Communication

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Asymmetric synthesis of chiral sulfoximines via the *S*-arylation of sulfinamides

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Supporting Information Placeholder

ABSTRACT: Optically active sulfoximines are a promising substance in medicinal chemistry. However, a methodology for preparing chiral sulfoximines in a stereoselective manner has been underdeveloped. Here, we report an asymmetric synthesis of chiral sulfoximines having an aryl group by the newly developed sulfur-selective arylation of easily accessible chiral sulfinamides. The utility of the present method is demonstrated by the asymmetric synthesis of a key intermediate of a COX-2 inhibitor.

Sulfoximines contain a hexavalent sulfur atom having one oxygen, one nitrogen and two carbon substituents.[1] Their sulfur atom is stereogenic center in the case where the two carbon substituents are not identical. Since chiral sulfoximines have distinctive properties such as a basic nitrogen atom and high solubility in polar solvents, they have recently been considered as promising bioisosteres in medicinal chemistry.[2] Some examples of bioactive sulfoximines are shown in Figure 1.[3] In general, the stereochemistry at the sulfur atom largely affects their biological activity. Accordingly, the development of a new methodology for a stereoselective synthesis of chiral sulfoximines could significantly accelerate an exploration of bioactive compounds containing such motifs.

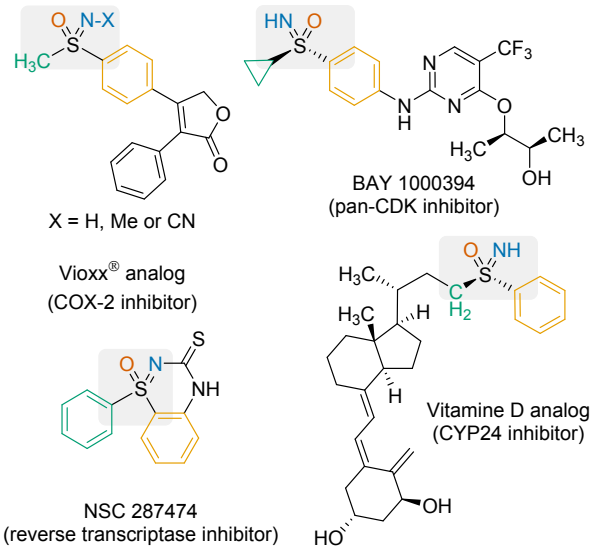


Figure 1. Examples of bioactive sulfoximines.

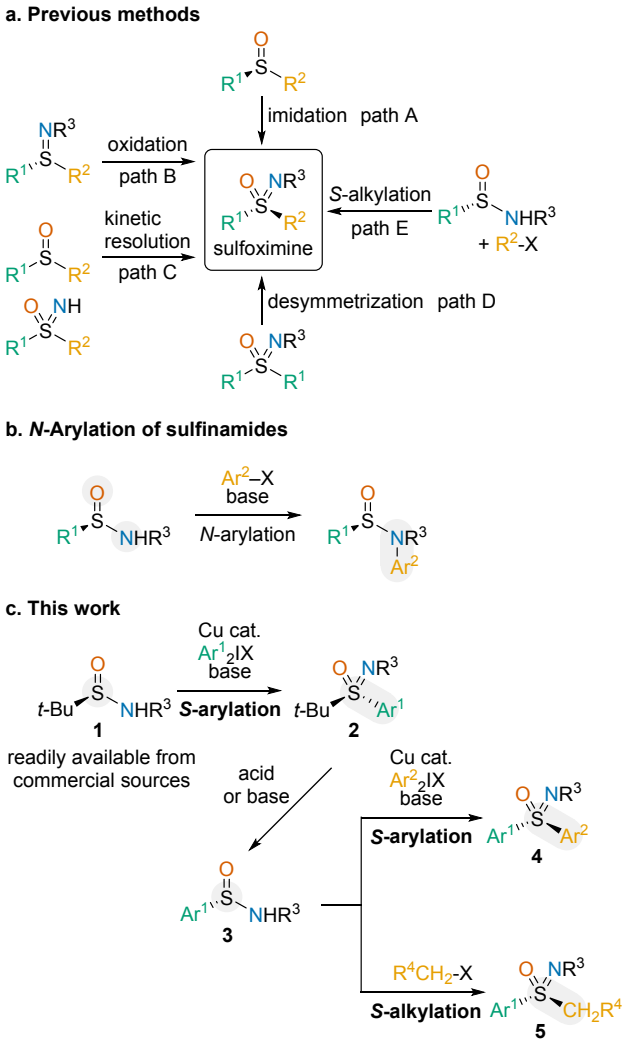


Figure 2. Strategies for the stereoselective synthesis of sulfoximines.

Asymmetric synthesis of chiral sulfoximines mainly relies on a stereospecific nitrene-transfer reaction to chiral sulfoxides (path A) as shown in Figure 2a.[4,5] Enantiomerically enriched chiral sulfoximines were also provided through stereospecific oxidation of enantioenriched sulfimides (path B), kinetic resolution of racemic sulfoxides or sulfoximines (path C) or desymmetrization

of prochiral sulfoximines (path D).[6-8] Additionally, we have recently developed an asymmetric synthesis of sulfoximines via a stereospecific *S*-alkylation of chiral sulfinamides with alkyl halides (R^2-X) (path E).[9] By employing this methodology, various dialkyl sulfoximines can be readily prepared in optically pure form. Chiral aryl sulfoximines are also important structural motifs in medicinal chemistry as shown in Figure1. In this context, we have become interested in the asymmetric synthesis of chiral aryl sulfoximines in optically pure form through the sulfur atom selective arylation of chiral sulfinamides. However, to the best of our knowledge, the arylation at the sulfur atom of sulfinamides has never been explored, probably because they react at the more nucleophilic nitrogen atom preferentially (Figure 2b).[10] Herein, we report the first sulfur-selective arylation of sulfinamides. A wide variety of optically pure sulfoximines can be prepared by the *S*-arylation of readily available (*R*)- or (*S*)-*tert*-butanesulfinamide derivative **1** with diaryliodonium salts under Cu catalysis (Scheme 2c).[11] Moreover, de-*tert*-butylation of the obtained chiral sulfoximines **2** with trifluoroacetic acid (TFA) or KO*t*-Bu enables the asymmetric synthesis of various chiral aryl sulfinamides **3.**[12,13] The resulting sulfinamides **3** were applied to the *S*-alkylation or the second *S*-arylation, affording various optically pure sulfoximines **4** and **5** with predictable stereochemistry.

Sulfoximines **2** having a *tert*-butyl group on the sulfur atom are known to be unstable under highly basic conditions.[12c] While the nucleophilicity of sulfinamides **1** would be improved by deprotonation, a strong base cannot be used in the synthesis of **2**. Therefore, a combination of a highly electrophilic aryl species and a weak base would be suitable to achieve the sulfur-selective arylation of a sulfinamide. In this context, we began our investigation by examining the sulfur-selective arylation with a diaryliodonium salt in the presence of a copper catalyst, because a highly reactive Cu(III)-Ar species for less reactive nucleophiles can be generated under mild conditions.[14] The steric and electronic properties of the nitrogen atom of a commercially available (*rac*)-*tert*-butanesulfinamide were tuned by introducing various protective groups to prevent the preferential *N*-arylation. In 1,2-dichloroethane (DCE) at 40 °C, sulfinamide derivatives (*rac*)-**1** were treated with 10 mol% of CuI, Ph_2IOTf and *i*-Pr_2NEt, and the results were shown in Scheme 1. Most protective groups were ineffective, and no desired *S*-arylation product was observed (Scheme 1a). In contrast, the reaction of (*rac*)-**1a** bearing an *N*-benzoyl group gave the *S*-arylation product in 33% yield albeit with low regioselectivity ((*rac*)-**2a**/(*rac*)-**6a** = 4.1/1) (Scheme 1b).[15] To our delight, replacement of the benzoyl group with a pivaloyl group resulted in the formation of the *S*-arylation product (*rac*)-**2b** exclusively. Based on these results, the pivaloyl group was selected as the protective group of choice for further studies.

Scheme 1. Effect of protective groups on the *S*-arylation

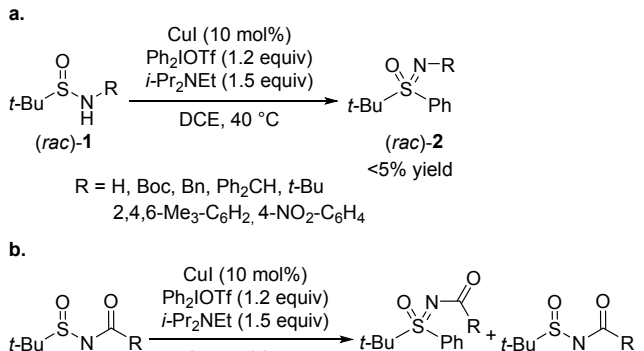
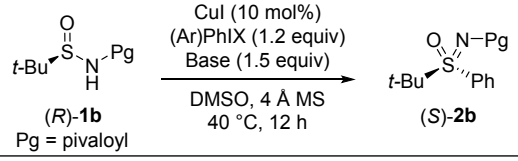


Table 1. Optimization of Reaction Conditions[a]



entry	(Ar)PhIX	base	yield (%)[b]
1[c]	Ph_2IOTf	*i*-Pr_2NEt	26
2[d]	Ph_2IOTf	*i*-Pr_2NEt	20
3	Ph_2IOTf	*i*-Pr_2NEt	55
4	Ph_2IOTf	DTBP	16
5	Ph_2IOTf	*N*-Me-pyrrolidine	39
6	Ph_2IOTf	Cy_2NMe	86
7	Ph_2IOTf	PMP	87
8	Ph_2IOTf	K_2CO_3	<5
9	Ph_2IOTf	NaH	<5
10	Ph_2IOTf	NaH+15-crown-5	33
11	Ph_2IBF_4	Cy_2NMe	85
12	(Mes)PhIOTf	Cy_2NMe	83
13[e]	Ph_2IOTf	Cy_2NMe	81
14[f]	Ph_2IOTf	Cy_2NMe	94
15[f,g]	Ph_2IOTf	Cy_2NMe	<5

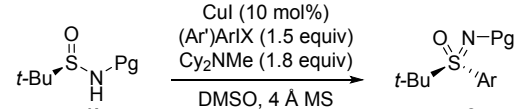
[a]Reactions were performed on a 0.1 mmol scale in 1.0 mL of DMSO. 4 Å MS were added at a concentration of 1.0 g/mmol. [b]Yields were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c]DCE as solvent. [d]MeCN as solvent. [e]$Cu(OTf)_2$ was used instead of CuI. [f]Performed with Ph_2IOTf (1.5 equiv) and Cy_2NMe (1.8 equiv) at 60 °C. [g]Without Cu catalyst. Mes = mesityl.

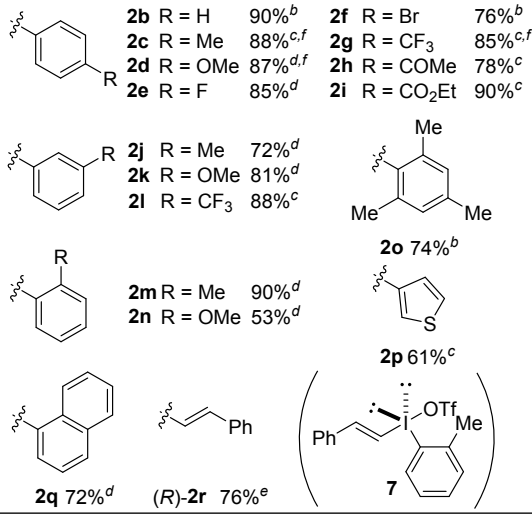
To improve the yield of **2b**, we then investigated effects of solvents and bases employing optically pure (*R*)-**1b** as a substrate (Table 1). Molecular sieves (4 Å) were added to the reaction mixture to prevent an unproductive hydrolysis of the diaryliodonium salt. Among solvents tested, DMSO was found to be optimal in terms of yield (entries 1–3). In these cases, the *N*-arylation product was not observed, suggesting that use of the pivaloyl group was crucial for achieving high regioselectivity. Use of 2,6-di-*tert*-butylpyridine (DTBP) instead of *i*-Pr_2NEt resulted in lower conversion of (*R*)-**1b** probably because of its low basicity (entry 4). With the less hindered amine such as *N*-Me-pyrrolidine, a diminished yield was observed (entry 5). In contrast, sterically hindered amines such as Cy_2NMe and 1,2,2,6,6-pentamethylpiperidine (PMP) promoted the desired reaction to give (*S*)-**2b** in high yield (entries 6 and 7). Use of inorganic bases led to decreased yields (entries 8–10). Similar reactivity was observed, with other diaryliodonium salts such as Ph_2IBF_4 and (Mes)PhIOTf instead of Ph_2IOTf (entries 11 and 12). $Cu(OTf)_2$ was also an effective catalyst for this *S*-arylation (entry 13). Finally, increasing the equivalents of the diaryliodonium salt and the amine allowed the formation of (*S*)-**2b** in 94% yield (entry 14). No reaction was observed in the absence of the copper catalyst (entry 15). Stereochemistry of (*S*)-**2b** was determined by single crystal X-ray diffraction, suggesting that the configuration at sulfur was retained during the sulfur–carbon bond formation.

We next investigated the scope of the present *S*-arylation with a series of diaryliodonium salts (Table 2). Diaryliodonium salts bearing an electron-donating methyl or methoxy group at the *para*-position afforded the corresponding sulfoximines in good yields (**2c** and **2d**). Halides such as F and Br at the *para*-position were well tolerated, allowing further functionalization by nucleophilic aromatic substitution reactions or cross-coupling reactions, respectively (**2e** and **2f**).[16] Use of symmetrical diaryliodonium salts (Ar = Ar′) bearing an electron-withdrawing groups such as CF_3,

acetyl or an ester group at the *para*-position gave the products in low yields (30–43% yields). On the other hand, employing unsymmetrical diaryliodonium salts bearing one bulky mesityl ligand (Ar′= Mes) led to improved yields (**2g**, **2h** and **2i**). The decreased yield with symmetrical diaryliodonium salts might be attributed to the formation of an undesired electron donor−acceptor (EDA) complex with the amine base or the sulfinamide.[17] Substituents at the *meta*- or *ortho*-position were also tolerated, albeit in moderate yield for *ortho*-methoxy group (**2j**–**2n**). Despite its large steric hindrance, a mesityl group was smoothly introduced in 74% yield (**2o**). Diaryliodonium salts having a 3-thiophenyl or 1-naphthyl substituent were found to be suitable substrates, giving *S*-arylation products (**2p** and **2q**) in good yields. α,β-Unsaturated sulfoximine (**2r**) was also successfully obtained by using iodonium salt **7**. Chiral HPLC analysis revealed that this *S*-arylation proceeded stereospecifically without racemization (**2c**, **2d** and **2g**). The practicability of our method was demonstrated with a 6 mmol scale of reaction, providing 1.38 g of (*S*)-**2b** in 82% yield without racemization.

Table 2. *S*-Arylation of (*R*)-1b[a]



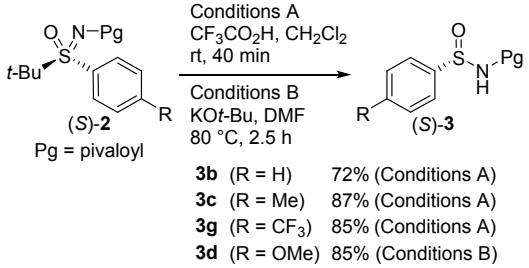


[a]Reactions were performed on a 0.1 mmol scale in 1.0 mL of DMSO. [b]Ar_2IOTf as (Ar')ArIX. [c](Mes)ArIOTf as (Ar')ArIX. [d]Ar_2IBF_4 as (Ar')ArIX. [e]Use of **7** instead of (Ar')ArIX. Performed for 48 h. [f]No racemization was confirmed by chiral HPLC.

Having demonstrated the *S*-arylation of (*R*)-**1b** on a range of diaryliodonium salts, we then explored de-*tert*-butylation of the arylation products (Scheme 2). De-*tert*-butylation of sulfoximines bearing phenyl, 4-methylphenyl or 4-trifluoromethylphenyl groups was carried out in the presence of TFA, and the corresponding sulfinamides (**3b**, **3c** and **3g**) were produced in high yield stereospecifically without racemization. On the other hand, the sulfoximine bearing an electron-rich 4-methoxyphenyl group was partially decomposed and racemized under above conditions.[18] To circumvent these undesired reactions, de-*tert*-butylation under basic conditions was examined, and treatment with KO*t*-Bu was found to give the corresponding product (**3d**) in high yield without racemization.

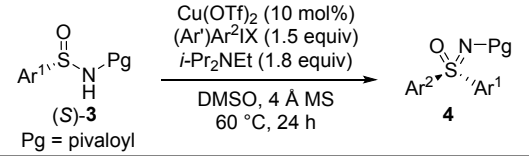
With these sulfinamides (*S*)-**3** having an aromatic group on the sulfur atom, we then investigated the asymmetric synthesis of chiral diaryl sulfoximines via the *S*-arylation (Table 3). Among amine bases tested, *i*-Pr_2NEt was found to be optimal for the *S*-arylation of (*S*)-**3** (details are provided in the Supporting Information). A range

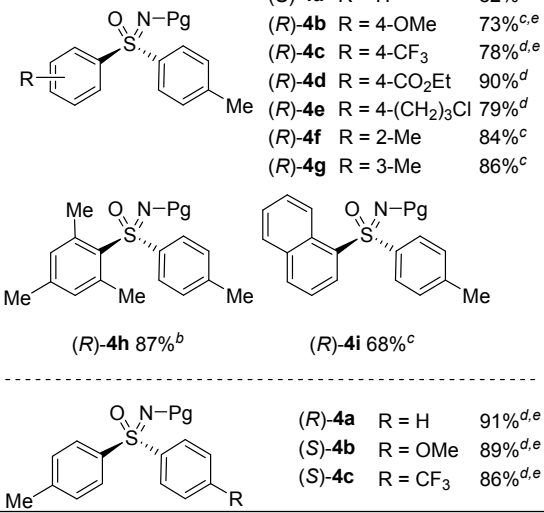
Scheme 2. De-*tert*-butylation of (*S*)-2



of diaryliodonium salts were applicable to the present method and the *S*-arylation of sulfinamide (*S*)-**3c** (Ar^1 = 4-methylphenyl) proceeded smoothly, affording the corresponding sulfoximines (**4a**–**4i**) in optically pure form. Notably, this method enables asymmetric synthesis of diaryl sulfoximines ((*S*)-**4a**) bearing sterically and electronically similar two aryl groups on the sulfur atom. The electron-rich *para*-methoxyphenyl group was readily introduced ((*R*)-**4b**). Use of diaryliodonium salts having the electron-withdrawing trifluoromethyl or ester group at the *para*-position resulted in good yields of (*R*)-**4c** and (*R*)-**4d**. Our method is compatible with the synthesis of a diaryl sulfoximine ((*R*)-**4e**) with a haloalkyl group, providing a platform for further functionalization. Methyl group at the *ortho*- or *meta*-position was also tolerated ((*R*)-**4f** and (*R*)-**4g**). Other aryl sulfinamides bearing phenyl, 4-methoxyphenyl or 4-trifluoromethylphenyl group were also applicable to the present method, and reactions with (Mes)(4-Me-C_6H_4)IOTf afforded the corresponding sulfoximines ((*R*)-**4a**, (*S*)-**4b** and (*S*)-**4c**) in optically pure form, respectively. Accordingly, a sequence consisting of the first *S*-arylation, de-*tert*-butylation and the second *S*-arylation was successfully applied to transform (*R*)-**1b** into various chiral diaryl sulfoximines, and either enantiomer can be formed by employing two diaryliodonium salts in reverse order.

Table 3. *S*-Arylation of (*S*)-3[a]

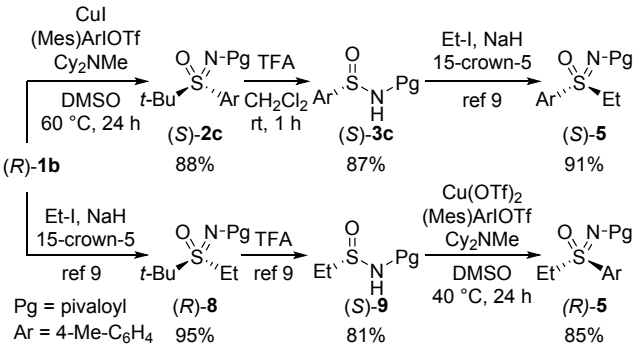




[a]Reactions were performed on a 0.1 mmol scale in 1.0 mL of DMSO. [b]$Ar^2{}_2IOTf$ as (Ar')Ar^2IX. [c]$Ar^2{}_2IBF_4$ as (Ar')Ar^2IX. [d](Mes)Ar^2IOTf as (Ar')Ar^2IX. [e]No racemization was confirmed by chiral HPLC.

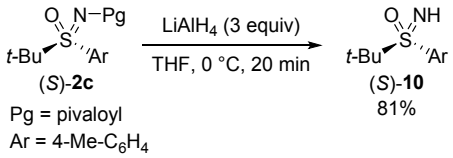
By using a combination of the present *S*-arylation and our previously reported *S*-alkylation,[9] a variety of chiral sulfoximines bearing both aryl and alkyl groups can be prepared in essentially complete optical purity (Scheme 3). (*S*)-*p*-Toluenesulfinamide (*S*)-**3c** was prepared by the *S*-arylation of (*R*)-*tert*-butanesulfinamide (*R*)-**1b** and the following TFA-mediated de-*tert*-butylation. The *S*-alkylation of the resulting sulfinamide (*S*)-**3c** with ethyl iodide gave (*S*)-sulfoximine (*S*)-**5**.[9] Remarkably, the application of the same chiral source (*R*)-**1b** to the *S*-alkylation and the subsequent *S*-arylation allowed the formation of the opposite enantiomer (*R*)-**5**. This result suggests that the present *S*-arylation is also applicable to sulfinamides with an alkyl group other than the *tert*-butyl group.

Scheme 3. Access to both enantiomers of sulfoximine 5 from the same chiral source



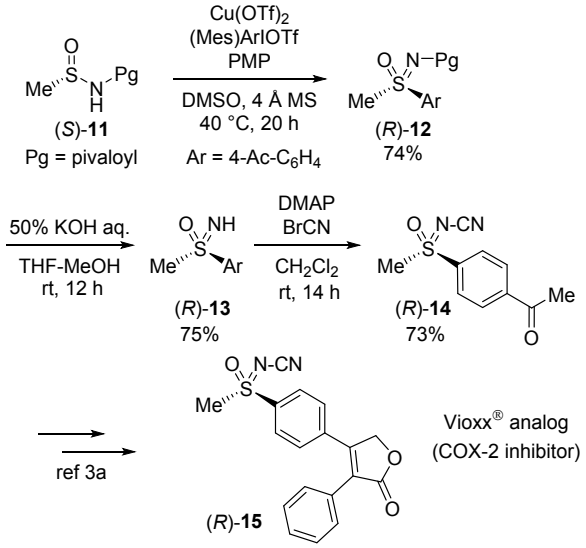
While the deprotection of the pivaloyl group can be achieved by hydrolysis under acidic or basic conditions, the competing de-*tert*-butylation of sulfoximines readily occurs.[12] On the other hand, treatment of sulfoximine (*S*)-**2c** with $LiAlH_4$ was found to give the *N*-unprotected sulfoximine (*S*)-**10** in high yield without loss of *tert*-butyl group on the sulfur atom (Scheme 4).[9]

Scheme 4. Removal of the pivaloyl group with $LiAlH_4$



To demonstrate the synthetic utility of the present *S*-arylation, the asymmetric synthesis of Vioxx® analog (*R*)-**15** was conducted (Scheme 5). Sulfoximine (*rac*)-**15** has a COX inhibitory activity with high COX-2 selectivity.[3a,3b] Generally, the biological activity of chiral sulfoximines is significantly affected by its absolute configuration. By employing our present method, enantiomerically pure (*R*)-**15** can be readily synthesized without an optical resolution. An *N*-unprotected sulfoximine (*R*)-**13** was prepared by the *S*-arylation of sulfinamide (*S*)-**11** and the subsequent basic hydrolysis.[15] An *N*-cyanation of the obtained sulfoximine (*R*)-**13** provided the known intermediate (*R*)-**14**.[19] Since racemic **14** was an intermediate in previous total synthesis of Vioxx® analog **15** by Bolm and co-workers, this work contributes to its formal asymmetric synthesis.[3a]

Scheme 5. Asymmetric synthesis of Vioxx® analog



In summary, we have developed an unprecedented *S*-arylation of the chiral sulfinamide derivatives having an alkyl or an aryl group by using the combination of the Cu(I) catalyst and diaryliodonium salts. Various chiral aryl sulfinamides are also obtained by the present arylation of *tert*-butanesulfinamide derivative, followed by de-*tert*-butylation under acidic or basic conditions. Additionally, the asymmetric synthesis of diaryl sulfoximines having sterically and electronically similar two aryl groups are also achieved by the second *S*-arylation of the obtained sulfinamides. By employing our present method, various chiral sulfoximines, including biologically active one, can be readily synthesized in optically pure form without an optical resolution.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interests.

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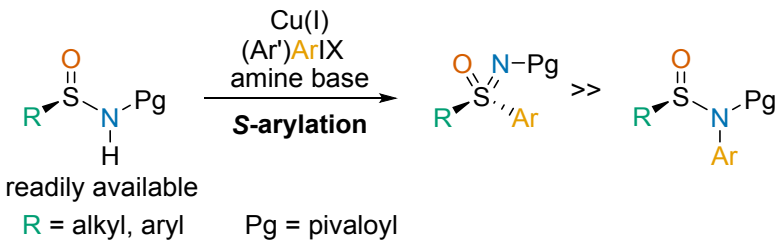
Cu(I)
(Ar')ArIX
amine base
S-arylation
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readily available
R = alkyl, aryl
Pg = pivaloyl