Asymmetric Synthesis of Chiral 1,3-Diamines

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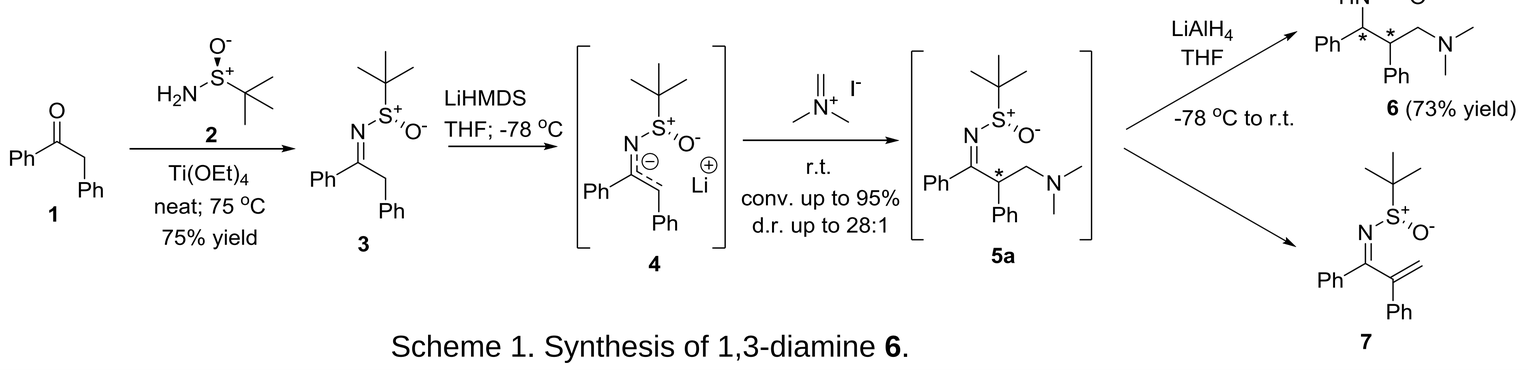
Goal

Asymmetric synthesis of 1,3-diamines by stereoselective introduction of Eschenmoser's salt in α-position of chiral *N*-sulfinyl imine.

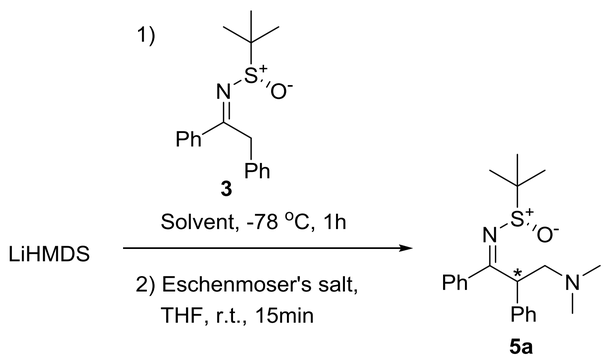


Scheme 1. Synthesis of 1,3-diamine **6**.

Chiral *N*-sulfinyl imine (**3**) can be successfully used in Mannich-type reaction with Eschenmoser's salt to produce *N*-sulfinyl-1-imino-3-amine (**5a**) in good diastereomeric ratio (up to 28 : 1) and conversion (Scheme 1). Because of undesired elimination of dimethylamine to furnish *N*-sulfinyl alkene (**7**), isolation of *N*-sulfinyl-1-imino-3-amine (**5a**) was not possible. Therefore, it was reduced *in situ* to corresponding 1,3-diamine **6** in good yield (up to 73%) and diastereomeric ratio (99:1).

Several theoretical rationalizations of the origin of diastereoselectivity in analogous reactions of Ellman's imine can be found in literature, however, they can hardly be applied to our system due to the complexity and substrate-dependent nature of the reaction. Our studies towards better understanding of the mechanism of Mannich-type reaction are underway.

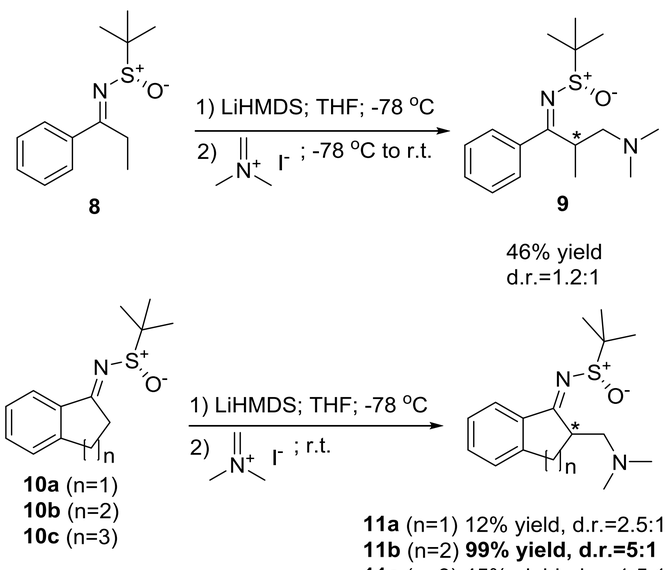
Screening of solvents



Entry	LiHMDS solvent	Solvent	LCMS, %		
			Substrate **3**	Product **5a**	Alkene **7**
1	**THF**	**THF**	**50**	**49 (d.r.=12:1)**	**<1**
2	THF	MeCN	28	60 (d.r.=1.1:1)	9
3	Toluene	Toluene	32	59 (d.r.=4.5:1)	9
4	Toluene	DCM	35	50 (d.r.=4:1)	10
5	Toluene	Monoglyme	54	16 (d.r.=7:1)	9

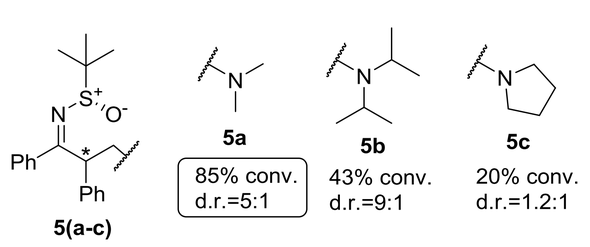
THF as a solvent provided the highest d.r.

Scope of *N*-sulfinyl imine



Ethyl substituent and 5- and 7- member cycles gave low to moderate results, indicating substrate dependant nature of the reaction.

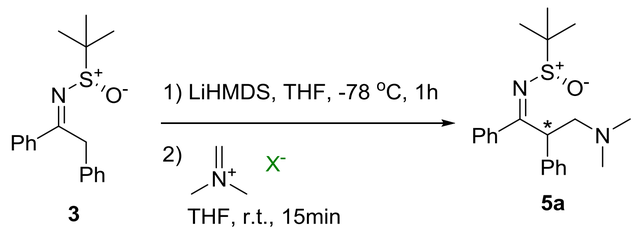
Scope of Eschenmoser's salt



1) 1.1 eq LiHMDS (1M, THF), THF, -78 °C, 1h
2) 1.5 eq Eschenmoser's salt, THF, -78 °C, o.n.

Stericaly smaller substituent in Eschenmoser's salt gave better results.

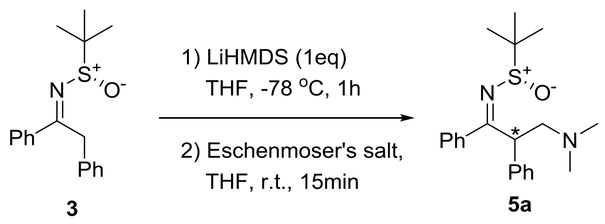
Anion effect of Eschenmoser's salt



Entry	X^-	LCMS, %		
		Substrate **3**	Product **5a**	Alkene **7**
1	**I^-**	**5**	**89 (d.r.=7:1)**	**6**
2	BF_4^-	19	53 (d.r.=4:1)	<1

BF_4^- anion does not improve nor yield, nor d.r.

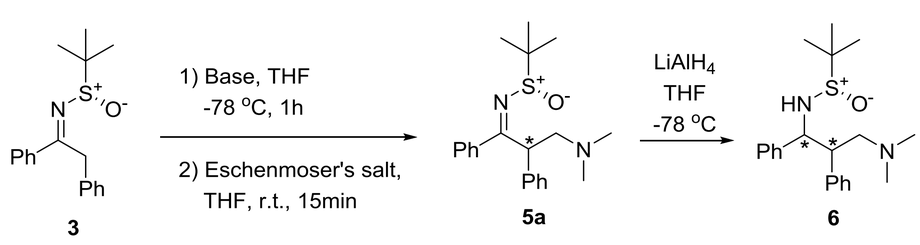
Rate of addition



Entry	Rate of LiHMDS addition	LCMS, %		
		Substrate **3**	Product **5a**	Alkene **7**
1	**0.1 mL/min**	**21**	**73 (d.r.=4:1)**	**<1**
2	2 mL/h	50	40 (d.r.=1.3:1)	5

Slow addition decreases yield and d.r. of product **5**

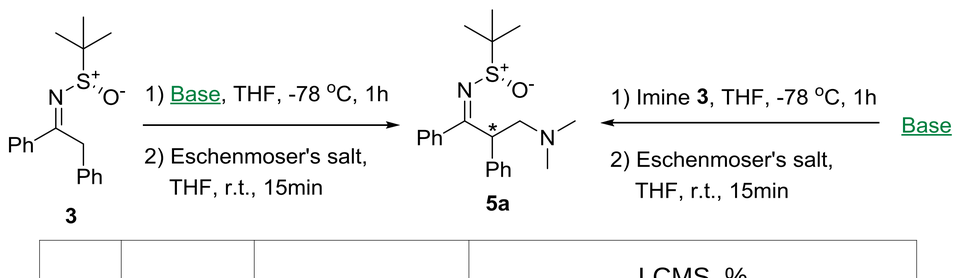
Screening of bases



Entry	Base, 1.3 eq	LCMS, %			Isolated yield of **6**, %
		Substrate **3**	Product **5a**	Alkene **7**	
1	MESLi	20	59 (d.r.=6:1)	14	23 (d.r.=3:1)
2	LiO^tBu	<1	48 (d.r.=9:1)	34	43 (d.r.=15:1)
3	NaO^tBu	56	8 (d.r.=9:1)	3	9 (d.r.=28:1)
4	KO^tBu	8	21 (d.r.=13:1)	70	27 (d.r.=29:1)
5	**LiHMDS**	**5**	**89 (d.r.=7:1)**	**6**	**73 (d.r.=99:1)**
6	NaHMDS	60	33 (d.r.=25:1)	7	-
7	KHMDS	25	45 (d.r.=26:1)	30	-
8	LDA	89	11 (d.r.=6:1)	<1	-

A. LiHMDS was chosen as a base as it gave the best results.
B. $LiAlH_4$ (compared to BH_3 and DIBAL) acquired product **6** in the best d.r. and yield.

Effect of base and order of addition



Entry	Base,1eq	Order of addition	LCMS, %		
			Substrate **3**	Product **5a**	Alkene **7**
1	LiHMDS	Base to imine	21	73 (d.r.=4:1)	<1
2		**Imine to base**	**50**	**49 (d.r.=12:1)**	**<1**
3	KHMDS	**Base to imine**	**36**	**54 (d.r.=23:1)**	**8**
4		Imine to base	31	53 (d.r.=9:1)	11
5	KO^tBu	Base to imine	52	32 (d.r.=30:1)	7
6		**Imine to base**	**41**	**53 (d.r.=28:1)**	**6**

A. Order of addition may have major effect on d.r. and yield.
B. Sub- or equimolar addition of base may increase d.r. and yield of the product **5**.

Supervisors: Dr. chem. K. Shubin, Dr. chem. E. Suna