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Chiral Auxiliaries for Asymmetric Radical Cyclization Reactions: Application to the Enantioselective Synthesis of (+)-Triptocallol

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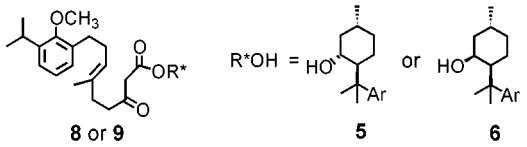
ABSTRACT



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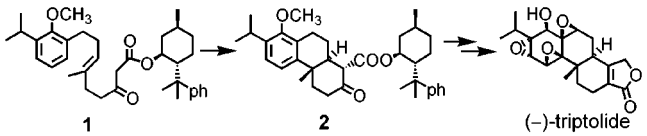
A series of epimeric 8-aryl menthyl derivatives 5a–d and 6a–l, prepared from the same chiral source (*R*)-pulegone, were employed as chiral auxiliaries in the asymmetric radical cyclization reactions of *β*-keto esters mediated by $Mn(OAc)_3$. Chiral precursors 8c and 8d provided the cyclization products 10c and 10d, respectively, as single isomers (dr > 99:1), whereas the cyclization of precursor 9k gave 13k with good stereoselectivity (dr = 24:1). Diastereomer 13e was employed as the key intermediate in the enantioselective synthesis of (+)-triptocallol in 90% ee.

The $Mn(OAc)_3$-mediated oxidative free-radical cyclization method has been widely used in the construction of polycyclic ring structures found in many natural products, especially terpenoids.[1,2] However, few asymmetric radical cyclizations have been reported.[3] Recently, we discovered a highly diastereoselective oxidative free radical cyclization reaction of *β*-keto esters mediated by $Mn(OAc)_3$,[4,5] in which (+)-8-phenylmenthol was employed as a chiral auxiliary and $Yb(OTf)_3$ as a catalyst to provide major diastereomer **2** (diastereomer ratio 38:1), a key intermediate for the total synthesis of (−)-triptolide (Scheme 1). However, (+)-8-phenylmenthol, derived from (*S*)-(−)-citronellol in several tedious steps,[6] is much more expensive than its enantiomer (−)-8-phenylmenthol. To improve the diastereoselectivities of radical cyclization reactions and to use inexpensive chiral source to construct the tricyclic skeleton of (−)-triptolide,

Scheme 1



1 2 (−)-triptolide

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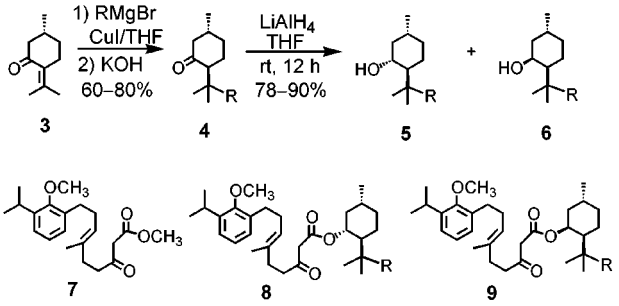
we would like to find suitable chiral menthyl derivatives to replace (+)-8-phenylmenthol. Furthermore, to synthesize both enantiomers of natural products in high optical purity from the same chiral source is very attractive for the development of more selective chiral drugs.[7] Here we report our efforts in developing new chiral auxiliaries for asymmetric radical cyclization reactions.

The chiral auxiliaries **5** and **6** were prepared following literature procedures (Scheme 2).[6,8] Ketone **4** was obtained

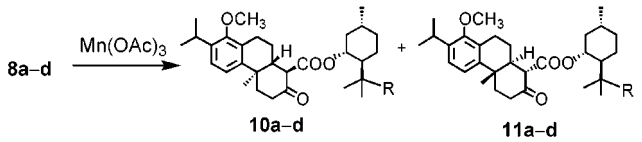
Scheme 2



by treating commercially available (*R*)-pulegone **3** with appropriate Grignard reagents in the presence of CuI. Reduction with $LiAlH_4$ generated two diastereomeric alcohols, **5** and **6**,[9] which were then incorporated into chiral β-keto esters **8** and **9** in 88−96% yields by ester exchange[10] with achiral precursor **7**[11] (Scheme 2).

The $Mn(OAc)_3$-mediated oxidative free-radical cyclization reactions of **8a**−**d** were carried out in degassed solvents in the presence of $Yb(OTf)_3$,[4,5,11] and the results are summarized in Table 1. When the aromatic group at the 8-position of chiral menthyl auxiliaries was changed from phenyl group (entry 1) to 3,5-disubstituted phenyl group (entries 2 and 3) or naphthyl group (entry 4), the diastereomer ratio was increased dramatically from 38:1 to more than 99:1. For the cyclization of **8c** or **8d**, one single isomer with three chiral centers was obtained in one step. It seems that increasing the steric bulkiness and electron density of the 8-aryl group

Table 1. $Mn(OAc)_3$-Mediated Asymmetric Radical Cyclization of Chiral Precursors **8a**−**d**[a]



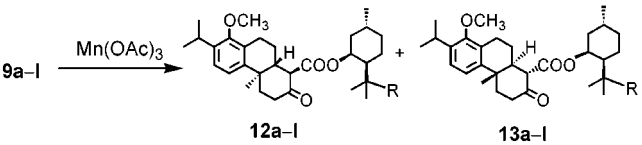
entry	substrates	R	dr (**10**:**11**)[b]	yield (%)[c]
1	**8a**	Ph	38:1	77
2	**8b**	3,5-$(MeO)_2C_6H_3$	86:1	75
3	**8c**	3,5-$(i\text{-}PrO)_2C_6H_3$	>99:1	53
4	**8d**	2-naphthyl	>99:1	67
5[d]	**8d**	2-naphthyl	24.5:1	44

[a] Unless otherwise indicated, all reactions were carried out with 1.0 equiv of $Yb(OTf)_3$ and 2.2 equiv of $Mn(OAc)_3{\cdot}2H_2O$ at 0.067 M substrate concentration, −5 to 0 °C in CF_3CH_2OH, 6−10 h. [b] The diastereomer ratio was determined by ^1H NMR (500 MHz, $CDCl_3$) analysis of the crude products. [c] Isolated yield. [d] Carried out at 50 °C in HOAc without $Yb(OTf)_3$, 1 h.

leads to higher diastereoselectivity. The important effect of Lewis acid $Yb(OTf)_3$ on this kind of asymmetric radical cyclization reaction was also confirmed (entry 4 vs 5).

Interestingly, the cyclization of **9a**−**l** gave **13a**−**l** as the major diastereomers (Table 2), which have the opposite

Table 2. $Mn(OAc)_3$-Mediated Asymmetric Radical Cyclization of Chiral Precursors **9a**−**l**[a]



entry	substrate	R	dr (**12**:**13**)[b]	yield (%)[c]
1	**9a**	3,5-$(CF_3)_2C_6H_3$	1:2.8	64
2	**9b**	*p*-$NO_2C_6H_4$	1:4.1	60
3[d]	**9b**	*p*-$NO_2C_6H_4$	1:6.0	55
4	**9c**	2,4-$(MeO)_2C_6H_3$	1:3.7	64
5	**9d**	*o*-$MeOC_6H_4$	1:4.5	60
6	**9e**	Ph	1:5.7	70
7	**9f**	*p*-Ph-C_6H_4	1:5.8	71
8	**9g**	*p*-$MeOC_6H_4$	1:6.7	72
9	**9h**	*m*-$MeOC_6H_4$	1:11.5	62
10	**9i**	3,4-$(MeO)_2C_6H_3$	1:11.2	64
11	**9j**	3,5-$(MeO)_2C_6H_3$	1:18.1	67
12	**9k**	3,5-$(i\text{-}PrO)_2C_6H_3$	1:24.2	55
13	**9l**	2-naphthyl	1:9.2	60

[a] Unless otherwise indicated, all reactions were carried out in degassed CF_3CH_2OH with 1.0 equiv of $Yb(OTf)_3$ and 2.2 equiv of $Mn(OAc)_3{\cdot}2H_2O$ at 0.067 M substrate concentration, −5 to 0 °C, 6−10 h. [b] The diastereomer ratio was determined by ^1H NMR (500 MHz, $CDCl_3$) analysis of the crude products. [c] Isolated yield (including both **12** and **13**). [d] At room temperature without $Yb(OTf)_3$, 26 h.

configuration for the tricyclic skeleton as compared to cyclization products **10a**−**d**. Low diastereomer ratios were

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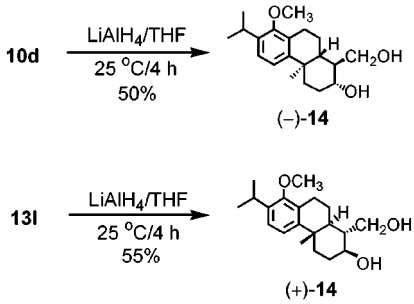
obtained when the chiral auxiliaries bearing electron-withdrawing groups or ortho-substitutents on the 8-phenyl group were employed (entries 1 and 2, 4 and 5). The cyclization of **9g**−**k** with electron-donating substituents, especially those at the meta positions of the 8-aryl ring, resulted in higher chiral induction (entries 8−12). Most significantly, diastereomer ratio of 1:24 was obtained for the cyclization reaction of **9k** (entry 12).

The absolute configuration of the resulting tricyclic skeleton was determined by using the following transformations (Scheme 3). Compounds **10d** and **13l** were reduced by

Scheme 3



$LiAlH_4$ to diols (−)-**14** ($[\alpha]_D$ −78°, *c* 0.50, EtOAc) and (+)-**14** ($[\alpha]_D$ +77 °, *c* 0.20, EtOAc), respectively (Scheme 3). Diols (−)-**14** and (+)-**14** gave the specific optical rotations and CD spectra of opposite signs, suggesting that they are mirror images. The absolute configuration of cyclization product **13e** was further confirmed by converting **13e** to natural product (+)-triptocallol (vide infra).[12a]

The opposite chiral induction obtained in the cyclization of **8** and **9** can be explained using the chelation models shown in Figure 1. In the presence of $Yb(OTf)_3$, the chelation of

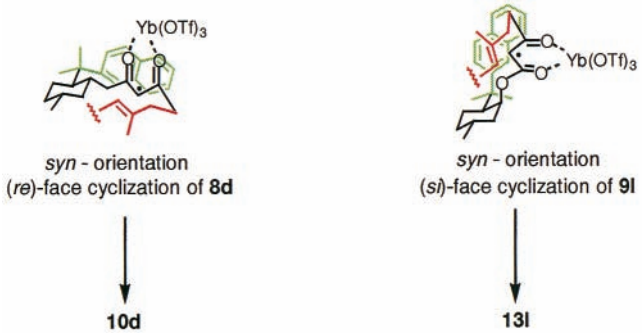


Figure 1. The transition state models of the radical cyclization in the presence of $Yb(OTf)_3$.

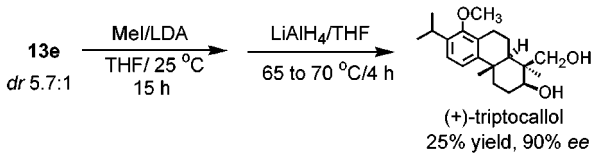
β-keto ester **8** to $Yb(OTf)_3$ would lock the two carbonyl groups in a *syn* orientation.[4] In the cyclization of **8d**, the 8-naphthyl group can effectively shield the (*si*)-face of the radical generated by Mn(III) oxidation and restrict the cyclization to the (*re*)-face to give **10d**. However, in the case of **9l**, the (*re*)-face is shielded and the (*si*)-face is more accessible, yielding **13l** as the major product. The π-stacking interaction[13] between the α-radical center and the 8-aryl group was invoked to explain the different stereoselectivities observed in the radical cyclization of **8d** and **9l**. In the ^1H NMR spectra, the protons α to the two carbonyl groups of **8d** showed more upfield chemical shifts (δ 2.38 and 2.22 ppm) than those of **9l** (δ 3.23 ppm), indicating that the equatorial β-keto ester group had much stronger π-stacking interactions with the 8-naphthalene ring than the axial one. Therefore, chiral precusor **8d** gave a single isomer **10d**, whereas precusor **9l** gave a lower diasteromer ratio (**13l**:**12l** = 9:1).

In addition, the π-stacking effect became stronger when the aromatic ring at the 8-position of the chiral auxiliary was substitued with more electron-releasing groups owing to the attraction of the electrophilic radical center and the electron-rich aromatic ring. As a result, the diastereomer ratio was enhanced by introducing electron-donating substituents on the aromatic ring. In contrast, the π-stacking effect was weakened when the aromatic ring was substitued with electron-withdrawing groups. In the absence of $Yb(OTf)_3$, the electronic repulsion between the electrophilic radical center and the electron-deficient aromatic ring would decrease and thus higher diastereomer ratio was obtained for the cyclization of **9b** (entry 2 vs 3).

As a result of the steric interactions, ortho substitution on the aromatic ring of the chiral auxiliary may cause a twist of aromatic plane and destroy the π-stacking interaction between the β-keto ester group and the aromatic ring. Therefore, the diastereoselectivity decreased significantly for the cyclization of **9c** and **9d** bearing ortho subsitutents (Table 2, entries 4 and 5). Among all the chiral auxiliaries examined, those with electron-releasing groups at *meta* positions gave the most effective chiral induction due to the electronic and steric effects (Table 2, entries 11 and 12).

The diastereomer **13e** was applied to the enantioselective synthesis of (+)-triptocallol, a terpenoid isolated from tissue cultures of *Tripterygium wilfordii*.[12a] Alkylation of **13e** (dr 5.7:1) with MeI,[14] followed by reduction with $LiAlH_4$, provided (+)-triptocallol ($[\alpha]$ = +54.8 °, *c* 0.18, CH_2Cl_2) in 25% yield and 90% ee (Scheme 4). The ^1H NMR spectrum

Scheme 4



of our synthetic (+)-triptocallol was identical to that of an authentic sample ($[\alpha]$ = +42.5° (*c* 0.4, $CHCl_3$))[12] supplied by Professor Takaishi.[15]

In summary, we have demonstrated that epimeric chiral auxiliaries derived from the same chiral source can be used

to control of the product configurations in the $Mn(OAc)_3$-mediated oxidative radical cyclization reactions. In addition, an enantioselective synthesis of (+)-triptocallol was accomplished in high selectivity. The manipulation of chiral auxiliaries utilized in the radical cyclization reactions may have tremendous potential in the asymmetric synthesis of either enantiomer of many polycyclic natural products. Work in that direction is in progress.

Acknowledgment. This work was supported by The University of Hong Kong and Hong Kong Research Grants Council.

Supporting Information Available: The preparation of chiral auxiliaries **5** and **6**, experimental details of the radical cyclization reactions of **8** and **9**, determination of diastereomer ratios of **10/11** and **12/13**, HPLC analysis of synthetic (+)-triptocallol, and the CD spectra of compounds (+)-**14** and (−)-**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) We thank Professor Yoshihisa Takaishi (University of Tokushima) for a copy of the ^{1}H NMR spectrum of natural (+)-triptocallol.