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Tandem Formation and [2,3] Rearrangement of Methylene Ammonium Ylides Derived from Amines and the Simmons–Smith Reagent

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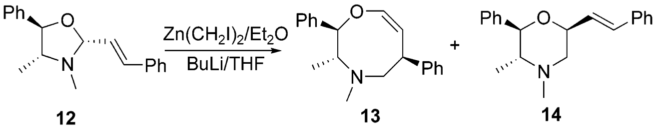
ABSTRACT



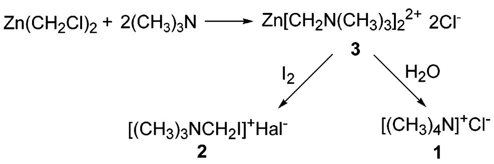
72% yield, >98% d.r.

5% yield, >98% d.r.

Zinc-complexed methylene ammonium ylides are formed from tertiary amines and the Simmons–Smith reagent. These stable entities can be activated with *n*-BuLi to allow reactions typical of ammonium ylides such as [2,3] rearrangements. In the case of oxazolidine 12, ylide formation, activation, and subsequent [2,3] rearrangement was highly efficient and occurred with very high diastereoselectivity.

Over 40 years ago, Wittig described the reaction of trimethylamine with a variation of the Simmons−Smith reagent $(ClCH_2)_2Zn$ generated from $CH_2N_2/ZnCl_2$, which on aqueous workup gave the quaternary ammonium salt **1** (Scheme 1).[1]

Scheme 1



Alternatively, quenching with iodine furnished the iodomethylammonium salt **2**. These reactions presumably occur via the *zinc-complexed ammonium ylide* **3**. It is surprising that this chemistry has remained completely dormant since this initial report, especially because the generation of ammonium ylides[2] without additional anion-stabilizing groups can be troublesome. Two methods have previously been employed to generate such ylides: fluoride-induced desilylation of α-trimethylsilylammonium salts[3] and the transmetalation of α-trimethylsilylammonium salts with *n*-BuLi.[4]

We felt that Wittig's zinc-complexed ammonium ylide offered some potential for generating unsubstituted ammonium ylides. However, Wittig's observations also caused us concern about the hurdles in attempting to exploit this process. Ammonium ylides are generally highly reactive intermediates that readily undergo Stevens rearrangements,[5] but the zinc-complexed ylide **3** was reported to be stable.

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[1] Wittig, G.; Schwarzenbach, K. *Liebigs Ann. Chem.* **1961**, *650*, 1.

[2] For a review on ammonium ylide, see: Markó, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; p 913. For a recent review on asymmetric ylide chemistry, see: Aggarwal, V. K.; Li, A. H.; Dai, L. X. *Chem. Rev.* **1997**, *97*, 2341.

[3] Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941.

[4] Maeda, Y.; Sato, Y. *J. Org. Chem.* **1996**, *61*, 5188.

[5] Stevens, T. S.; Creighton, E. M.; Gordon, A. B.; Macnicol, M. *J. Chem. Soc.* **1928**, 3193.

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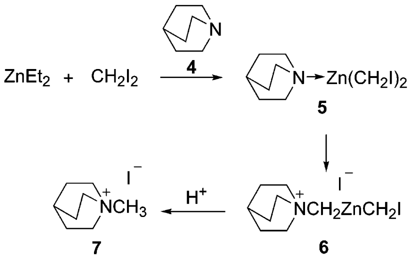
Was this due to the known lower propensity of the metal-free ammonium ylide related to **3** to undergo the Stevens rearrangement,[6] or was this due to the stability associated with the formation of a zinc complex? In this paper, we show that the latter explanation is correct and describe a method for converting the stable zinc-complexed ammonium ylide into a reactive one.

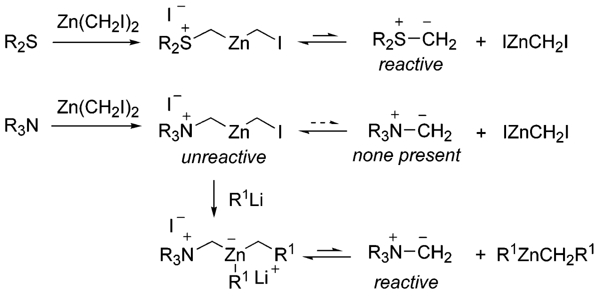
We began our studies by repeating Wittig's reaction, although we used the more user-friendly Furukawa protocol[7] for generation of the Simmons–Smith reagent and employed quinuclidine rather than trimethylamine, and some useful observations were made. Treatment of quinuclidine **4** with the Simmons–Smith reagent in diethyl ether resulted in the formation of a white precipitate after a few minutes at −10 °C. Interestingly, if the reaction was worked up at this stage, quinuclidine was regenerated, indicating that amine–zinc complex **5** had been formed. Workup of the reaction mixture after 2 days at 0 °C gave the methylammonium salt **7**, which is presumably formed from the zinc-complexed ammonium ylide **6** (Scheme 2).

Scheme 2



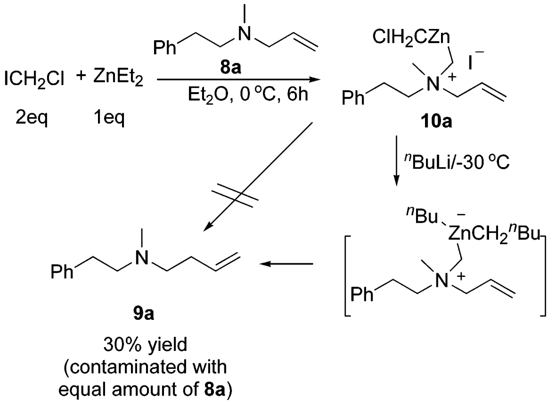
To test whether the lack of rearrangement of the zinc-complexed ammonium ylide was related to the stability associated with the [2.2.2] bicyclic amine, an alternative amine with a high propensity for both [1,2] and [2,3] rearrangements was sought. Thus, unsaturated amine **8a** was selected and treated with the Simmons–Smith reagent. However, no rearrangement products or cyclopropanes[8] were formed, but as before, the N-methylated ammonium salt was isolated instead. This indicates that the zinc-complexed ammonium ylide is completely unreactive. We were surprised at the complete lack of reactivity of these ylides, especially because sulfides are known to react with the Simmons–Smith reagent to give zinc-complexed sulfonium ylides, which readily participate in [2,3] rearrangements,[9] epoxidations,[10] and aziridinations.[11] Presumably, in the sulfide case, there is a significant amount of the free ylide, which participates in these reactions, whereas ammonium ylides, being much less stable,[12] remain tightly bound to the zinc cation, resulting in an insignificant amount of the free ylide (Scheme 3).

Scheme 3



We reasoned that formation of an ate complex should render the organozinc reagent more reactive, as dissociation to form a zinc free ylide now seemed more feasible (Scheme 3). A number of additives were tested,[13] and it was found that *n*-BuLi was effective. The product of [2,3] sigmatropic rearrangement **9a** was formed upon treatment of the zinc-complexed ammonium ylide **10a** with *n*-BuLi, albeit in low yield (Scheme 4).

Scheme 4



During optimization of the reaction conditions, our first observation was that the choice of the Simmons–Smith reagent was crucial. When the reagent generated from 1 equiv

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(6) Meada, Y.; Sato, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1491.

(7) (a) Furukara, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1968**, 3495. (b) Furukara, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1969**, *25*, 2647.

(8) Allylic amines bearing a *non-nucleophilic nitrogen* readily undergo cyclopropanation with the Simmons–Smith reagent; see: Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761.

(9) (a) Kozarych, Z.; Cohen, T. *Tetrahedron Lett.* **1982**, *23*, 3019. (b) Charette, A. B.; Marcoux, J. F.; Molinaro, C.; Beauchemin, A.; Brochu, C.; Isabel, E. *J. Am. Chem. Soc.* **2000**, *122*, 4508.

(10) (a) Aggarwal, V. K.; Ali, A.; Coogan, M. P. *J. Org. Chem.* **1997**, *62*, 8628. (b) Aggarwal, V. K.; Coogan, M. P.; Stenson, R. A.; Jones, R. V. H; Fieldhouse, R.; Blacker, J. *Eur. J. Org. Chem.* **2002**, *2*, 319.

(11) Aggarwal, V. K.; Stenson, R. A.; Jones, R. V. H.; Fieldhouse, R.; Blacker, J. *Tetrahedron Lett.* **2001**, *42*, 1587.

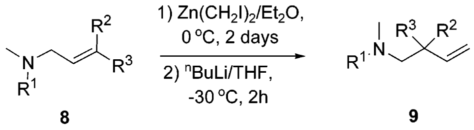
(12) pK_a values of Et$_3$N$^+$CH$_2$Ph and Bu$_2$S$^+$CH$_2$Ph are 30.8 and 18.8, respectively: Cheng, J. P.; Liu, B; Zhao, Y. Y.; Sun, Y.; Zhang, X; Lu, Y. *J. Org. Chem.* **1999**, *64*, 604.

(13) We have tried MeONa and *pseudo*-ephedrine salts made from 1 equiv of (1*R*,2*R*)-*pseudo*-ephedrine/1 equiv of LiHMDS or NaHMDS and 1 equiv of (1*R*,2*R*)-*pseudo*-ephendrine/2 equiv of *n*-BuLi as additives in THF solution at 0 °C. In all cases, no neutral amines were obtained after workup.

of $ZnEt_2$ and 2 equiv of ICH_2Cl was treated with the tertiary amine **8a**, a small amount of cyclopropane byproduct was observed in addition to the rearrangement product. When the Simmons–Smith reagent was generated from 1 equiv of $ZnEt_2$ and 1 equiv of ICH_2Cl or 1 equiv of CH_2I_2 and treated with amine **8a**, low conversion to **9a** was observed. However, the species generated from 1 equiv of $ZnEt_2$ and 2 equiv of CH_2I_2 had the desired balance of reactivity and selectivity. With 1.1 equiv of of this reagent (generated from 1.1 equiv of $ZnEt_2$ and 2.2 equiv of CH_2I_2), we observed that the amine was totally consumed and the rearrangement product was the only product obtained. This was important, as it was difficult to separate the rearrangement product from the starting material or any other byproducts. TBME, diethyl ether, benzene, and toluene were superior to other solvents, and reaction in diethyl ether gave the highest yield.

These optimized conditions were then applied to a series of tertiary allylamines (Table 1).

Table 1. [a]



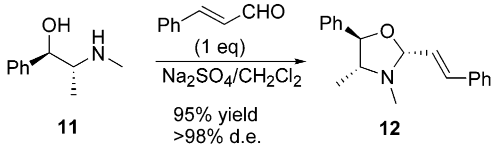
substrate	R¹	R²	R³	yield (%)
8a	$Ph(CH_2)_2$	H	H	70
8b	$Ph(CH_2)_2$	CH_3	CH_3	50
8c	$Ph(CH_2)_2$	H	Ph	76
8d	$PhCH_2$	H	H	30[b]

[a] Stoichiometry of the process is $ZnEt_2$:CH_2I_2:amine:^{n}BuLi = 1.1:2.2:1:3.9. [b] Starting material (24%) was recovered; a small amount of Sommelet–Hauser rearrangement product was observed.

Although the product from **8a** could potentially arise from either a [1,2] or [2,3] rearrangement, the product from substrates **8b** and **8c** proved that [2,3] sigmatropic rearrangement occurred exclusively. The benzylamine derivative **8d** gave a lower yield of the [2,3] rearrangement product **9d**. In addition to recovery of a small amount of starting material, a small amount of Sommelet–Hauser rearrangement[14] product was also observed.

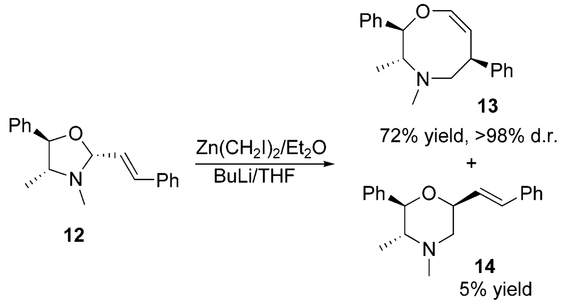
Oxazolidine derivatives provided additional opportunities to probe the scope and the stereochemical consequences of the novel rearrangement process. Oxazolidine **12** was prepared in a facile manner from (1*R*,2*R*)-*pseudo*-ephedrine and cinnamaldehyde in the presence of Na_2SO_4. A single diastereomer was formed in high yield,[15] the relative stereochemistry of which was assigned by analogy with previous reports on related substrates (Scheme 5).[16]

Scheme 5



Treatment of oxazolidine **12** with our standard optimized procedure furnished the ring-expanded product **13**, derived from [2,3] sigmatropic rearrangement in 72% yield as a single diastereoisomer. A small amount of the morpholine derivative **14** was also isolated, again, as a single diastereoisomer (Scheme 6).

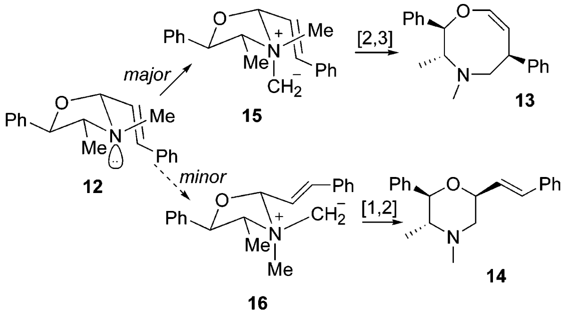
Scheme 6



The relative stereochemistry of the eight-membered ring was determined by X-ray crystallography, and the relative stereochemistry of the [1,2] rearrangement product was determined by NOESY NMR.

The formation of **13** can be rationalized by considering the possible TSs for rearrangement and the possible diastereomers (**15**/**16**) generated upon ylide formation. Of the two possible diastereomers, ylide **15** is expected to be the major isomer due to the known preference for alkylation/ylide formation of five-membered ring heterocycles to occur cis to adjacent substituents as a result of the favored conformation of the ring (Scheme 7).[17,18c] Subsequent [2,3] sigmatropic rearrangement of ylide **15** has to occur on the (*s*)-cis conformer of the alkene to furnish the (*Z*)-oxazocine **13**.[18]

Scheme 7



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[14] Sommelet, M.; Hauser, C. R. *Hebd. Seances Acad. Sci*. **1937**, *205*, 56.

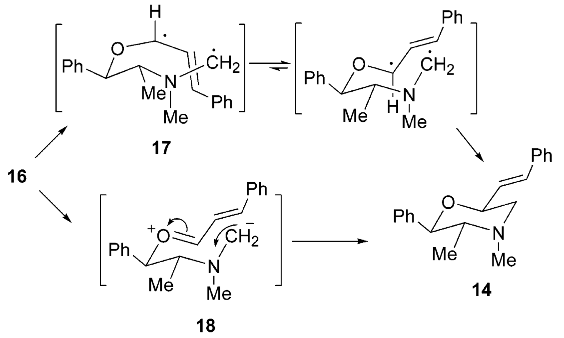
[15] (a) Khruscheva, N. S.; Loim, N. M.; Sokolov, V. L.; Makhaev, V. D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2425. (b) Huche, M.; Aubouet, J.; Pourcelot, G.; Berlan, J. *Tetrahedron Lett*. **1983**, *24*, 585. (c) Hassan, A.; Rene, G.; Robert, C. *Tetrahedron Lett*. **1982**, *23*, 503. (d) Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron*, **1984**, *40*, 1803.

[16] Hussain, A.; Wyatt, P. B. *Tetrahedron* **1993**, *49*, 2123.

The (*s*)-trans conformer of **15** places the alkene too far away from the ylide carbon to effect cyclization. [2,3] Sigmatropic rearrangement of ylide **16** in the (*s*)-trans conformation (the (*s*)-cis conformer places the groups too far apart) would lead to formation of the (*E*)-isomer of the eight-membered ring compound.[18a,c] However, such rings are highly strained and their formation must be accompanied by a higher activation barrier. In this case, an alternative pathway for rearrangement emerges: the Stevens rearrangement to give morpholine **14** (Scheme 7).[19]

While morpholine **14** could indeed have arisen from a Stevens rearrangement of ylide **16**,[20] the stereochemistry of the product caused us concern, as such intramolecular rearrangements usually proceed with retention of stereochemistry.[21] In our case, clean inversion was observed. It is possible that the neighboring oxygen atom and cinnamyl groups confer added stability to the radical intermediate **17**, allowing time for bond rotation to occur prior to ring closure. Alternatively, it is possible that the intermediate ylide undergoes ring opening to give oxonium ion **18**[22], which is then trapped by the carbanion to give compound **14**. This mechanism does involve an intermediate non-stabilized carbanion, but this may be stabilized by the zinc salts present in solution (Scheme 8).

Scheme 8



In conclusion, we have shown that amines react with the Simmons−Smith reagent to give zinc-complexed ammonium ylides, which are highly stable. Even amines bearing allyl groups showed no indication of rearrangement. This indicates that Wittig's inference of the formation of a zinc-complexed ammonium ylide was primarily due to the stability of the metal-complexed ylide and not due to the reduced propensity for rearrangement. In addition, we have described a protocol for converting the easily accessible, stable zinc-complexed ammonium ylides into reactive species. This involves addition of *n*-BuLi, which converts the zinc complex into a much more reactive zincate complex that is capable of undergoing [2,3] rearrangement.

Acknowledgment. We thank Chirotech for financial support.

Supporting Information Available: Spectroscopic data and experimental procedures for compounds **8a−d**, **9a−c**, and **12−14** and X-ray crystallography of compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Glaeske, K. V.; West, F. G. *Org. Lett.* **1999**, *1*, 31.

(18) For other examples of rearrangements of ammonium ylides to give eight-membered rings, see: (a) Clark, J. S.; Hodgson, P. B. *Tetrahedron Lett.* **1995**, *36*, 2519. (b) Wright, D. L.; Weekly, R. M.; Groff, R.; McMills, M. C. *Tetrahedron Lett.* **1996**, *37*, 2165. (c) Vedejs, E.; Hagen, J. P.; Roach, B. L.; Spear, K. L. *J. Org. Chem.* **1978**, *43*, 1185.

(19) For another example in which one diastereoisomer of an ylide undergoes [2,3] rearrangement and the other diastereomer undergoes a [1,2] rearrangement, see ref 18b.

(20) Ylide **15** would not be expected to undergo Stevens rearrangement, as [2,3] sigmatropic rearrangements are generally faster processes than [1,2] rearrangements. Mageswaran, S.; Ollis, W. D.; Sutherland, I. O.; Thebtaranonth, Y. *J. Chem. Soc., Chem. Commun.* **1971**, 1494. For a review on Stevens rearrangements, see ref 2.

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(22) For other examples of ylides derived from acetals/thioacetals undergoing effectively a [1,2] rearrangement, see: (a) Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; Leusen, D. V. *J. Org. Chem.* **1984**, *49*, 1917. (b) Trauner, D.; Porth, S.; Opatz, T.; Bats, J. W.; Giester, G.; Mülzer, J. *Synthesis* **1998**, 653. (c) Mülzer, J.; Trauner, D.; Bats, J. W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1970.