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Stereo- and Regiochemical Aspects of the Mitsunobu Reaction in Synthesis of Chiral Amino Ether Ligands for Asymmetric Reactions

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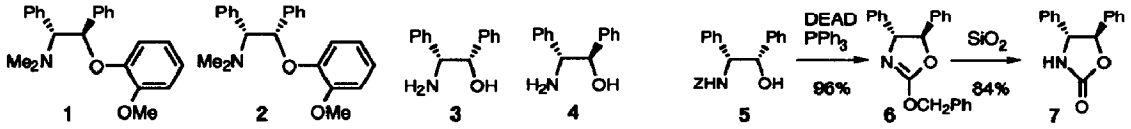
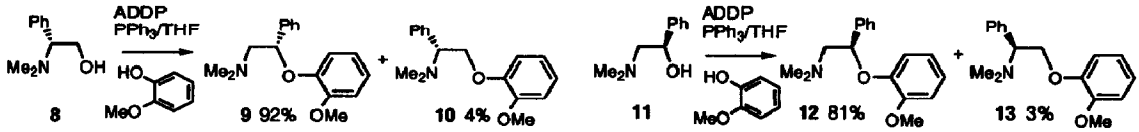
Abstract: *Combination of the neighboring amino group participating Mitsunobu reaction and cyclic sulphamidate procedure provided efficient stereo- and regioselective synthesis of chiral amino ether ligands for asymmetric reactions.*

As part of our studies aimed at asymmetric reactions,[1] we designed new chiral amino ether ligands **1** and **2** that are expected to be available by the Mitsunobu reaction of the corresponding amino alcohols **3** and **4**. During studies, we have observed intriguing stereo- and regiochemical outcome of the Mitsunobu reaction. The Mitsunobu reaction is a powerful procedure for nucleophilic displacement of alcohol groups with inversion of configuration.[2] However, it has been attracted recent attention in that neighboring group participation alters the stereo- and regiochemical outcome. Farina observed concurrent inversion and retention in allylic alcohols.[3] The reaction of alcohols bearing amino group in vicinal relationship is much more intriguing. Freedman reported the net retention and scrambles of regiochemistry in aminoindanols.[4] However, Lipshutz and Miller reported the clean inversion in carbamates bearing a vicinal relationship to a hydroxy function,[5] unlikely secondary amides that proceed with net retention via oxazoline formation.[6]

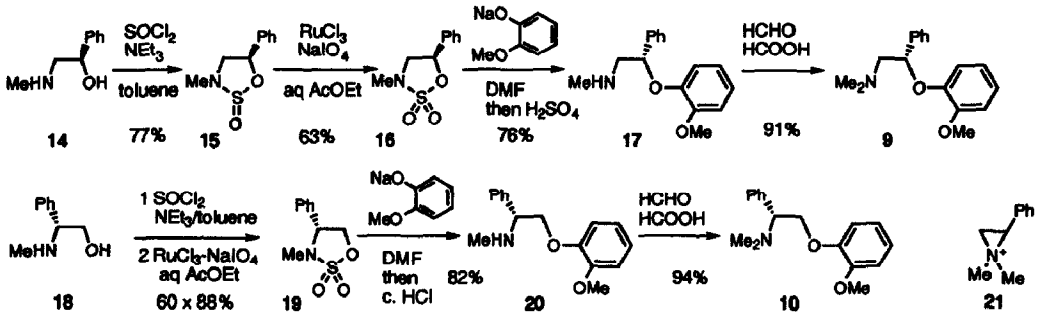


Encouraged by Lipshutz's report,[5] (1*R*,2*S*)-2-amino-1,2-diphenylethanol **3** was converted to *Z*-alcohol **5** which was then treated with 2-methoxyphenol under Mitsunobu conditions. On the contrary to expectation, the product was oxazoline **6** which was converted to cyclic urethane **7** through silica gel column chromatography.[7] Stereochemistry was confirmed by direct comparison with **7** prepared from **4**.

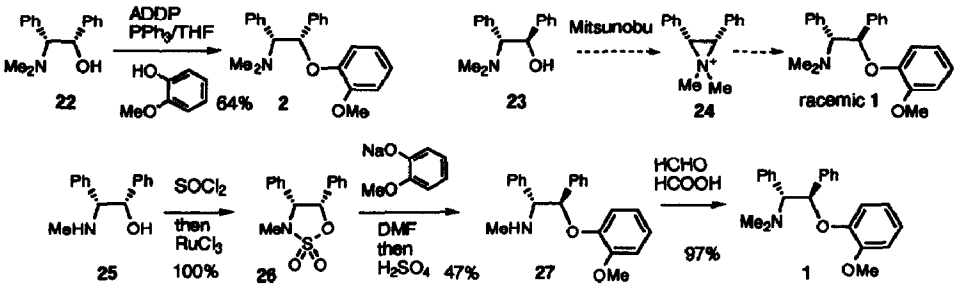
Disappointed by the results, we determined to study the reaction systematically. At first, the reaction of *R*-2-dimethylamino-2-phenylethanol **8** with 2-methoxyphenol in the presence of DEAD and PPh_3 in THF was carried out to give **9** in 56% yield, instead of **10**. Chemical yield of **9** was dramatically improved to 92% by using ADDP.[8] Regioisomer **10** was also isolated in 4% yield. Similarly, treatment of *R*-2-dimethylamino-1-phenylethanol **11** gave the same product **12** as **9** but with opposite absolute configuration.



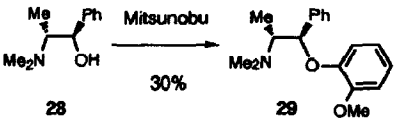
The absolute configuration was confirmed by synthesis of **9** from *R*-2-methylamino-1-phenylethanol **14** via cyclic sulphamidate **16** to give **17** which was methylated to **9**.[9] Regiochemistry of the Mitsunobu product was determined by synthesis of **10** from *R*-2-methylamino-2-phenylethanol **18** via cyclic sulphamidate **19**. These reactions clearly indicated the formation and regioselective opening of the intermediate aziridinium ion **21** to afford **9**, **10**, **12** and **13** in Mitsunobu reaction.



The Mitsunobu reaction of (1*R*,2*S*)-2-dimethylamino-1,2-diphenylethanol **22** with 2-methoxyphenol provided the corresponding amino ether **2** with net retention of stereochemistry in 64% yield. On the contrary, Mitsunobu reaction of **23** failed and afforded a mixture of intractable products, probably due to failure in forming sterically unfavorable aziridinium ion **24**. The optically pure **1** was successfully obtained from **25** via cyclic sulphamidate **26** in 46% total yield.



Regioselective opening at the benzylic carbon of aziridinium ion and net retention of stereochemistry were demonstrated by synthesis of **29** from *N*-methyl-pseodoephedrine **28** under Mitsunobu conditions.



These reactions demonstrated well the formation and regioselective opening of the aziridinium intermediate as well as stereochemical aspects of the neighboring group participating Mitsunobu reaction. Application of these new chiral ligands into enantioselective reactions are in progress in our laboratories.[10]

References and Notes

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