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Asymmetric Induction in the Neber Rearrangement of Simple Ketoxime Sulfonates under Phase-Transfer Conditions: Experimental Evidence for the Participation of an Anionic Pathway

Takashi Ooi, Makoto Takahashi, Kanae Doda, and Keiji Maruoka*
Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

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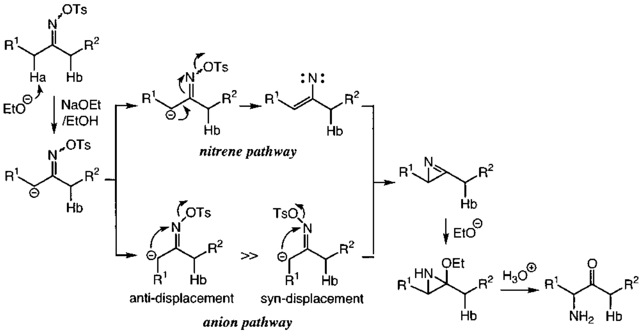
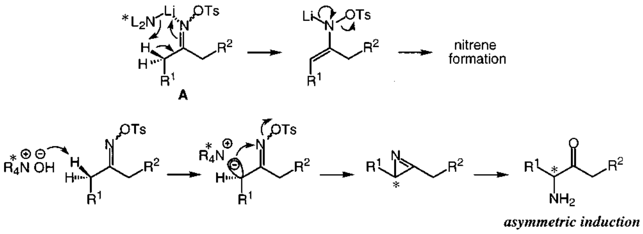
Since its discovery in 1926,[1] the Neber rearrangement of oxime sulfonates has been recognized as one of the promising methods for the preparation of a variety of α-amino ketones of both mixed alkyl−aryl and cyclic types,[2,3] primary structures often encountered in biologically active compounds.[4] The reaction is usually carried out in ethanolic sodium ethoxide and the plausible mechanistic pathways have been classified into: (i) initial removal of an α-proton followed by loss of the tosylate moiety produces unsaturated nitrene, which is converted to an azirine (nitrene pathway), and (ii) displacement at nitrogen and leaving of the tosyloxy function take place in a concerted manner after an α-proton abstraction (anion pathway) as illustrated in Scheme 1.[2a,5,6] Previous studies generally support the former mechanism, where the product distribution is governed by the relative acidity of α-protons H_a and H_b, and initial stereochemistry of the oxime sulfonate is irrelevant.[2a,5] On the other hand, the stereochemistry would seem to be important in the latter mechanism, because the *anti*-displacement would be strongly favored over the *syn*-displacement.[5] If this process is operative, employment of chiral base could result in the discrimination of two enantiotopic α-protons, giving optically active α-amino ketones. However, deprotonation by commonly used chiral lithium amides is believed to proceed through cyclic structure **A** via the coordination of lithium to nitrogen, eventually producing an unsaturated nitrene with loss of the asymmetry (Scheme 2).[7,8] In this context, we have been interested in the utilization of tetraalkylammonium hydroxide for the generation of a carbanion at the α-position under phase-transfer conditions.[9] This could further be achieved in an enantioselective manner by the use of chiral quaternary ammonium salts, enabling the first experimental demonstration of the substantial involvement of anion pathway in the Neber rearrangement of simple ketoxime sulfonates. In this communication, we wish to describe our preliminary results.

Scheme 1

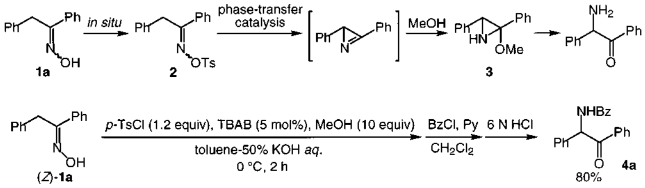


We initiated our search for appropriate phase-transfer reaction conditions with the oxime tosylate of benzyl phenyl ketone (**2**) as a model substrate. Taking the well-known instability of oxime sulfonates into consideration, we envisioned that **2** could be derivatized in situ from the parent ketoxime **1a** under the reaction conditions of the rearrangement. After screening inorganic bases and solvents under liquid−liquid as well as solid−liquid phase-transfer conditions using tetrabutylammonium bromide (TBAB) as a representative catalyst, we found that treatment of (*Z*)-**1a** with *p*-toluenesulfonyl chloride (1.2 equiv), TBAB (5 mol %) and MeOH (10 equiv) in toluene−50% KOH aqueous solution (volume ratio = 3:1) at 0 °C for 2 h, and subsequent benzoylation followed by acidic hydrolysis afforded the protected α-amino ketone **4a** in 80% isolated yield as shown in Scheme 3. The presence of methanol turned out to be crucial to obtain high yield by the in situ derivatization of the initially formed azirine to the more stable methoxy aziridine **3**. It should be noted that attempted reaction without TBAB under otherwise identical conditions gave only the corresponding tosylate **2** and none of the rearranged product was detected.

Scheme 2



Scheme 3



With this information in hand, we set out to study the asymmetric Neber rearrangement using chiral quaternary ammonium bromides as catalysts. If the expected carbanion was generated at the α-position under the optimized phase-transfer conditions, then pairing it with a chiral ammonium cation of an appropriate structure should lead to asymmetric induction, providing unequivocal experimental evidence for the participation of the anion pathway. Indeed, exposure of (*Z*)-**1a** to the present liquid−liquid phase-transfer conditions with structurally rigid, C_2-symmetric quaternary ammonium bromide **5a** as a catalyst (5 mol %)[10] followed by the benzoylation and hydrolysis gave rise to **4a** in 60% yield with 30% ee (entry 1 in Table 1). Here, switching the catalyst from **5a** to **5b**

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* To whom correspondence should be addressed. E-mail: maruoka@kuchem.kyoto-u.ac.jp.

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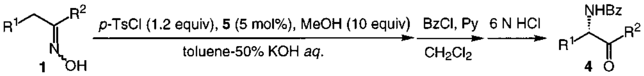
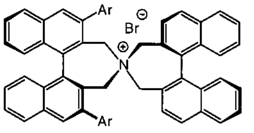
Table 1. Asymmetric Induction in the Neber Rearrangement by Chiral Phase-Transfer Catalysis[a]



entry	oxime R^1	oxime R^2	oxime geometry	catalyst	condition (°C, h)	yield[b] (%)	% ee[c] (config)[d]
1	Ph	Ph (**1a**)	(*Z*)	**5a**	0, 72	60	30 (*S*)
2				**5b**	0, 19	86	35 (*S*)
3				**5c**	0, 48	80	51 (*S*)
4			(*E*)	**5c**	0, 48	61	racemic
5	Ph	*p*-F−Ph (**1b**)	(*Z*)	**5b**	0, 19	95	50
6				**5c**	0, 43	90	63
7				**5c**	0, 68	81	70[e]

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of *p*-TsCl and 10 equiv of MeOH in the presence of 5 mol % of **5** in toluene−50% KOH aq (volume ratio = 3:1) under the given reaction conditions. [b] Isolated yield. [c] Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD) with hexane−2-propanol as solvent. [d] Determined, after reduction with NaBH$_4$/MeOH, by comparison with the optical rotation of *N*-benzoyl adduct of commercially available (1*S*,2*R*)-(+)-1,2-diphenyl-2-aminoethanol. [e] Use of mesitylene as solvent.

and **5c** enhanced the enantioselectivity to 35% ee and 51% ee, respectively (entries 2 and 3).[11,12] A noteworthy observation is the fact that the reaction with (*E*)-**1a** under otherwise similar conditions afforded racemic **4a** in 61% yield, suggesting the intervention of the nitrene pathway rather than the unfavorable *syn*-displacement (entry 4). More compelling results were obtained in the rearrangement of the oxime **1b** derived from benzyl *p*-fluorophenyl ketone, where the corresponding protected amino ketone **4b** was obtained in 95% yield, 50% ee with **5b** and 90% yield, 63% ee with **5c**, respectively (entries 5 and 6). It is worthy of comment that use of mesitylene in place of toluene further increased the enantioselectivity to 70% ee (entry 7).



(*S*,*S*)-**5a** [Ar = β-Np] [β-Np-NAS-Br]
5b [Ar = 6-CF$_3$-(2-Np)]
5c [Ar = 4-CF$_3$-Ph]

The effectiveness of the chiral quaternary ammonium bromide **5** in inducing the stereoselectivity can be rationalized by postulating the transition-state model, in which the conformation of the catalyst−substrate ion pair would be fixed so that the possible π−π interactions are fully appreciated (Figure 1). This hypothetical transition state could explain the beneficial effect of electron-deficient 3,3′-aromatic substituents of **5** on the enantioselectivity as well as the absolute configuration of the rearranged product **4**.[13] Interestingly, use of more electron-rich *p*-methoxyphenylsulfonyl chloride in the reaction of (*Z*)-**1b** under the influence of **5c** led to the production of more enantioenriched **4b** (80% yield, 73% ee).[14]

In conclusion, we have successfully utilized liquid−liquid phase-transfer catalysis for the Neber rearrangement of simple ketoxime sulfonates and unambiguously demonstrated the participation of the anion pathway by the employment of optically pure, C_2-symmetric chiral quaternary ammonium bromides as catalysts. This provides not only a new mechanistic insight but also an opportunity for extending the full synthetic utility of this classical yet useful rearrangement along with optimization of the enantioselective reaction.

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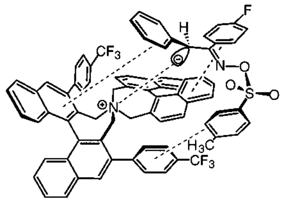

Figure 1. Transition-state model for the asymmetric Neber rearrangement of (*Z*)-**1b** with **5c**.

Supporting Information Available: Representative experimental procedures as well as spectroscopic characterization of catalyst **5** and all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) According to the report by House and Berkowitz (ref 5), we explicitly illustrate a carbanion from which the azirine can be formed in both ways. However, a totally concerted process wherein proton removal and intramolecular displacement occur concomitantly is also conceivable as an anionic pathway, and our results presented in this manuscript do not rule out this mechanism. We acknowledge the reviewer for valuable comments on this point.
(7) We examined the reaction of (*Z*)-**1a** with representative chiral lithium amides and *n*-BuLi-chiral diamine complexes, where the desired product **4a** was obtained in low yields with 1−5% ee. See the Supporting Information for details.
(8) A few examples of asymmetric Neber reaction have recently been reported; (a) For reaction with a chiral auxiliary, see: Piskunova, I. P.; Eremeev, A. V.; Mishnev, A. F.; Vosekalna, I. A. *Tetrahedron* **1993**, *49*, 4671. For a cinchona alkaloid-mediated reaction, see: (b) Verstappen, M. M. H.; Ariaans, G. J. A.; Zwanenburg, B. *J. Am. Chem. Soc.* **1996**, *118*, 8491. (c) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I. *Tetrahedron Lett.* **2000**, *41*, 5363. (d) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Ezpeleta, J. M. *J. Org. Chem.* **2000**, *65*, 3213. For recent review on 2*H*-azirines as synthetic tools, see: Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; Manuel de los Santos, J. *Eur. J. Org. Chem.* **2001**, 2401.
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(11) In the reaction with the catalyst **5c**, intermediary optically active methoxy aziridine **3** was isolated by silica gel column chromatography as a diastereomeric mixture in a ratio of 1.4:1 after conversion to its *N*-benzoate. See the Supporting Information for characterization.
(12) Attempted rearrangement of (*Z*)-**1a** with *O*-allyl-*N*-(9-anthracenylmethyl)-cinchonidinium bromide[15] as catalyst under otherwise similar conditions proceeded sluggishly at 0 °C and eventually produced **4a** in 35% yield with 15% ee after stirring at room temperature for 24 h.
(13) Treatment of (*Z*)-oxime mesylate of benzyl *p*-fluorophenyl ketone with **5c** and MeOH in toluene−50% KOH aqueous solution at 0 °C for 48 h furnished **4b** in 73% yield with 13% ee. The observed substantial decrease of the enantiomeric excess suggests the importance of the π−π interaction between tosyloxy moiety of oxime sulfonate and 3,3′-aromatic substituent of the catalyst to fix the conformation.
(14) Performed in mesitylene−50% KOH aq at 0 °C for 48 h.
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