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# A Stereocontrolled Access to Ring-Fused Piperidines through a Formal [2+2+2] Process

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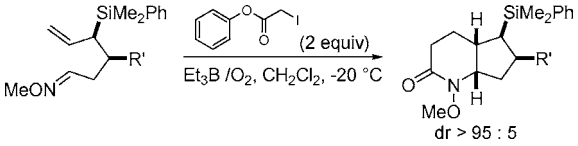
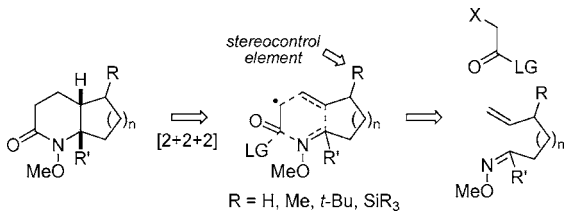
## ABSTRACT




**A formal [2+2+2] process has been devised that allows the stereocontrolled formation of ring-fused piperidines from allylsilanes possessing an oxime moiety. The cascade involves an intermolecular radical addition of an α-iodoacetate onto an allylsilane double bond, which is followed by a 5-*exo*-trig cyclization onto an oxime and is completed by the formation of the amide bond by nucleophilic attack of the amine onto the ester function.**

The piperidine substructure can be found in numerous natural products and is also present in a wide range of biologically relevant targets currently under preclinical and clinical tests.[1] We envisioned that 2,3-ring-fused piperidines could be elaborated through a simple strategy based on a formal [2+2+2] process, in which two bonds of the piperidine ring would be formed through radical reactions, the last one being the result of an ionic nucleophilic process (Scheme 1). The first C−C bond would thus be generated through an intermolecular addition of a radical species onto an olefin, followed by the formation of the second C−C bond through a rapid 5- or 6-*exo*-trig cyclization of the resulting radical onto an oxime. Pioneering studies by Bartlett, Hart, and Naito have shown that such cyclizations are usually faster than those involving simple olefins.[2] The resulting alkoxyaminyl radical would then cyclize to produce the corresponding six-membered ring lactam in a "one-pot" operation. Three new stereogenic centers could also be created and stereochemistry would be controlled by a resident allylic substituent.

**Scheme 1.** Formal Radical-Ionic [2+2+2] Cascade for the Stereocontrolled Synthesis of Ring-Fused Piperidines




Precedents from our laboratory[3] have shown that an allylic silicon group is particularly well suited in this context as it leads to improved reaction rate during intermolecular addition of electrophilic radical species onto olefins and efficiently controls the stereochemical outcome of the whole transformation, leading to high levels of 1,2- and 1,5-diastereocontrol. Its synthetic utility is also enhanced by the possible

(1) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *23*, 3679−3681.

(2) (a) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631−1633. (b) Bartlett, P. A.; Mc Laren, K. L.; Ring, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633−1634. (c) Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 1140−1157. (d) Ueda, M.; Miyabe, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6190−6193. (e) Miyabe, H.; Ueda, M.; Fujii, K.; Nishimura, A.; Naito, T. *J. Org. Chem.* **2003**, *68*, 5618−5626.

(3) (a) James, P.; Landais, Y. *Org. Lett.* **2004**, *6*, 325−328. (b) James, P.; Felpin, F.-X.; Schenk, K.; Landais, Y. *J. Org. Chem.* **2005**, *70*, 7985−7995. (c) James, P.; Schenk, K.; Landais, Y. *J. Org. Chem.* **2006**, *71*, 3630−3633.

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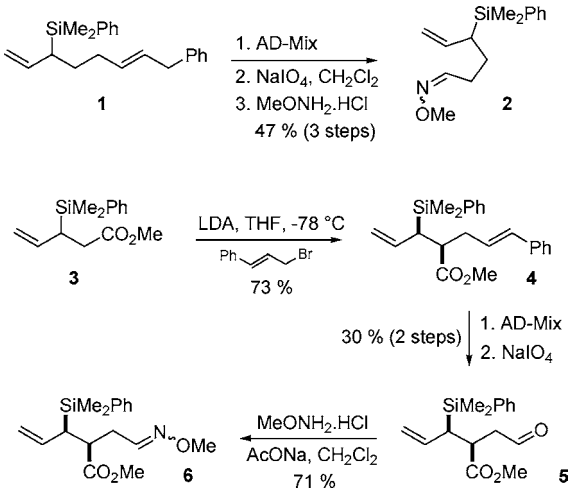
C−Si bond oxidation,[4] thus allowing the introduction of an additional hydroxy group. We report in this Letter our preliminary results on this straightforward approach to ring-fused piperidines using a cascade of radical and ionic processes.

Several allylsilane-oximes were thus prepared from the corresponding aldehydes, available from dienes having an allylsilane moiety (Scheme 2). Access to the aldehyde

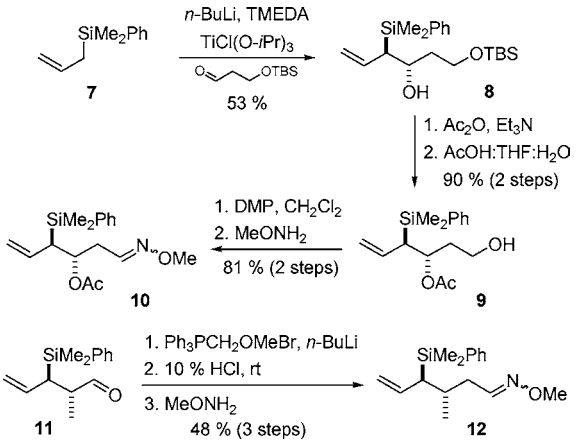
**Scheme 2.** Preparation of Oximes **2** and **6**




function involved a regioselective dihydroxylation of one of the double bonds of **1** and **4**, followed by oxidation of the resulting diol. Use of Sharpless chiral ligands allowed good regiocontrol during the dihydroxylation step, with the disubstituted olefin reacting faster than that of the allylsilane. This strategy thus afforded useful aldehydes having an allylsilane moiety in generally good yields. Oximes **2** and **6** (*E*/*Z* mixture) were then at hand by simply reacting the crude aldehyde with methylhydroxylamine hydrochloride in the presence of a base.

Allylsilane **10** was prepared starting from phenyldimethylallylsilane **7** through the route depicted below (Scheme 3).

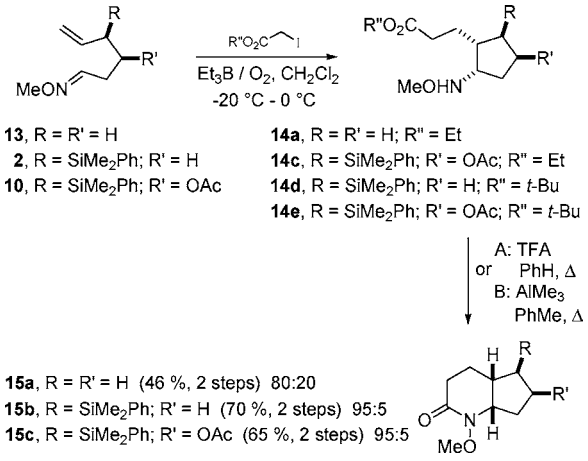
**Scheme 3.** Preparation of Oximes **10** and **12**




Reetz−Yamamoto titanium-mediated allylation of **7** with 3-TBS-protected hydroxy propanal led to the $\beta$-hydroxysilane **8** as a unique diastereomer in moderate yield. Acetylation of the secondary alcohol followed by desilylation of the primary alcohol led to **9**, which was oxidized (DMP) and subsequently transformed into oxime **10** (*E*/*Z* mixture). In parallel, homologation of aldehyde **11** through a Wittig reaction, followed by hydrolysis of the resulting enol ether into the corresponding aldehyde led finally to oxime **12** in good overall yield.

Our preliminary investigations started with the cyclization of simple olefin **13** devoid of an allylic substituent, using ethyl iodoacetate (2 equiv) and $Et_3B$ as an initiator (4 equiv) (Scheme 4). Addition, then cyclization occurred smoothly

**Scheme 4.** Two-Pot Preparation of Lactams **15a−c**




but provided the monocyclic compound **14a** in 80% yield as an 8:2 mixture of cis/trans diastereomers, without traces of the desired lactamized product. Complete lactamization was finally observed with conditions A or B, leading to **15a** in reasonable overall yield. This protocol was then extended to allylsilanes **2** and **10**. It was anticipated that addition of α-halo esters to allylsilanes might bring in additional problems such as halogen atom transfer.[5] Addition of an α-iodoacetate onto an allylsilane under radical conditions may thus be followed by a fast iodine atom transfer, generating a $\beta$-iodosilane known to $\beta$-eliminate spontaneously even under mild conditions to produce the corresponding olefin.[6] When the reaction was applied to allylsilane **2**, the corresponding cyclopentane **14b** (not shown) was, however, produced in a very satisfying 95:5 ratio of cis/trans isomers (84%), demonstrating that iodine transfer was probably slow as compared to cyclization,[7] and that the

(4) (a) Fleming, I. *Chemtracts*: *Org. Chem.* **1996**, 1−64. (b) Landais, Y.; Jones, G. *Tetrahedron* **1996**, *52*, 7599−7662.

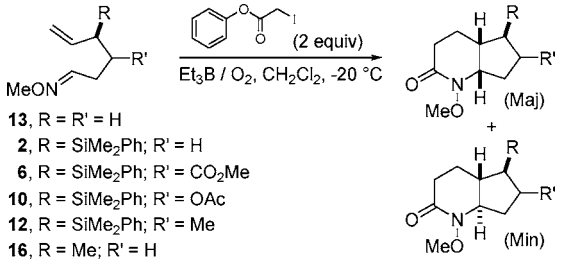
(5) Rate constants for 5-*exo*-trig cyclizations onto oximes and iodine atom transfer from α-iodoacetate have been estimated: $k \approx 3 \times 10^7$ and $k \approx 10^7$ M·s$^{-1}$, respectively. Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543−17594.

(6) (a) Porter, N. A.; Zhang, G.; Reed, A. D. *Tetrahedron Lett.* **2000**, *41*, 5773−5777. (b) Guindon, Y.; Guérin, G.; Chabot, C.; Ogilvie, W. *J. Am. Chem. Soc.* **1996**, *118*, 12528−12535.

silicon group controlled efficiently the stereochemistry of the two stereogenic centers.[3] Attempted purification of the crude mixture onto silica gel led to 45% of the *cis*-cyclopentane **14b**, along with 37% of the desired lactam **15b**.[8] A similar observation was made with allylsilane **10**. Direct lactamization on the crude reaction mixture, using conditions A or B, finally led to **15b** and **15c** in good overall yield. Interestingly, when using *tert*-butyliodoacetate, **14d**−**e** were isolated in good yield (74% and 78%) and were resistant to further lactamization on silica gel.

These preliminary results were encouraging and showed that the silicon group led to an excellent transfer of chirality during the 5-*exo*-trig cyclization. However, a stepwise formation of the fused bicyclo[4.3.0] system was not yet satisfying and our next efforts focused toward a one-pot process. It was finally found that simply introducing a better leaving group on the ester function allowed the two steps to be performed in a single-pot operation. By using phenyliodoacetate[9] as the radical precursor, lactams were thus obtained in one pot, in excellent yield and high stereoselectivity under mild conditions (Table 1). A high level of

**Table 1.** One-Pot Preparation of Lactams **15**−**19**




**13**, R = R' = H
**2**, R = $SiMe_2Ph$; R' = H
**6**, R = $SiMe_2Ph$; R' = $CO_2Me$
**10**, R = $SiMe_2Ph$; R' = OAc
**12**, R = $SiMe_2Ph$; R' = Me
**16**, R = Me; R' = H
**17**, R = *t*-Bu; R' = H

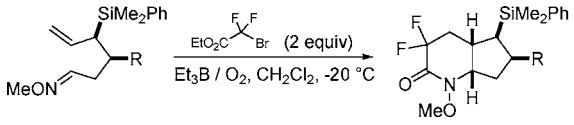
| entry | olefin | $Et_3B$ (equiv) | product | cis/trans[a] | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **13** | 2 | **15a** | 76:24 | 69 |
| 2 | **2** | 3 | **15b** | >95:5 | 76 |
| 3 | **10** | 3 | **15c** | >95:5 | 78 |
| 4 | **6** | 3 | **15d** | >90:10 | 61 |
| 5 | **12** | 3 | **15e** | >95:5 | 85 |
| 6 | **16** | 6 | **18** | 85:13.5:1.5[c] | 51 |
| 7 | **17** | 6 | **19** | >95:5 | 47 |

[a] Ratio estimated from $^1H$ NMR of the crude reaction mixture. [b] Isolated yield. [c] Ratio estimated through GC.

stereocontrol was obtained with bulky substituents in the allylic position. Complete 1,2- and 1,5-stereocontrol was thus observed with allylic $PhMe_2Si$ and *t*-Bu groups at −20 °C (entries 2−5 and 7, Table 1). The reaction was found to be more sluggish with precursors having an alkyl group in the allylic position (6 equiv of $Et_3B$ are required in this case, entries 6 and 7) and less efficient in terms of yield.[10] The process was generally high yielding with allylsilanes, and the reaction conditions tolerate various functional groups, including *β*-silyl acetates (**10**) which are prone to Peterson elimination under Lewis acidic conditions.

We also found that introduction of electron-withdrawing substituents α to the ester function of the radical precursor allowed the formation of lactams in a single-pot operation (Scheme 5). In this case, the presence of the phenyl ester

**Scheme 5.** Addition of Bromodifluoroacetate to Allylsilanes



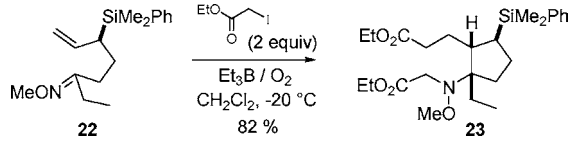

**2**, R = H
**10**, R = OAc

**20**, R = H (53 %, 71 % corr)
**21**, R = OAc (65 %)

group is not required, and **20** and **21** are formed from **2** and **10**, respectively, in reasonable yields and high diastereocontrol (>95:5). To our knowledge this is the first successful intermolecular radical addition of α,α-difluoroacetate to olefins.[11]

The study was also extended to precursors possessing a ketoxime function. In contrast with the results above, addition of ethyl iodoacetate (2 equiv) to allylsilane **22** (Supporting Information) led to monocyclized product **23** in which two fragments of acetate had been incorporated, the reaction proceeding with high yield and complete diastereocontrol (Scheme 6). Interestingly when the reaction was repeated

**Scheme 6.** Addition of Ethyl Iodoacetate to Ketoximes




**22** **23**

with ethyl xanthate,[12] the same product was formed, albeit in lower yield, indicating that the formation of the α-amino ester moiety occurred probably through a radical process. This result is also noteworthy as it shows that 5-*exo*-trig cyclization on a disubstituted $sp^2$ center is still favored relative to iodine-atom transfer.[13]

A tentative rationalization of the observed cascade is proposed below (Figure 1). The electrophilic radical species **I** is formed by abstraction of halogen from the α-haloester precursor. This then adds selectively onto the olefin to generate the radical intermediate **II**. This step is probably fast with electron-rich allylsilanes to form stabilized *β*-silyl

(7) Iodine-atom transfer followed by regeneration of the *β*-silyl radical under the reaction conditions ($Et_3B$) may not be completely ruled out.
(8) It is noteworthy that **14a** requires forcing conditions to lactamize and does not cyclize on silica as compared to silicon analogues.
(9) Phenyliodoacetate was prepared from phenol in two steps (Supporting Information).
(10) Polar effects are likely at the origin of these differences in reactivity between allylsilanes and their alkylated analogues.[3]
(11) Itoh, T.; Sakabe, K.; Kudo, K.; Ohara, H.; Takagi, Y.; Kihara, H.; Zagatti, P.; Renou, M. *J. Org. Chem.* **1999**, *64*, 252−265.
(12) Tournier, L.; Zard, S. Z. *Tetrahedron Lett.* **2005**, *46*, 455−459.
(13) Analogous 5-*exo*-trig cyclizations on trisubstituted olefins are known to be slower than addition on disubstituted olefins.

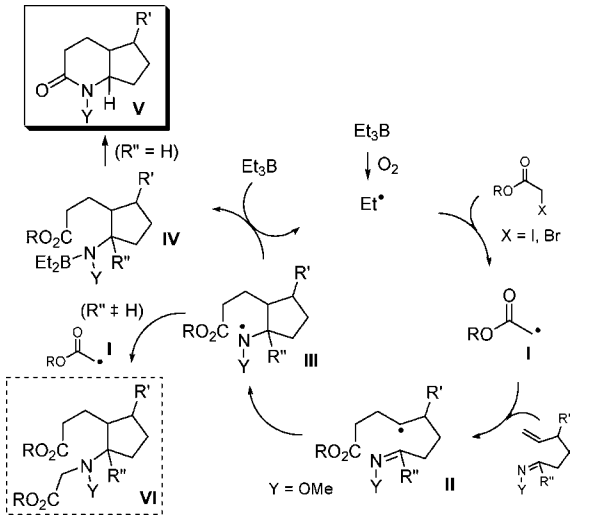



**Figure 1.** Tentative mechanistic rationale of the cascade.

radical **II**. This rapidly cyclizes through a 5-*exo*-trig process, providing the alkoxyaminyl radical **III**. When R″ is a hydrogen, **III** likely reacts with $Et_3B$ to regenerate an ethyl radical and boron amide **IV**, which cyclizes through an ionic process to form the bicyclic lactam **V**. Activation of the ester function through precoordination with $BEt_2$ may occur, accelerating the process. However, the nature of the leaving OR group on the ester is crucial for this step as demonstrated by the rapid lactamization observed when R = OPh as compared with R = OEt. When R″ is not a hydrogen, steric hindrance around the alkoxyaminyl radical probably prevents the formation of **IV** and provides **III** with enhanced kinetic stability. The latter thus possesses enough lifetime to recombine with **I** to provide bis-addition product **VI**. Experiments aiming at trapping intermediate **III** (R″ = Et) with more persistent benzyl radicals led to the corresponding benzyl-protected aminoxide in low yield, indicating that *N*-alkylation to form **23** occurred most likely through a recombination of two radical species (**I** and **III**) and not through an ionic pathway.[12,14]

In conclusion, we reported here a "one-pot" stereocontrolled elaboration of five-membered-ring fused piperidines through a new formal [2+2+2] process, involving a cascade of radical and ionic transformations. The bicyclic systems thus obtained may be elaborated further, for instance through oxidation of the C−Si bond.[15] This strategy should find applications in the synthesis of a number of natural products of biological interest. Work along these lines is in progress in our laboratory.

**Acknowledgment.** We gratefully acknowledge the CNRS, MENRT (grant to E.G.), the Institut Universitaire de France, and COST-D28 for financial support. We also thank Prof S. Zard (Ecole Polytechnique, Palaiseau) for fruitful discussions and Prof. J.-C. Quirion (University of Rouen) for a generous gift of ethyl bromodifluoroacetate.

**Supporting Information Available:** Detailed experimental procedures and spectral and analytical data for all precursors and cyclized products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) When **22** was treated with a mixture of ethyl iodoacetate and benzyl iodide, under radical conditions ($Et_3B/O_2$), a mixture of **23** and a monocyclized product having a NBn(OMe) group were formed in various amounts depending on the iodide ratio.

(15) This was demonstrated with the oxidation of compound **15b**, using Fleming buffered conditions[4] (KBr, AcONa, AcOOH; 82% yield).