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Effect of the Leaving Group on the Alkylation Diastereoselectivity of the Schöllkopf Chiral Auxiliary

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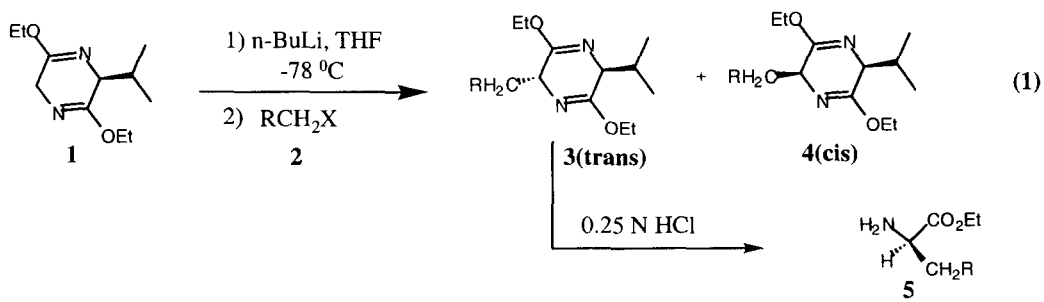
Summary: *Tosylates, diphenylphosphates and bromides were employed to study the effect of the leaving group on the alkylation diastereoselectivity of the Schöllkopf chiral auxiliary* ***1*** *at aliphatic, benzylic, propargylic and allylic electrophilic centers. The diastereoselectivity generally follows the pattern: diphenylphosphate > tosylate > bromide. In terms of both diastereoselectivity and yield, each leaving group possesses a different advantage.*

In the early 1980s Schöllkopf developed an excellent chiral auxiliary **1** to prepare a large variety of amino acids.[1] As shown in equation 1, the metalation and subsequent diastereoselective alkylation of the bis-lactim ether **1** provided dominant trans selectivity (see **3**), the products of which were hydrolyzed to furnish amino acid esters **5**. Bis-lactim ether **1** can be readily prepared from L-valine and glycine on large scale[2] and is now commercially available in both enantiomeric forms. Numerous applications of this Schöllkopf chiral auxiliary in the synthesis of optically active unnatural amino acids have been reported, including the synthesis of the antitumor agents OF 4949-III/IV,[3a] α-deuteriated α-amino acids[3b] and tryptophan analogues.[2] In a few cases, however, alkylation of the Schöllkopf chiral auxiliary suffered from poor diastereoselectivity. Attempts to overcome this drawback have been carried out by modification of the chiral auxiliary through replacement of the isopropyl group in the bis-lactim ether **1** with bulkier groups such as t-butyl to increase the diastereoselectivity.[4] Although the alkylation selectivity was increased, the relative cost and availability of those modified bis-lactim ethers[4] have limited their utilization. Because of the popularity of the bis-lactim ether **1**, in this letter the focus has been shifted from the Schöllkopf chiral auxiliary itself to the electrophiles (see **2**). More specifically, a variety of leaving groups have been employed to provide a simple and practical solution to the problem mentioned above. Studies of the effect of the leaving group on alkylation diastereoselectivity were carried out by employing the bromide, tosylate and diphenylphosphate (see **2**) to effect alkylations of the bis-lactim ether **1** at aliphatic, benzylic, propargylic and allylic electrophilic centers.



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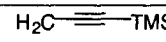
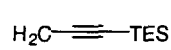
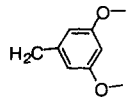
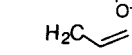
The diphenylphosphates and tosylates were readily prepared by treatment of the corresponding alcohols with diphenyl chlorophosphate or p-toluenesulfonyl chloride, respectively, in ethyl ether in the presence of base. Alkylations of bis-lactim ether **1** were carried out in THF at –78 ^{0}C for 6 hours. Diastereoselectivity was determined by ^{1}H NMR spectroscopy. The results are depicted in Table 1.

Table 1. Effect of the leaving group on the alkylation selectivity of the bis-lactim ether **1.**

Entry	(XCH_2R) $-CH_2R$	-X					
		-Br		-OTs		$-OP(O)(OPh)_2$	
		Yield %	% de	Yield %	% de	Yield %	% de
1		81	43	82	83	80	95
2		90	14	89	71	90	96
3		86	71	80	92	42	98
4		88	97	82	67	40	97
5	CH_2CH_3	80	71	82	90	24	98

As shown in Table 1, alkylation with the diphenylphosphates furnished exceptionally high diastereoselectivity (>95%) in all cases. The tosylate provided better diastereoselectivity than the bromide with the exception of one case (entry 4, Table 1). Bromide, has been the leaving group most commonly employed, unfortunately, it provided the poorest selectivity in most cases. In terms of both alkylation yield and selectivity, however, both tosylate and diphenylphosphate exhibited specific advantages. At the propargylic position (entries 1 and 2), diphenylphosphate was the best group to effect efficient and selective alkylation. In the allylic position (entry 4), the bromide was the leaving group of choice. At the aliphatic and benzylic positions (entries 3, 5), tosylate provided the best results when the alkylation yield was balanced against stereoselectivity.

Examination of the yields and diastereoselectivities in Table **1** provides a rational basis for the selection of alkylating agent in the Schöllkopf approach to amino acids. In most cases diphenylphosphate and tosylate were found to be far superior to bromide, although the allylic system in entry 4 proves to be an exception. Further work is underway to understand the high %de achieved with the diphenylphosphates.

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