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A re-investigation of Modena's protocol for the asymmetric oxidation of prochiral sulfides

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Abstract—The reactivity of commercially available or easily accessible hydroperoxides has been conveniently exploited for the achievement of highly efficient and enantioselective catalytic modifications of Modena's protocol for the asymmetric oxidation of sulfides. A notably enhanced enantioselectivity has been obtained by exploiting a concomitant process of stereoconvergent kinetic resolution taking place under catalytic conditions.

1. Introduction

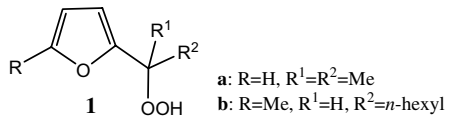
The metal-catalyzed asymmetric oxidation of prochiral sulfides represents one of the most popular approaches for the synthesis of chiral sulfoxides, whose importance both as chirality controllers and biologically significant compounds is well documented.[1]

In 1984, Kagan[2] and Modena[3] discovered independently that the combinations of Ti(O*i*-Pr)$_4$/(*R*,*R*)-diethyl tartrate (DET)/H_2O (1:2:1) and Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET (1:4) promoted the asymmetric oxidation of sulfides by using *tert*-butyl hydroperoxide (TBHP) as oxidant. The early suggestion of the involvement of the same catalytic species in both protocols was then excluded because of the differences observed in the oxidation of 2-substituted 1,3-dithiane derivatives[4] and in the influence of temperature.[5]

Subsequently, an extensive investigation by Kagan resulted in the achievement of a highly enantioselective stoichiometric procedure[6] and pointed out the necessity of a very careful control of the experimental conditions (temperature, mode of stirring, order and time of addition of the reagents) required for the preparation of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET/H_2O (1:2:1) system. Furthermore, the catalytic version[4a,7] of a modified Kagan's procedure was based on the employment of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET/*i*-PrOH (1:4:4) catalyst and the presence of 4 Å molecular sieves were found to have a beneficial effect on the level of enantioselectivity. In the following years, the interest of several research groups was focused on the influence exerted by different chiral ligands so that many modifications of Kagan's catalytic procedure were reported in the literature and involved the use of 1,2-diols,[8] binaphthols,[9] triethanolamines[10] and 1,2-amino alcohols[11] as chiral auxiliaries.

Rather surprisingly, over the same period, very little attention was paid to Modena's protocol in spite of its operational simplicity and good levels of diastereo- and enantioselectivity observed in the asymmetric oxidation of 1,3-dithiolanes,[12] 1,3-dithiane-2-carboxylates.[4c]

In recent years the ready availability of a new class of renewable hydroperoxides of type **1**[13] (Fig. 1) has allowed the achievement of stoichiometric and catalytic procedures[14] for the enantioselective oxidation of sulfides using, respectively, Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET (1:4) and Ti(O*i*-Pr)$_4$/(*R*)-BINOL/H_2O (1:2:1) catalysts. It is noteworthy, however, that in both cases, high values of enantiomeric excess (ee) could be obtained through a combined process of asymmetric sulfoxidation and



1

a: R=H, R^1=R^2=Me
b: R=Me, R^1=H, R^2=*n*-hexyl

Figure 1.

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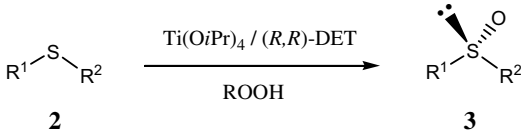
stereoconvergent kinetic resolution of the enantioenriched sulfoxides with a reduction of the chemical yields.

Since the achievement of new *catalytic* procedures affording chiral sulfoxides in high yields and ees still represents a very appealing target, the original stoichiometric Modena's protocol was re-investigated with particular attention paid to the influence exerted by different oxygen donors ROOH on the efficiency and enantioselectivity of the conversion **2**→**3** (Scheme 1).



2 **3**

Scheme 1.

2. Results and discussion

In the preliminary phase, methyl *p*-tolyl sulfide was chosen as a model compound and the reactivity of commercially available TBHP and cumyl hydroperoxide (CHP) was examined under the typical conditions of Modena's protocol in the presence of catalytic amounts of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET (1:4) system (Scheme 1, Table 1). At −20 °C, the oxidation by TBHP proceeded with a moderate level of efficiency and enantioselectivity (entry 1) while at a higher temperature (entry 2), only a notable increase of yield could be observed. The use of CHP, as oxidant, at −20 °C afforded much more satisfactory results since very good yields and ees could be obtained in a much reduced reaction time (entry 3). However, the occurrence of the reaction at 0 °C (entry 4) resulted only in a lower chemoselectivity since an appreciable amount of sulfone (16%) could be isolated.

Table 1. Asymmetric sulfoxidation of Me–S–*p*-tolyl by different ROOH

Entry	ROOH	Ti(IV) (equiv)	Reaction time (h)	Temp (°C)	Yield[a] (%)	ee[b] (%)
1	TBHP	0.3	46	−20	54(0)	64
2	TBHP	0.3	23	0	83(4)	64
3	CHP	0.3	6	−20	93(4)	85
4	CHP	0.3	4	0	80(16)	85
5	**1a**	0.3	3	0	93(3)	78
6	**1b**	0.3	24	−20	92(4)	89
7	**1a**	0.2	2	0	82(3)	69
8	**1b**	0.2	23	−20	79(9)	62

[a] All the yields refer to isolated chromatographically pure compounds. The values in parentheses refer to sulfone yields. In all entries, 1.7 equiv of ROOH were used in the presence of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET in the ratio 1/4.
[b] Predominant (*R*)-enantiomer.

Methyl *p*-tolyl sulfide was then submitted to treatment with the easily accessible furyl hydroperoxides **1a** and **b**[14] under the same conditions as TBHP and CHP. It is notable that at −20 °C, **1a** proved to be almost completely unreactive; however a good yield and ee were obtained by carrying out the reaction at 0 °C (entry 5). Conversely, the employment of **1b** resulted in a very chemoselective oxidation, which was found to proceed at −20 °C in a highly efficient and enantioselective way (entry 6). Furthermore, in both cases the decrease of catalyst loading (entries 7 and 8) caused the formation of the sulfoxide in rather lower yields and ees.

In order to assess the general validity of the above reported results, several sulfides were submitted to treatment with furyl hydroperoxides **1a** and **b** under the optimized conditions [0.3 equiv of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET (1:4) system]. In the case of **1a**, although a very good efficiency could be observed in all the entries 1–4 (Table 2), the asymmetric oxidation afforded the corresponding sulfoxides with ees only in the 53–78% range. Very interestingly, the employment of **1b**, as oxidant, allowed the attainment of high yields and ees (up to 91%) (entries 5–12) and, furthermore, because of the enhanced chemoselectivity, only in entry 11 was the formation of the over-oxidation product in a non-negligible amount (10%) detected.

Table 2. Catalytic asymmetric sulfoxidation of R^1–S–R^2 by **1a**,**b**

Entry	ROOH	R^1	R^2	Product	Yield[a] (%)	ee[b] (%)
1	**1a**	*p*-Tolyl	Me	**3a**	93(3)	78
2	**1a**	*p*-MeOC$_6$H$_4$	Me	**3b**	92(4)	75
3	**1a**	*p*-ClC$_6$H$_4$	Me	**3c**	73(6)	76
4	**1a**	Ph	Et	**3d**	98(0)	53
5	**1b**	*p*-Tolyl	Me	**3a**	92(4)	89
6	**1b**	*p*-MeOC$_6$H$_4$	Me	**3b**	96(3)	86
7	**1b**	*p*-ClC$_6$H$_4$	Me	**3c**	89(6)	87
8	**1b**	Ph	Me	**3e**	92(6)	91
9	**1b**	2-Naphthyl	Me	**3f**	77(0)	81
10	**1b**	Ph	Et	**3d**	81(n.d.)[d]	77
11	**1b**	*p*-NO$_2$C$_6$H$_4$	Me	**3g**	80(10)	87
12	**1b**	*n*-Octyl	Me	**3h**	67(0)	72[c]

[a] All the yields refer to isolated chromatographically pure compounds. The values in parentheses refer to sulfone yields. In all entries, 1.7 equiv of **1a** and **b** were used in the presence of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET in the ratio 1/4.
[b] Predominant (*R*) enantiomer.
[c] The ee was determined by ^{1}H NMR (400 MHz) in the presence of (*R*)-(−)-(3,5-dinitrobenzoyl)-α-phenylethylamine as shift reagent.
[d] Not determined.

It is noteworthy that the catalytic procedure of asymmetric sulfoxidation seemed to be more enantioselective than the stoichiometric one: in fact, the oxidation of Me–S–*p*-tolyl with **1b**, performed in the presence of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET (1:4) under conditions ensuring significant reduction of the concomitant process of kinetic resolution, was reported[14] to take place in 74% ee (97% yield), while in entry 5, methyl *p*-tolyl sulfoxide was obtained in 89% ee (92% yield). In a similar way, a notable improvement of enantioselectivity was observed in the case of Me–S–Ph, as clearly shown by the comparison of the literature data for the stoichiometric sulfoxidation (78% ee, 89% yield) with the ones of entry 8 (91% ee, 92% yield).

The promising results obtained in the preliminary phase, Table 1 (entries 3 and 4), stimulated a further investiga-

tion on the reactivity of CHP in the presence of varying amounts of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET (1:4) catalyst. Me–S–*p*-tolyl was again chosen as the model compound. As clearly shown in Table 3, rather similar levels of enantioselectivity have been observed by using catalyst loading in the range 0.1–1.0 equiv (entries 1–4), while a sharp drop has been observed both in yield and ee derived from the employment of 0.05 equiv of catalyst (entry 5).

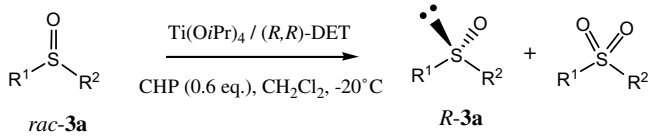
Table 3. Asymmetric sulfoxidation of Me–S–*p*-tolyl by CHP

Entry	Ti(IV) (equiv)	Time (h)	Yield[a] (%)	ee[b] (%)
1	1.00	6	84(0)	90
2	0.30	6	93(4)	85
3	0.15	24	95(5)	90
4	0.10	24	96(2)	85
5	0.05	26	79(2)	60

[a] All the yields refer to isolated chromatographically pure compounds. The values in parentheses refer to sulfone yields. In all the entries, 1.7 equiv of **1a** and **b** were used in the presence of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET in the ratio 1:4.
[b] Predominant (*R*)-enantiomer.

A previous report[15] pointed out the occurrence of a process of kinetic resolution of racemic sulfoxides by treatment with CHP in the presence of stoichiometric amounts of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET (1:4). This finding suggested the possibility of increasing the level of enantioselectivity of the catalytic procedure by a combined process of asymmetric sulfoxidation and kinetic resolution of the enantioenriched sulfoxides. Therefore, the experiment of entry 2 was repeated in the presence of 1.4 equiv of CHP and, after the oxidation was prolonged for 48 h, the expected (*R*)-sulfoxide was isolated in 80% yield and 97% ee. The appropriate choice of CHP/sulfide stoichiometric ratio allowed the achievement of a very high ee without affecting in a dramatic way the efficiency of the process, since methyl *p*-tolyl sulfone was obtained in only 16% yield.

The involvement of a stereoconvergent process of kinetic resolution in this latter reaction was further confirmed by submitting *rac*-methyl *p*-tolyl sulfoxide **3a** to treatment with CHP in the presence of 0.3 equiv of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET (1:4) under the conditions depicted in Scheme 2.



Scheme 2.

In fact, after 24 h, unreacted sulfoxide was isolated in 70% yield and 35% ee [as the predominant (*R*)-enantiomer] and a stereoselection factor $S = 13.9$ was calculated.[16]

As shown in Table 4, the catalytic approach proved to be successful with a series of sulfides, especially in the presence of 0.3 and 0.15 equiv of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET (1:4) complex and, with the exception of entries 4 and 11 over-oxidation was greatly reduced, the sulfoxides were obtained in high ees and yields.

Table 4. Catalytic asymmetric sulfoxidation of R^1–S–Me by CHP

Entry	R^1	Ti(IV) (equiv)	Product	Yield[a] (%)	ee[b] (%)
1	*p*-Tolyl	0.30	**3a**	93(4)	85
2	*p*-MeOC$_6$H$_4$	0.30	**3b**	87(5)	85
3	Ph	0.30	**3e**	95(3)	91
4	*p*-NO$_2$C$_6$H$_4$	0.30	**3g**	66(10)	84
5	*p*-ClC$_6$H$_4$	0.30	**3c**	95(5)	89
6	*n*-Octyl	0.30	**3h**	90(5)	83[c]
7	*p*-Tolyl	0.15	**3a**	95(5)	91
8	*p*-ClC$_6$H$_4$	0.15	**3c**	93(7)	89
9	*p*-MeOC$_6$H$_4$	0.15	**3b**	92(8)	89
10	Ph	0.15	**3e**	89(9)	92
11	*n*-Octyl	0.15	**3h**	72(25)	69[c]
12	*p*-Tolyl	0.10	**3a**	96(2)	85
13	*p*-MeOC$_6$H$_4$	0.10	**3b**	93(6)	80

[a] All the yields refer to isolated chromatographically pure compounds. The values in parentheses refer to sulfone yields. In all entries, 1.7 equiv of CHP were used in the presence of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET in the ratio 1:4. Reaction time: 6 h (entries 1–6), 24 h (entries 7–13).
[b] Predominant (*R*)-enantiomer.
[c] The ee was determined by ^{1}H NMR (400 MHz) in the presence of (*R*)-(−)-(3,5-dinitrobenzoyl)-α-phenylethylamine as shift reagent.

In an attempt to increase the level of enantioselectivity the conversion, **2**→**3** was performed under the typical conditions required by the combined process of asymmetric sulfoxidation and kinetic resolution (Table 5).

Table 5. Combined asymmetric oxidation of R^1–S–Me and kinetic resolution of R^1–SO–Me by CHP

Entry	R^1	Product	Ti(IV) (equiv)	Yield[a] (%)	ee[b] (%)
1	*p*-Tolyl	**3a**	0.3	80(16)	97
2	*p*-MeOC$_6$H$_4$	**3b**	0.3	65(32)	>99
3	Ph	**3e**	0.3	82(16)	97
4	*p*-Tolyl	**3a**	0.15	86(12)	91
5	*p*-Tolyl	**3a**	0.1	96(4)	80

[a] All the yields refer to isolated chromatographically pure compounds. The values in parentheses refer to sulfone yields. In all entries, 1.7 equiv of CHP were used in the presence of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET in the ratio 1:4.
[b] Predominant (*R*)-enantiomer.

However, appreciable improvements were achieved only in the presence of 0.3 equiv of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET (1:4) catalyst (entries 1–3), although in entry 2 the formation of the corresponding sulfoxide took place in the highest ee at the expense of the chemical yield.

As previously reported in the introduction, the stoichiometric Modena protocol for the enantioselective oxidation of sulfides has scarcely been explored and some modifications of the original procedure are based on the employment of simple or polyfunctional furyl hydroperoxides in substitution of TBHP.[13] Therefore, in order to broaden the field of this investigation, CHP was reacted with several sulfides in the presence of a stoichiometric amount of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET (1:4) complex.

Under the optimized conditions of entries 1–6 (Table 6) the asymmetric sulfoxidation was found to proceed with complete chemoselectivity, high efficiency and enantioselectivity.

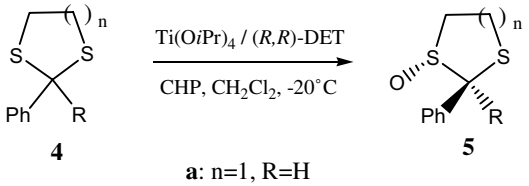
Table 6. Stoichiometric asymmetric oxidation of R^1–S–R^2 by CHP

Entry	R^1	R^2	Product **3**	Time (h)	Yield[a] (%)	ee[b] (%)
1	*p*-Tolyl	Me	**3a**	6	84(0)	90
2	2-Naphthyl	Me	**3f**	24	90(0)	92
3	*o*-$MeOC_6H_4$	Me	**3i**	40	99(0)	92
4	Ph	Et	**3d**	40	95(0)	70
5	*p*-$NO_2C_6H_4$	Me	**3g**	24	60(0)	87
6	*n*-Octyl	Me	**3h**	24	73(0)	91[c]
7	*p*-Tolyl	Me	**3a**	24	95(0)	91
8	Ph	Et	**3d**	72	73(15)	75[d]
9	Ph	Me	**3e**	26	72(20)	97[d]
10	*p*-ClC_6H_4	Me	**3c**	24	80(15)	96[d]

[a] All the yields refer to isolated chromatographically pure compounds. The values in parentheses refer to sulfone yields. In all the entries 1.2 equiv of CHP were used in the presence of 1 equiv of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET in the ratio 1:4.
[b] Predominant (*R*)-enantiomer.
[c] The ee was determined by ^{1}H NMR (400 MHz) in the presence of (*R*)-(−)-(3,5-dinitrobenzoyl)-α-phenylethylamine as shift reagent.
[d] In these entries 1.4 equiv of CHP were used.

More prolonged reaction times (entries 7 and 8) or the use of slightly increased CHP/sulfide ratios (entries 9 and 10) promoted the usual process of stereoconvergent kinetic resolution, leading to the chiral sulfoxides in higher yields or ees. The stereochemical outcome of entry 6 (91% ee) can be considered of particular importance since dialkyl sulfides are known to usually suffer asymmetric oxidation with moderate enantioselectivity.

Finally the modified Modena's protocol allowed significant improvements in the asymmetric sulfoxidation of cyclic 2-subsituted 1,3-thioacetals of type **4** (Scheme 3, $n = 1$) since the usual treatment afforded the corresponding mono-sulfoxides **5** in complete diastereoselectivity and high enantioselectivity (Table 7, entries 1 and 2).



Scheme 3.

It is notable that, under catalytic conditions [0.3 equiv of Ti(IV) complex], **5a** was obtained as single diastereoisomer in 95% yield and 74% ee (entry 3). Conversely, in spite of a high diastereoselectivity, a very low ee was observed in the case of the six-membered thioacetale **4c** (entry 4), confirming the poor results previously reported for the oxidation of 2-alkyl- or 2-aryl-2-substituted 1,3-dithianes by the typical Kagan and Modena procedures.

Table 7. Asymmetric mono-sulfoxidation of **4** by CHP

Entry	R	*n*	Time (h)	Product	Yield[a] (%)	ee[b] (%)
1	H	1	23	**5a**	73(>99/1)	89
2	Me	1	24	**5b**	95(>99/1)	91
3	H	1	6	**5a**	95(>99/1)	74[c]
4	H	2	40	**5c**	68(>99/1)	10

[a] All the yields refer to isolated chromatographically pure compounds. In all entries, 1.2 equiv of CHP were used in the presence of 1 equiv of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET in the ratio 1:4. Values in parentheses refer to *trans*/*cis* diastereoisomeric ratios calculated according to Refs. 17 (**5a**,**b**) and 18 (**5c**).
[b] Ees were determined by HPLC by using a Daicel Chiralcel OD column.
[c] In this entry 0.3 equiv of Ti(IV) complex were used.

3. Conclusion

In conclusion, a careful investigation into the original stoichiometric Modena's procedure has allowed the achievement of highly enantioselective *catalytic* modifications based on the use of CHP or easily recyclable furyl hydroperoxides, as oxygen donors, in the presence of reduced amounts (down to 10%) of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET (1:4) complex. A further enhancement of the level of enantioselectivity has been obtained through a stereoconvergent process of kinetic resolution accompanying the asymmetric sulfoxidation under catalytic conditions. Finally, it is noteworthy that the stoichiometric version of Modena's protocol (oxidant CHP) afforded very high ees and yields both in the oxidation of sulfides and the stereoselective mono-sulfoxidation 2-aryl-substituted 1,3-dithiolanes.

4. Experimental

4.1. Materials and general methods

All the reactions were performed in flame-dried glassware under an atmosphere of dry argon. All the solvents were of reagent grade and were dried and distilled immediately before use (CH_2Cl_2 from calcium hydride). Purifications were performed by flash chromatography (Merck silica gel), by elution with light petroleum (40–70 °C)/ethyl acetate mixtures. Starting materials and all other reagents, unless otherwise indicated, were purchased from Aldrich or Fluka and used without further purification. All the reactions were monitored by thin layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualized by UV light or by $KmnO_4$ spray test. The NMR spectra (Bruker DRX 400 (^{1}H 400 MHz; ^{13}C 100 MHz)), were performed in $CDCl_3$ solution and referenced to residual $CHCl_3$ (7.26 ppm (^{1}H); 77.23 ppm (^{13}C)). Optical rotations were measured on a Jasco Dip-1000 using the Na lamp. HPLC analyses were performed with Waters Associates equipment (Waters, 2487 Dual λ absorbance detector) using a Daicel Chiralcel OB column with the exception of **5a**–**c** (Daicel Chiralcel OD column). Furyl hydroperoxides **1a** and **b** were prepared according to Ref. 14. Structures and absolute configurations of compounds **3a** and **b**,[6c] **3c**,[6a] **3d**,[19] **3e**–**i**[6c] were assigned by comparison with literature data (^{1}H NMR and sign of the specific rotation).

4.2. Standard procedure for the stoichiometric asymmetric sulfoxidation

A solution of (*R*,*R*)-diethyl tartrate (0.415 g, 2.0 mmol), titanium tetraisopropoxide (0.142 g, 0.50 mmol) and sulfide (0.50 mmol) in dry CH_2Cl_2 (3.5 mL) under an argon atmosphere was stirred at room temperature for 5 min. Then the temperature was cooled to −20 °C and after 20 min a solution of cumyl hydroperoxide (1.2 mmol in 3.5 mL of dry CH_2Cl_2) was slowly added. After the appropriate reaction time, a solution of 10% Na_2SO_3 (2 mL) was added and the solution stirred for about 1 h. Then the resulting gel was recovered with ethyl acetate (20 mL) and filtered on a short pad of SiO_2. After removing the solvent under reduced pressure, the crude oil was purified by silica gel flash chromatography (eluent starting from Et_2O to a mixture 1:1 Et_2O/ethyl acetate) to afford the pure sulfoxide.

4.3. Standard procedure for the catalytic asymmetric sulfoxidation

In all the *catalytic* procedures, a Ti(IV) complex was used at the same concentration (0.047 M). In a typical experimental procedure, a solution of (*R*,*R*)-diethyl tartrate (0.124 g, 0.60 mmol), titanium tetraisopropoxide (0.043 g, 0.15 mmol) and sulfide (1.0 equiv) in dry CH_2Cl_2 (1.6 mL) under an argon atmosphere was stirred at room temperature for 5 min. Then the temperature was cooled to −20 °C and after 20 min a solution of hydroperoxide (1.7 equiv in 1.6 mL of dry CH_2Cl_2) slowly added. After the appropriate reaction time, the above reported procedure for stoichiometric sulfoxidation was followed for the work-up.

4.4. Standard procedure for the catalytic kinetic resolution

The above reported procedure for the catalytic sulfoxidation was used with the substitution of sulfide with racemic methyl *p*-tolyl sulfoxide. The reagents were added to dry CH_2Cl_2 in the following order: sulfoxide (1.0 equiv), (*R*,*R*)-diethyl tartrate (1.2 equiv), titanium tetraisopropoxide (0.3 equiv), 0.6 equiv of cumyl hydroperoxide were employed.

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