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Enantiocontrol in the [2,3]-Wittig-rearrangement

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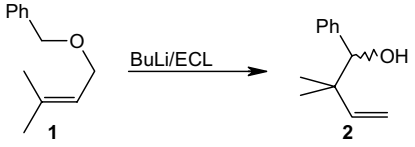
Abstract—The enantioselective [2,3]-Wittig rearrangement of benzyl prenyl ether has been studied. Treatment of this ether with butyl lithium bearing diamines or bis(oxazoline)s as external chiral ligands (ECL) gave the expected alcohol in up to 66% ee, the highest reported for this transformation. The optimum ECL is based on the bis(oxazoline) system and the C5 substituent on the bis(oxazoline) is crucial to determining both the degree and sense of asymmetric induction.

1. Introduction

The [2,3]-Wittig rearrangement has been widely used in asymmetric synthesis,[1] however the vast majority of these syntheses have used enantioenriched substrates, with the chirality transferred to the product. However, with the ever increasing range of asymmetric deprotonation procedures available,[2] the development of a general enantioselective variant is highly desirable.



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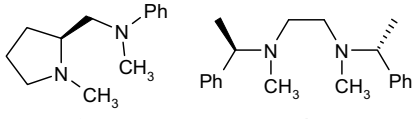
There are a number of examples of an enantioselective version of this important transformation.[3] Nakai reported the asymmetric [2,3]-Wittig rearrangement of (*E*)-crotyl propargylic ethers mediated by (−)-sparteine and bis(oxazoline)s with the products being formed in ees of between 2% and 89%, however the benzyl (*Z*)-crotyl ethers gave the corresponding alcohols in ees of 24–40%.[4a] Manabe studied the asymmetric Wittig rearrangement of diprop-2-ynyl ethers and achieved moderate ees with a pseudoephedrine derived external chiral ligand (ECL);[5] also included in this paper was the rearrangement of benzyl prenyl ether **1** giving the benzyl alcohol **2** in 68% yield and 40% ee. However, in our hands the synthesis and purification of the pseudoephedrine-derived ligand has proved problematic, although the product **2** was formed in 79% yield but with only 34% ee using an impure form of the ligand.[6] Gibson also reported the highly enantioselective [2,3]-Wittig rearrangement of benzyl ethers when complexed to chromium carbonyls (ees up to 96%).[7] Herein we report a systematic study of the asymmetric [2,3]-Wittig rearrangement of benzyl prenyl ether **1**, mediated by butyl lithium/external chiral ligand (ECL) complexes.[8]

2. Results and discussion

The first ECL studied were those based on the (*S*)-Proline and (*R*)-(+)-α-methylbenzylamine framework **3** and **4**. The complex between diamine **3** and *n*-BuLi in either THF or toluene gave no rearrangement; with diamine **4** in THF the product could be isolated in 40% yield, with an ee of 14% (Table 1, entry 1).



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As seen in Table 1 a switch to toluene as solvent with BuLi/**4** gave 10% yield under standard conditions (entry 2) whereas 23% was isolated if the reaction was kept at −78 °C for 5 h (entry 3). The ees for these reactions were 18% and 20%, respectively. We then looked at the effect of source and equivalents of BuLi (entries 4–9) and it was found that optimum conditions of 2 equiv of *n*-BuLi in the presence of diamine **4** at −78 to 0 °C for 3 h gave

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Table 1. Diamine ECL/BuLi mediated [2,3]-Wittig rearrangement

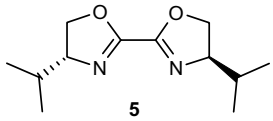
Entry	ECL[a]	Conditions[b]	BuLi (equiv)	Solvent	Yield %	Ee % (configuration)
1	**4**	−78 °C for 15 min warming to 0 °C for 8.5 h	*n*-BuLi (1)	THF	40	14 (*S*)
2	**4**	−78 °C for 15 min warming to 0 °C for 3 h	*n*-BuLi (1)	Toluene	10	18 (*S*)
3	**4**	−78 °C for 5 h	*n*-BuLi (1)	Toluene	23	20 (*S*)
4	**4**	−78 °C for 5 h	*n*-BuLi (2)	Toluene	56	19 (*S*)
5	**4**	−78 °C for 15 min warming to 0 °C for 3 h	*n*-BuLi (2)	Toluene	78	20 (*S*)
6	**4**	−78 °C for 15 min warming to 0 °C for 3 h	*s*-BuLi (1)	Toluene	11	12 (*S*)
7	**4**	−78 °C for 5 h	*s*-BuLi (1)	Toluene	0	—
8	**4**	−78 °C for 15 min warming to 0 °C for 3 h	*s*-BuLi (2)	Toluene	30	12 (*S*)
9	**4**	−78 °C for 5 h	*s*-BuLi (2)	Toluene	25	15 (*S*)

[a] The ECL was always used in a 1:1 ratio with the ether.
[b] The effect of additives HMPA, TMEDA and lithium chloride on these reactions was detrimental in terms of ee, and in most cases yield also.

the expected product in 78% yield with an ee of 20% (entry 5).

Nakai's report[4] of an asymmetric deprotonation protocol based on butyl lithium with a bis(oxazoline) acting as an ECL prompted us to explore this possibility.

A six-membered chelate is formed between the ECL used by Nakai **7** and the lithium ion of butyl lithium and it was initially reasoned that formation of a five-membered ring chelate may be tighter and thus enhance the efficient transfer of chirality from the ligand to the substrate and thus increase enantioselectivity. To this end the bis(oxazoline) **5** and pyridyl-oxazoline **6** were prepared.



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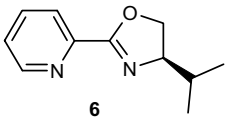

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Under the standard conditions (addition of BuLi at −78 °C), in ether, THF, hexane or toluene, no expected product was isolated in the presence of **5** or **6**. It was reasoned that there was a reaction between the ligand and butyl lithium: this was reinforced by the observation that no ligand could be isolated after work-up.[9] Reduction of the reaction temperature to −110 °C resulted in formation of the expected product in the presence of **5** (Table 2). To date we have been unable to find conditions that allow the rearrangement to be effected in the presence of ligand **6**.

n-Butyl lithium complexed to ligand **5** in THF, toluene or hexane was unable to mediate the reaction, with starting material being recovered. Changing to *tert*-butyl lithium proved more fruitful (Table 2). However, THF was an ineffective solvent as the alcohol could only be isolated in a yield of 2% (entries 1 and 2), and ether as solvent gave no expected product (entry 3). Toluene as solvent resulted in the formation of alcohol in 17% yield and 19% ee (entry 4). No expected product was formed in hexane under these conditions, however under more dilute conditions the alcohol was isolated in 11% yield with an ee of 27% (entry 5). Pre-mixing benzyl prenyl ether with ligand prior to addition of *tert*-butyl lithium increased both yield and ee (13% and 33%, respectively, entry 6). As expected keeping the reaction at −110 °C for 6 h increased enantioselectivity to 36% and the yield further increased to 35% (entry 7).

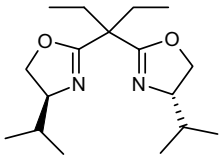
Under our preferred conditions (entry 8, Table 2) the bis(oxazoline) utilised by Nakai **7**, provided the expected alcohol in 74% yield with an ee of 33%. However, we were also interested in investigating the importance of the C5 substituent on enantioselectivity as there is the possibility of a buttressing effect where the configuration of C4 is more efficiently transferred to the substrate by being forced towards the chelated lithium ion by steric

Table 2. Bis(oxazoline) ECL/*t*-BuLi mediated [2,3]-Wittig rearrangement

Entry	ECL[a]	Conditions	Solvent	Yield %	Ee % (configuration)
1	**5**	−78 °C for 5 h	THF	0	—
2	**5**	−110 °C for 5 h and warming to rt for 16 h	THF[b]	2	5 (*S*)
3	**5**	−110 °C for 5 h and warming to rt for 16 h	Ether	0	—
4	**5**	−110 °C for 5 h and warming to rt for 16 h	Toluene	17	19 (*S*)
5	**5**	−110 °C for 5 h and warming to rt for 16 h	Hexane	11	27 (*S*)
6	**5**	−110 °C for 5 h and warming to rt for 16 h	Hexane[b]	13	33 (*S*)
7	**5**	−110 °C for 6 h	Hexane[b]	35	36 (*S*)
8	**7**	−78 °C for 5 h and warming to rt for 16 h	Hexane	74	33 (*S*)
9	**8**	−78 °C for 5 h and warming to rt for 16 h	Hexane	31	62 (*S*)
10	**9**	−78 °C for 5 h and warming to rt for 16 h	Hexane	11	25 (*R*)
11	**10**	−78 °C for 5 h and warming to rt for 16 h	Hexane	39	66 (*R*)
12	**10**	−78 °C for 5 h and warming to rt for 16 h	Hexane[c]	47	62 (*R*)

[a] 1.45 equiv of ECL and 1.5 equiv of *t*-BuLi (to ether) were used.
[b] The ether and external chiral ligand were pre-mixed.
[c] 2 equiv of *t*-BuLi with respect to ECL were used in this reaction.

repulsion due to the presence of bulky substituents. It was practically simpler to target the ligands with a gem dimethyl linkage rather than the gem diethyl as used by Nakai and thus ligands **8**, **9** and **10** were prepared.



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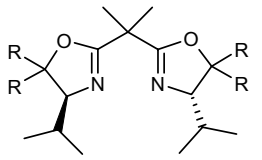

R = H **8**; R = CH_3 **9**; R = Ph **10**

Much to our surprise the gem di-methyl equivalent of Nakai's ligand **8** gave the expected product in a much higher ee of 62% in favour of the (*S*)-enantiomer, albeit in an lower yield of 31% (Table 2, entry 9). Encouraged by this result we went on to look at the ligand **9** with methyl groups on C5 (Table 2, entry 10), however this resulted in the product being isolated in a lower yield of 11% and with a disappointing ee of 25%, although the sense of asymmetric induction has now reversed with the (*R*)-enantiomer being favoured. This trend continued when the highly sterically encumbered tetraphenyl substituted ligand **10** was used under these conditions, with the isolated yield increasing to 39%. The ee was much improved to 66%, but once again in favour of the (*R*)-enantiomer (Table 2, entry 11). The yield of this reaction can be increased to 47% by using 2 equiv of *t*-BuLi with respect to the ECL without significant detriment to the enantioselection (Table 2, entry 12).

3. Conclusion

In summary we have developed an asymmetric deprotonation protocol using butyl lithium/bis(oxazoline) complexes effective for mediating the [2,3]-Wittig rearrangement of benzyl prenyl ether in ees of up to 66%. The enantioselectivity of the reaction is highly sensitive to the structure of the bis(oxazoline). Changing from a gem diethyl bridge on the bis(oxazoline) to a gem dimethyl results in an improvement in enantioselection from 33% to 62%. Furthermore the C5 substituent of the bis(oxazoline) also plays a pivotal role in enantiocontrol of this reaction. Changing from hydrogen at C5 through methyl to phenyl results in the reversal of enantioselection from 62% *S* to 66% *R*.

This is the first time that a simple modification of an ECL, derived from the same chiral source (L-valine) has produced (*R*)- or (*S*)-**2** via [2,3]-Wittig rearrangement. Furthermore this is a significant increase on the highest reported ee for this transformation.

Acknowledgements

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