluene–EtOAc, 20:1) gave 4b (62%) as a colorless oil.

IR (NaCl): 2924, 1956, 1716, 1492, 1083, 1033 cm–1.


2-(2-(2-(2-Phenylbuta-2,3-dienyl)phenyl p-Tolyl) (S)-Sulfoxide (4a)

Following the general procedure starting from sulfoxide 1a and propargyl bromide (2a) with flash chromatography (toluene–EtOAc, 20:1) gave 4a (92%) as a colorless oil.

1H NMR (200 MHz, CDCl3): δ = 2.09, 143.2, 141.6, 141.4, 137.2, 130.7, 130.4, 129.8, 127.7, 125.7, 124.9, 88.4, 75.9, 29.7, 18.5.

2-[2-(Vinylideneheptyl)phenyl]-p-Tolyl (S)-Sulfoxide (4e)
Following the general procedure starting from sulfoxide 1a and oct-2-ynyl mesylate (2f) with flash chromatography (toluene–EtOAc, 20:1) gave 4e (65%) as a colorless oil.

[α]D 20 –127.8 (c 1.03, CHCl3).

1H NMR (300 MHz, CDCl3): δ = 7.00–7.96 (m, 1 H), 7.54–7.42 (m, 4 H), 7.31–7.26 (m, 5 H); 4.46–4.47 (m, 2 H), 3.35–3.36 (m, 2 H), 2.40 (s, 3 H), 1.4–1.34 (m, 3 H).

13C NMR (50 MHz, CDCl3): δ = 206.8, 143.7, 141.4, 137.4, 130.7, 130.5, 129.9, 129.8, 127.7, 125.8, 124.8, 102.3, 35.3, 31.5, 27.0, 22.4, 21.3, 14.0.


2-[(R)-Penta-3,4-dien-2-yl]phenyl-p-Tolyl (S)-Sulfoxide (4f)
Following the general procedure starting from sulfoxide 1b and propargyl bromide (2a) with flash chromatography (toluene–EtOAc, 20:1) gave 4f (76%) as a colorless oil; mixture of diastereomers.

[α]D 20 –206.1 (c 0.4, acetone).

IR (NaCl): 2971, 2923, 1956, 1680 cm–1.

MS (FAB): m/z (%) = 283 ([M + H+] 100), 241 (36), 149 (12), 139 (18).

HRMS: m/z [M + H+] calc for C19H18O+S: 283.1151; found: 283.1151.

Analytical. Calcd for C19H18O+S: C, 76.56; H, 6.42; S, 11.35. Found: C, 75.83; H, 6.46; S, 10.98.

2-(R)-3-Methylpent-3-ene-2-ylphenyl-p-Tolyl (S)-Sulfoxide (4g)
Following the general procedure starting from sulfoxide 1b and 1-bromombut-2-ene (2c) with flash chromatography (toluene–EtOAc, 20:1) gave 4g (51%) as a colorless oil; mixture of diastereomers.

[α]D 20 –169.9 (c 0.3, acetone).

IR (NaCl): 2971, 2923, 1593, 1680 cm–1.

1H NMR (200 MHz, CDCl3): δ (major diastereomer) = 7.93–7.90 (m, 1 H), 7.50–7.10 (m, 7 H), 5.26 (q, J = 6.4 Hz, 1 H), 4.84–4.79 (m, 2 H), 4.10–3.90 (m, 2 H), 2.35 (s, 3 H), 0.99 (d, J = 6.4 Hz, 3 H); δ (minor diastereomer) = 7.93–7.90 (m, 1 H), 7.50–7.10 (m, 7 H), 4.97 (q, J = 6.4 Hz, 1 H), 4.69–4.64 (m, 2 H), 4.10–3.90 (m, 1 H), 2.35 (s, 3 H), 1.24 (d, J = 6.4 Hz, 3 H).

13C NMR (50 MHz, CDCl3): δ = 207.9, 144.0, 142.3, 141.7, 131.3, 130.0, 129.9, 127.7, 127.6, 126.1, 124.7, 95.1, 76.6, 33.1, 21.6, 20.5.

MS (FAB): m/z (%) = 283 ([M + H+] 100), 241 (36), 149 (12), 139 (18).

HRMS: m/z [M + H+] calc for C19H18Os+S: 283.1151; found: 283.1151.

2-[(R)-1-Phenylpent-3-ene-2-yl]phenyl-p-Tolyl (S)-Sulfoxide (4i)
Following the general procedure starting from sulfoxide 1c and propargyl bromide (2a) with flash chromatography (toluene–EtOAc, 20:1) gave 4i (40% conversion) as an inseparable mixture with 1c as a colorless oil; single diastereomer.

1H NMR (300 MHz, CDCl3): δ = 7.86–7.85 (m, 1 H), 7.37–7.03 (m, 2 H), 5.25–5.18 (m, 1 H), 4.65–4.62 (m, 2 H), 4.21–4.15 (m, 1 H), 3.07–2.58 (m, 2 H), 2.24 (s, 3 H).

2-[(R)-3-Methyl-1-phenylpent-3-ene-2-yl]phenyl-p-Tolyl (S)-Sulfoxide (4j)
Following the general procedure starting from sulfoxide 1c and 1-bromombut-2-ene (2c) with flash chromatography (toluene–EtOAc, 20:1) gave 4j (68%) as a colorless oil; single diastereomer.

[α]D 20 –35.7 (c 0.43, CHCl3).

IR (NaCl): 2960, 1958, 1712, 1593, 1469, 1030 cm–1.

1H NMR (300 MHz, CDCl3): δ = 7.62 (d, J = 8.4 Hz, 1 H), 7.46–6.92 (m, 12 H), 8.44–8.42 (m, 2 H), 4.16–4.11 (m, 1 H), 3.20–2.74 (m, 2 H), 2.34 (s, 3 H), 1.61 (d, J = 3.1 Hz, 3 H).

13C-NMR (75 MHz, CDCl3): δ = 206.6, 144.2, 142.6, 141.1, 139.9, 131.5, 129.8, 129.1, 128.4, 128.2, 128.0, 127.9, 126.1, 125.9, 125.7, 101.9, 77.2, 44.8, 40.7, 21.3, 18.3.

MS (FAB): m/z (%) = 373 ([M + H+] 100), 234 (7), 143 (6).

HRMS: m/z [M + H+] calc for C23H19O+S: 373.1613; found: 373.1620.

2-[(R)-Hepta-1,2,6-trien-4-yl]phenyl-p-Tolyl (S)-Sulfoxide (4k)
Following the general procedure starting from sulfoxide 1d and propargyl bromide (2a) with flash chromatography (toluene–EtOAc, 20:1) gave 4k (64%) as a colorless oil; mixture of diastereomers.

[α]D 20 –11.6 (c 0.4, acetone).

IR (NaCl): 2968, 2925, 1593, 1469, 1030 cm–1.

1H NMR (300 MHz, CDCl3), δ (major diastereomer) = 7.99 (d, J = 7.5 Hz, 1 H), 7.50–7.20 (m, 7 H), 5.30–5.20 (m, 2 H), 5.00–4.90 (m, 2 H), 4.80–4.70 (m, 2 H), 3.92–3.88 (m, 1 H), 2.50–2.38 (m, 1 H), 2.30–1.95 (m, 1 H); δ (minor diastereomer) = 7.99 (d, J = 7.5 Hz, 1 H), 7.50–7.20 (m, 7 H), 5.30–5.20 (m, 2 H), 5.00–
(1H NMR (300 MHz, CDCl3); δ (major diastereomer) = 7.98–7.97 (m, 1 H), 7.52–7.24 (m, 7 H), 5.50–5.39 (m, 2 H), 5.00–4.95 (m, 2 H), 4.85–4.72 (m, 2 H), 3.65–3.60 (m, 1 H), 2.50–2.38 (m, 1 H), 2.38 (s, 3 H), 1.99–1.90 (m, 2 H), 1.60 (t, J = 3.1 Hz, 1 H); δ (minor diastereomer) = 7.98–7.97 (m, 1 H), 7.52–7.24 (m, 7 H), 5.50–5.39 (m, 2 H), 5.00–4.95 (m, 2 H), 4.85–4.72 (m, 2 H), 3.65–3.60 (m, 1 H), 2.50–2.38 (m, 1 H), 2.38 (s, 3 H), 1.99–1.90 (m, 2 H), 1.60 (t, J = 3.1 Hz, 1 H).)

IR (NaCl): 3058, 2923, 1684, 1595, 1491, 1083, 1054, 1030, 1349, 758 cm–1.


(1H NMR (300 MHz, CDCl3); δ (major diastereomer) = 7.99–7.98 (m, 1 H), 7.53–7.24 (m, 7 H), 5.49–5.40 (m, 2 H), 4.84–4.72 (m, 2 H), 3.65–3.60 (m, 1 H), 2.50–2.38 (m, 1 H), 2.38 (s, 3 H), 1.99–1.90 (m, 2 H), 1.60 (t, J = 3.1 Hz, 1 H); δ (minor diastereomer) = 7.98–7.97 (m, 1 H), 7.52–7.24 (m, 7 H), 5.50–5.39 (m, 2 H), 5.00–4.95 (m, 2 H), 4.85–4.72 (m, 2 H), 3.65–3.60 (m, 1 H), 2.50–2.38 (m, 1 H), 2.38 (s, 3 H), 1.99–1.90 (m, 2 H), 1.60 (t, J = 3.1 Hz, 1 H).)

IR (NaCl): 3058, 2923, 1684, 1117, 1032, 810, 758 cm–1.

HRMS: m/z [M + H+] calcd for C23H22OS: 359.1467; found: 359.1467.

Following the general procedure starting from sulfoxide 1b and (R)-4-phenylbut-3-yn-2-yl mesylate ([R]-2g) with flash chromatography (toluene–EtOAc, 20:1) gave 4m (73%) as a colorless oil; single diastereomer.

[α]D20 = –93.9 (c 1.1, CH2Cl2).

IR (NaCl): 3058, 2923, 1684, 1117, 1032, 810, 758 cm–1.


Following the general procedure starting from sulfoxide 1a and (S)-4-phenylbut-3-yn-2-yl mesylate ([S]-2g) with flash chromatography (toluene–EtOAc, 20:1) gave 4n (76%) as a colorless oil; single diastereomer.

[α]D20 = 191.0 (c 1.85, CHCl3).

IR (NaCl): 3058, 2923, 1684, 1117, 1032, 810, 758 cm–1.


Following the general procedure starting from sulfoxide 1a and (S)-4-phenylbut-3-yn-2-yl mesylate ([S]-2g) with flash chromatography (toluene–EtOAc, 20:1) gave 4n (76%) as a colorless oil; single diastereomer.

[α]D20 = 191.0 (c 1.85, CHCl3).

IR (NaCl): 3058, 2923, 1684, 1117, 1032, 810, 758 cm–1.


Following the general procedure starting from sulfoxide 1a and (S)-4-phenylbut-3-yn-2-yl mesylate ([S]-2g) with flash chromatography (toluene–EtOAc, 20:1) gave 4n (76%) as a colorless oil; single diastereomer.

[α]D20 = 191.0 (c 1.85, CHCl3).

IR (NaCl): 3058, 2923, 1684, 1117, 1032, 810, 758 cm–1.


Following the general procedure starting from sulfoxide 1a and (S)-4-phenylbut-3-yn-2-yl mesylate ([S]-2g) with flash chromatography (toluene–EtOAc, 20:1) gave 4n (76%) as a colorless oil; single diastereomer.

[α]D20 = 191.0 (c 1.85, CHCl3).

IR (NaCl): 3058, 2923, 1684, 1117, 1032, 810, 758 cm–1.
3 H). 2.38 (s, 3 H), 1.83 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 7.0 Hz, 3 H).

13C NMR (75 MHz, CDCl3): δ = 205.8, 143.8, 142.0, 136.3, 131.2, 131.0, 130.1, 128.3, 128.0, 127.5, 127.4, 126.7, 126.6, 126.5, 124.6, 109.9, 90.8, 34.9, 30.8, 21.4, 14.2.

(aS)-2-[(R)-3-Prop-1-enylidene]heptan-2-ylphenyl p-Tolyl (S)-Sulfonoxide (4q)

Following the general procedure starting from sulfoxide 1b and rac-oct-3-yn-2-yl mesylate (rac-2) with flash chromatography (toluene–EtOAc, 20:1) gave 4q (53%) as a colorless oil; mixture of diastereomers 93:7; 86% de [HPLC (2 Chiralpak OD columns, hexane–PrOH, 95:5; flow rate 0.3 mL/min); tk = 59.7 (major), 69.7 (minor)].

[a]D20 = 20.9 (c 0.50, CHCl3).

IR (NaCl): 2921, 1958, 1690, 1595, 1492, 1032 cm–1.

MS (ESI): m/z (%) = 287 (M + H+, 100), 229 (53), 207 (10).


1H NMR (400 MHz, CDCl3); δ = 7.98–7.90 (m, 1 H), 7.42–7.13 (m, 7 H), 3.12–2.99 (m, 1 H), 2.32 (s, 3 H), 1.58–1.46 (m, 2 H), 1.25–0.98 (m, 7 H), 0.85 (d, J = 6.7 Hz, 3 H).

13C NMR (100 MHz, CDCl3); δ = 146.0, 143.2, 142.1, 131.9, 130.4, 127.9, 127.1, 126.4, 125.2, 122.0, 38.4, 37.1, 34.9, 29.9, 23.2, 21.6, 14.4.

(1R)-1-(Pentan-2-yl-2-[(S)-p-tolylsulfinyl])benzene (7)

The product was obtained starting from a diastereomeric mixture of 4f (94:6) or 3b/3b¢ (90:10), following the procedure for hydrogenation with PtO2.20 To a soln of 4f or 3b/3b¢ in EtOH (5 mL) with a hydrogen balloon was added PtO2 (10 mol%). The reaction was followed by TLC and when the reaction was complete, the mixture was filtered through celite and solvent was eliminated under reduced pressure, followed by flash chromatography (n-hexane–EtOAc, 8:1) to give 7 as a colorless oil; yield: 85% (4f/4f¢), 79% (3b/3b¢).

[a]D20 = –84.4 (c 1.7, CHCl3).

IR (NaCl): 2958, 2928, 1595, 1493, 1160, 1083, 1033 cm–1.

1H NMR (300 MHz, CDCl3); δ = 7.88–7.85 (m, 1 H), 7.42–7.14 (m, 7 H), 3.10–3.03 (m, 1 H), 2.28 (s, 3 H), 1.17 (d, J = 6.8 Hz, 3 H), 1.17–0.77 (m, 7 H).

13C NMR (75 MHz, CDCl3); δ = 146.2, 142.0, 141.8, 141.5, 131.2, 129.8, 129.7, 126.9, 126.3, 124.7, 39.1, 34.1, 21.9, 21.2, 20.4, 13.9.

MS (ESI): m/z (%) = 287 (M + H+), 100), 229 (53), 207 (10).

HRMS: m/z [M + H+] calcd for C16H15OS: 287.1454; found: 287.146.

(2R)-2-Phenylhexane (6)17

Over a soln of the sulfoxide 5 (± 5) (0.05 mmol) in THF (5 mL) at 0 °C was added n-BuLi (0.5 mmol). After 10 min the mixture was hydrolyzed with sat. NH4Cl (5 mL), extracted with Et2O (3 × 5 mL) and the solvent was eliminated under reduced pressure. The residue oil was purified by flash chromatography (pentane) to give 6; yield: 60%.

[a]D20 = –97.7 (c 0.1, EtOH). The negative sign of the specific optical rotation matched with that described in the literature2 for the R-enantiomer.

1H NMR (400 MHz, CDCl3); δ = 7.35–7.01 (m, 5 H), 2.66–2.58 (m, 1 H), 1.55–1.11 (m, 6 H), 1.22 (m, 3 H), 0.85 (m, 3 H).

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References


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8. The copper between brackets, [Cu], indicates that the stoichiometric ligand/copper ratio is not known.
