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The Metallation of Troeger's Base

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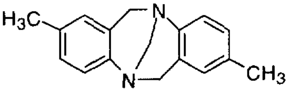
Summary: Complexation of Troeger's base with boron trifluoride etherate followed by treatment with n-BuLi results in the formation of an anion. This reacts with electrophiles stereoselectively to give alkylation products in good to excellent yields. Copyright © 1996 Elsevier Science Ltd

Troeger's base is a fascinating molecule which has received much attention in recent years as a template around which to construct unique architectures for molecular recognition.[1] The use of Troeger's base as a ligand for asymmetric processes has only begun to be examined. Transition metal complexes of Troeger's base are known.[2] Recently, such complexes have been used as catalysts in the hydrosilylation of alkynes, though this methodology did not attempt to take advantage of the chirality of **1**.[3a] Troeger's base has also been used as a chiral modifier in the enantioselective hydrogenation of ethyl pyruvate.[3b] As part of a program centering on the construction of new chiral ligands and auxiliaries for asymmetric processes from **1** and the related Kagan's ether **2**,[4] we have begun investigating the chemistry of both of these systems particularly with respect to benzylic functionalization.



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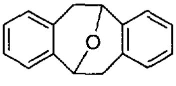

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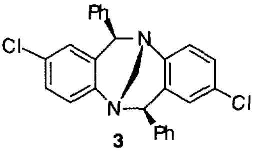
The synthesis of Troeger's base and its congeners is straightforward and involves the condensation of an appropriately substituted aniline with formaldehyde producing chiral (but racemic) products in good to excellent yields.[5] The use of formaldehyde or an equivalent precludes the formation of derivatives of Troeger's base which are functionalized. Only a few such derivatives are known as exemplified by **3** and **4**.[6,7] Our plans for the development of chiral species from Troeger's base called for ready access to such derivatives. We envisaged benzylic metallation as a convenient route to the desired compounds.



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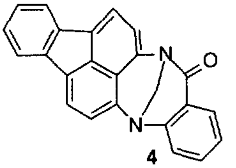

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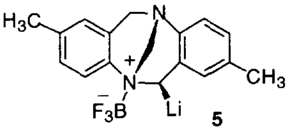

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The work of Kessar was particularly inspiring in this regard. He recently reported that the metallation of amines such as tetrahydroisoquinolines could be greatly facilitated by pre-complexation of the amine with boron trifluoride.[8] We decided to apply this methodology to Troeger's base. This report describes our successful, preliminary results in the metallation of Troeger's base using the Kessar approach.[9]

Treatment of a 0.2 M solution of Troeger's base in THF at 0 ^{o}C with one equivalent of BF_3-Et_2O followed by cooling to -78 °C and treatment with one equivalent of n-BuLi for thirty minutes resulted in a deep orange-red solution of organolithium **5**. This reacted with a selection of electrophiles stereoselectively to produce the adducts **6** in moderate to excellent yields. The results are summarized in the Table.

The reaction has not been optimized, nor have the full range of potential electrophiles been examined. Benzylic, allylic and primary alkyl halides reacted well (Table, entries 1-5). The stereochemistry of the adducts was assigned based on the assumption that electrophiles approached the anion from the less hindered convex face of the dibenzobicyclo[3.3.1] framework. Reactive electrophiles such as chlorotrimethylsilane and MEM chloride also work well. The reaction with furfural produced a 1.7:1 mixture of diastereomers, as assessed by examination of the ^1H NMR of the crude reaction mixture.[10] These were presumed to be epimeric at the carbinol carbon. This was confirmed by Swern oxidation, which led to a single ketone **6m** in 84% yield.

Other carbonyl functional groups including ketone, chloroformate and ester reacted with **5**. Interestingly, the

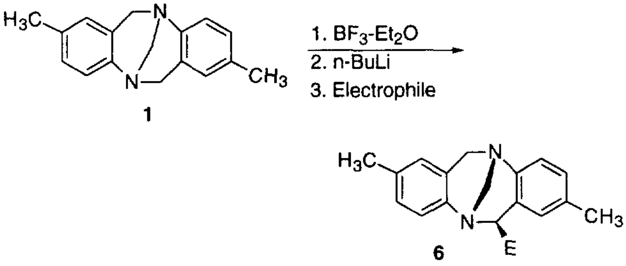


Table. Alkylation of Troeger's Base

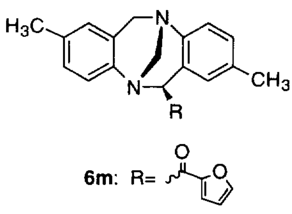
Entry	Electrophile	Product	Yield(%)[a]
1	$PhCH_2Br$	**6a**	68
2	2-(3-bromopropyl)furan	**6b**	75
3	allyl bromide	**6c**	62
4	CH_3I	**6d**	87
5	5-iodo-1-pentene	**6e**	76
6	TMSCl	**6f**	66
7	MEMCl	**6g**	84
8	furfural	**6h**	66[b]
9	Ph_2CO	**6i**	66
10	iBuOCOCl	**6j**	62
11	p-tBuPhCO$_2$Me	**6k**	13[c]
12	$C_2Br_2Cl_4$	**6l**	0[d]

[a]Yield after chromatographic purification. [b]Obtained as a 1.7:1 mixture of diastereomers. Characterized as ketone **6m**. [c]Major product was **7**. [d]Major product was **6n**.

major product with methyl para t-butylbenzoate was not the ketone **6k** but a different compound to which we have tentatively assigned the structure shown by alcohol **7**. This was obtained in 25% yield (Table, entry 11). The stereochemical assignment of **7** is based on the fact that both the ^1H and ^{13}C NMR do not exhibit signs of symmetry. Hence, the Troeger's base fragments in **7** must possess the same relative configuration (no mirror plane) and the reaction of **6k** with **5** must take place with a high degree of stereoselectivity.

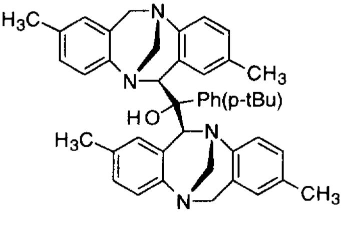
Finally, attempted bromination of **5** failed (Table, entry 12). Presumably in the course of work up, the brominated adduct was hydrolyzed. The corresponding hemi-aminal **6n** was isolated in 72% yield.

In Troeger's base, the nitrogen lone pairs are approximately gauche to the exo hydrogens of the benzylic methylene groups. We anticipated that the lone pair-lone pair repulsion which presumably inhibits deprotonation in amines like tetrahydroisoquinolines would not be as significant a problem in this case. Indeed, treatment of **1** with n-BuLi in THF under the same conditions as above followed by alkylation with benzyl bromide resulted in the formation of **6a** in 14% yield (69% based on recovered material). While it is clear that the rate of deprotonation of Troeger's base is greatly enhanced by precomplexation with boron trifluoride, this result suggests that it may not be necessary at all.



6m: R=

6n: R= OH



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In summary, we have developed the first general entry to derivatives of Troeger's base functionalized at a benzylic methylene position. The metallation step is greatly facilitated by precomplexing **1** with boron trifluoride, though metallation can take place in the absence of this Lewis acid. The availability of Troeger's base in optically pure form via asymmetric transformation and progress in the asymmetric synthesis of analogues of Troeger's base promise a diverse supply of enantiomerically pure substrates to which this chemistry can be applied.[11]

Further development of this chemistry,[12] other methods for the benzylic functionalization of **1** (and **2**) and the generation and application of new families of chiral ligands for asymmetric reactions and catalysis[13] are in progress and will be reported in due course.[14,15]

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References and Notes

1. (a) Vögtle, F. *Fascinating Molecules in Organic Chemistry;* Wiley: Chichester, 1992; pp 237-49. (b) Bag, B.G. *Curr. Sci.* **1995**, *68*, 279.
2. ur-Rahman, S. *J. Chem. Soc. Pak.* **1987**, *9*, 503.
3. (a) However, its potential in asymmetric catalysis was acknowledged. See: Goldberg, Y.; Alper, H. *Tetrahedron Lett.* **1995**, *36*, 369. (b) Minder, B.; Schuerch, M.; Mallat, T.; Baiker, A. *Catal. Lett.* **1995**, *31*, 143.
4. For leading references, see: Harmata, M.; Murray, T. *J. Org. Chem.* **1989**, *54*, 3761.

5. (a) Bag, B.G.; Maitra, U. *Synth. Commun.* **1995**, *25*, 1849. (b) Sucholeiki, I.; Lynch, V.; Phan, L.; Wilcox, C.S. *J. Org. Chem.* **1988**, *53*, 98.
6. (a) Metlesics, W.; Tavares, R.; Sternbach, L.H. *J. Org. Chem.* **1966**, *31*, 3356. (b) Shenbor, M.I.; Smirnov, G.M. *Vopr. Khim. Khim. Tekhnol.* **1976**, *43*, 24; (CA 87:68019).
7. (a) Analogues substituted on the bridging methylene are also known. For example, see: Johnson, R.A.; Gorman, R.R.; Wnuk, R.J.; Crittenden, N.J.; Aiken, J.W. *J. Med. Chem.* **1993**, *36*, 3202. (b) Analogues in which a benzylic methylene and the bridging methylene are connected have been prepared. For example, see: Jircitano, A.J.; Sommerer, S.O.; Shelley, J.J. *Acta Crystallogr., Sect. C* **1994**, *C50*, 445.
8. Kessar, S.V. Singh, P.; Vohra, Kaur, N.P.; Singh, K.N. *J. Chem. Soc., Chem. Commun.* **1991**, 568.
9. Benzylic epimers of **3** are converted to **3** by treatment with sodium hydride, presumably the result of benzylic metallation, at least in an equilibrium sense. See reference 6a.
10. This mixture was not rigorously characterized. ^{1}H NMR data of the reaction product suggested two compounds in a 1.7:1 ratio based on integration of peaks assigned to the methyl groups of both diastereomers. That the compounds were epimeric at the carbinol center was confirmed by oxidation, which led to a single ketone.
11. (a) Wilen, S.H.; Qi, J.Z. *J. Org. Chem.* **1991**, *56*, 485. (b) Maitra, U.; Bag, B.G.; Rao, P.; Powell, D. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2049.
12. For example, in a single experiment, treatment of Troeger's base with two equivalents of Lewis acid and base followed by alkylation with benzyl bromide gave a dibenzyl derivative of Troeger's base which was C2 symmetric (by ^{13}C NMR) but in an unoptimized yield of only 18%.
13. Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis;* Wiley: New York, 1995.
14. All new compounds exhibited satisfactory ^{1}H and ^{13}C NMR and IR spectral data as well as satisfactory combustion analysis or high resolution exact mass data.
15. General experimental procedure. Preparation of **6a**: To a flame-dried, round-bottom flask equipped with a stir bar, septum and nitrogen balloon was added 104.3 mg of Troeger's base and 2 mL of dry THF. The solution was cooled to 0 ^{o}C in an ice bath and stirred for 10 min. To this solution was added 54 ul of BF_3-Et_2O and the solution was stirred from 20 min. The solution was then cooled to -78 ^{o}C in a dry ice/isopropanol bath and allowed to stir for 10 min. n-BuLi (185 ul of 2.45 M hexanes solution) was then added. The resulting deep orange-red solution was stirred for 15 min. Benzyl bromide (55 ul) was then added dropwise via syringe. The deep orange-red color dissappeared by the end of the addition leaving a faint yellow solution. After stirring for 30 min. at -78 ^{o}C the reaction was quenched by the careful addition of water (5 mL). The reaction mixture was transferred to a separatory funnel, the layers separated and the aqueous layer extracted with ethyl ether (3x5 mL). The combined organic layers were washed with water (2x5 mL) and brine (1x5 mL). The organic layer was dried (Na_2SO_4). Filtration and removal of solvent in vacuo gave crude product which was purified by flash chromatography.

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