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TETRAHEDRON

Sparteine-Mediated Enantioselective [2,3]-Wittig Rearrangement of Allyl *ortho*-Substituted Benzyl Ethers and *ortho*-Substituted Benzyl Prenyl Ethers

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ABSTRACT: The (-)-sparteine-mediated enantioselective [2,3]-Wittig rearrangement of *N,N*-dialkyl-*o*-allyloxymethylbenzamides and *o*-substituted benzyl prenyl ethers has been investigated. Enantiomeric excess up to 60% was observed as for the reaction with *N,N*-diethyl-*o*-allyloxymetylbenzamide. From the mechanistic investigations, it was suggested that the stereoinformation was introduced at the deprotonation step. Substoichiometric amount of (-)-sparteine (0.2 equiv.) did not decrease the enantioselectivity. Introduction of functional groups other than carbamoyl group did not enhance the enantioselectivity in this rearrangement.

INTRODUCTION

Enantioselective and diastereoselective [2,3]-Wittig rearrangement reactions are powerful tools in the synthesis of natural products such that having more than one chiral carbon centers in the molecules. A number of successful studies have been reported for the diastereoselective [2,3]-Wittig rearrangement [1—7] starting from chiral substrates, while the studies that dealt with [2,3]-Wittig rearrangement reaction of achiral substrates and chiral ligand—base complex achieved to unsatisfactory results to date [8—13]. Attractive challenges of Nakai *et al.*,[8] and Manabe[11] showed the enantioselective [2,3]-Wittig rearrangement of unsubstituted allylic benzyl ether derivatives by (-)-sparteine even in low enantiomeric excess.

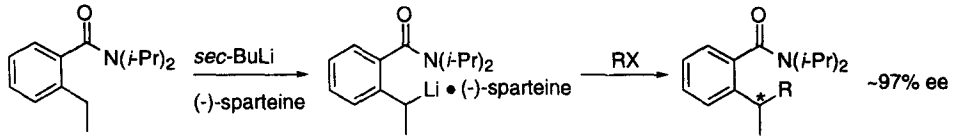

Chart 1

In the meantime, among the well studied heteroatomic substituents promoted lateral metalation-substitution reactions[14], α- and lateral lithiation-substitution reactions mediated by (-)-sparteine, well studied by Hoppe[15, 16, 17], Beak[18, 19] etc., are successful examples of the enantioselective version. Especially, Beak *et al.* have shown (-)-sparteine mediated highly enantioselective metalation-substitution reactions of *N,N*-dialkyl-*o*-ethylbenzamides (Chart 1).

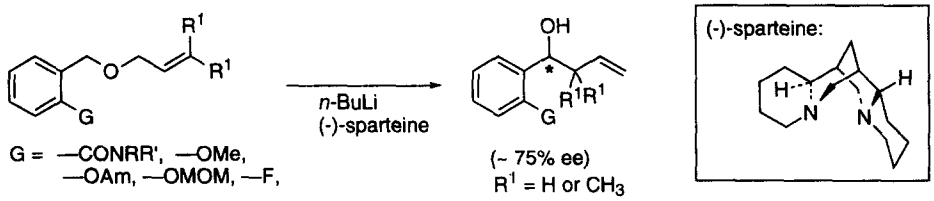

Chart 2

Based on these results, we expected on the effects of the heteroatomic substituent, located at ortho position of allyl benzyl ethers and presumably involved in coordination with a ligand and a base, on

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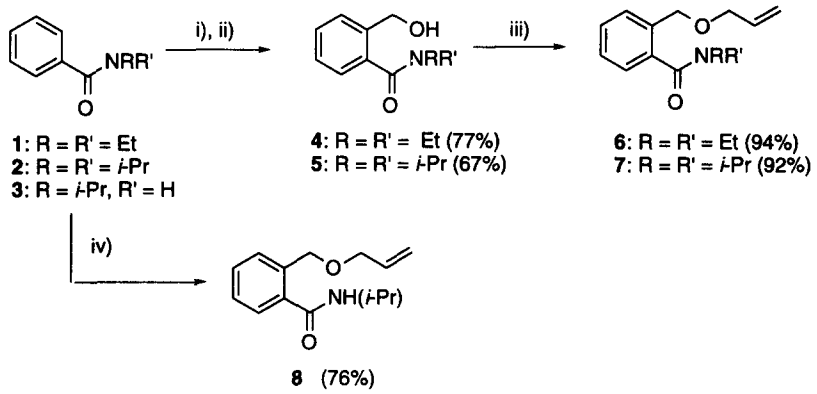
[2,3]-Wittig rearrangement of allyl benzyl ethers. Previously, we have briefly communicated the enantioselective [2,3]-Wittig rearrangement *via* (-)-sparteine-mediated lateral metalation of *N,N*-dialkyl-*o*-allyloxymethylbenzamides and *o*-substituted benzyl prenyl ethers and have shown that the *o*-carbamoyl group could effectively assist to transfer the stereoinformation by coordinating with the (-)-sparteine—*n*-BuLi complex[20](Chart 2).

We wish to report here the details about the studies on (-)-sparteine-mediated [2,3]-Wittig rearrangement of *o*-substituted allylic benzyl ether derivatives including the mechanistic investigation directed for the development of the catalytic asymmetric [2,3]-Wittig rearrangement.

RESULTS AND DISCUSSION

Scheme 1 illustrates the synthesis of *N,N*-diethyl-*o*-allyloxymethylbenzamide (**6**). Compound (**6**) was synthesized by the reaction of allylbromide with **4**, which was prepared by *ortho*-metalation of the starting *N,N*-diethylbenzamide followed by sodium borohydride reduction[21].

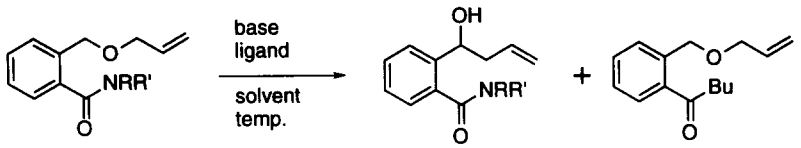
Scheme 1



Reagents and Conditions: i) 1) *sec*-BuLi / TMEDA / THF / -78 °C, 2) DMF / -78 °C to room temp. ii) $NaBH_4$ / MeOH / 0 °C. iii) NaH / allyl bromide / THF. iv) 1) 2.2 equiv. *sec*-BuLi / 2.2 equiv. TMEDA / THF / -78 °C, 2) 

Initial results in Table 1 show that the reaction with no ligand (at -78 °C) afforded only 8% yield of desired rearranged compound (**9**) with substantial amounts of aryl butyl ketone (**12**) resulting from nucleophilic attack of *n*-BuLi on the amide carbonyl, and the reaction at -95 °C gave recovery of the starting material (entries 1 and 2). The addition of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) increased the formation of the desired compound in 47% and reduced the generation of undesired aryl butyl ketone (entry 3). Table 1 also shows that (-)-sparteine-mediated [2,3]-Wittig rearrangement of *N,N*-diethyl-*o*-allyloxymethylbenzamide (**6**) under various conditions. In diethyl ether, low enantiomeric excess was observed with the opposite sense of selectivity compared with that in pentane and toluene, while in toluene, poorer enantioselectivity was observed than shown in pentane (entries 4, 6 and 7). Use of 2.2 equivalent of *n*-BuLi and 2.2 equivalent of (-)-sparteine in pentane at -95 °C afforded the best selectivity (60% ee) without recovery of the starting material (entry 10). To improve the enantioselectivity and to suppress the formation of undesired aryl butyl ketone, we prepared *N,N*-diisopropyl-*o*-allyloxymethylbenzamide (**7**) and *N*-isopropyl-*o*-allyloxymethylbenzamide (**8**) as illustrated in Scheme 1. As the result, in the reaction with **7**, the introduction of the bulkier substituent could not enhance the enantioselectivity and could not reduce the formation of aryl butyl ketone.

Table 1



6: R = R' = Et
7: R = R' = *i*-Pr
8: R = *i*-Pr, R' = H

9: R = R' = Et
10: R = R' = *i*-Pr
11: R = *i*-Pr, R' = H

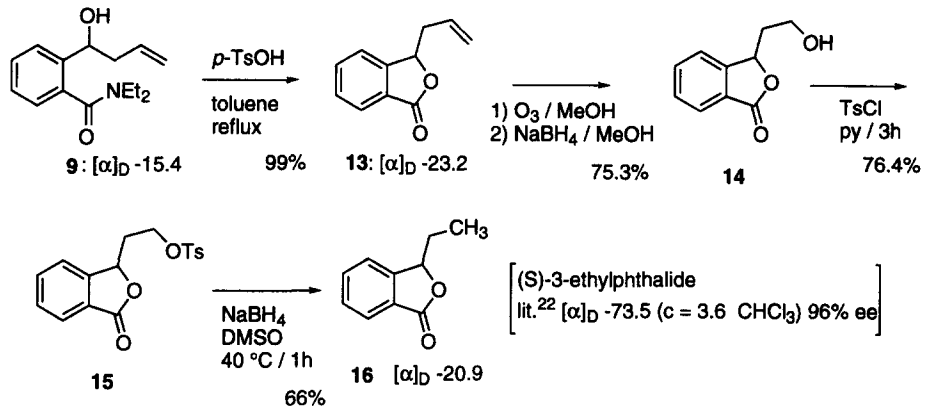
12

entry	Compds. No.	base equiv.	ligand equiv.	temp.	solvent	time	Products No.	yield %	ee	$[\alpha]_D$
1	**6**	1.1 *n*-BuLi	—	-78	pentane	3h	**9 (12)**	8 (63)	—	—
2	**6**	1.1 *n*-BuLi	—	-95	pentane	3h	**9 (12)**	0 (trace)	—	—
3	**6**	1.1 *n*-BuLi	1.1 TMEDA	-78	pentane	3h	**9 (12)**	47 (34)	—	—
4	**6**	1.1 *n*-BuLi	1.1 (-)-sparteine	-78	pentane	3h	**9 (12)**	45 (29)	50 (S)	-22.4
5	**6**	1.1 *n*-BuLi	1.1 (-)-sparteine	-95	pentane	3h	**9 (12)**	40 (14)	55 (S)	-23.0
6	**6**	1.1 *n*-BuLi	1.1 (-)-sparteine	-78	ether	3h	**9 (12)**	52 (37)	4 (R)	+3.3
7	**6**	1.1 *n*-BuLi	1.1 (-)-sparteine	-78	toluene	3h	**9 (12)**	58 (16)	7 (S)	-3.8
8	**6**	1.1 *sec*-BuLi	1.1 (-)-sparteine	-78	pentane	3h	**9 (12)**	50 (12)	11 (R)	+4.9
9	**6**	2.2 *n*-BuLi	2.2 (-)-sparteine	-78	pentane	3h	**9 (12)**	65 (11)	44 (S)	-15.4
10	**6**	2.2 *n*-BuLi	2.2 (-)-sparteine	-95	pentane	3h	**9 (12)**	83 (13)	60 (S)	-25.6
11	**6**	2.2 *n*-BuLi	0.2 (-)-sparteine	-95	pentane	6h	**9 (12)**	44 (30)	48 (S)	-18.2
12	**7**	2.2 *n*-BuLi	2.2 (-)-sparteine	-78	pentane	3h	**10 (12)**	86 (14)	37 (R)	+13.3
13	**7**	2.2 *n*-BuLi	2.2 (-)-sparteine	-95	pentane	3h	**10 (12)**	73 (4)	19 (R)	+7.4
14	**8**	3.3 *n*-BuLi	3.3 (-)-sparteine	-78	pentane	3h	**11 (12)**	10 (0)	75 (S)	-9.15

But it is noteworthy that the reaction with **7** showed the slightly lower ee (37%) but with the opposite sense of selectivity (entries 12, 13). In the case of **8**, the poor solubility of **8** in pentane led to the product in quite low chemical yield (10%), even though the highest enantioselectivity (75% ee) was observed (entry 14).

% ee and the absolute configurations of enantio-enriched compounds

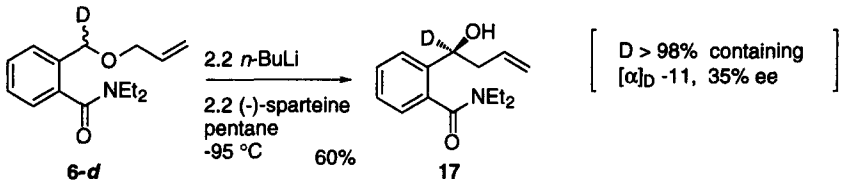
The % ee's were obtained by HPLC analysis on a CHIRALCEL OD column (250 x 4.6 mm I. D.) using *n*-hexane : *i*-propanol = 200 : 1 as eluent (flow rate 0.5 ml / min) at 254 nm (As for **9, 10, 11, 19b** , the % ee's were obtained after conversion to the corresponding 3-substituted phthalide as shown in Scheme 2). The absolute configurations of the main enantiomer **9, 10, 11, 19b** were determined, after chemical modifications, by comparison with the optical rotations of the known compounds[22] (For example, the (S) absolute configuration of **9** was determined as shown in Scheme 2).



Scheme 2

Mechanistic investigations

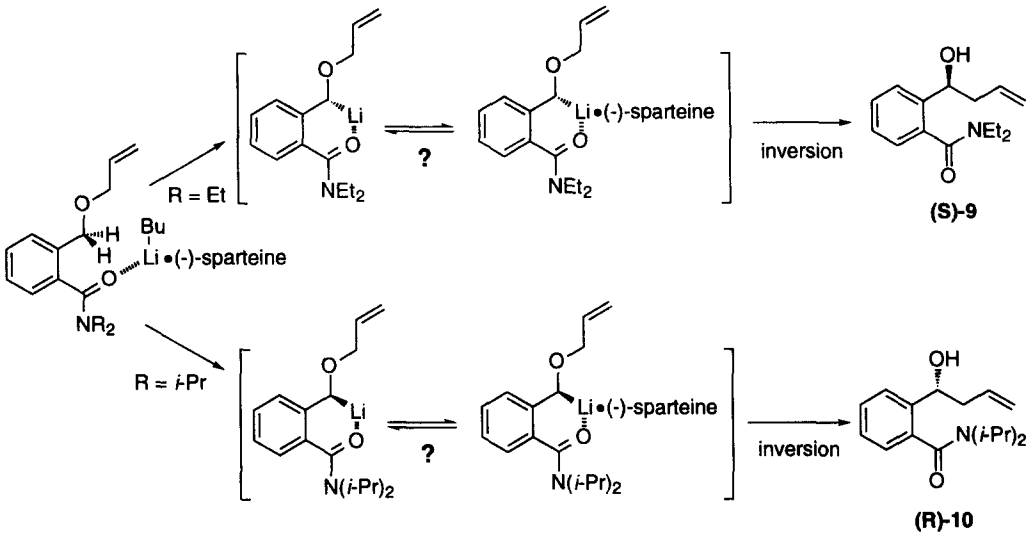
Prior to discuss the reason for the opposite selectivity between *N,N*-diethylcarbamoyl group and *N,N*-diisopropylcarbamoyl group described above, we tried to establish whether the enantioselectivity of this rearrangement was introduced at the deprotonation step or after the deprotonation.



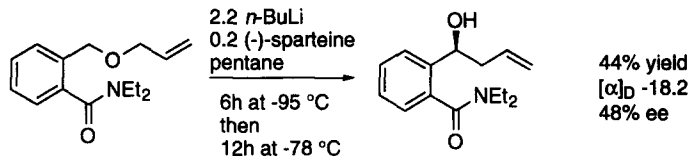
Scheme 3

We carried out the similar rearrangement of a racemic α-deuterated benzyl ether derivative (**6-*d***) with *n*-BuLi—(-)-sparteine complex. As shown in Scheme 3, deuterated product (**17**) with 98 % *d*-content was obtained in 60% yield, but the % ee was significantly decreased to 35 %. This result suggests that the enantioselectivity is predominantly determined at the deprotonation step. Furthermore the fact that the presence of (-)-sparteine (ligand) is crucial for the promotion of this rearrangement (see Table 1, entries 2, 5) suggests the enantioselective deprotonation pathway. Thus it seems that the stereoinformation is introduced at the deprotonation step and the opposite selectivity between *N,N*-diethylcarbamoyl group and *N,N*-diisopropylcarbamoyl group can be rationalized as that *n*-BuLi—(-)-sparteine complexes coodinated with the carbamoyl groups take different orientations between *N,N*-diethylcarbamoyl group and *N,N*-diisopropylcarbamoyl group to abstract one of the two prochiral hydrogens and the resulting chiral lithium salts rearrange to give the corresponding products as shown in Chart 3[23]. However, we need further investigations to confirm whether the chiral lithium salts include the equilibration between the uncomplexed and the complexed species with (-)-sparteine (Chart 3). The results and the mechanistic studies mentioned above prompted us to carry out the similar rearrangement but with the substoichiometric amount of (-)-sparteine directed for the catalytic asymmetric [2,3]-Wittig rearrangement. The reaction with 0.2 equivalent of (-)-sparteine (2.2 equivalent of *n*-BuLi) at -95 °C gave desired rearranged product in 44% chemical yield with 48% ee (Table 1, entry 11 and Scheme 4).

Chart 3. Proposed Mechanism of Enantioselective [2,3]-Wittig Rearrangement *via* Asymmetric Deprotonation Pathway

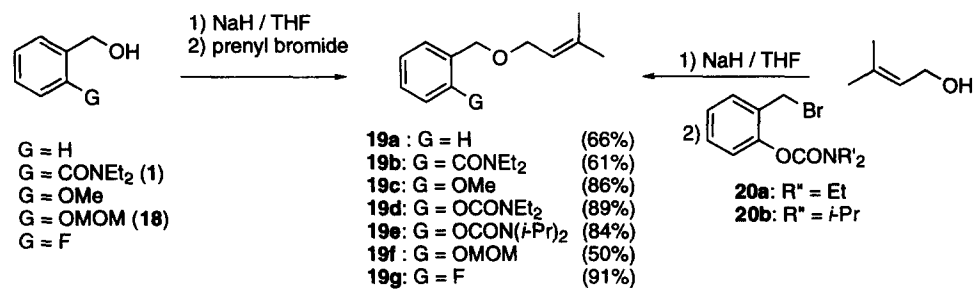


Scheme 4



This result shows that (-)-sparteine is potential as a catasylst. Extension studies were tried on [2,3]-Wittig rearrangement of the slightly modified substrates, *o*-substituted benzyl prenyl ethers (Scheme 5, Table 2).

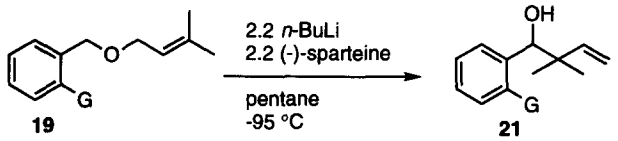
Scheme 5



The compounds (**19a, 19b, 19c, 19f** and **19g**) were prepared in the same way as those of *N,N*-dialkyl-*o*-allyloxymethylbenzamides. As for the synthesis of **19d** and **19e**, the benzyl bromide derivatives (**20a** and **20b**), which were prepared by the NBS bromination of *N,N*-dialkyl *O*-*o*-tolylcarbamates, were condensed with 3-methyl-2-butene-1-ol (prenol). As can be seen from Table 2, *N,N*-diethyl-*o*-(3-methyl-2-butenyl)oxymethylbenzamide (**19b**) gave the highest enantioselectivity (62% ee) (entry 2). The presence of *o*-methoxy and *o*-OCON(*i*-Pr)2 groups, both of which were known as strong directed

metalation groups, did not enhance the enantioselectivities (entries 3, 5). *o*-Methoxymethoxy adduct (**21f**) was obtained in 20% ee. *o*-Fluoro derivative (**19g**) gave a product with 16% ee.

Table 2



19 **21**

entry	G	products	yield (%)	S. M. (%)[a]	ee	$[\alpha]_D$
1	H	**21a**	60	30	21 (S)[b]	-10.1
2	$CONEt_2$	**21b**	71	0	62 (S)[c]	-24.8
3	OMe	**21c**	49	41	12[d]	-6.1
4	$OCONEt_2$	**21d**	0[e]	0	—	—
5	$OCON(i\text{-}Pr)_2$	**21e**	60	24	10[d]	+5.1
6	OCH_2OCH_3	**21f**	50	45	20[d]	-7.8
7	F	**21g**	68	0	16[d]	-6.6

a: Yield of the recovered starting material. b: The absolute configuration is known[10].
c: The absolute configuration of main enantiomer **21b** was determined , after converted to 3-*tert*-butylphthalide, by comparison with that of known compound[22]. d: The absolute configurations are unassigned. e: Exclusive C-O cleavage was observed to form *o*-hydroxy benzyl prenyl ether.

CONCLUSION

The *N,N*-diethylcarbamoyl group acts as an efficient director in the (-)-sparteine-mediated enantioselective [2,3]-Wittig rearrangement of *o*-substituted benzyl allyl ethers. The presence of *N,N*-diisopropylcarbamoyl group gave a product with a similar but opposite enantioselectivity to that of *N,N*-diethylcarbamoyl group. The reaction mechanism was investigated using racemic *d*-containing *N,N*-diethyl-*o*-allyloxymethylbenzamide and it was suggested that the stereoinformation was introduced at the deprotonation step. However, we still need to consider what the real intermediate is and to confirm how the intermediate proceeds to the product. The enantioselectivity in the rearrangement was not decreased even with the substoichiometric amount (0.2 equiv.) of (-)-sparteine. Introduction of the several heteroatomic functional groups other than carbamoyl groups did not enhance the enantioselectivity in this system.

ACKNOWLEDGEMENTS We wish to thank Professor Victor Snieckus (Department of Chemistry, Queen's University, Canada) for informative discussions and advice.

EXPERIMENTAL

All materials not explicitly mentioned were purchased from Wakenyaku Co., Nacalai Tesque Co., and Aldrich Chemical Co. ^{1}H-NMR spectra were recorded on a JEOL JNM-FX-270 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are recorded in parts per million (ppm) relative to TMS. ^{13}C-NMR spectra were proton decoupled and recorded on a JEOL JNM-FX-270 spectrometer using the carbon signal of the deuterated solvent as the internal standard. Mass spectra (MS) were obtained on JMS-HX / HX-110A instruments. Optical rotation were measured on a DIP 360 (Japan Spectroscopic Co.) polarimeter at the sodium D-line and ambient temperature. Analytical HPLC

was performed on a Waters 510 / 486 unit and the wavelength detector was operated at 254 nm. Chiral HPLC analyses were performed using CHIRALCEL OD columns at room temperature unless stated otherwise. Enantiomeric purity assays using chiral HPLC columns were completed with both racemic and enantioenriched materials and repeated at least once in order to ensure accuracy of the method used. Melting points were measured on a Yanagimoto micro melting point apparatus without correction. Flash chromatography was performed with silica gel (C-200) obtained from Wakenyaku Co. Analytical thin layer chromatography was performed on Merck Silica gel 60 F_{254} alminium sheets and the visualization was accomplished by UV lamp. THF was distilled from sodium / benzophenone under an argon atmosphere. Pentane and diethyl ether were distilled from Calcium hydride under an argon atmosphere. Toluene was distilled from sodium. (-)-Sparteine and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) were distilled from calcium hydride under nitrogen and stored under argon. Solutions of *n*-BuLi in hexanes and *sec*-BuLi in cyclohexane were obtained from KANTO CHEMICAL CO. or Aldrich and titrated periodically according to the method of Watson and Eastham[24]. A -78 °C bath refers to a mixture of dry ice in acetone and a -95 °C bath refers to a mixture of dry ice and liquid nitrogen in acetone.

_N,N_-Diethyl-_o_-hydoxymethylbenzamide (4)

A solution of *N,N*-diethylbenzamide (1.77 g, 10 mmol) in freshlly distilled tetrahydrofuran (THF) (30 mL) was added to a -78 °C solution of *sec*-BuLi (12 mL, 12 mmol, 1.0 M in cyclohexane) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (1.8 mL, 12 mmol) in dry THF (80 mL) *via* cannula and the solution was maintained at -78 °C under argon. After 40 min, *N,N*-dimethylformamide (DMF) (3.1 mL, 40 mmol) was added to the reaction mixture and the mixture was stirred at -78 °C for 1h and warmed to room temperature. The reaction mixture was treated with sat. NH_4Cl aq. and then concentrated. Extraction with ethyl acetate (30 mL x 3), wash with water, brine, dryness over $MgSO_4$, concentration to a small volume afforded a crude aldehyde (2.3 g) as an yellow oil. A crude aldehyde (2.3 g) was dissolved in methanol (50 mL) and 420 mg of $NaBH_4$ was addd dropwise at 0 °C. After 30 min stirring at room temperature, the reaction mixture was treated with sat. NH_4Cl aq. and extracted with ethyl acetate. Organic phase was washed with water and brine and then dried over $MgSO_4$. Concentration to a small volume *in vacuo* gave crude product. Purification by flash chromatography (hexane: ethyl acetate = 1:2) afforded 1.6 g (77%) of pure **4** as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.08 (t, 3H, *J* = 6.93 Hz), 1.27 (t, 3H, *J* = 6.93 Hz), 3.21 (q, 2H, *J* = 6.93 Hz), 3.57 (q, 2H, *J* = 6.93 Hz), 3.85 (m, 1H), 4.50 (m, 2H), 7.21—7.46 (m, 4H). Anal calcd. for $C_{12}H_{17}NO_2$: H, 8.21; C, 69.57; N, 6.76. Found: H, 8.27; C, 69.86; N, 6.69.

_N,N_-Diethyl-_o_-allyloxymethylbenzamide (6)

To a stirred suspension of NaH (690 mg as 60% oil suspension, 17.3 mmol, prewashed with hexane) in 50 mL of THF at 0 °C, a solution of **4** (2.76 g, 13.3 mmol) in 15mL of THF was slowly added. The mixture was sirred for 15 minutes at room temperature. The mixture was cooled to 0 °C again and allyl bromide (1.5 mL, 17.3 mmol) was added dropwise and the mixture was stirred at room temperature for 20h. Sat. NH_4Cl aq. was added to the reaction mixture and the mixture was extracted with Et_2O. The extract was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexane: ethyl acetate = 3:2) gave **6** (3.09 g, 94%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.05 (t, 3H, *J* = 6.93 Hz), 1.25 (t, 3H, *J* = 6.93 Hz), 3.14 (q, 2H, *J* = 6.93 Hz),

3.55 (m, 2H), 4.03 (m, 2H), 4.51 (s, 2H), 5.16—5.33 (m, 2H), 5.86—6.00 (m, 1H), 7.18—7.48 (m, 4H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 12.7, 13.8, 38.7, 42.9, 69.7, 71.8, 117.1, 125.5, 127.6, 128.7, 128.9, 134.6, 134.8, 136.6, 170.3. Anal calcd. for $C_{15}H_{21}NO_2$: H, 8.50; C, 72.87; N, 5.67. Found: H, 8.72; C, 72.62; N, 5.42.

***N,N*-Diethyl-*o*-(1-hydroxy-3-butenyl)benzamide (9). (-)-Sparteine-mediated [2,3]-Wittig rearrangement of *N,N*-diethyl-*o*-allyloxymethylbenzamide (Typical procedure).**

To a -78 °C solution of (-)-sparteine (0.51 mL, 2.2 mmol) and *n*-BuLi (1.4 mL, 2.2 mmol, 1.53 M in hexane) in 35 mL of freshly distilled pentane, a solution of **6** (494 mg, 2.0 mmol) in pentane (10 mL) was slowly added *via* cannula. The resulting purple mixture was stirred for 3h at -78 °C and then warmed to room temperature. The reaction mixture was treated with sat. NH_4Cl aq. and separated. Aqueous phase was extracted three times with ethyl acetate and organic phase was combined, washed with water and brine, dried over $MgSO_4$, then concentrated to a small volume *in vacuo*. Purification by flash chromatography gave 226.4 mg (45%) of *N,N*-diethyl-*o*-(1-hydroxy-3-butenyl)benzamide (**9**) and 146 mg (29%) of aryl butyl ketone (**12**). **9**: $[\alpha]_D$ -22.4 (c, 1.31 $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.09 (t, 3H, *J* = 6.93 Hz), 1.27 (t, 3H, *J* = 6.93 Hz), 2.60 (m, 2H), 3.13—3.67 (m, 5H), 4.68 (bs, 1H), 5.08—5.18 (m, 2H), 5.74—5.89 (m, 1H), 7.17—7.53 (m, 4H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 12.5, 13.8, 38.9, 43.2, 117.6, 117.7, 125.6, 127.2, 129.1, 134.8, 140.8, 171.1. Anal calcd. for $C_{15}H_{21}NO_2$: H, 8.50; C, 72.87; N, 5.67. Found: H, 8.61; C, 72.63; N, 5.50. **12**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.94 (t, 3H, *J* = 7.26 Hz), 1.32—1.74 (m, 4H), 2.92 (m, 2H), 4.06 (m, 2H), 4.78 (s, 2H), 5.17—5.36 (m, 2H), 5.89—6.04 (m, 1H), 7.31—7.71 (m, 4H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 13.7, 22.2, 26.2, 29.5, 70.0, 71.5, 116.6, 126.7, 127.8, 128.1, 131.1, 134.5, 136.8, 138.8. Anal calcd for $C_{15}H_{20}O_2$: H, 8.62; C, 77.59. Found: H, 8.47; C, 77.37.

***N,N*-Diisopropyl-*o*-hydroxymethylbenzamide (5)**

According to the procedure described in the synthesis of **4**, a solution of *N,N*-diisopropylbenzamide (4.1 g, 20 mmol) in 50 mL of THF was added to a solution of *sec*-BuLi (20 mL, 24 mmol, 1.2 M in cyclohexane) and TMEDA (3.6 mL, 24 mmol) in 150 mL of THF at -78 °C. After 40 min, DMF (6.2 mL, 80 mmol) was added to the reaction mixture and worked up. A crude aldehyde was dissolved in 60 mL of MeOH at 0 °C and $NaBH_4$ (760 mg, 20 mmol) was added by portions. Purification by flash chromatography (*n*-hexane : ethyl acetate = 2 : 3) afforded 3.15 g (67%) of *N, N*-diisopropyl-*o*-hydroxymethylbenzamide as a white solid. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.14 (m, 6H), 1.57 (m, 6H), 3.54 (m, 2H), 3.83 (m, 1H), 4.42 (m, 1H), 4.65 (m, 1H), 7.18 (m, 1H), 7.27—7.45 (m, 3H). Anal calcd. for $C_{14}H_{21}NO_2$: H, 8.94; C, 71.49; N, 5.96. Found: H, 9.24; C, 71.38; N, 5.93.

***N,N*-Diisopropyl-*o*-allyloxymethylbenzamide (7)**

According to the procedure described in the synthesis of **6**, a solution of **5** (1.5 g, 6.4 mmol) in 10 mL of THF was added dropwis to a stirred suspension of NaH (305 mg as 60% oil suspension, 7.7 mmol, prewashed with hexane) in 30 mL of THF at 0 °C. Allyl bromide (0.66 mL, 7.7 mmol) was added dropwise and the mixture was worked up. Purification by flash chromatography (hexane : ethyl acetate = 2 : 1) gave **7** (1.62 g, 92%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.10 (d, 6H, *J*= 6.60 Hz), 1.56 (d, 6H, *J* = 6.93 Hz), 3.50 (m, 1H), 3.71 (m, 1H), 4.06 (ddd, 2H, *J* = 5.83, 1.32, 0.99 Hz), 4.45 (d, 1H, *J* = 11.55 Hz), 4.61 (d, 1H, *J* = 11.55 Hz), 5.20 (m, 1H), 5.30 (m, 1H), 5.95 (m, 1H), 7.13 (m, 1H), 7.25—7.37 (m, 2H), 7.46 (m, 1H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 20.5, 45.6, 50.8, 69.5, 71.9, 117.3,

124.7, 127.5, 128.2, 129.0, 134.6, 137.9, 169.9. Anal calcd. for $C_{17}H_{25}NO_2$: H, 9.09; C, 74.18; N, 5.09. Found: H, 9.12; C, 74.44; N, 4.98.

Allyl chloromethyl ether

According to the literature (Org. Syn. *Collective Volume 6* p101—103.), anhydrous hydrogen chloride was passed through the mixture of allyl alcohol (16.3 mL, 0.26 mol) and paraformaldehyde (8.0 g, 0.26 mol). The mixture was maintained at 20—25 °C and the bubbling of hydrogen chloride was continued for 2h. The two clear homogenuous layers were sparated, and the upper layer is diluted with 80 mL of pentane and dried over anhydrous $MgSO_4$ for 3h at 0 °C, with stirring. The filtrate containing 1 - 2 g of anhydrous calcium chloride was concentrated on a rotary evaporator to afford 16 g (58%) of crude product. This crude allyl chloromethyl ether was used without further purification. However, crude material was distilled at 70 mmHg from anhydrous calcium chloride, affording very pure allyl chloromethyl ether (bp. 43 °C / 70 mmHg). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.24 (m, 2H), 5.27—5.35 (m, 2H), 5.52 (s, 2H), 5.93 (m, 1H).

***N*-Isopropyl-*o*-allyloxymethylbenzamide (8)**

To a -78 °C solution of *sec*-BuLi (11.3 mL, 11 mmol, 0.97 M in cyclohexane) and TMEDA (1.7 mL, 11 mmol) in 15 mL of anhydrous THF, *N*-isopropylbenzamide (815 mg, 5 mmol) in THF (15 mL) was added *via* cannula. The mixture was maintained at -78 °C for 1h and then quenched with 1.6 g (15 mmol) of allyl chloromethyl ether (dissolved in 10 mL of THF). The mixture was further stirred for 1h at -78 °C and treated with sat. NH_4Cl aq. at -78 °C. The mixture was concentrated *in vacuo* and extracted three times with ethyl acetate. The combined organic phase was washed with water, brine, and dried over anhydrous $MgSO_4$ and concentrated. Purification by flash chromatography gave 880 mg (75%) of **8** as colorless solid. Recrystallization from hot hexane gave pure compound as colorless needles. mp 65—67 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.25 (d, 6H, J = 6.27 Hz), 4.10 (m, 2H), 4.29 (m, 1H), 4.58 (s, 2H), 5.30 (m, 2H), 5.96 (m, 1H), 7.21—7.77 (m, 5H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 22,8, 41.8, 71.1, 117.5, 126.8, 128.6, 129.3, 130.1, 130.8, 133.9, 137.2, 167.6. Anal calcd for $C_{14}H_{19}NO_2$. H, 8.15; C, 72.10; N, 6.01. Found: H, 8.22; C, 72.04: N, 6.01.

***N,N*-Diisopropyl-*o*-(1-hydroxy-3-butenyl)benzamide (10). [2,3]-Wittig rearrangement of 7 by the typical procedure used for 9**

To a stirred suspension of (-)-sparteine (0.37 mL, 1.60 mmol) and *n*-BuLi (1.00 mL, 1.60 mmol, 1.6 M in hexane) in 15 mL pentane at -78 °C, a solution of **7** (200 mg, 0.73 mmol) in 5mL of pentane was added *via* cannula and the deep red suspension was stirred at -78 °C for 3h. After worked up, purification by flash chromatography gave 173 mg (86%) of **10** and 24 mg (12%) of **12**. **10**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.12 (m, 6H), 1.56 (m, 6H), 2.60 (m, 2H), 3.35—3.55 (m, 1H), 3.82 (m, 1H), 4.68 (m, 1H), 5.06—5.20 (m, 2H), 5.80 (m, 1H), 7.14 (d, 1H, J = 7.26 Hz), 7.28 (m, 1H), 7.37 (m, 1H), 7.49 (m, 1H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 20.1, 20.2, 20.4, 20.5, 20.6, 39.7, 43.2, 45.9, 50.1, 70.3, 72.2, 117.2, 117.7, 124.7, 125.1, 126.6, 127.2, 127.5, 128.7, 134.9, 136.1, 137.3, 140.5, 170.7, 171.1. Anal calcd for $C_{17}H_{25}NO_2$: H, 9.09; C, 74.18; N, 5.09. Found: H, 9.11; C, 74.10; N, 5.21.

***N*-Isopropyl-*o*-(1-hydroxy)-3-butenylbenzamide (11) . [2,3]-Wittig rearrangement reaction of 8**

To a -78 °C solution of (-)-sparteine (0.77 mL, 3.3 mmol) and *n*-BuLi (2.2 mL, 3.3 mmol, 1.5 M in hexane) in 15 mL of freshly distilled pentane, a solution of **8** (233 mg, 1.0 mmol) in pentane (15 mL) was slowly added *via* cannula. After worked up, purification by flash chromatography gave 23.4 mg

(10%) of **11**. $[\alpha]_D$ -9.15 (c 2.34 $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.27 (m, 6H), 2.61 (m, 2H), 4.25 (m, 1H), 4.56 (bs, 1H), 4.78 (m, 1H), 5.08 (m, 2H), 5.79 (m, 1H), 6.09 (m, 1H), 7.29—7.45 (m, 4H). HRMS (FAB+) calcd for $C_{14}H_{20}NO_2$ (MH) 234.1495. Found: 234.1501

3-Allylphthalide (13)

p-TsOH•H_2O (50 mg) was added to the toluene (3 mL) solution of enantio-enriched rearranged product (**9**) (64 mg, 0.26 mmol, $[\alpha]_D$ -15.4) and the mixture was refluxed for 30 min under argon atmosphere. The mixture was diluted with ethyl acetate and added 10 mL of NH_4Cl aq. and separated. The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with water, brine and dried over $MgSO_4$. After concentrated to the small volume, crude residure was purified by flash chromatography for HPLC analysis. 44.8 mg (99%). The enantiomeric excess was found to be 44%. The enantiomeric excess was obtained by HPLC on CHIRALCEL OD column (250 x 4.6 mm, I. D.) from Daicel co. using *n*-hexane : *i*-propanol = 200 : 1 as eluent (flow rate 0.5 ml / min) at 254 nm. $[\alpha]_D$ -23.2 (c 4.0 $CHCl_3$) ^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.60—2.81 (m, 2H), 5.14—5.22 (m, 2H), 5.53 (m, 1H), 5.69—5.84 (m, 1H), 7.48 (d, 1H, *J* = 7.25 Hz), 7.53 (dd, 1H, *J* = 7.26, 7.59 Hz), 7.68 (dd, 1H, *J* = 7.25, 7.59 Hz), 7.90 (d, 1H, *J* = 7.59 Hz). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 38.5, 80.1, 119.6, 121.9, 125.7, 126.1, 129.1, 131.1, 133.8, 149.2, 170.3. Anal calcd for $C_{11}H_{10}O_2$: H, 5.75; C, 75.86. Found: H, 5.81; C, 75.67.

The % ee's of compounds 10 and 11

As the same way, **10** (80 mg, 0.29 mmol, $[\alpha]_D$ +13.3) was converted to 3-allylphthalide (50.5 mg, 99%). $[\alpha]_D$ +18.8 (c 5.0 $CHCl_3$). The enantiomeric excess was found to be 37%.

11 (21 mg, 0.09 mmol, $[\alpha]_D$ -9.15) was converted to 3-allylphthalide (10 mg, 64%). $[\alpha]_D$ -48.6 (c 1.0 $CHCl_3$). The enantiomeric excess was found to be 75%.

Successive two step procedures for 3-(2-hydroxy)ethylphthalide (14)

To a -60 °C solution of 3-allyl phthalide (**13**) (86 mg, 0.5 mmol, $[\alpha]_D$ -23.0) in MeOH (40 mL), O_3 gas was flowed. The colorless solution changed to pale blue within 15 min. After 10 min further stirring at -10 °C, excess $NaBH_4$ (500 mg) in MeOH was added. The mixture was concentrated *in vacuo*, added sat. NH_4Cl aq., and extracted three times with chloroform. The combined organic layer was washed with water, brine, and dried over $MgSO_4$ and then concentrated to a small volume. 67 mg (75.3%). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.92 (m, 1H), 2.33 (m, 1H), 3.96 (m, 2H), 5.70 (dd, 1H, *J* = 3.30, 9.56 Hz), 7.50 (m, 1H), 7.53 (m, 1H), 7.70 (m, 1H), 7.92 (m, 1H). HRMS (FAB+) calcd for $C_{10}H_{11}O_3$ (MH) 179.07083. Found: 179.0706.

3-(2-*p*-Toluenesulfonyloxy)ethylphthalide (15)

To the chloroform solution of **14** (50 mg, 0.28 mmol), pyridine (0.05 mL, 0.56 mmol) and *p*-toluenesulfonyl chloride (107 mg, 0.56 mmol) was added at 0 °C. The mixture was stirred at room temperature for 3h. The mixture was treated with NH_4Cl aq. and separated. The aqueous phase was extracted with chloroform and the combined organic phase was washed with water and brine, dried over $MgSO_4$ and then concentrated to the small volume. Purification by flash chromatography gave 71 mg (76.4%) of pure **15**. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.97 (m, 1H), 2.47 (s, 3H), 2.48 (m, 1H), 4.28 (m, 2H), 5.55 (m, 1H), 7.37 (m, 2H), 7.44 (m, 1H), 7.56 (m, 1H), 7.72 (m, 1H), 7.80 (m, 2H), 7.83 (m, 1H). HRMS (FAB+) calcd. for $C_{17}H_{17}SO_5$ (MH) 333.07971. Found: 333.0792.

3-Ethylphthalide (16)

The DMSO (2 mL) solution of **15** (30 mg, 0.09 mmol) and $NaBH_4$ (37 mg, 1 mmol) was stirred for 1h at 40 °C. The mixture was treated with NH_4Cl aq. and extracted with ether. The ether layer was washed with water and brine, dried over $MgSO_4$ and then concentrated. Purification by flash chromatography (*n*-hexane : ethyl acetata = 3 : 1) afforded 10 mg (66%) of 3-ethylphthalide. $[\alpha]_D$ -20.9 (c 0.23 $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.01 (m, 3H), 1.83 (m, 1H), 2.13 (m, 1H), 5.46 (m, 1H), 7.44 (m, 1H), 7.53 (m, 1H), 7.68 (m, 1H), 7.90 (m, 1H). HRMS (FAB+) calcd for $C_{10}H_{11}O_2$ (MH) 163.0759. Found: 163.0763.

***N,N*-Diethyl-*o*-hydoxy(deuteriomethyl)benzamide (4-*d*)**

A solution of *N,N* -diethylbenzamide (2.2 g, 12.4 mmol) in freshlly distilled THF (30 mL) was added to a stirred solution of *sec*-BuLi (14.1 mL, 13.7 mmol, 0.97 M in cyclohexane) and TMEDA (2.06 mL, 13.7 mmol) in dry THF (80 mL) *via* cannula and the solution was maintained at -78 °C under argon. After 40 min, DMF (2.9 mL, 37.3 mmol) was added to the reaction mixture and the mixture was stirred at -78 °C for 1h and warmed to room temperature. The reaction mixture was treated with sat. NH_4Cl aq. and then concentrated. Extraction with ethyl acetate (30 mL x 3), wash of organic layers by water, brine, dried over $MgSO_4$ and concentration afforded a crude product (2.58 g) as an yellow oil.

A crude aldehyde (1.0 g) was dissolved in methanol (10 mL) and added 200 mg of $NaBD_4$ (Sodium borodeuteride, 98 atom % D) dropwise at 0 °C. After 30min stirring at room temperature, the reaction mixture was treated with sat. NH_4Cl aq. and extracted with ethyl acetate. Organic phase was washed with water and brine and then dried over $MgSO_4$. Concentration to a small volume *in vacuo* gave crude product. Purification by flash chromatography (hexane:ethyl acetate = 1:1) afforded 550 mg (54%) of pure **4-*d*** as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.10 (m, 3H), 1.28 (m, 3H), 3.24 (m, 2H), 3.58 (m, 3H), 4.50 (m, 1H), 7.22—7.47 (m, 4H).

***N,N*-Diethyl-*o*-allyloxy(deuteriomethyl)benzamide (6-*d*)**

A solution of **4-*d*** (450 mg, 2.16 mmol) in 5mL of THF was slowly added to a stirred suspension of NaH (104 mg as 60% oil suspension, 2.6 mmol, prewashed with hexane) in 10 mL of THF at 0 °C. Allyl bromide (0.23 mL, 2.6 mmol) was added dropwise and stirred for 20h and worked up according to the procedure described in the synthesis of **6**. Purification by flash chromatography (hexane:ethyl acetate = 3:2) gave **6-*d*** (361 mg, 67.4%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.04 (m, 3H), 1.25 (m, 3H), 3.14 (m, 2H,), 3.56 (m, 2H), 4.02 (m, 2H), 4.49 (bs, 1H), 5.24 (m, 2H), 5.92 (m, 1H), 7.18—7.47 (m, 4H). LRMS (FAB+) calcd for $C_{15}H_{21}DNO_2$ (MH) 249. Found: 249.

N*, *N*-Diethyl-*o*-(1-deuterio-1-hydroxy-3-butenyl)benzamide (17). [2,3]-Wittig rearrangement of 6-*d

To a -95 °C solution of (-)-sparteine (0.41 ml, 1.77 mmol) and *n*-BuLi (1.18 ml, 1.77 mmol, 1.5 M in hexane) in 10 mL of freshly distilled pentane, a solution of **6-*d*** (200 mg, 0.8 mmol) in pentane (5 mL) was slowly added *via* cannula. The resulting purple mixture was stirred for 3h at -95 °C and then worked up according to the typical procedure. Purification by flash chromatography gave 124 mg (62%) of **17** and 65 mg (36%) of aryl butyl ketone. $[\alpha]_D$ -11.15 (c 1.649 $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.09 (m, 3H), 1.26 (m, 3H), 2.59 (m, 2H), 3.19 (m, 2H), 3.56 (m, 2H), 5.07—5.17 (m, 2H), 5.81 (m, 1H), 7.17—7.53 (m, 4H). HRMS (FAB+) calcd. for $C_{15}H_{21}DNO_2$ (MH) 249.17143. Found: 249.1704. **17** was converted to 3-allyl-3-deuterio phthalide (94%, $[\alpha]_D$ -20.6 (c 2.4 $CHCl_3$)). The enantiomeric excess was found to be 35%.

[2,3]-Wittig rearrangement reaction of 6 with 0.2 equivalent of (-)-sparteine

To a -95 °C solution of (-)-sparteine (0.043 mL, 0.2 mmol) and *n*-BuLi (1.4 mL, 2.2 mmol, 1.53 M in hexane) in 15 mL of freshly distilled pentane, a solution of **6** (237 mg, 1.0 mmol) in pentane (5 mL) was slowly added *via* cannula. The resulting purple mixture was stirred for 6h at -95 °C and then stirred for 12h at -78 °C. The reaction mixture was worked up according to the typical procedure. Purification by flash chromatography gave 104 mg (44%) of **9** ($[\alpha]_D$ -18.2) and 68 mg (30%) of **12**.

***N,N*-Diethyl-*o*-(3-methyl-2-butenyloxymethyl)benzamide (19b)**

According to the procedure described in the synthesis of **6**, a solution of **4** (1.5 g, 7.2 mmol) in 10 mL of THF was slowly added to a stirred suspension of NaH (316 mg as 60% oil suspension, 7.9 mmol, prewashed with hexane) in 30 mL of THF at 0 °C. Then 1-bromo-3-methyl-2-butene (prenyl bromide) (1.0 mL, 8.6 mmol) was added dropwise. Work-up and purification by flash chromatography (eluted with hexane:ethyl acetate = 3:2) gave **19b** (1.2 g, 61%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.04 (m, 3H), 1.26 (m, 3H), 1.66 (s, 3H), 1.74 (s, 3H), 3.14 (m, 2H), 3.56 (m, 2H), 4.02 (m, 2H), 4.48 (s, 2H), 5.33—5.39 (m, 1H), 7.16—7.52 (m, 4H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 12.7, 13.7, 18.0, 25.7, 38.6, 42.9, 67.3, 69.4, 121.0, 125.4, 127.4, 128.6, 128.9, 135.0, 136.5, 136.9, 170.3. Anal. Calcd. for $C_{17}H_{25}NO_2$: H, 9.16; C, 74.13; N, 5.09. Found: H, 9.19; C, 73.77; N, 4.65.

***o*-Methoxybenzyl prenyl ether (19c)**

To a stirred suspension of NaH (880 mg as 60% oil suspension, 22.0 mmol, prewashed with hexane) in 50 mL of THF at 0 °C, a solution of *o*-methoxy benzyl alcohol (2.73 g, 20 mmol) in 7 mL of THF was slowly added. Then 1-bromo-3-methyl-2-butene (prenyl bromide) (2.66 mL, 23 mmol) was added dropwise. Work-up and purification by flash chromatography (hexane:ethyl acetate = 10:1) gave the product (3.55 g, 86%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.67 (s, 3H), 1.75 (s, 3H), 3.82 (s, 3H), 4.05 (m, 2H), 4.54 (s, 2H), 5.42 (m, 1H), 6.84—7.40 (m, 4H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 17.8, 25.6, 55.1, 66.6, 66.7, 110.0, 120.2, 121.3, 126.8, 128.3, 128.8, 136.6, 157.0. Anal. calcd for $C_{13}H_{18}O_2$: H, 8.8; C, 75.68. Found: H, 8.79; C, 74.48.

***N,N*-Diethyl *O*-*o*-(1-bromomethyl)phenylcarbamate (20a)**

N,N-Diethyl *O*-*o*-tolylcarbamate (2.07 g, 10 mmol) and 1.8 g of NBS (*N*-bromo succinimide) were dissolved in 25 mL of $CHCl_3$. 0.1 g of AIBN was added and the reaction mixture was refluxed for 5 hours. Floating precipitates formed was filtrated off and the filtrate was concentrated to a small volume. Purification by flash chromatography (hexane: ethyl acetate = 10:1) afforded 650 mg (23%) of **20a** as an yellow oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.20 (m, 6H), 3.37—3.57 (m, 4H), 4.45 (s, 2H), 7.14—7.40 (m, 4H). LRMS calcd for $C_{12}H_{18}NO_2Br$ (MH^+) 286, 288. Found, 286, 288.

***N,N*-Diethyl *O*-*o*-(3-methyl-2 butenyl)oxymethylphenylcarbamate (19d)**

To a stirred suspension of NaH (134 mg as 60% oil suspension, 3.38 mmol, prewashed with hexane) in 5 mL of THF at 0 °C, prenol (0.34 mL, 3.35 mmol) was slowly added. The mixture was sirred for 15 minutes at room temperature and then cooled to 0 °C again. **20a** (967 mg, 3.38 mmol) in THF (3 mL) was added dropwise to the mixture. The mixture was stirred at room temperature for 20h and added Sat. NH_4Cl aq. After extracted with ether, the extract was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo.* Purification by flash chromatography (hexane : ethyl acetate = 3:1) gave 873 mg (89%) of **19d** as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.18—1.30 (m, 6H), 1.65 (s, 3H), 1.74 (s, 3H), 3.35—3.50 (m, 4H), 4.00 (m, 2H), 4.49 (s, 2H), 5.35—5.41 (m, 1H), 7.09—7.47 (m,

4H). Anal. Calcd. for $C_{17}H_{25}NO_3$: H, 8.65; C, 70.06; N, 4.81. Found: H, 8.66; C, 68.51; N, 4.49 as $C_{17}H_{25}NO_3 \cdot 1/2H_2O$

N,N-Diisopropyl O-(2-bromomethyl)phenylcarbamate (20b)

N,N-Diisopropyl *O*-*o*-tolylcarbamate (2.35g, 10 mmol) and 2.85g (16 mmol) of NBS were dissolved in 25 mL of chloroform. 0.3 g Of AIBN was added and the reaction mixture was refluxed for 12h. Floating precipitates formed was filtered off and the filtrate was concentrated to small volume. Purification by flash chromatography (hexane : ethyl acetate = 20: 1) afforded 2.07 g (66%) of **20b** as an yellow oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.31—1.40 (m, 12H), 4.02—4.16 (m, 2H), 4.45 (s, 2H), 7.11—7.42 (m, 4H). Anal calcd for $C_{14}H_{20}NO_2Br$: H, 6.42; C, 53.51; N, 4.46; Br, 25.43. Found: H, 6.58; C, 53.46; N, 4.48; Br, 25.21.

N,N-Diisopropyl O-o-(3-methyl-2-butenyloxymethyl)phenylcarbamate (19e)

To a stirred suspension of NaH (144 mg as 60% oil suspension, 3.6 mmol, prewashed with hexane) in 10 mL of THF at 0 °C, a solution of prenol (0.36 mL, 3.6 mmol) was slowly added. The mixture was stirred for 15 min at room temperature. The mixture was cooled to 0 °C again and **20b** (1.04 g, 3.3 mmol) in THF (10 mL) was added dropwise and the mixture was stirred at room temperature for 20h. Sat. NH_4Cl aq. was added to the reaction mixture and the mixture was extracted with ether. The extract was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (hexane : ethyl acetate = 3:1) gave 886 mg (84%) of **19e** as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.33 (m, 12H), 1.64 (s, 3H), 1.74 (s, 3H), 4.04 (m, 4H), 4.48 (s, 2H), 5.38 (m, 1H), 7.05—7.49 (m, 4H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 18.0, 20.5, 21.5, 25.8, 46.0, 47.0, 66.8, 66.9, 121.1, 122.4, 125.3, 128.4, 129.2, 131.1, 136.9, 149.2, 154.0. Anal calcd. for $C_{19}H_{29}NO_3$: H, 9.15; C, 69.5; N, 4.27. Found: H, 8.97; C, 69.73; N, 4.29 as $C_{19}H_{29}NO_3 \cdot 1/2H_2O$

o-Methoxymethoxybenzyl alcohol (18)

According to the procedure described in the synthesis of **4**, methoxymethoxybenzene (2,76 g, 20 mmol) in 30 mL of THF was slowly added to a stirred solution of *sec*-BuLi (20 mL, 24 mmol.2 M soln. in cyclohexane) and TMEDA (3.6 mL, 24 mmol) in 150 mL of THF at -78 °C. DMF (6.2 mL, 80 mmol) was added to the mixture and worked up. To a crude aldehyde in 50 mL of methanol at 0 °C, $NaBH_4$ (760 mg, 20 mmol) was added by portions. Work-up procedure and purification by flash chromatography (hexane: ethyl acetate = 3:2) gave 1.95 g (58%) of **18** as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.27 (t, 1H, J = 6.60 Hz), 3.50 (s, 3H), 4.71 (d, 2H, J = 6.60 Hz), 5.24 (s, 2H), 7.01 (ddd, 1H, J = 7.59, 7.26, 0.99 Hz), 7.11 (d, 1H, J = 8.25 Hz), 7.23—7.33 (m, 2H). Anal calcd for $C_9H_{12}O_3$: H, 7.14; C, 64.29. Found: H, 7.38; C, 64.15.

o-Methoxymethoxybenzyl prenyl ether (19f)

To a stirred suspension of NaH (312 mg as 60% oil suspension, 7.8 mmol, prewashed with hexane) in 30 mL of THF at 0 °C, a solution of **18** (1.2 g, 7.14 mmol) in 10 mL of THF was slowly added. The mixture was treated with 1-bromo-3-methyl-2-butene (prenyl bromide) (0.91 mL, 7.8 mmol). Work-up and purification by flash chromatography (hexane: ethyl acetate = 5:1) gave **19f** (831 mg, 50%) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.67 (s, 3H), 1.75 (s, 3H), 3.48 (s, 3H), 4.04 (m, 2H), 4.57 (s, 2H), 5.20 (s, 2H), 5.42 (m, 1H), 6.97—7.42 (m, 4H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 18.0, 25.8, 56.0, 66.8, 94.4, 113.9, 121.3, 121.7, 127.7, 128.5, 129.1, 136.9, 154.8. Anal calcd. for $C_{14}H_{20}O_3$: H, 8.47; C, 71.19. Found: H, 8.66; C, 71.22.

o-Fluorobenzyl prenyl ether (19g)

To a stirred suspension of NaH (440 mg as 60% oil suspension, 11 mmol, prewashed with hexane) in 25 mL of THF at 0 °C, *o*-fluorobenzyl alcohol (1.26 g, 10 mmol) in 5 mL of THF was slowly added. The mixture was treated with 1.27 mL of 1-bromo-3-methyl-2-butene. Work-up and purification by flash chromatography (hexane: ethyl acetate = 10:1) afforded 1.76 g (91%) of **19g** as colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.67 (s, 3H), 1.76 (s, 3H), 4.03 (m, 2H), 5.40 (m, 1H), 6.99—7.46 (m, 4H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 18.1, 25.9, 65.4, 65.5, 67.0, 115.1, 115.4, 121.1, 124.1, 124.2, 125.7, 125.9, 129.2, 129.3, 130.2, 137.5, 159.1, 162.7. Anal. Calcd. for $C_{12}H_{15}OF$: H, 7.79; C, 74.18; F, 9.79. Found: H, 7.75; C, 74.25; F, 9.79.

***N,N*-Diethyl-*o*-(2,2-dimethyl-1-hydroxy-3-butenyl)benzamide (21b). [2,3]-Wittig rearrangement of 19b**

To a -95 °C solution of (-)-sparteine (0.51 mL, 2.2 mmol) and *n*-BuLi (1.45 mL, 2.2 mmol, 1.53 M in *n*-hexane) in freshly distilled pentane (20 mL), **19b** (275 mg, 1.0 mmol) in pentane was slowly added *via* cannula. After 3h at -95 °C, the reaction mixture was worked up according to the typical procedure. Purification by flash chromatography gave 174 mg (63%) of **21b** and 86 mg (33%) of aryl butyl ketone. **21b**: $[\alpha]_D^{28}$ -24.8 (c 1.583 $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.97—1.28 (m, 12H), 3.09—3.31 (m, 4H), 3.83 (m, 1H), 4.94—5.16 (m, 2H), 5.91—6.13 (m, 1H), 7.12—7.70 (m, 4H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 13.7, 20.3, 24.8, 38.9, 40.9, 46.3, 64.8, 114.9, 122.8, 123.4, 125.5, 129.1, 133.3, 142.4, 144.8, 171.1. Anal calcd for $C_{17}H_{25}NO_2$: H, 9.16; C, 74.13; N, 5.09. Found: H, 9.13; C, 74.08; N, 4.82. The % ee of **21b** was determined as follows: *p*-TsOH•H_2O (150 mg) was added to the toluene (10 mL) solution of (170 mg) of **21b** ($[\alpha]_D$ -24.8) and the mixture was refluxed for 30 min under argon atmosphere. The mixture was diluted with ethyl acetate and added 10 mL of NH_4Cl aq. and separated. The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with water, brine and dried over $MgSO_4$. After concentrated to the small colume, the residue was purified by flash chromatography to afford 100 mg (80%) of the pure 3-(1,1-dimethyl-2-propenyl)phthalide as a colorless oil. The enantiomeric excess was found to be 62%. $[\alpha]_D$ -23.44 (c 0.887 $CHCl_3$) ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.27 (s, 3H), 5.08—5.20 (m, 2H), 5.23 (s, 1H), 5.89 (dd, 1H, *J* = 10.88, 17.48 Hz), 7.49—7.91 (m, 4H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 20.4, 25.9, 41.8, 95.0, 115.0, 121.1, 123.2, 126.1, 129.1, 133.3, 142.4, 147.8, 169.1.

3-*tert*-Butylphthalide

To determine the absolute configuration of main enantiomer of **21b**, 3-*tert*-Butylphthalide was obtained from 3-(1,1-dimethyl-2-propenyl)phthalide ($[\alpha]_D$ -23.44) by the same procedure as shown in Scheme 2. $[\alpha]_D$ -6.7 (c 0.15 $CHCl_3$) ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.92 (s, 9H), 5.14 (s, 1H), 7.30—7.90 (m, 4H).

***o*-Methoxy-(2,2-dimethyl-1-hydroxy-3-butenyl)benzene (21c). [2,3]-Wittig rearrangement of 19c**

To a -95 °C solution of (-)-sparteine (0.51 mL, 2.2 mmol) and *n*-BuLi (1.45 mL, 2.2 mmol, 1.53 M soln. in *n*-hexane) in freshly distilled pentane (20 mL), **19c** (206 mg, 1.0 mmol) in pentane (5 mL) was slowly added *via* cannula. After 3h at -95 °C, the reaction mixture was worked up according to the typical procedure. Purification by flash chromatography gave 100 mg (49%) of **21** as a colorless oil. The enantiomeric excess was found to be 12%. $[\alpha]_D^{23}$ -6.12 (c 3.464 $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.03 (s, 3H), 2.56 (m, 1H), 3.80 (s, 3H), 4.84 (m, 1H), 5.02 (dd, 1H, *J* = 1.32, 17.49 Hz), 5.07 (dd, 1H, *J* = 1.32, 10.89 Hz), 5.96 (dd, 1H, *J* = 10.89, 17.49 Hz), 6.85—7.30 (m, 4H).

^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 21.7, 24.1, 43.0, 55.1, 75.5, 110.5, 112.8, 120.1, 128.2, 129.1, 129.2, 145.5, 157.0. Anal calcd. for $C_{13}H_{18}O_2$: H, 8.8; C, 75.68. Found: H, 9.04; C, 75.63.

***N,N*-Diisopropyl *O*-(*o*-(2,2-dimethyl-1-hydroxy-3-butenyl)phenylcarbamate (21e) [2,3]-Wittig rearrangement of 19e**

To a -95 °C solution of (-)-sparteine (0.39 mL, 1.72 mmol) and *n*-BuLi (1.12 mL, 1.72 mmol, 1.53 M soln. in *n*-hexane) in freshly distilled pentane (20 mL), **19e** (250 mg, 0.78 mmol) in pentane (5 mL) was slowly added *via* cannula. After 3h at -95 °C, the reaction mixture was worked up according to the typical procedure. Purification by flash chromatography gave 149 mg (60%) of **21e** as a colorless oil. The enantiomeric excess was found to be 10%. $[\alpha]_D$ +5.10 (c 1.253 $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.05 (s, 3H), 1.31 (m, 12H), 3.87—4.22 (m, 2H), 4.75 (m, 1H), 5.00—5.11 (m, 2H), 5.98 (dd, 1H, *J* = 10.55, 17.49 Hz), 7.02—7.51 (m, 4H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 20.5, 21.4, 21.6, 24.5, 42.3, 46.0, 47.0, 73.8, 113.2, 122.3, 124.7, 128.0, 128.8, 133.7, 144.9, 154.0. Anal. calcd. for $C_{17}H_{25}NO_3 \bullet CH_3OH$: H, 9.40; C, 68.38; N, 3.99. Found: H, 9.19; C, 68.22; N, 4.03.

***o*-Methoxymethoxy-(2,2-dimethyl-1-hydroxy-3-butenyl)benzene (21f). [2,3]-Wittig rearrangement of 19f**

To a -95 °C solution of (-)-sparteine (0.51 mL, 2.2 mmol) and *n*-BuLi (1.45 mL, 2.2 mmol, 1.53 M soln. in *n*-hexane) in freshly distilled pentane (20 mL), **19f** (236 mg, 1.0 mmol) in pentane (5 mL) was slowly added *via* cannula. After 3h at -95 °C, the reaction mixture was worked up according to the typical procedure. Purification by flash chromatography gave 110 mg (50%) of **21f** as a colorless oil. The enantiomeric excess was found to be 20%. $[\alpha]_D$ -7.8 (c 2.045 $CHCl_3$) ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.06 (s, 3H), 2.36 (m, 1H), 3.48 (s, 3H), 4.91 (m, 2H), 5.05 (dd, 1H, *J* = 1.32, 17.49 Hz), 5.10 (dd, 1H, *J* = 1.32, 10.56 Hz), 5.97 (dd, 1H, *J* = 10.56, 17.49 Hz), 6.96—7.35 (m, 4H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 21.6, 24.2, 43.0, 56.1, 74.5, 94.8, 113.1, 113.7, 121.2, 128.3, 129.0, 129.7, 145.3, 155.0. HRMS (FAB+) calcd for $C_{14}H_{21}O_3$ (MH) 237.14913. Found: 237.1483

***o*-Fluoro-(2,2-dimethyl-1-hydroxy-3-butenyl)benzene (21g). [2,3]-Wittig rearrangement of 19g**

To a -95 °C solution of (-)-sparteine (0.65 mL, 2.84 mmol) and *n*-BuLi (1.85 mL, 2.84 mmol, 1.53 M in hexane) in 20 mL of freshly distilled pentane, a solution of **19g** (250 mg, 1.29 mmol) in pentane (5 mL) was slowly added *via* cannula. The mixture was stirred for 3h at -78 °C and then worked up according to the typical procedure. Purification by flash chromatography gave 170 mg (68%) of **21g**. The enantiomeric excess was found to be 16%. $[\alpha]_{D30}$ -6.65 (c, 1.293 $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.05 (s, 3H), 4.85 (m, 1H), 5.08 (dd, 1H, *J* = 1.32, 17.48 Hz), 5.15 (dd, 1H, *J* = 1.32, 10.56 Hz), 5.94 (dd, 1H, *J* = 10.56, 17.48 Hz), 6.96—7.45 (m, 4H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 20.9, 23.9, 42.7, 73.0, 114.0, 114.6, 115.0, 123.4, 123.5, 128.0, 128.2, 128.6, 128.8, 129.1, 129.2, 144.5, 158.3, 161.9. Anal. calcd. for $C_{12}H_{15}OF$: H, 7.79; C, 74.18; F, 9.79. Found: H, 8.04; C, 74.18; F, 9.51.

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