Journal of Organometallic Chemistry, *473* (1994) 93–99

Carbon–carbon bond forming reactions *via* new organosamarium(III) intermediates

Masahiro Murakami and Yoshihiko Ito

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Kyoto 606-01 (Japan)

(Received December 15, 1993; in revised form December 22, 1993)

Abstract

New carbon–carbon bond forming reactions *via* organosamarium(III) intermediates, developed in our laboratory, are reviewed. (α-Iminoalkyl)samarium(III) intermediates are generated by treatment of organic halides and 2,6-xylyl isocyanide with samarium(II) iodide. Subsequent reactions with carbonyl compounds produce α-hydroxy imines, which are hydrolyzed to the corresponding α-hydroxy ketones. Unsymmetrical α-diketones are synthesized by autoxidation of α-hydroxy imines. The use of 4-(tert-butyldimethylsiloxy)-2,6-xylyl isocyanide in the SmI_2-mediated three-component coupling reaction has led to the stereoselective syntheses of 2-amino alcohols *via* reduction and subsequent oxidative *N*-de-arylation. Double insertion of 2,6-xylyl isocyanide into an organic halide mediated by SmI_2 provides an efficient synthetic method for hydroxy diketones and vicinal triketones. (α-Aminoalkyl)samarium(III), generated through formation of a radical from *N*-(*o*-iodobenzyl)amine, its translocation and a subsequent one-electron transfer, is used as a new α-amino carbanion equivalent.

Key words: Samarium; Carbon–carbon bond formation

1. Introduction

Samarium(II) iodide is a strong one-electron transfer reducing agent. Since the appearance of the seminal paper by Kagan *et al.* in 1980 [1], reactions of samarium(II) iodide have been extensively studied in the field of synthetic organic chemistry and have led to many interesting and useful results. Several reviews are available on this rapid progress [2]. This review covers our recent studies on new carbon–carbon bond forming reactions involving (α-iminoalkyl)samarium(III) intermediates [3]. A new method of generating an α-amino carbanion equivalent is also presented [4] (Fig. 1).

2. Synthesis of α-hydroxy ketones by SmI_2-mediated three-component coupling

Metallation of the isocyano carbons by α-addition of organometallic compounds to isocyanides results in the formation of (α-iminoalkyl)metal compounds, which can be subsequently utilized as synthetic equivalents of acyl anions [5]. Our research in the field of organosamarium chemistry was initiated by an interest in the introduction of a samarium metal onto an isocyano carbon atom. When 2,6-xylyl isocyanide (1) was treated with samarium(II) iodide, no reaction took place even in the presence of HMPA as co-solvent [6] and the isocyanide 1 was recovered. Next, an organic halide was treated with two equivalents of samarium(II) iodide in the presence of the inert isocyanide 1 in THF containing HMPA at −15°C. The deep purple color of samarium(II) iodide disappeared in 3 h and the following aqueous work-up afforded an aldimine. This result suggested the formation of the (α-iminoalkyl) samarium(III) intermediate 2 by coupling of an organic halide with isocyanide (1) (Scheme 1).

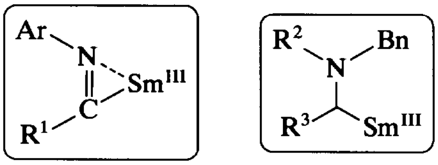
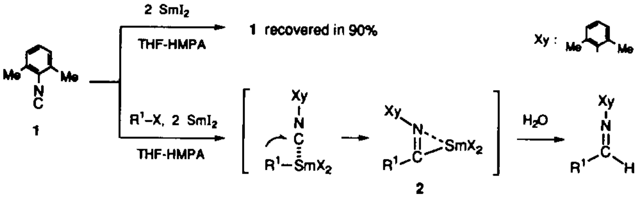


Fig. 1.

Correspondence to: Dr. Y. Ito.

Elsevier Sequoia.

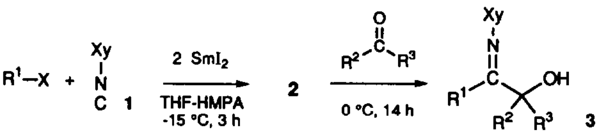


Scheme 1.

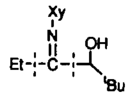
When a carbonyl compound was added to the reaction mixture after disappearance of the deep purple color, α-hydroxy imine (**3**) was formed, supporting the involvement of the intermediate **2** [3b] (Table 1).

Primary and secondary alkyl bromides and iodides successfully coupled with isocyanide (**1**) and the resulting (α-iminoalkyl)samarium(III) species underwent the second coupling both with aldehydes and with ketones. Notably, not enolization but addition to the carbonyl group took place even with cyclopentanone which is exceptionally prone to enolization. The success of the reaction with cyclopentanone implies that (α-iminoalkyl)samarium(III) (**2**) is highly nucleophilic and still less basic. Selective 1,2-addition proceeded with α,β-unsaturated ketones. Various functional groups were tolerated under the reductive conditions for the initial coupling of organic halides with **1**. Neither carbon–carbon double nor triple bonds, including terminal bonds, were affected. Trimethylsilyl and pivaloyl groups, which are often cleaved by organolithium and Grignard reagents, could be employed for protection of hydroxyl groups. Furthermore, benzyl and tetrahydropyranyl ethers were also suitable for the protective group.

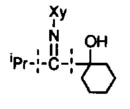
TABLE 1. Three-component coupling of organic halides, **1** and carbonyl compounds



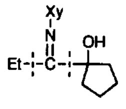
Product **3**, yield (%) [a]



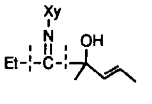
3a, 94



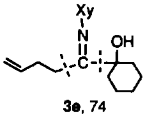
3b, 99



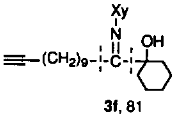
3c, 99



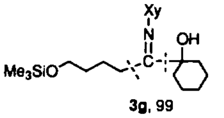
3d, 94



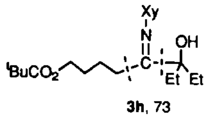
3e, 74



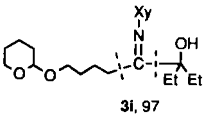
3f, 81



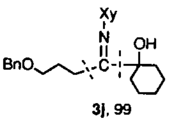
3g, 99



3h, 73



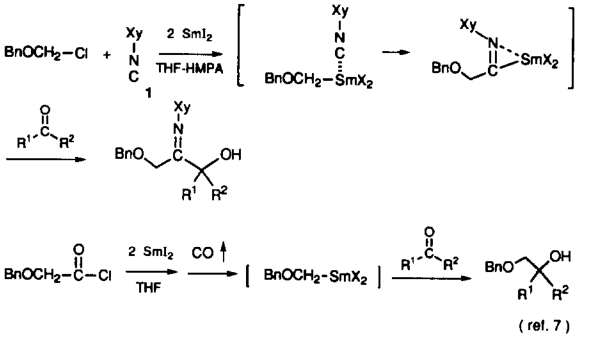
3i, 97



3j, 99

---

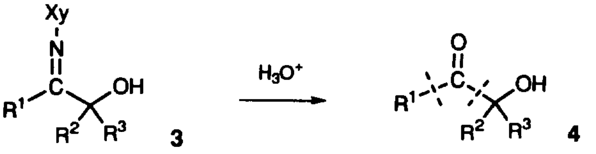
[a] Isolated yields based on organic halides.



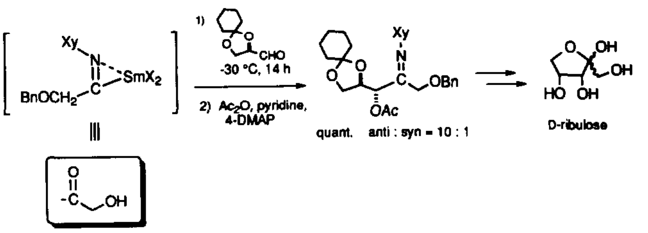
Scheme 2.

Of note was the use of benzyl chloromethyl ether as the starting halide [3a]. It has been reported that the samarium(II) iodide-mediated reaction of an α-alkoxy acetyl chloride results in the extrusion of carbon monoxide, giving (alkoxymethyl)samarium(III) [7]. In contrast, the present reaction proceeds in the reverse direction, *i.e.* isocyanide (**1**) is inserted into (alkoxymethyl)samarium(III) in spite of its isoelectronic structure with carbon monoxide. The resulting (α-iminoalkyl)samarium(III) also added to carbonyl compounds to yield α,α′-dioxy *N*-substituted imines (Scheme 2). α-Hydroxy imines **3** were transformed to the corresponding α-hydroxy ketones **4** in good yield by acid-catalyzed hydrolysis of the imino group. Thus, the samarium(II) iodide-mediated three-component coupling of organic halides, 2,6-xylyl isocyanide, and carbonyl compounds provides a facile preparative method for α-hydroxy ketones (Scheme 3).

In particular, hydrolysis of α,α′-dioxy *N*-substituted imines could be performed under extremely mild conditions, presenting a useful and practical approach to the synthesis of α,α′-dihydroxy ketones. The (α-iminoalkyl)samarium(III) acted as a synthetic equivalent to (α-hydroxy acetyl) anion. This method of construction



Scheme 3.



Scheme 4.

of α,α'-dihydroxy ketones was successfully applied to the stereoselective synthesis of D-*erythro*-2-pentulose (D-ribulose) [3a] (Scheme 4).

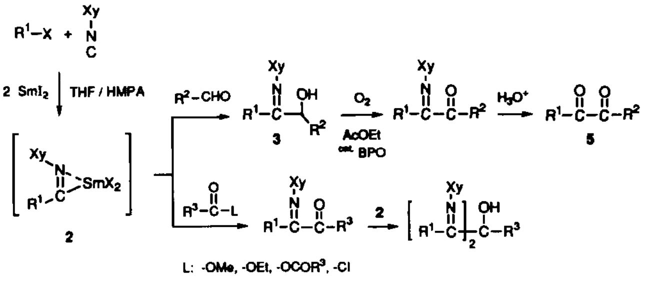
3. Synthesis of unsymmetrical α-diketones *via* autoxidation of α-hydroxy imines

α-Keto imines are attractive precursors of α-diketones. Attempted direct acylation of (α-iminoalkyl)samarium(III) intermediate **2** with various acylating agents was unsuccessful, because the α-keto imine once formed is so electrophilic and is attacked by **2** again to afford a tertiary alcohol as the major product. However, autoxidation of α-hydroxy imines provided an alternative synthetic pathway to α-keto imines [3c]. α-Hydroxy imines were readily oxidized by a simple procedure of bubbling oxygen into a refluxing solution of α-hydroxy imines in AcOEt in the presence of a catalytic amount of benzoyl peroxide. The imino group of the α-keto imine thus obtained was hydrolyzed by treatment with aqueous acid affording the corresponding unsymmetrical α-diketone **5** (Scheme 5).

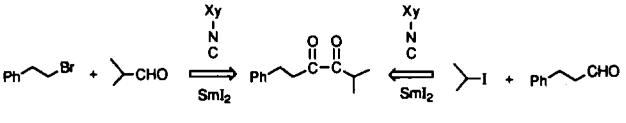
According to the present method, the same unsymmetrical α-diketone can be synthesized *via* two synthetic routes, *i.e.* one incorporating R^1 from an organic halide and R^2 from an aldehyde, and the other *vice versa* (Scheme 6).

4. Stereoselective synthesis of 2-amino alcohols

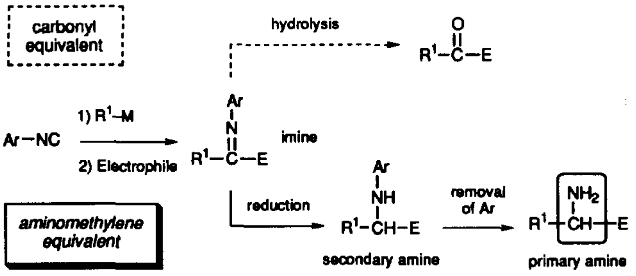
α-Hydroxy ketones and unsymmetrical α-diketones have been synthesized *via* (α-iminoalkyl)samarium(III) intermediates. In these transformations, the nitrogen atom derived from the isocyanide is ultimately lost by hydrolysis and, consequently, the isocyanide is used as a masked carbonyl synthon. It could reveal the intrinsic synthetic value of the isocyanide, one inaccessible from carbon monoxide, if the imino group of the product could be unmasked without the loss of the nitrogen atom. Reduction of the produced imine to a secondary amine and subsequent removal of the *N*-substituent constitute a feasible approach along these lines, wherein the isocyanide is used as an aminomethylene equivalent (Scheme 7).



Scheme 5.

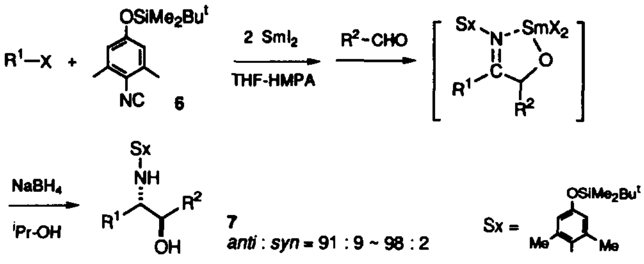


Scheme 6.

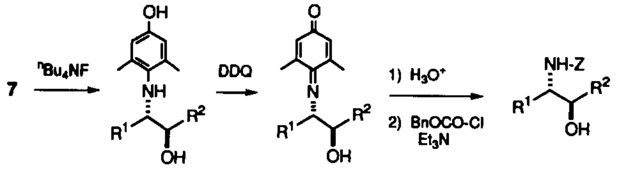


Scheme 7.

Taking into account that a *p*-oxyphenyl group can be oxidatively removed from a nitrogen atom [8], 4-(tert-butyldimethylsiloxy)-2,6-xylyl isocyanide (**6**) was prepared from commercially available 3,5-xylenol [3d]. It was found that isocyanide **6** successfully coupled with an organic halide and a carbonyl compound. The resulting reaction mixture was treated *in situ* with $NaBH_4$, one of the simplest hydride reducing agents, affording anti-2-(arylamino) alcohol (**7**) selectively. Notably, the addition of 2-propanol to the mixture as a co-solvent improved the selectivity significantly (Scheme 8).



Scheme 8.



Scheme 9.

The 2-(arylamino) alcohols 7 were de-arylated *via* desilylation with TBAF followed by oxidation with DDQ to afford the corresponding 2-(primary amino) alcohols in high yield (Scheme 9).

The stereoselection observed in the hydride reduction is reasonably attributed to the attack of hydride from the less-hindered side of the five-membered ring involving chelation of the samarium atom with the oxygen and nitrogen atoms of the α-oxy-*N*-arylimine (Fig. 2).

The present stereoselective synthetic method of 2-amino alcohols was applied to the synthesis of a ceramide, the hydrophobic skeleton of glycosphingolipids. The α-oxy imine was prepared by coupling of benzyl chloromethyl ether, the isocyanide **6** and 2-hexadecenal. Reduction with $NaBH_4$ gave the corresponding anti-2-amino alcohol stereoselectively. Temporary introduction of a palmitoyl group, removal of the aryl group, and migration of the palmitoyl group led to the synthesis of the (+)-ceramide **8**. Thus, a convenient and general synthetic route to ceramides was established (Scheme 10).

5. Synthesis of α-hydroxy aldehydes by SmI_2-mediated coupling of ketones and isocyanide (1)

Reduction of ketones by samarium(II) iodide in the presence of isocyanide (**1**) afforded α-hydroxy aldimines after aqueous work-up [3b]. It has been reported that ytterbium metal reacts with benzophenone to produce η^2-benzophenone dianion–Yb complex [9]. Therefore, the present reaction may involve η^2-ketone–samarium (III) complex, which adds to isocyanide. However, all attempts to trap the resulting (α-iminoalkyl)samarium (III) intermediate with carbonyl compounds failed. α-Hydroxy aldimines thus obtained were converted to the corresponding α-hydroxy aldehydes by alkylation of the imino nitrogen with methyl triflate followed by hydrolysis (Scheme 11).

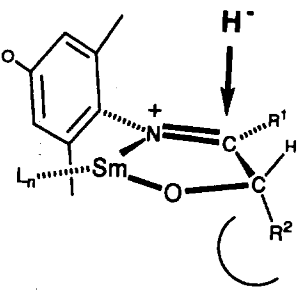
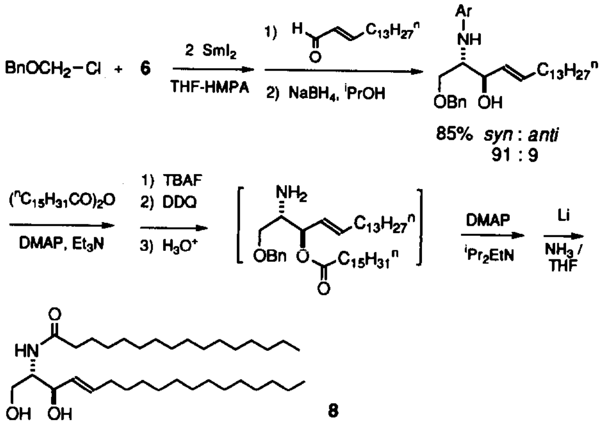


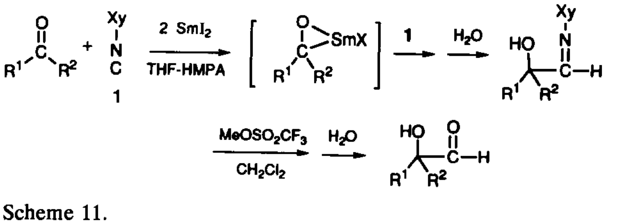
Fig. 2. Proposed model for hydride attack to the five-membered chelation intermediate.



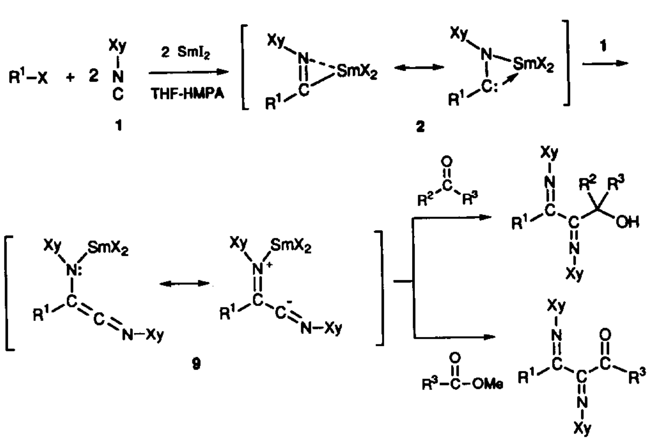
Scheme 10.

6. SmI_2-mediated double insertion of isocyanide (1) into organic halides

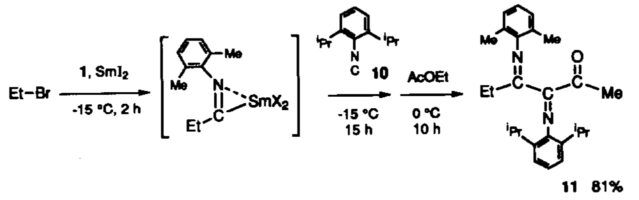
Selective double insertion of isocyanide (**1**) into an organic halide is efficiently mediated by samarium(II) iodide providing a useful synthetic method for vicinal di- and tricarbonyl compounds [3e]. When an organic halide was treated with two equivalents of 2,6-xylyl isocyanide (**1**) and samarium(II) iodide in THF/HMPA at −15°C for 10 h, (α-iminoalkyl)samarium(III) (**2**), the initial intermediate, underwent the second coupling with **1** to afford organosamarium species **9**. The ketenimine structure may be presumed on the basis of the structures of the related actinide metal complexes [10]. The intermediate **9** reacted with ketones and aldehydes to produce α-hydroxy diimines. In marked contrast to the (α-iminoalkyl)samarium(III) (**2**), the intermediate **9** was successfully acylated with esters to produce the corresponding α-keto diimine selectively. This difference in the reactivity patterns of **2** and **9** may be



Scheme 11.



Scheme 12.

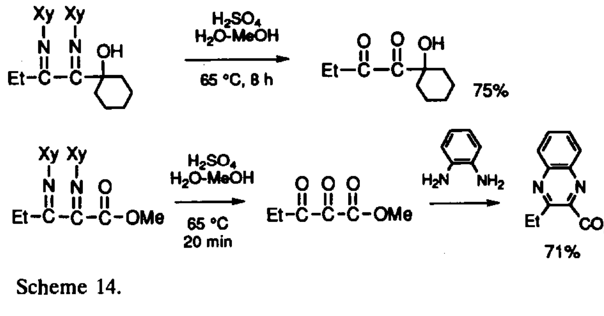


Scheme 13.

ascribed to their η^2-type and ketenimine structures. It should be noted that three C–C bonds were formed between four molecules in one stage to construct an α-hydroxy diimine or an α-keto diimine (Scheme 12).

Stepwise coupling with different isocyanides **1** and **10** led to the formation of a cross double insertion product **11** (Scheme 13).

The diimines thus obtained were hydrolyzed in acidic media to the corresponding polycarbonyl compounds. Of particular interest is the fact that this procedure provides a novel method for the construction of 1,2,3-tricarbonyl functionality, which has recently attracted much attention since it is a peculiar structural feature of the powerful immunosuppressants [11] (Scheme 14).



Scheme 14.

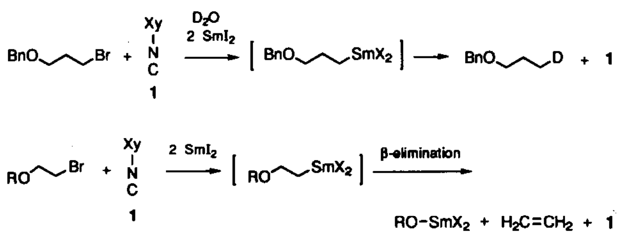
7. Mechanistic interpretation of SmI_2-mediated coupling of an organic halide with isocyanide 1

When the samarium(II) iodide-mediated reaction of an alkyl halide with isocyanide (**1**) was carried out in the presence of D_2O, no coupling reaction of the alkyl halide with **1** took place and a deuterated alkane with a high percent of deuterium incorporation (R–D:R–H > 95:5) was obtained. Whereas reactions with alkyl halides bearing oxy-substituents at the α-, γ-, or δ-positions worked well, only β-oxy substituted alkyl halides like 2-(trimethylsiloxy)ethyl bromide and 2-(benzyloxy)ethyl bromide failed to react with the isocyanide. Benzyl alcohol was obtained in the case of 2-(benzyloxy)ethyl bromide. The formation of benzyl alcohol may be accounted for by assuming the intermediacy of a (β-oxyalkyl)samarium(III), which undergoes β-elimination (Scheme 15).

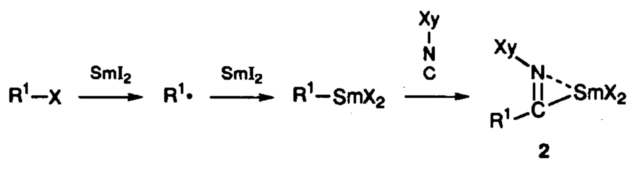
These findings support the following route for the generation of the (α-iminoalkyl)samarium(III) species **2**; an alkylsamarium(III) is formed by means of rapid successive one-electron transfers from 2 equivalents of samarium(II) iodide to an organic halide. The alkylsamarium(III) species undergoes α-addition to the isocyanide. On the basis of the structures of η^2-(α-iminoalkyl)erbium and -yttrium complexes [12], a η^2complex is the likely structure of the (α-iminoalkyl)samarium(III) species **2** (Scheme 16).

8. Generation of carbanions

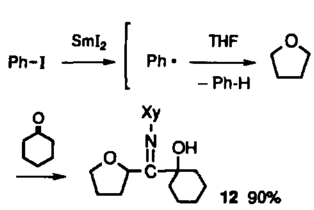
It has been reported that phenyl and vinyl radicals involved in samarium(II) iodide-mediated reactions abstract a hydrogen atom from the THF solvent more



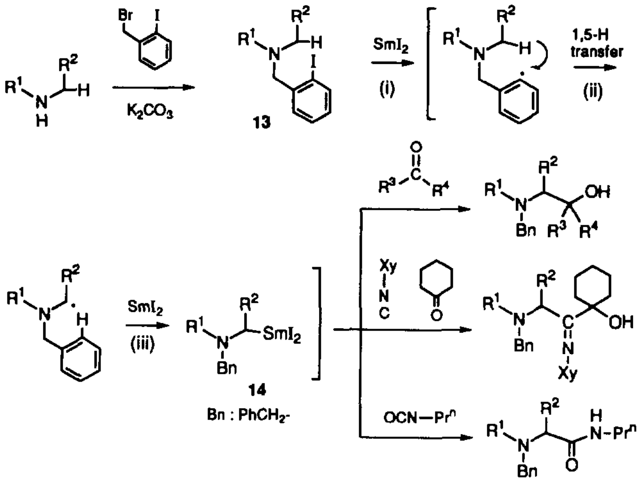
Scheme 15.



Scheme 16.



Scheme 17.



Scheme 18.

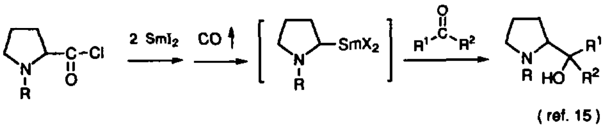
rapidly than they are reduced by samarium(II) iodide [6,13]. The hydrogen transfer generates α-tetrahydrofuryl radical. Indeed, it was found that the use of iodobenzene or vinyl bromide in the samarium-mediated three-component coupling reaction resulted in the formation of THF-containing adduct **12** (Scheme 17).

Synthetic exploitation of this type of hydrogen transfer was attempted and a new method for the generation of a carbanion equivalent α to amino nitrogens was developed [4]. Tertiary amines **13** having a pendant at the *o*-iodobenzyl group on the nitrogen were easily prepared in high yield by treatment of secondary amines with *o*-iodobenzyl bromide in aqueous K_2CO_3/THF. The C–C bond formation took place at the α-position of the nitrogen upon treatment of **13** with samarium(II) iodide in the presence of electrophiles in tetrahydropyran containing HMPA. Cyclic and acyclic tertiary amines coupled with various electrophiles including enolizable ketones, isocyanates and isocyanides. The results of deuterium incorporation experiments support the following reaction pathway to α-amino organosamarium(III) **14** as the transient intermediate: (i) de-iodination of the *o*-iodobenzyl group by SmI_2 giving the corresponding aryl radical; (ii) an intramolecular 1,5-hydrogen atom transfer producing the α-amino radical [14]; (iii) one electron transfer from SmI_2 to the α-amino radical giving **14** (Scheme 18).

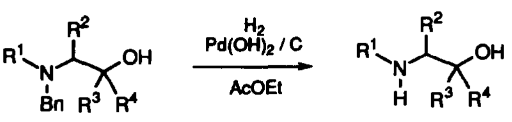
Recently, Kagan *et al.* reported that α-amino organosamarium(III) is also generated *via* extrusion of carbon monoxide from α-amino acid chloride [15] (Scheme 19). It should be noted that isocyanide (**1**) showed the opposite reactivity pattern towards α-amino organosamarium(III) as well as α-alkoxy organosamarium(III) (see Schemes 2 and 18).

It should be noted that the pendent benzyl group in the product can be removed by hydrogenation to give the secondary amine. Therefore, the reaction provides a useful method for the synthesis of a variety of nitrogen containing compounds including 2-amino alcohols and α-amino acid derivatives (Scheme 20).

Metallation by hydrogen-metal exchange has been mostly carried out by abstraction of protons under strongly basic conditions using alkyllithium or lithium amide [16]. The present reaction, which is composed of a delivery of radical center from the pendent benzyl group to the α-position of nitrogen and a subsequent one-electron transfer, offers a new method for metalation.



Scheme 19.



Scheme 20.

9. Conclusions

Several new C–C bond forming reactions involving organosamarium(III) intermediates have been developed. The reactions described here provide a new and convenient synthetic method for α-hydroxy ketones and aldehydes, hydroxy diketones, vicinal triketones, and 2-amino alcohols, demonstrating the outstanding efficiency of SmI_2-mediated reactions. The compatibility of various functionalities with the reaction conditions fulfills the requirements for the construction of a multi-functional carbon framework.

Acknowledgement

We gratefully acknowledge the intellectual and practical contributions of our co-workers whose names are given in the references.

References

1 P. Girard, J.L. Namy and H.B. Kagan, *J. Am. Chem. Soc., 102* (1980) 2693.

2 (a) H.B. Kagan and J.L. Namy, *Tetrahedron, 42* (1986) 6573; (b) J. Soderquist, *Aldrichim. Acta, 24* (1991)15; (c) G.A. Molander, *Chem. Rev., 92* (1992) 29.

3 (a) M. Murakami, T. Kawano and Y. Ito, *J. Am. Chem. Soc., 112* (1990) 2437; (b) M. Murakami, T. Kawano, H. Ito and Y. Ito, *J. Org. Chem., 58* (1993) 1458; (c) M. Murakami, I. Komoto, H. Ito and Y. Ito, *Synlett,* (1993) 511; (d) M. Murakami, H. Ito and Y. Ito, *J. Org. Chem., 58* (1993) 6766; (e) M. Murakami, H. Masuda, T. Kawano, H. Nakamura and Y. Ito, *J. Org. Chem., 56* (1991) 1.

4 M. Murakami, M. Hayashi and Y. Ito, *J. Org. Chem., 57* (1992) 793.

5 (a) G.E. Niznik, W.H. Morrison and H.M. Walborsky, *J. Org. Chem., 39* (1974) 600; (b) M.J. Marks and H.M. Walborsky, *J. Org. Chem., 46* (1981) 5405; (c) M.J. Marks and H.M. Walborsky, *J. Org. Chem., 47* (1982) 52; (d) M. Murakami, H. Ito and Y. Ito, *J. Org. Chem., 53* (1988) 4158; (e) M. Murakami, H. Ito, W.A.W. Bakar, A.B. Baba and Y. Ito, *Chem. Lett.,* (1989) 1603.

6 J. Inanaga, M. Ishikawa and M. Yamaguchi, *Chem. Lett.,* (1987) 1485.

7 M. Sasaki, J. Collin and H.B. Kagan, *Tetrahedron Lett., 29* (1988) 4847.

8 T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York, 1991, p. 400.

9 (a) Z. Hou. H. Yamazaki, K. Kobayashi, Y. Fujiwara and H. Taniguchi, *J. Chem. Soc., Chem. Commun.,* (1992) 722; (b) Z. Hou, H. Yamazaki, Y. Fujiwara and H. Taniguchi, *Organometallics, 11* (1992) 2711.

10 K.G. Moloy, P.J. Fagan, J.M. Manriquez and T.J. Marks, *J. Am. Chem. Soc., 118* (1986) 56.

11 M.K. Rosen and S.L. Schreiber, *Angew. Chem., Int., Ed. Engl., 31* (1992) 384.

12 (a) W.J. Evans, T.P. Hanusa and J.H. Meadows, *Organometallics, 6* (1987) 295; (b) W.J. Evans, J.H. Meadows, W.E. Hunter and J.L. Atwood, *Organometallics, 2* (1983) 1252.

13 T.L. Fevig, R.L. Elliott and D.P. Curran, *J. Am. Chem. Soc., 110* (1988) 5064.

14 (a) S.M. Bennete and D.L.J. Clive, *J. Chem. Soc., Chem. Commun.,* (1986) 878; (b) D.C. Lathbury, P.J. Parsons and I. Pinto, *J. Chem. Soc., Chem. Commun.,* (1988) 81; (c) A.D. Borthwick, S. Caddick and P.J. Parsons, *Tetrahedron Lett., 31* (1990) 6911; (d) V. Snieckus, J.C. Cuevas, C.P. Sloan, H. Liu and D.P. Curran, *J. Am. Chem. Soc., 112* (1990) 896; (e) D.P. Curran, A.C. Abraham and H. Liu, *J. Org. Chem., 56* (1991) 4335.

15 J. Collin, J.L. Namy, G. Jones and H.B. Kagan, *Tetrahedron Lett., 33* (1992) 2973.

16 D.J. Ager, in T.A. Hase (ed.), *Unpoled Synthons*, Wiley, New York, 1987, p. 101.