Asymmetric Catalysis

Practical Asymmetric Synthesis of Vicinal Diamines through the Catalytic Highly Enantioselective Alkylation of Glycine Amide Derivatives**

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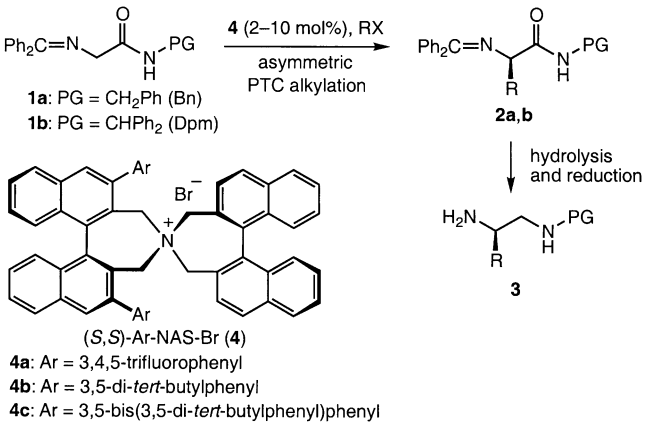
Optically active vicinal diamines are of great medicinal importance, as they are incorporated in a variety of compounds that display a broad spectrum of biological activity.[1] In organic synthesis, there has also been considerable interest in this class of compounds because of their use as chiral ligands and auxiliaries in asymmetric synthesis.[2] Accordingly, numerous efforts have been made toward their stereoselective preparation, and a number of useful methodologies have been elaborated.[3] Unfortunately, however, only a few practical and general procedures are available even for the asymmetric synthesis of monosubstituted vicinal diamines.[4]

Although the reduction of amides derived from natural α-amino acids is probably one of the most straightforward methods for the synthesis of optically active monosubstituted vicinal diamines,[5] critical structural limitations on the availability of α-amino acids (existing chiral pool) and possible partial racemization encountered in the formation of the amide constitute severe drawbacks. The direct stereoselective introduction of the required side chain onto glycine amides has emerged as a powerful strategy to overcome this intrinsic problem. However, the successful catalytic asymmetric functionalization of prochiral glycine amide derivatives has never been reported, and all previous examples have been diastereoselective transformations involving substrates with chiral auxiliaries.[6] Herein we report the first highly enantioselective phase-transfer catalytic (PTC) alkylation of protected glycine amides **1** with the designer chiral quaternary ammonium salt **4** as the catalyst.[7] The chiral ammonium enolate generated from **1b** and **4c** was found to be very reactive and underwent smooth alkylation even with less reactive *secondary* alkyl halides, thereby facilitating the practical catalytic asymmetric synthesis of a broad range of optically active monosubstituted vicinal diamines (Scheme 1).

First, we examined the feasibility of the stereoselective alkylation of prochiral glycine amide derivatives under phase-transfer catalytic conditions by using the benzophenone Schiff base **1a** of *N*-benzylglycinamide as a representative substrate[8] and the N-spiro chiral quaternary ammonium bromide **4a** as the catalyst. Treatment of **1a** with benzyl bromide (1.2 equiv) and **4a** (2 mol%) in toluene/aqueous KOH (50%) (3:1) at 0°C for 10 h gave only a trace amount of the corresponding alkylation product **2a** (R = CH_2Ph). In contrast, the reaction proceeded smoothly under similar con-



Scheme 1. Practical synthesis of a wide range of optically active vicinal diamines through the asymmetric phase-transfer catalytic alkylation of **1** in the presence of the catalyst (*S*,*S*)-**4**. RX = primary, secondary, allylic, or benzylic alkyl halide.

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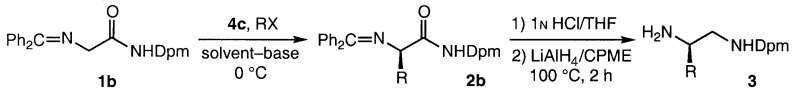
ditions with the catalyst **4b**, which has the substituent 3,5-di-*tert*-butylphenyl, to furnish **2a** (R = CH_2Ph) almost quantitatively with 36% *ee*. This result suggested that the steric effect of the 3,3′ aromatic substituent of the catalyst is more important than the electronic effect of this group on the reactivity. Compound **2a** (R = CH_2Ph) was obtained with higher enantioselectivity (69% *ee*) when **4c**, which is sterically more hindered, was employed. We then focused on screening the amide substituent, based on these initial results. The diphenylmethyl (Dpm) derivative **1b** was a good substrate, and the phase-transfer catalytic benzylation of **1b** in the presence of **4c** afforded the desired α-amino amide **2b** (R = CH_2Ph) in 98% yield with 92% *ee* (Table 1, entry 1).

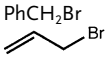
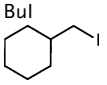
Next, we studied the transformation of **2b** (R = CH_2Ph) into the corresponding vicinal diamine. We found that acidic hydrolysis of the imine functionality of **2b** (R = CH_2Ph) followed by treatment with $LiAlH_4$ in cyclopentyl methyl ether (CPME)[9] afforded the optically active partially protected vicinal diamine **3** (R = CH_2Ph) in 96% yield without loss of enantiomeric excess (Table 1, entry 1).[10] This procedure facilitates the straightforward preparation of a variety of optically active vicinal diamines with primary alkyl side chains. Representative examples are shown in Table 1. A saturated aqueous solution of CsOH was used to ensure consistently high chemical yields in the alkylation with less reactive alkyl halides (Table 1, entries 3 and 4).

This system, which consists of the amide **1b** and the chiral catalyst **4c**, is remarkably reactive, thus enabling the hitherto difficult catalytic asymmetric alkylation of a glycine anion equivalent with simple secondary alkyl halides.[11,12] For instance, the reaction of **1b** with 2-iodopropane (5 equiv) under otherwise similar conditions gave **2b** (R = *i*Pr) in 82% yield with 82% *ee* (Table 1, entry 5). The use of mesitylene in place of toluene enhanced the enantioselectivity to 90% *ee*, and increasing the catalyst loading to 5 mol% led to improvement of the chemical yield (Table 1, entries 6 and 7).[13] Moreover, various cycloalkyl side chains could be introduced in satisfactory chemical yields with excellent enantioselectivities when 2–10 mol% of **4c** was used as the catalyst (Table 1, entries 8–10). Regardless of the steric demand of the newly introduced side chain at the α position, the resulting α-alkyl α-amino amides **2b** can be readily converted into the corresponding optically active partially protected vicinal diamine **3** in excellent chemical yields, as shown in Table 1 and Scheme 2, thus greatly expanding the scope of the present method. Reprotection of the free amine in **3** gave **5**, which could be derivatized further to the partially protected diamine hydrochloride **6** (91%) by simple hydrogenolysis (Scheme 2).

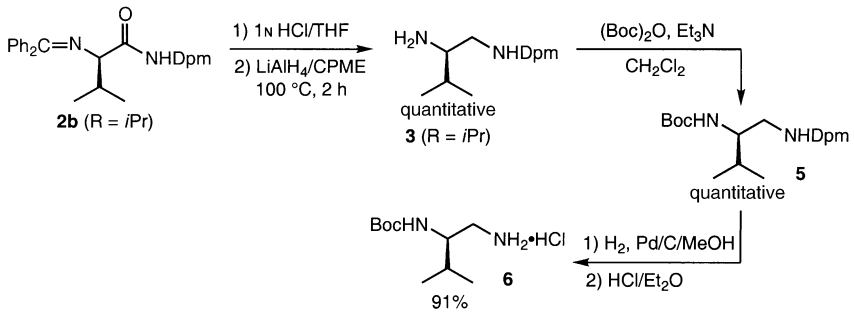
Finally, our approach has been successfully extended to the catalytic asymmetric synthesis of optically active vicinal diamines with sterically congested quaternary stereogenic centers. Thus, vigorous stirring of a mixture of the alanine diphenylmethyl amide derived aldimine Schiff base **7**, iodocyclopentane (5 equiv), $CsOH·H_2O$ (5 equiv), and **4c** (2 mol%) in mesitylene at 0°C for 3 h gave α-amino amide **8** almost quantitatively with 93% *ee*. Subsequent hydrolysis and reduction of **8** cleanly produced the corresponding partially protected diamine **9** (96%),[14] which is not readily accessible by other asymmetric methodologies (Scheme 3).

Table 1: Asymmetric synthesis of optically active vicinal diamines by the catalytic enantioselective phase-transfer alkylation of **1b**.[a]



Entry	RX	**4c** [mol%]	Solvent	Base[b]	*t* [h]	Yield of **2b** [%][c]	*ee* [%][d]	Yield of **3** [%][c]
1[e]	$PhCH_2Br$	2	toluene	KOH	3	98	92 (*R*)	96
2[e]		2	toluene	KOH	2	99	98 (*R*)	88
3[e]	BuI	2	toluene	CsOH	3	94	97 (*R*)	91
4[e]		2	toluene	CsOH	3	82	98 (*R*)	92
5		2	toluene	CsOH	5	82	82 (*R*)	
6		2	mesitylene	CsOH	5	81	90 (*R*)	
7		5	mesitylene	CsOH	5	90	90 (*R*)	>99
8		2	mesitylene	CsOH	3	91	96	97
9[f]		10	mesitylene	CsOH	5	71	95	90
10		10	mesitylene	CsOH	3	80	89	85

[a] Unless otherwise specified, the reaction was carried out with 5 equivalents of RX in the presence of a catalytic amount of **4c** under the reaction conditions given. [b] Aqueous KOH (50%) or saturated, aqueous CsOH. [c] Yield of the isolated product. [d] Enantiopurity was determined by HPLC analysis of the alkylated imine on a chiral phase (Daicel Chiralcel OD (entry 1), Chiralcel OD-H (entry 2), and Chiralpak AD (entries 3–10)) with hexane/2-propanol as the solvent. The absolute configuration of the major enantiomer (given in brackets) was determined by comparison of the HPLC retention time with that of an authentic sample that had been synthesized independently. [e] RX: 1.2 equivalents. [f] Iodocyclohexane: 10 equivalents.



Scheme 2. Facile derivatization of optically active **2b** (R = *i*Pr) to the corresponding differently protected diamines **3** (R = *i*Pr), **5**, and **6**. Boc = *tert*-butoxycarbonyl.

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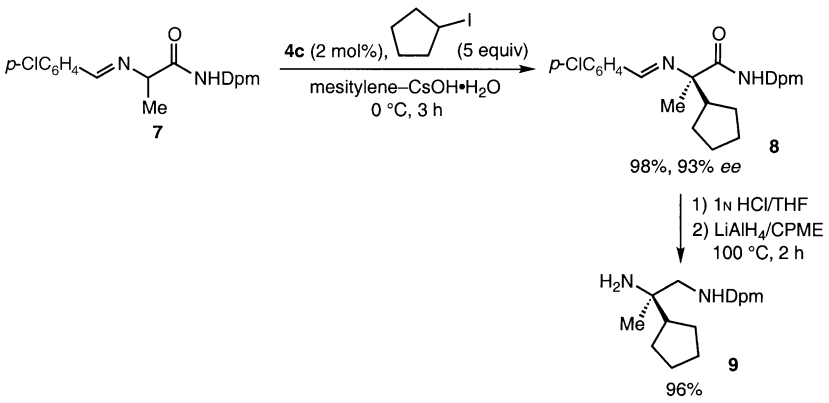

Scheme 3. Catalytic asymmetric synthesis of the vicinal diamine **9**, which possesses a sterically congested quaternary stereogenic center.

In conclusion, we have presented a practical procedure for the asymmetric synthesis of vicinal diamines based on the catalytic highly enantioselective alkylation of **1b** under phase-transfer conditions in the presence of the designer chiral quaternary ammonium bromide **4c**. As this substrate–catalyst combination enables the previously difficult catalytic asymmetric construction of α-alkyl α-amino amides that contain a tertiary β carbon center,[15] our approach offers efficient access to structurally diverse optically active vicinal diamines, including those with sterically very congested quaternary α carbon centers.

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Keywords: alkyl halides · alkylation · asymmetric catalysis · phase-transfer catalysis · vicinal diamines

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[14] The absolute configuration of the product **8** was determined to be *R* by X-ray crystallographic analysis after conversion into a dipeptide with *N*-benzyloxycarbonyl-L-alanine; see Supporting Information.
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