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N-Silyl-Tethered Radical Cyclizations: A New Synthesis of γ-Amino Alcohols

Christophe Blaszykowski, Anne-Lise Dhimane, Louis Fensterbank, and Max Malacria*

Laboratoire de Chimie Organique, UMR CNRS 7611, Université Pierre et Marie Curie, Case 229, 4 place Jussieu, 75252 Paris Cedex 05, France

malacria@ccr.jussieu.fr

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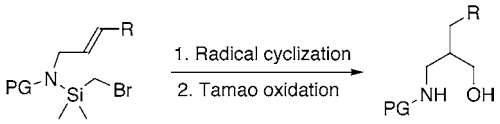
ABSTRACT



Various allylic and propargylic amines bearing a protecting group (PG) have been employed in *N*-silyl-tethered radical cyclizations. The resulting silapyrrolidine adducts could be smoothly oxidized, creating access to γ-amino alcohols. The silylation, radical cyclization, and oxidation reactions could be consolidated in a one-pot process.

The concept of temporary linking reacting partners in view of overcoming unfavorable entropy effects, forcing regioselectivity, and controlling stereoselectivity has been well-illustrated over the last two decades.[1] Several approaches have been designed relying, for instance, on pivotal atoms such as boron (boronate tethers),[2] sulfur,[3] Lewis acidic salts,[4] and more prominently silicon (siloxanes, silaketals, and silyl ethers).[5] All these linkages are based on at least one alcohol component. In contrast, amines that are key substrates in organic synthesis have been little involved for that purpose[6] and only sporadic reports of *N*-silyl-tethered Sakurai-type reaction,[7] Diels−Alder cycloaddition,[8] Zr-mediated cyclization,[9] hydrosilylation,[10] silylformylation,[11] and bis-silylation[12] have appeared. Interestingly, to the best of our knowledge, the *N*-silyl linkage has never been utilized in the context of radical chemistry. So we turned our attention to the possibility of developing a nitrogen version of the bromomethyldimethylsilyl (BMDMS) allyl[13] and propargyl ether[14] radical cyclizations (Scheme 1). We first examined the preparation of *N*-silyl precursors **2**, with the concern that aminosilanes are more fragile substrates than the corresponding ethers,[15]

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(5) For reviews, see: (a) Bols, M.; Skydstrup, T. *Chem. Rev.* **1995**, *95*, 1253−1277. (b) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813−854. (c) Gauthier, D.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289−2338.

(6) For an exemple based on phosphonamide species, see: Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. *Org. Lett.* **2001**, *3*, 3939−3942 and references therein.

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(13) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298−2300. (b) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500−501.

(14) Magnol, E.; Malacria, M. *Tetrahedron Lett.* **1986**, *27*, 2255−2256.

(15) Si−N bond is 77 kcal/mol, about 24 kcal/mol weaker than the Si−O bond. For a discussion of this, see: Armitage, D. A. In *The Chemistry of the Silicon−Heteroatom Bond*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1991; pp 365−445.

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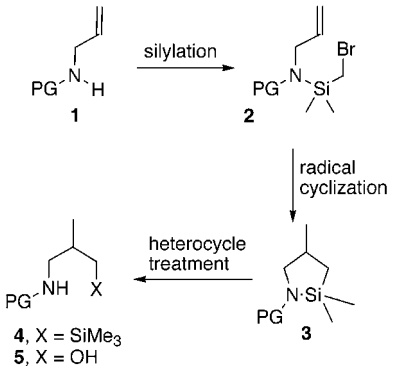
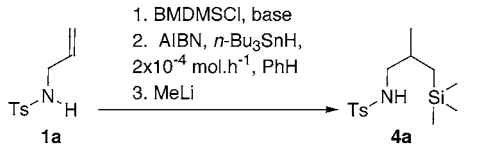
Scheme 1. *N*-Silyl-Tethered Radical Cyclization



and that the bromomethyl group could also be a supplementary source of instability.[16] The latter was in part confirmed by a preliminary experiment: while N-Boc allylamine could be cleanly silylated with trimethylsilyl chloride (70% after chromatography), only untractable material was obtained with BMDMS chloride. Moreover, no precursor **2** could be isolated with a benzyl protecting group (PG), whereas the tosyl one showed moderate stability. In contrast, N-TMS and N-phenyl precursors have been obtained efficiently (> 70% yield).

These findings suggested to us that it could be necessary to conduct the silylation, radical cyclization, and further heterocycle **3** treatment in a one-pot operation. This principle was initially tested on tosylallylamine **1a** as shown in Scheme 2. Thus, silylation of **1a** with BMDMSCl in the presence of

Scheme 2

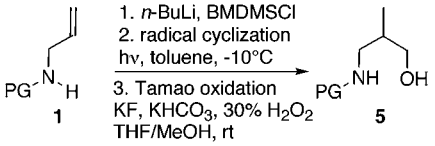


base	radical initiation	yield (%) of **4a**
Et_3N, DMAP	Δ	28
Et_3N, DMAP	hν (sun lamp), 10°	62
n-BuLi	hν (sun lamp), 10°	69

Et_3N and DMAP, followed by a slow addition of tributyltin hydride in thermal initiation conditions and methyllithium treatment provided the expected branched amine **4a** in 28% overall yield, with 47% recovery of **1a**. Although this result demonstrated the feasability of the one-pot reaction, we suspected that the aminosilane decomposed to some extent in these thermal conditions in the presence of ammonium salts.[17] So we examined the possibility of running this sequence at lower temperatures by using photochemical initiation conditions. This proved to be beneficial since **4a** was obtained in a better yield (62%), accompanied by only 18% of **1a**. Optimization of the conditions was achieved by running an irreversible deprotonation of the amine with *n*-BuLi and using photochemical initiation (69% of **4a**, Scheme 2).

We then pursued the use of an allyl partner as a radical acceptor, varying the nature of the PG on amines **1**, and focused on the preparation of γ-amino alcohols **5** after final Tamao oxidation (Table 1). Our initial result (entry 1) with

Table 1.



entry	amine **1**, PG	**5**, yield (%)
1	**1a**, Ts	**5a**, 23[a]
2	**1a**, Ts	**5a**, 63[b]
3	**1b**, Ph	**5b**, 18[c]
4	**1b**, Ph	**5b**, 65[d]
5	**1c**, Bn	**5c**,
6	**1d**, Boc	**5d**, 75

[a] Siloxane dimer was isolated in 44% yield. [b] $HBF_4.OEt_2$ treatment was run prior to Tamao oxidation. [c] Bromoanilines were also isolated in 44% yield. [d] KF/MeOH treatment was run prior to Tamao oxidation.

a Ts protecting group showed that the preparation of a γ-amino alcohol derivative was possible; however, the yield was modest (23% **5a**), due to the reluctant oxidation of the siloxane (−Si−O−Si− dimer)[8,18] that is formed during the Tamao oxidation. So we had to have recourse to a HBF_4 treatment prior to the oxidative treatment in order to cleave the N−Si bond and generate a fluorosilane that could be smoothly oxidized as proved by the increased yield of **5a** in entry 2 (63%). The aniline precursor **1b** (entry 3) also gave a satisfactory yield of cyclized adducts. However, the expected product **5b** (18%) was accompanied by 44% monobrominated adducts in *para* and *ortho* positions (3:1 ratio) on the aniline ring. Examination of the ^1H NMR of the crude product of the radical cyclization showed that this bromination pathway was not taking place at that stage. Presumably, the Tamao conditions would promote the

(16) Survey of literature data shows that only very few of these substrates with no functionality have been described; see: (a) Niederprüm, H.; Simmler, W. *Chem. Ber.* **1963**, *96*, 965−975. (b) Yoder, C. H.; Cader, B. M. *J. Organomet. Chem.* **1982**, *233*, 275−279 and references therein.

(17) For a discussion of the cleavage of aminosilanes with ammonium salts, see: Anderson, H. H. *J. Am. Chem. Soc.* **1951**, *73*, 5802−5803. See also refs 15 and 16a.

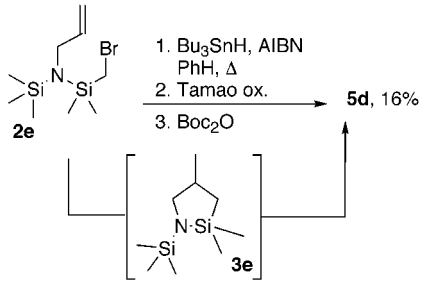
(18) Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, *269*, C37−C39. (b) Tamao, K. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 861−878.

(19) For related oxidative brominations, see: Narender, N.; Srinavasu, P.; Ramakrishna Prasad, M.; Kulkarni, S. J.; Raghavan, K. V. *Synth. Comm.* **2002**, *32*, 2313−2318 and references therein.

(20) Compound **2e** has been prepared by two consecutive N-silylations of allylamine (72% yield) and been found to be stable to aqueous workup and bulb to bulb distillation. For a rationalization of this stability, see: Schorr, M.; Schmitt, W. *Phosphorus, Sulfur, Silicon* **1992**, *68*, 25−35.

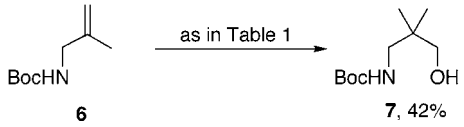
oxidation of Bu_3SnBr to a Br^+ species[19] that would be readily intercepted by the activated aniline moiety. To preclude this side reaction, a treatment of the crude cyclization product, prior to Tamao oxidation, with KF in methanol followed by a filtration over Celite eliminated most of the tin residues and inorganic salts, which allowed the improvement of the yield of **5b** to 65% (entry 4). Finally, the one-pot process proved to be completely inapplicable to benzyl precursor **1c** (entry 5) but very versatile in the case of Boc amine **1d**, giving birth to 75% yield of product **5d** (entry 6).

Scheme 3



A notable feature of all these reactions is their complete regioselectivity in favor of the 5-*exo-trig* process, and this has to be compared with the results of Nishiyama in the silyl ether series, who always observed the 6-*endo* mode on allylic systems without terminal functionality.[13a] This was further

Scheme 4



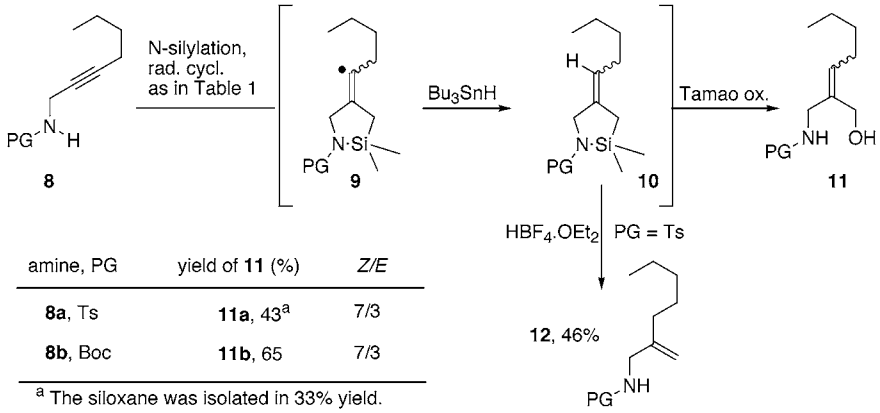
confirmed by the radical cyclization of the precursor **2e**,[20] which provided only the silapyrrolidine **3e** as judged by the NMR spectra of the crude product (Scheme 3). Then, an unprecedented one-pot Tamao oxidation and Boc protection sequence furnished the previously synthesized Boc adduct **5d** in 16% overall yield (this yield being presumably lowered by the volatility of intermediate **3e**).

More astonishingly, only a trace (<2%) of 6-*endo* cyclization was observed with methallyl precursor **6**, which followed cleanly the 5-*exo* mode (Scheme 4). This result strongly contrasts with Nishiyama's results involving the corresponding methallyl BMDMS ether precursor, which reacts in a 2:1 6-*endo* versus 5-*exo* reversed selectivity.[13a] Presumably, a slower 5-*exo-trig* process as well as a still unfavorable 6-*endo* process would account for the slightly depressed, but consistent with the literature, yield of this transformation.

Finally, propargyl precursors of type **8** could be engaged in this process to give versatile γ-amino alcohols **11** as a 7:3 mixture of *Z*/*E* diastereomers (Scheme 5). This stereochemical assignment was based on NOE measurements and ^{13}C NMR γ-gauche effects.[21] In the case of the tosyl precursor **8a**, we faced the same problem of siloxane formation, which is reluctant to undergo oxidation and results in a lesser yield of **11a**. Additional treatment by $HBF_4{\cdot}OEt_2$ is not the solution here since it resulted in the formation of allylamine **12**. The overall transformation **8a** → **12** is also worthy of note. Boc precursor **8b** reacted cleanly and gave the same ratio of stereoisomers. This moderate (*Z*)-stereoselectivity originates from a reduction of the vinyl radical, which displays the minimized allylic strain between the alkyl chain and the more remote CH_2-heteroatom moiety[22] (the C−Si bond is approximately 30% longer than the C−N bond).

In conclusion, we have reported the first examples of radical cyclizations of BMDMS amino derivatives. We have worked out a new and efficient access to γ-amino alcohols by combining the N-silylation, radical cyclization, and oxidation steps in a one-pot process. Tuning of the reaction conditions (notably at the oxidation stage) according to the nature of the amine protecting group has been devised. Numerous γ-amino alcohol derivatives exhibit important

Scheme 5



amine, PG	yield of **11** (%)	*Z*/*E*
8a, Ts	**11a**, 43[a]	7/3
8b, Boc	**11b**, 65	7/3

[a] The siloxane was isolated in 33% yield.

biological activities,[23] and our efforts are now devoted toward these targets. Moreover, thanks to the trivalent nature of the pivotal nitrogen atom, further applications focusing on the attachment of chiral auxiliaries for an asymmetric version or grafting to polymers in view of supported synthesis are under investigation.

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Supporting Information Available: Experimental procedures and spectral data for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) For a model of the reduction of vinyl radicals, see: Journet, M.; Malacria, M. *J. Org. Chem.* **1992**, *57*, 3085−3093.

(23) See for instance: Lee, J.; Park, S.-U.; Kim, J.-Y.; Kim, J.-K.; Lee, J.; Oh, U.; Marquez, V. E.; Beheshti, M.; Wang, Q.-J.; Modarres, S.; Blumberg, P. M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2909−2914.