Tetrahedron: *Asymmetry* 19 (2008) 1167–1170

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: http://www.elsevier.com/locate/tetasy

Highly enantioselective [2,3]-Wittig rearrangement of functionalized allyl benzyl ethers: a novel approach to lignan synthesis

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ARTICLE INFO

Article history:
Received 3 March 2008
Accepted 9 April 2008
Available online 26 May 2008

ABSTRACT

Highly enantioselective [2,3]-Wittig rearrangement of functionalized allyl benzyl ethers was accomplished using a chiral di-*tert*-butyl bis(oxazoline) ligand. The reaction proceeded with excellent diastereo- and enantioselectivity when no methoxy substituent was present at the *ortho*-position on the benzyl group. On the other hand, the enantioselectivity was drastically decreased in the presence of an *ortho*-methoxy group.

1. Introduction

The [2,3]-Wittig rearrangement is a strategy used to provide building blocks for the synthesis of natural products, since two stereocenters are constructed simultaneously with high diastereoselectivity.[1] Recently, an asymmetric [2,3]-Wittig rearrangement with an external chiral ligand has been investigated (Fig. 1).

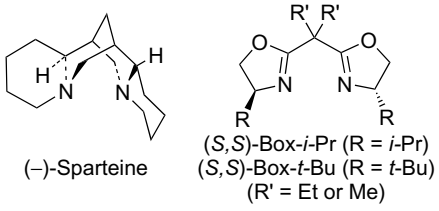
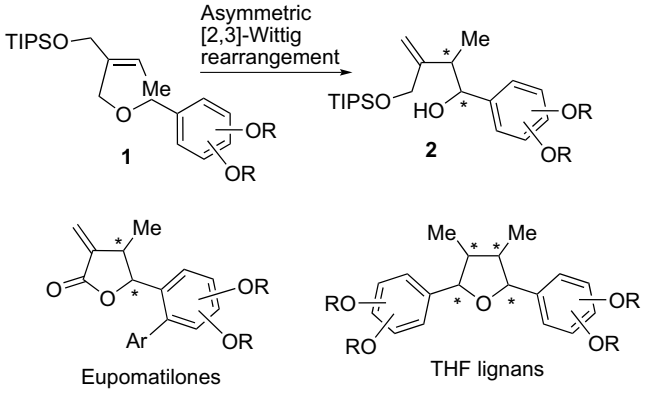


Figure 1. External chiral ligands for [2,3]-Wittig rearrangement.

Kang pioneered the asymmetric [2,3]-Wittig reaction using an external chiral ligand for alkenyl propargyl ethers[2] and the enantioselectivity was improved by Nakai up to 89% ee by applying a chiral diisopropyl bis(oxazoline) (Box-*i*-Pr).[3] On the other hand, the enantioselectivity remained moderate to low for benzyl ether-type substrates. Manabe[4] first reported an asymmetric [2,3]-Wittig rearrangement of alkenyl benzyl ethers using a chiral amino ether ligand, wherein (*Z*)-crotyl benzyl ether predominantly afforded the *syn*-adduct with 64% ee. For (*Z*)-crotyl benzyl ether, Nakai's ligand was not effective (40% ee).[3] In Kimachi's study using (−)-sparteine for *ortho*-functionalized benzyl ethers, the enantioselectivity did not exceed 60% ee.[5] Breeden improved the selectivity for benzyl prenyl ether up to 66% ee with inversion of enantioselectivity by employing a modified Box-*i*-Pr bearing *gem*-diphenyl group at the C5 position of two oxazoline rings.[6] To obtain an enantioselectivity more than 85% ee, conversion of the aryl group into tricarbonylchromium complex was required as described in Gibson's report.[7]

Over the course of our synthetic studies on lignans,[8] we investigated the asymmetric [2,3]-Wittig rearrangement of benzylic ethers **1** as a key reaction (Scheme 1).

Lignans are phenylpropanoid dimers and possess a variety of frameworks and substitution patterns on aryl groups. In addition, they have interesting biological activities such as cytotoxic, antiviral, antifungal, immunosuppressive, antiasthmatic, and antioxidant activities.[9] We envisioned a chiral benzylic alcohol derivative **2** as a key intermediate for various lignans, which can be synthesized by asymmetric [2,3]-Wittig rearrangement of oxygenated benzyl ether **1**, as shown in Scheme 1. We were interested in Honda's work regarding the synthesis of kallolide A and pinnatin A, in which an asymmetric [2,3]-Wittig reaction of cyclic furfuryl ethers



Scheme 1.

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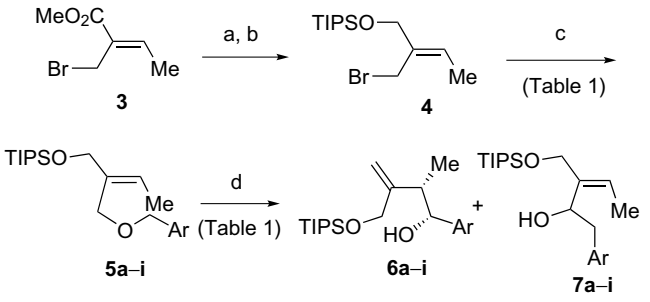
doi:10.1016/j.tetasy.2008.04.025

using chiral di-*tert*-butyl bis(oxazoline) (Box-*t*-Bu) ligand proceeded with a very high selectivity (93% ee), albeit in a low yield (19%).[10] In spite of the prominent selectivity, application of the Box-*t*-Bu ligand to asymmetric [2,3]-Wittig rearrangement was limited to this cyclic substrate. We started a systematic study of asymmetric [2,3]-Wittig rearrangements of various oxygenated benzyl ethers using the Box-*t*-Bu ligand.

Herein, we report a highly diastereo- and enantioselective asymmetric [2,3]-Wittig rearrangement of oxygenated benzylic ethers using an external chiral ligand. We also found that an *ortho*-methoxy substituent affected the regiochemistry of deprotonation and enantioselectivity.

2. Results and discussion

The known unsaturated ester **3**[11] was converted into triisopropylsilyl (TIPS) ether **4** in 84% yield in two steps. Substrates **5a–i** were readily synthesized by the nucleophilic substitution of **4** with alkoxides from various benzylic alcohols (Scheme 2 and Table 1). Using substrates **5a–i**, we investigated the [2,3]-Wittig rearrangement with *t*-BuLi in tetrahydrofuran (THF). The results are shown in Scheme 2 and Table 1. The reaction of unsubstituted benzyl ether **5a** afforded only a product arising from [2,3]-Wittig rearrangement in 86% yield (entry 1). The diastereoselectivity was very high, and the *syn* product was produced exclusively. In the case of the 4-methoxybenzyl derivative **5b**, the reaction afforded the desirable [2,3]-Wittig product **6b** in 44% yield accompanied by 17% of the [1,2]-Wittig product **7b** (entry 2). The [2,3]-Wittig rearrangement product **7b** resulted from the deprotonation of the allylic proton rather than the benzylic proton. The structure of the [1,2]-Wittig rearrangement product **7b** was confirmed by a two-dimensional $^{1}H/^{13}C$-heteronuclear multiple bond correlation (HMBC) experiment.



Scheme 2. Reagents and conditions: (a) DIBAL, CH_2Cl_2, −20 °C; (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt (84% in two steps); (c) $ArCH_2OH$, *t*-BuOK, THF, rt (Table 1); and (d) *t*-BuLi, THF, −78 °C (Table 1).

The regioselectivity of the deprotonation was improved when the 3-methoxybenzyl derivative **5c** and the 2-methoxybenzyl derivative **5d** were used (entries 3 and 4). No [1,2]-Wittig rearrangement product was observed, and the yields of **6c** and **6d** increased to 64% and 68%, respectively. We also examined the reaction of dimethoxybenzyl derivatives **5e–h** with diverse substitute patterns (entries 5–8) and trimethoxybenzyl ether **5i** (entry 9), and some of these aryl groups were found in natural lignans. In these compounds, only 3,4-dimethoxybenzyl derivative **5e** afforded [1,2]-Wittig rearrangement product **7e**, but the ratio of the by-product was smaller than that with the 4-methoxybenzyl derivative **5b**.

The decrease in the regioselectivity of the deprotonation in the 4-methoxybenzyl ether **5b** probably originated from the weak acidity at the benzylic position by the electron-donating resonance effect of a *para*-methoxy group. Therefore, the acidity was recovered in 3-methoxybenzyl ether **5c**. In contrast, it was found that the 2-methoxy substituent in **5d**, with the positive resonance effect, promotes the deprotonation at the benzylic position, thereby improving the regioselectivity and the yield. The high regioselectivity in **5d** would be due to the lateral metallation effect by coordinating to the countercation of the base.

The relative stereochemistry of the [2,3]-Wittig rearrangement product **6d** was confirmed by conversion into known γ-lactones *syn*- and *anti*-**8**, as shown in Scheme 3.[12] The ^{1}H and ^{13}C NMR spectral data were identical to the published data. The relative stereochemistry of other [2,3]-Wittig rearrangement products was confirmed by comparison of the ^{1}H NMR data with the data for **6d** and 1-*epi*-**6d** (*anti*-isomer of **6d**), which was prepared by oxidation of **6d** followed by diastereoselective reduction with L-Selectride® (Scheme 3).

Coupling constants between the C1- and C2-methine protons were $J = 4.0$ Hz in **6d** (*syn*-isomer) and $J = 8.3$ Hz in 1-*epi*-**6d** (*anti*-isomer), respectively. Those of products **6a–i** ranged from 3.4 to 4.4 Hz, thereby indicating their *syn*-stereochemistry. A similar empirical rule was also reported by Nakai.[13]

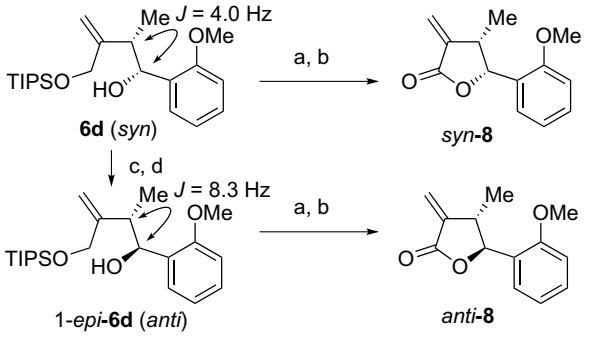
The asymmetric version of [2,3]-Wittig rearrangement was conducted with *t*-BuLi in hexane in the presence of (*S*,*S*)-2,2′-(dimethylmethylene)bis(4-*tert*-butyl-2-oxazoline) **9**[14] as an external chiral ligand. The results are summarized in Scheme 4 and Table 2. Unsubstituted benzyl ether **5a** afforded the *syn*-isomer **6a** exclusively in 65% yield with unprecedented high diastereo- and enantioselectivity (>98% de and 98% ee) (entry 1). High selectivity was also observed in 4-methoxybenzyl ether **5b** and 3-methoxybenzyl ether **5c** (entries 2 and 3).

Unexpectedly, the enantioselectivity was greatly decreased in 2-methoxybenzyl ether **5d** (entry 4). A similar tendency was observed in dimethoxybenzyl ethers **5e–h** and trimethoxybenzyl ether **5i**. In contrast, while 3,4- and 3,5-dimethoxybenzyl ethers **5e** and **5f** showed comparatively high enantioselectivity (entries

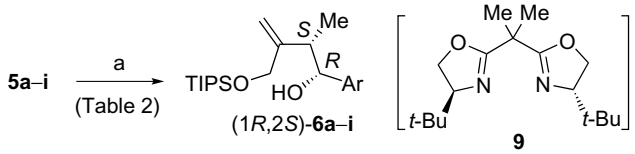
Table 1
Synthesis of benzylic ethers **5a–i** and [2,3]-Wittig rearrangement

Entry	Ar	Benzylic ether	Yield[a,b] (%)	[2,3]-Rearranged product	Yield[b,c] (%)	[1,2]-Rearranged product	Yield[b,c] (%)
1	Phenyl	**5a**	75	**6a**	86	**7a**	0
2	4-Methoxyphenyl	**5b**	63	**6b**	44	**7b**	17
3	3-Methoxyphenyl	**5c**	80	**6c**	64	**7c**	0
4	2-Methoxyphenyl	**5d**	85	**6d**	68	**7d**	0
5	3,4-Dimethoxyphenyl	**5e**	85	**6e**	43	**7e**	6
6	3,5-Dimethoxyphenyl	**5f**	74	**6f**	93	**7f**	0
7	2,3-Dimethoxyphenyl	**5g**	85	**6g**	72	**7g**	0
8	2,5-Dimethoxyphenyl	**5h**	85	**6h**	58	**7h**	0
9	3,4,5-Trimethoxyphenyl	**5i**	77	**6i**	79	**7i**	0

[a] Reactions were carried out using benzylic alcohol (2 equiv), *t*-BuOK (2.2 equiv) in THF at rt for 16 h.
[b] Isolated yield.
[c] Reactions were carried out using benzylic ether (1 equiv), *t*-BuLi (10 equiv) in THF at −78 °C for 2 h.



Scheme 3. Reagents and conditions: (a) TBAF, THF, rt; (b) cat. TEMPO, cat. *n*-Bu_4NI, NCS, CH_2Cl_2–H_2O, pH 8.6, rt (50% for *syn*-**8** and 85% for *anti*-**8** each in two steps); (c) cat. TPAP, NMO, CH_2Cl_2–CH_3CN (9:1), 4 Å MS, rt (98%); and (d) L-Selectride®, THF, −78 °C then 30% H_2O_2, acetone, rt (91%).



Scheme 4. Reagents and conditions: (a) *t*-BuLi, (*S*,*S*)-Box-*t*-Bu **9**, hexane, −78 °C (Table 2).

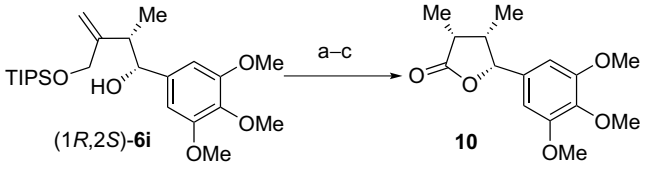
Table 2
Asymmetric [2,3]-Wittig rearrangement of benzylic ethers **5a–i**[a]

Entry	Ar	Product	Yield[b] (%)	ee[c] (%)
1	Phenyl	**6a**	65	98
2[d]	4-Methoxyphenyl	**6b**	34	98
3	3-Methoxyphenyl	**6c**	75	95
4	2-Methoxyphenyl	**6d**	73	8
5	3,4-Dimethoxyphenyl	**6e**	32	87
6	3,5-Dimethoxyphenyl	**6f**	72	99
7	2,3-Dimethoxyphenyl	**6g**	58	17
8	2,5-Dimethoxyphenyl	**6h**	58	22
9	3,4,5-Trimethoxyphenyl	**6i**	76	85

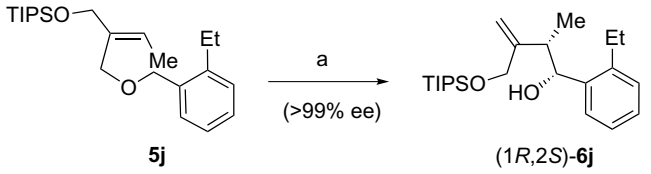
[a] Reactions were carried out using benzylic ether (1 equiv), *t*-BuLi (10 equiv), and (*S*,*S*)-Box-*t*-Bu **9** (5 equiv) in hexane at −78 °C for 2 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] A trace of [1,2]-Wittig rearrangement product was produced as a by-product.

5 and 6), 2,3- and 2,5-dimethoxybenzyl ethers **5g** and **5h** with an *ortho*-methoxy substituent afforded products with low enantiomeric excess (entries 7 and 8). The 3,4,5-trimethoxybenzyl ether **5i**, bearing no methoxy group at the *ortho*-position, afforded a product with high enantiomeric excess (entry 9).[†]

The absolute configuration of the secondary alcohols was determined by a modified Mosher method,[15] after conversion of alcohols **6b–d** into the corresponding (+)- and (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters. Thus, the stereochemistry of the major products was determined as (1*R*,2*S*). The absolute configuration of the other products was assumed by analogy with them. The assignment was also confirmed by conversion of **6i** (85% ee) into known γ-lactone **10** {$[\alpha]_D^{21} = +67.3$ (*c* 0.34, $CHCl_3$)} and comparison of the specific rotation {lit.[16] $[\alpha]_D^{23} = +57.1$ (*c* 0.2, $CHCl_3$)} (Scheme 5). Since the γ-lactone **10** is a synthetic intermediate of 3-*epi*-eupomatilone 6,[16] we have achieved a formal synthesis of 3-*epi*-eupomatilone 6.



Scheme 5. Reagents and conditions: (a) TBAF, THF, rt, (b) cat. TEMPO, cat. *n*-Bu_4NI, NCS, CH_2Cl_2–H_2O, pH 8.6, rt; (c) H_2, cat. $Rh(PPh_3)_3Cl$, toluene, rt (40% in three steps).



Scheme 6. Reagents and conditions: (a) *t*-BuLi, (*S*,*S*)-Box-*t*-Bu **9**, hexane, −78 °C (69%).

The effect of the 2-methoxy group is unclear, but the oxygen appears to play an important role in the effect. In order to confirm the role of the 2-methoxy group, we synthesized the 2-ethylbenzyl equivalent **5j** in 63% yield by the general procedure shown in Scheme 2. The asymmetric [2,3]-Wittig reaction of **5j** afforded **6j** in 69% yield and with excellent enantioselectivity (>99% ee) (Scheme 6) in contrast to that of 2-methoxybenzyl ether **5d** (8% ee).[‡] Presumably, coordination of the methoxy group to the lithium cation rather than the steric effect would retard the high selectivity. Further studies including the reaction mechanism are in progress.

3. Conclusion

In conclusion, we have investigated the [2,3]-Wittig rearrangement of various benzyl ethers. As a result, we have found that (*S*,*S*)-Box-*t*-Bu **9** is an effective ligand for oxygenated benzylic ethers. The substitution of the methoxy group affected the chemical yield and enantioselectivity, depending on its position. The products will become versatile intermediates for the synthesis of lignans.

Acknowledgements

We acknowledge the financial support of a Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (No. 18590097) and Osaka Ohtani University Research Fund (Pharmaceutical Sciences).

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[†] The reaction of **5b** using (−)-sparteine was sluggish and the expected **6b** was not obtained. Instead, S_N2' reaction of *t*-BuLi to **5b** and elimination of triisopropylsilanolate occurred with 53% yield along with 41% recovery of **5b**.

[‡] The absolute configuration of **6j** was determined by the modified Mosher method.

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