J|A|C|S
ARTICLES
Published on Web 09/11/2004

Thiyl Radical-Mediated Cleavage of Allylic C−N Bonds: Scope, Limitations, and Theoretical Support to the Mechanism

Stéphanie Escoubet,[†] Stéphane Gastaldi,[†] Vitaliy I. Timokhin,[†,‡] Michèle P. Bertrand,*[,†] and Didier Siri[§]

Contribution from the Laboratoire de Chimie Moléculaire Organique, UMR 6517, Boite 562, Faculté des Sciences St Jérôme, Université d'Aix-Marseille III, Avenue Normandie-Niemen, 13397 Marseille Cedex 20, France, Department of Physical Chemistry, Institute of Physical Chemistry, National Academy of Sciences of Ukraine, 3A Naukova Street, 79060, Lviv, Ukraine, and Laboratoire de Chimie Théorique et Modélisation Moléculaire, UMR 6517, Boite 521, Faculté des Sciences St Jérôme, Université de Provence, Avenue Normandie-Niemen, 13397 Marseille Cedex 20, France

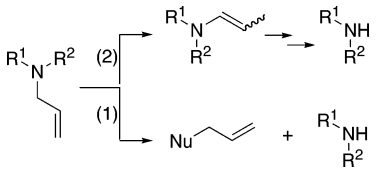
Received January 9, 2004; E-mail: michele.bertrand@univ.u-3mrs.fr

Abstract: Thiols mediate the radical isomerization of allylic amines into enamines. The reaction results in the cleavage of the allylic C−N bond, after treatment with aqueous HCl. The mechanism involves the abstraction of an allylic hydrogen α to nitrogen by thiyl radical, followed by a return hydrogen transfer from the thiol to the carbon γ to nitrogen in the intermediate allylic radical. The scope and limitations of the reaction with respect to the nature of the thiol, to the structure of the allylic chain, and to the nature of the substituents at nitrogen were investigated. The experimental results were interpreted on the ground of DFT calculations of the C−Hα BDE in the starting allylic amines, and of the C−Hγ BDE in the resulting enamines. The efficiency of the initial hydrogen transfer is the first requirement for the reaction to proceed. A balance must be found between the S−H BDE and the two above-mentioned C−H BDEs. The incidence of stereoelectronic factors was analyzed through NBO calculations performed on the optimized geometries of the starting allylic amines. Additional calculations of the transition structures and subsequent tracing of the reaction profiles were performed for the abstraction of Hα from both the allyl and the prenyl derivatives by *p*-TolS•. The latter allowed us to estimate the rate constant for the abstraction of hydrogen by thiyl radical from an *N*-prenylamine and an *N*-allylamine.

Introduction

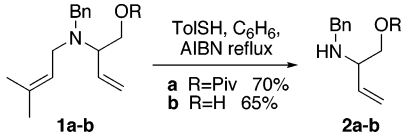
The methodologies allowing the cleavage of allylic C−N bonds can be roughly classified into two groups (Scheme 1).

Scheme 1



In the protocols belonging to the first group, the amino group is submitted to such experimental conditions as to become a leaving group which is displaced by a nucleophile.[1] The methods of the second type proceed through the migration of the double bond, leading to an enamine which is then cleaved upon acidic treatment.[2]

Our group has long been involved in the field of sulfur-centered radicals-mediated cyclization of 1,6-dienes.[3,4] As reported in a preliminary note,[5] while investigating the addition of *p*-thiocresol to dienes **1a**,**b** (in which the nitrogen atom bears two different allylic moieties), we discovered by accident an unexpected deprenylation reaction (eq 1).[6]



(1)

None of the isomeric pyrrolidines **3a**,**b** (Figure 1) that would have been produced through an addition/cyclization/hydrogen transfer sequence were formed. The only products, isolated in 65 or 70% yield depending on the starting material, were the

[†] Université d'Aix-Marseille III.

[‡] National Academy of Sciences of Ukraine. Present address: Department of Chemistry, University of Wisconsin−Madison, 1101 University Ave., Madison, WI 53706.

[§] Université de Provence.

(1) (a) Merzouk, A.; Guibé, F.; Loffet, A. *Tetrahedron Lett.* **1992**, *33*, 477. (b) Garro-Hélion, F.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109. (c) Lemaire-Audoire, S.; Savignac, M.; Genêt, J.-P.; Bernard, J.-M. *Tetrahedron Lett.* **1995**, *36*, 1267. (d) Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932. (e) Kapnang, H.; Charles, G. *Tetrahedron Lett.* **1983**, *24*, 3233. (f) Olofson, R. A.; Yamamoto, Y. S.; Wancowicz, D. J. *Tetrahedron Lett.* **1977**, *18*, 1563. (g) Ito, H.; Taguchi, T.; Hauzawa, Y. *J. Org. Chem.* **1993**, *58*, 774. For a special case of photochemical release of amine, see also: (h) Schoenleber, R. O.; Giese, B. *Synlett* **2003**, 501.

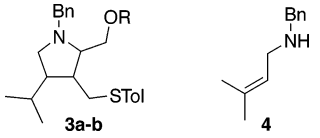


Figure 1.

amines **2a**,**b** that resulted from the cleavage of the prenyl group. This experimental observation was all the more intriguing as no trace of prenyl benzylamine (**4**) (Figure 1), that would have resulted from the cleavage of the most highly branched allylic C−N bond, was detected.

A series of blank experiments led to the conclusion that both the thiol and the radical initiator were needed for the reaction to proceed, which of course pointed to a radical mechanism. This article describes all the studies that were carried out in order to determine the scope and limitations of this reaction. As disclosed in the following discussion, the reaction involves the thiyl radical-catalyzed migration of the double bond, leading to the corresponding enamine, which is then hydrolyzed. Theoretical calculations of S−H and C−H bond dissociation energies were performed using density functional theory (DFT) in order to reach a better understanding of the factors controlling the reactivity of thiols toward a series of allylic amines (cf. Table 2 for S−H BDEs, and Table 3 for the C−H BDEs obtained by using UB3LYP/6-311++G(3df,3pd) and UB3LYP/6-31+G(d,p) single-point energies on UB3LYP/6-31+G(d,p)-optimized geometries[7a]). The incidence of stereoelectronic factors was analyzed by using the natural bond orbital method (NBO).[7b]

Results and Discussion

(a) Reactivity of Prenylamines in the Presence of a Stoichiometric Amount of Thiol. A series of amines bearing only one allylic chain was selected to investigate the reaction mechanism (Figure 2).

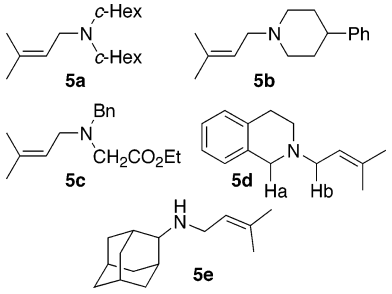
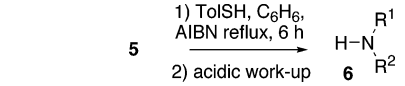


Figure 2.

Table 1. Deprenylation of Tertiary and Secondary Amines



substrate	product	yield, %
5a	**6a**	97,[a] 64[b]
		79[e]
		98[c]
5b	**6b**	77[a]
		57[d]
5c	**6c**	57[a]
5d	**5d**	25% recovery[a]
5e	**6e**	98[a]

[a] TolSH, 1.2 equiv. [b] *hν*, room temperature. [c] TolSH, 0.1 equiv. [d] TolSH, 0.2 equiv. [e] TolSH, 1.2 equiv, CH_3CN, reflux.

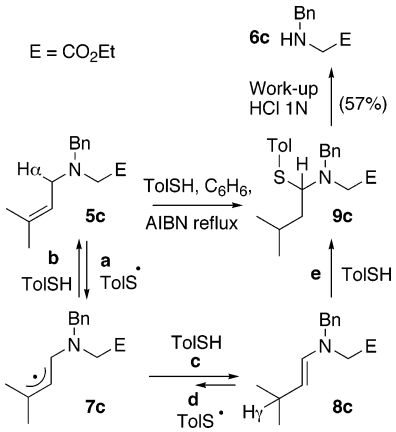
Reactions using a stoichiometric amount of thiol (1.2 equiv) were carried out first. The results are summarized in Table 1 (conditions described in footnote *a*). Yields varied within the range of 57−98%, except for **5d**, which was partially recovered unchanged (25% based on ^{1}H NMR using pentamethylbenzene as internal standard). Most of the starting material was degraded into unidentified products; however, 1,2,3,4-tetrahydroisoquinoline (**6d**) was not detected. In a blank experiment, **6d** was reacted with TolSH (1.2 equiv) in the presence of AIBN for 7 h. Based on the ^{1}H NMR spectrum of the crude mixture, 63% remained unchanged. If ever it had been formed throughout the deprenylation of **5d**, it should have been detected.

It can be noted that the reaction also worked at reflux in acetonitrile (conditions described in Table 1, footnote *e*), and at room temperature under photochemical initiation, but gave lower yields (conditions described in footnote *b*).

As shown in Scheme 2, when **5c** was allowed to react with *p*-thiocresol (1.2 equiv) in the presence of AIBN in benzene at reflux, thioaminal **9c** was identified as the precursor of amine **6c** from the analysis of the ^{1}H NMR spectrum of the crude reaction mixture.[8] This confirmed the validity of the above-

(2) (a) Gigg, R.; Conant, R. *J. Carbohydr. Chem.* **1983**, *1*, 331. (b) Mori, M.; Ban, Y. *Chem. Pharm. Bull.* **1976**, *24*, 1992. (c) Moreau, B.; Marquet, A. *Tetrahedron Lett.* **1977**, *30*, 2591. (d) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224. (e) Laguzza, B. C.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 1483. (f) Mitsudo, T.-A.; Zhang, S.-W.; Satake, N.; Kondo, T.; Watanabe, Y. *Tetrahedron Lett.* **1992**, *33*, 5533. (g) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781. (h) Picq, D.; Cottin, M.; Anker, D.; Pacheco, H. *Tetrahedron Lett.* **1983**, *24*, 1399. (i) Carless, H. A. J.; Haywood, D. J. *J. Chem. Soc., Chem. Commun.* **1980**, 980. (j) Tomori, H.; Shibutami, K.; Ogura, K. *Heterocycles* **1997**, *44*, 213. (k) Hubert, A. J.; Moniotte, P.; Goebbels, G.; Warin, R.; Teyssie, P. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1954. (l) Barolo, P.; Rossi, P. F. *Ann. Chim. (Rome)* **1969**, *59*, 268. (m) Hubert, A. J.; Georis, A.; Warin, R.; Teyssié, P. *J. Chem. Soc., Perkin Trans. 2* **1972**, 366. (n) Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1978**, *100*, 3949. (o) Yamamoto, A.; Kitazume, S.; Pu, L. S.; Ikeda, S. *J. Am. Chem. Soc.* **1971**, *93*, 371. (p) Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **1998**, *39*, 4679. For the catalytic isomerization of *N*-allylamines, see also: (q) Novak, B. M.; Cafmeyer, J. T. *J. Am. Chem. Soc.* **2001**, *123*, 11083.
(3) (a) De Riggi, I.; Gastaldi, S.; Surzur, J.-M.; Bertrand, M. P.; Virgili, A. *J. Org. Chem.* **1992**, *57*, 6118. (b) De Riggi, I.; Nouguier, R.; Surzur, J.-M.; Bertrand, M. P.; Jaime, C.; Virgili, A. *Bull. Soc. Chim. Fr.* **1993**, *130*, 229. (c) Bertrand, M. P.; De Riggi, I.; Lesueur, C.; Gastaldi, S.; Nouguier, R.; Jaime, C.; Virgili, A. *J. Org. Chem.* **1995**, *60*, 6040. (d) Bertrand, M. P.; Gastaldi, S.; Nouguier, R. *Tetrahedron Lett.* **1996**, *37*, 1229. (e) Lesueur, C.; Nouguier, R.; Bertrand, M. P.; Hoffmann, P.; De Mesmaeker, A. *Tetrahedron* **1994**, *50*, 5369. (f) Bertrand, M. P.; Lesueur, C.; Nouguier, R. *Carbohydrate Lett.* **1995**, *1*, 393. (g) Bertrand, M. P.; Gastaldi; S.; Nouguier, R. *Tetrahedron* **1998**, *54*, 12829. (h) Nouguier, R.; Gastaldi, S.; Stien, D.; Bertrand, M.; Renaud, P. *Tetrahedron Lett.* **1999**, *40*, 3371.
(4) For general reviews, see: (a) Bertrand, M. P.; Ferreri, C. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 485−503. (b) Chatgilialoglu, C.; Bertrand, M. P.; Ferreri, C. In *S-Centered Radicals*; Alfassi, Z. B., Ed.; Wiley: Chichester, 1999; pp 312−354. (c) Crich D. In *Organosulfur Chemistry*; Page, P., Ed.; Academic Press: London, 1995; Vol. 1, pp 49−88. (d) Chatgilialoglu, C.; Guerra, M. In *Supplement S: The Chemistry of Sulphur-Containing Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1993; pp 363−394.
(5) Bertrand, M. P.; Escoubet, S.; Gastaldi, S.; Timokhin, V. I. *J. Chem. Soc., Chem. Commun.* **2002**, 216.
(6) Gastaldi, S. Thesis, Marseille, 1997.
(7) (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.11.4; Gaussian, Inc.: Pittsburgh, PA, 1998. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

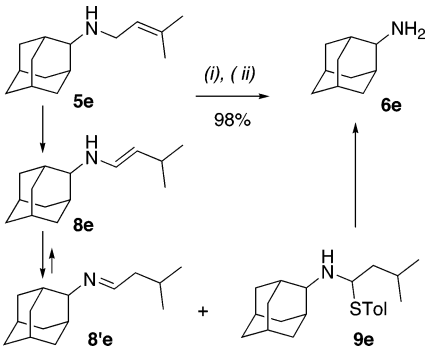
Scheme 2



mentioned hypothesis, according to which *p*-TolS• radical would abstract an allylic hydrogen atom from **5c** to form radical **7c**, stabilized by the delocalization of both the π-system and the nitrogen lone pair (step **a**).[9] The first step might be reversible. According to literature data,[10,11] the forward reaction would be slightly exothermic (ΔH_{298}(S−H) = 354.9 ± 4.1 kJ mol^{-1},[10a] ΔH_{298}(C−Hα) = 345.6 ± 3.3 kJ mol^{-1} [11]). The subsequent reverse transfer of a hydrogen atom from the thiol, back to the carbon-centered radical, would lead to the most stable olefin, i.e., the enamine **8c**.

It is important to point out that the two hydrogen atom transfers involved in the above mechanism benefit from favorable polar effects since the electrophilic sulfur-centered radical generates a nucleophilic carbon-centered radical in step **a**, and vice versa in step **c**. In this reaction, the thiyl radical acts as an "acidic polar reversal catalyst" as defined by Roberts.[12] Although thiols are known as being excellent hydrogen atom donors,[4,13] the reverse reaction, i.e., hydrogen abstraction by thiyl radicals, is involved in biologically important processes,[14,15] and has given rise recently to useful synthetic applications.[16] The addition of thiols to enamines is a well-known reaction[17] that would explain the formation of **9c** which is ultimately cleaved upon treatment.[18]

Scheme 3[a]



[a] Reagents and conditions: (i) TolSH, 1.2 equiv, AIBN, C_6H_6, 6 h reflux; (ii) Purolite 150.

The mechanism is general; it applies to all the tertiary amines in the series. Owing to the greater stability of the enamine, the reaction should be displaced toward **8**, provided a balance is found between the S−H BDE and the two C−H BDEs. In an ideal situation, the S−H bond should be stronger than the C−Hα bond but weaker than the C−Hγ bond. If such were not the case, then the absence of recovered starting material would imply that the addition of the thiol to the enamine plays a crucial role in displacing the equilibrium through the consumption of **8**, leading to **9**.

As exemplified with **5e**, the same experimental conditions apply to secondary amines. However, the latter results in a primary amine (**6e**) which is less easy to recover after acid−base workup. A treatment on ion-exchange resin led to a significant improvement in the yield of **6e**. It is noteworthy that the cleavage of **5e** proceeds through the isomerization of enamine **8e** into the corresponding imine **8′e** (Scheme 3). The only intermediates detected in this case from the ^{1}H and ^{13}C NMR spectra of the crude mixture were imine **8′e** and thioaminal **9e** [the characteristic signals of the functional group

(8) **9c** was characterized by the signal of the proton α to the heteroatoms at 4.50 ppm (dd, J = 7.6 and 6.0 Hz) and by the signal of the functional carbon at 76.6 ppm. Similarly, thioaminal **9b** was formed from **5b** and characterized by signals at 4.26 ppm (t, J = 7.5 Hz) and 82.0 ppm from the ^{1}H and ^{13}C NMR spectra of the crude reaction mixture before acidic workup.

(9) Alternatively, an electron transfer from the amine to *p*-TolS• followed by the abstraction of a proton α to nitrogen in the resulting radical cation might also explain the formation of **7c**.

(10) For theoretical discussions and recent measurements, see: (a) Borges dos Santos, R. M.; Muralha, V. S. F.; Correia, C. F.; Guedes, R. C.; Costa Cabral, B. J.; Martinho Simoes J. A. *J. Phys. Chem. A* **2002**, *106*, 9883. (b) Chandra, A. K.; Nam, P.-C.; Nguyen, M. T. *J. Phys. Chem. A* **2003**, *107*, 9182. For earlier reports, see: (c) Denisov, E. T. *Russ. J. Phys. Chem. (Engl. Transl.)* **1996**, *70*, 238. (d) McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493. (e) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1982**, *47*, 3224. (f) Zavitsas, A. A.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **1995**, *117*, 10645 and refs cited therein. (g) Janousek, B. K.; Reed, K. J.; Braumann, J. I. *J. Am. Chem. Soc.* **1980**, *102*, 3125. For additional critical analysis of various calculations methods, see also: (h) Yao, X.-Q.; Hou, X.-J.; Jiao, H.; Xiang, H.-W.; Li, Y.-W. *J. Phys. Chem. A* **2003**, *107*, 9991. (i) Johnson, E. R.; Clarkin, O. J.; DiLabio, G. A. *J. Phys. Chem. A* **2003**, *107*, 9953. (j) Feng, Y.; Wang, J.-T.; Huang, H.; Guo, Q.-X. *J. Chem. Comput. Sci.* **2003**, *43*, 2005. (k) Parkinson, C. J.; Mayer, P. M.; Radom, L. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2305.

(11) Dombrowski, G. W.; Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R. *J. Org. Chem.* **1999**, *64*, 427.

(12) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25.

(13) *Sulfur-Centered Reactive Intermediates in Chemistry and Biology*; Chatgilialoglu, C., Asmus, K.-D., Eds.; NATO ASI Series; Plenum Press: New York, 1990.

(14) For selected representative studies, see: (a) Pogocki, D.; Schöneich, C. *Free Radicals Biol. Med.* **2001**, *31*, 98. (b) Robins, M. J.; Ewing, G. J. *J. Am. Chem. Soc.* **1999**, *121*, 5823. (c) Silva, D. J.; Stubbe, J.; Samano, V.; Robins, M. J. *Biochemistry* **1985**, *24*, 754. (d) Zhao, R.; Lind, J.; Merenyi, G.; Eriksen, T. E. *J. Chem. Soc., Perkin Trans. 2* **1997**, 569. (e) Schöneich, C.; Asmus, K. D.; Von Bruchhausen, F. *Biochem. Biophys. Res. Commun.* **1989**, *161*, 113. (f) Nauser, T.; Schöneich, C. *J. Am. Chem. Soc.* **2003**, *125*, 2042. (g) Ferreri, C.; Constantino, C.; Perrotta, L.; Landi, L.; Mulazzani, Q. G.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **2001**, *123*, 4459. (h) Ferreri, C.; Constantino, C.; Faraone M. M. R.; Formisano, C.; Landi, L.; Chatgilialoglu, C. *Free Radicals Biol. Med.* **2002**, *33*, 1516.

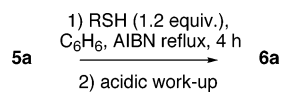
(15) (a) Rauk, A.; Armstrong, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 4185. (b) Rauk, A.; Armstrong, D. A.; Berges, J. *Can. J. Chem.* **2001**, *79*, 405. (c) Rauk, A.; Armstrong, D. A.; Fairlie, D. P. *J. Am. Chem. Soc.* **2000**, *122*, 9671. (d) Rauk, A.; Yu, D.; Armstrong, D. A. *J. Am. Chem. Soc.* **1998**, *120*, 8848. (e) Rauk, A.; Yu, D.; Armstrong, D. A. *J. Am. Chem. Soc.* **1997**, *192*, 208.

(16) (a) Dang, H.-S.; Roberts, B. P.; Sekhon, J.; Smits, T. M. *Org. Biomol. Chem.* **2003**, 1330. (b) Dang, H.-S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1161. (c) Cai, Y.; Dang, H.-S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2449. (d) Roberts, B. P.; Smits, T. M. *Tetrahedron Lett.* **2001**, *42*, 3663. (e) Dang, H.-S.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2452. (f) Roberts, B. P.; Smits, T. M. *Tetrahedron Lett.* **2001**, *42*, 137. (g) Dang, H.-S.; Roberts, B. P. *Tetrahedron Lett.* **2000**, *41*, 8595. (h) Dang, H.-S.; Roberts, B. P. *Tetrahedron Lett.* **1999**, *40*, 8929. (i) Dang, H.-S.; Roberts, B. P. *Tetrahedron Lett.* **1999**, *40*, 4271. (j) Dang, H.-S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, *67*. (k) Dang, H.-S.; Roberts, B. P. *J. Chem. Soc., Chem. Commun.* **1998**, 1145. (l) Dang, H.-S.; Roberts, B. P. *Tetrahedron Lett.* **1995**, *36*, 3731.

(17) Lawesson, S.-O.; Jakobsen, H. J.; Larsen, E. H. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 461.

(18) An intramolecular example of such a radical−polar crossover reaction, competing with thiyl radical cyclization, had been reported in an early work; see: Kaafarani, M.; Crozet, M. P.; Surzur, J.-M. *Bull. Soc. Chim. Fr.* **1987**, 885.

Table 2. Influence of the Nature of the Thiol on the Deprenylation of **5a**



RSH	TolSH	MeO_2CCH_2SH	*n*-OctylSH
conversion, %	100	78	57
pK_a[a]	6.5	7.8	10.9
$\Delta H°_{298}$(S−H),[b] kJ mol^{-1}	354.9[10a] ± 4.1		370.7[10g] ± 8.4
$\Delta H°_{298}$(S−H), kJ mol^{-1}	318.2[c] 339.1[d]	366.8[c]	351.1[c] 360.9[d]

[a] Solvent H_2O (cf. ref 10d; 10.9 refers to *n*-BuSH). [b] Experimental values, cf. refs 10a−g (370.7 kJ mol^{-1} refers to EtSH). [c] ZPE-corrected values calculated with the Gaussian-98 molecular orbital package (UB3LYP/6-311++G(3df,3pd)//UB3LYP/6-31+G(d,p)); the value for *n*-OctylSH refers to the value calculated for *n*-BuSH. [d] Values calculated at the G3MP2 level.

appear at 4.19 ppm (br t, $J = 6.2$ Hz) and 74.8 ppm for **9e**; and at 7.70 ppm (t, $J = 4.8$ Hz) and 162 ppm for **8′e**].

(b) Influence of the Nature of the Thiol, and of Its Use in Catalytic Amounts. The influence of the nature of the thiol was investigated through a series of comparative experiments carried out on amine **5a**. In this particular case, in the presence of a stoichiometric amount of thiol, none of the intermediate **8a** or **9a** could be identified from the crude mixture before workup. The instability of thioaminal **9a** is possibly related to the steric bulk of the two cyclohexyl groups: a significant amount of dicyclohexylamine (**6a**) is formed directly in the reaction medium, possibly because of residual water in the solvent. The conversion was determined from the ^{1}H NMR analysis of the crude mixture.[19] The results obtained with *p*-TolSH, $HSCH_2CO_2Me$, and *n*-OctylSH are reported in Table 2. All the experiments were carried out in refluxing benzene under strictly identical conditions, and the crude reaction mixture was analyzed in all cases after 4 h. Only the reaction performed with *p*-thiocresol went to completion within 4 h. The conversion was 78% in the presence of methyl thioglycolate; it was even lower (57%) when *n*-octanethiol was used.

The conversion correlates to the pK_a of the thiol: the more acidic the thiol, the higher the conversion, as if the addition of the thiol to the enamine was an important factor for the reaction to reach completion. However, the pK_a is not the only parameter varying in the series, since there is a concomitant change in the S−H bond dissociation energy (calculated and experimental BDEs are reported in Table 2). Hydrogen atom transfers are sensitive to enthalpic effects: the stronger the S−H bond, the faster step **a**. The drawback is that at the same time, step **c** should be slowed (cf. Scheme 2). Whenever there is no kinetic limitation, and if the enamine is stabilized enough compared to the parent allylic amine, the same results should be obtained whatever the amount of thiol (stoichiometric or catalytic). Comparative results are reported in Table 1 (conditions described in footnotes *c* and *d*) for *p*-thiocresol-mediated reactions. The yields are quite similar under both sets of experimental conditions. In the presence of a catalytic amount of thiol, the presence of enamines **8a** and **8b**, originating from **5a** and **5b**, could be detected in 56% and 50% yield, respectively, in the crude mixture before hydrolysis. Yields were determined by

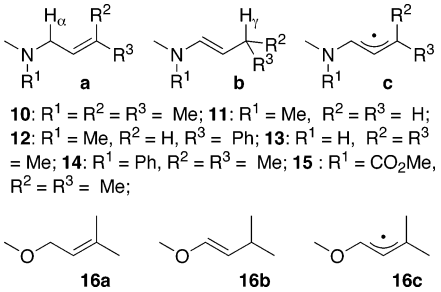


Figure 3.

^{1}H NMR in the presence of pentamethylbenzene as internal standard. They are based on the characteristic signals of the vinylic proton β to nitrogen (**8a**, dd, $J = 6.8$ and 14.0 Hz at 4.10 ppm; **8b**, dd, $J = 7.4$ and 14.1 Hz at 4.53 ppm).

It must be noted that the reaction of **5a** with a stoichiometric amount of either methyl thioglycolate or *n*-octanethiol reached completion after heating in the presence of AIBN for 7 h (95% yield). In contrast, the corresponding catalytic reactions led to much lower yields [recovered **5a** (43%), **6a** (35%) with methyl thioglycolate (0.2 equiv); recovered **5a** (60%), **6a** (40%) with *n*-OctylSH (0.2 equiv); all the yields are based on ^{1}H NMR using pentamethylbenzene as internal standard, after 7 h at reflux].

(c) Theoretical Support: DFT Calculations of C−Hα and C−Hγ BDEs, and NBO Calculations. The experimental results were supported by DFT calculations. For a series of selected model compounds (Figure 3), calculations were performed on the enamines and on the parent allylic amines. Additional calculations of the corresponding delocalized radicals were also carried out in order to determine the C−Hα and C−Hγ bond dissociation energies for each structure. The C−Hα BDEs in various amines, and consequently the radical stabilization energies (RSE) of the corresponding radicals, have been recently determined by photoacoustic calorimetry, and the experimental results were corroborated by theoretical calculations.[11,20] Numerous studies have been devoted to C−H BDEs in α-amino acid derivatives and peptides due to their incidence in biological processes.[15] Only one recent article was found concerning specifically *N*-benzyl- and *N*-allylamines.[11]

An experimental value of 345.6 ± 3.3 kJ mol^{-1} at 295 K has been reported for the C−Hα BDE in triallylamine.[11] A value of 323.8 kJ mol^{-1} was calculated for *N*,*N*-dimethyl-allylamine.[11] For the sake of homogeneity, we have performed DFT calculations on the whole series. The comparative data using two different basis sets for single-point energies are summarized in Tables 3 and 7. Geometry optimization was conducted without any constraint using the UB3LYP/6-31+G(d,p) method. Zero-point energies and temperature corrections were calculated using the specified scaling factor (0.9804).

The most stable conformations of amines **10a** and **13a** correspond to the antiparallel orientation of the nitrogen lone pair and the C−Hα bond to be cleaved. Such is not the case for **11a** and **12a**. Owing to the negligible energy difference between the most stable conformer and the antiparallel arrangement in these two particular cases (1.5 and 1.6 kJ mol^{-1},

(19) The ratio was determined from the ^{1}H NMR spectrum. It is based on the signal of the vinylic proton in **5a** (t at 5.17 ppm) and the total integration of the protons of the cyclohexyl moiety α to nitrogen (tt at 2.55 ppm).

(20) (a) Wayner, D. D. M.; Clark, K. B.; Rauk, A.; Yu, D.; Armstrong, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 8925. (b) Lalevée, J.; Allonas, X.; Fouassier, J.-P. *J. Am. Chem. Soc.* **2002**, *124*, 9613. For earlier reports, see references cited therein.

Table 3. Calculated Total Energies (*E*) for Allylic Amines, Enamines, and the Corresponding Radicals; C−Hα and C−Hγ BDEs (ZPE Corrected); ΔH, ΔG at 298 K

	UB3LYP/6-31+G(d,p)				UB3LYP/6-311++G(3df,3pd)//UB3LYP/6-31+G(d,p)				
structure	E^a	$BDE_{298}{}^b$	$\Delta H_{298}{}^b$	$\Delta G_{298}{}^b$	E^a	$BDE_{298}{}^b$	$\Delta H_{298}{}^b$	$\Delta G_{298}{}^b$	$BDE_{298}^{corr}{}^d$
10a	−330.53199	307.9	−19.6	−17.5	−330.61996	301.2	−21.0	−18.9	328.5
10b	−330.53987	327.5			−330.62835	322.2			340.6
10c	−329.90403				−329.99254				
11a	−251.88895	303.3[c]	−39.7	−39.4	−251.95775	296.9	−40.7	−40.4	324.2
11b	−251.90426	343.0[c]			−251.97344	337.6			356.0
11c	−251.26276				−251.33199				
12a	−482.96290	298.2	−16.0	−16.5	−483.08992	291.5	−17.8	−18.3	318.8
12b	−482.96920	314.2			−483.09689	309.3			327.7
12c	−482.33922				−482.46681				
13a	−291.22210	307.0	−21.0	−17.8	−291.30075	300.6	−22.3	−19.1	327.9
13b	−291.23025	328.0			−291.30938	322.9			341.3
13c	−290.59399				−290.67309				
14a	−522.28462	309.4	−16.3	−21.8	−522.42221	304.2	−16.4	−21.9	331.5
14b	−522.29173	325.7			−522.42936	320.6			339.0
14c	−521.65663				−521.79422				
15a	−519.12389	311.6	−9.7	−4.6	−519.27592	306.3	−11.0	−5.9	333.6
15b	−519.12787	321.3			−519.28041	317.3			335.7
15c	−518.49315				−518.64522				
16a	−311.08432	326.5	−3.7	−1.6	−311.17278	321.3	−4.4	0.9	348.6
16b	−311.08638	330.2			−311.17510	325.7			344.1
16c	−310.44909				−310.53753				

[a] In hartrees. [b] In kJ mol^{-1}. [c] C−Hα BDE = 301.5 kJ mol^{-1}, and C−Hγ BDE = 342.8 kJ mol^{-1} at the UB3LYP/6-31G(d) level. [d] Isodesmic corrections (see text).

respectively), and to the low rotational barrier around the C−N bond,[21] the values reported in Table 3 refer in all cases to the antiparallel conformers for the sake of homogeneity.

DFT methods are known to be more reliable for relative BDE calculations than for absolute BDE calculations. Accurate BDEs could not be anticipated; therefore, the BDEs are underestimated. The underestimation can be as high as 40−60 kJ mol^{-1}.[10j] If one compares the value of the C−Hα BDE calculated for *N*,*N*-dimethyl-allylamine (**11a**) to the value measured for triallylamine,[11] it can be noted that the DFT calculations performed at the UB3LYP/6-31+G(d,p) level underestimate the BDE by 42.3 kJ mol^{-1}. As shown in Table 3, the use of a smaller basis set, i.e., 6-31G(d), does not lead to significant changes in the BDE values. The use of the larger basis set (6-311++G(3df,3pd)) to calculate single-point energies increases the gap with respect to the experimental value. However, more reliable relative values should be anticipated from the larger basis set including diffuse functions.[10j]

As mentioned previously, the only experimental value that could be taken as a reference is that of the C−Hα BDE in triallylamine.[11] To our knowledge, no value can be found in the literature for the C−Hγ BDE. Isodesmic corrections based on the reactions in eqs 2 and 3 were applied.

$$R{-}H + (CH_2{=}CHCH_2)_2N\dot{C}HCH{=}CH_2 \rightarrow R^{\bullet} + (CH_2{=}CHCH_2)_2NCH_2CH{=}CH_2 \quad (2)$$

$$R{-}H + (CH_2{=}CHCH_2)_2NCH{=}CH\dot{C}H_2 \rightarrow R^{\bullet} + (CH_2{=}CHCH_2)_2NCH{=}CHCH_3 \quad (3)$$

The BDEs evaluated from G3MP2 calculations for both C−Hα in triallylamine (339.6 kJ mol^{-1}, 6 kJ mol^{-1} below the experimental value) and C−Hγ (357.4 kJ mol^{-1}) in the corresponding enamine were used as benchmarks. The same BDEs calculated at the UB3LYP/6-311++G(3df,3pd) level (312.3 and 339.0 kJ mol^{-1}, respectively) were used to determine the corresponding corrective terms. Therefore, 27.3 and 18.4 kJ mol^{-1} were added to the BDEs determined at the UB3LYP/6-311++G(3df,3pd) level of theory for C−Hα and C−Hγ, respectively.

The DFT calculations at the UB3LYP/6-311++G(3df,3pd) level that are reported in Table 2 also underestimate the S−H BDE in *p*-thiocresol by 36.7 kJ mol^{-1}. This observation is consistent with the most recent reports on the subject that issued while this work was in progress.[10a,h−j] Owing to the similarity in the difference between the experimental and the calculated values for both *p*-thiocresol and the amines, the following discussion is based strictly on the comparison of corrected C−H BDEs values to the S−H BDE calculated with the G3MP2 method, i.e., 339.1 kJ mol^{-1}.

The solvent effects were evaluated for both **10a**−**c** and **11a**−**c** and *p*-thiocresol using the SCIPCM model using the 6-31+G(d) basis set (Table 4).[22] These values can be compared to the values calculated in the gaseous phase using the 6-31+G(d,p) basis set. It can be noted that the S−H BDE is lowered by 9.9 kJ mol^{-1} in benzene and by 10.4 kJ mol^{-1} in acetonitrile. It is slightly more lowered than the C−H BDEs that are lowered only by 3.1−4.2 kJ mol^{-1} depending on the solvent for C−Hα, and by 3.3−5.7 kJ mol^{-1} for C−Hγ. The effects of solvent were neglected, since the values in Table 4 do not contradict the following discussion based on the relative data in the gaseous phase. Furthermore, the polarizable continuum model may not be a good model to account for specific interactions between

(21) The rotation around the C−N bond is not restricted. A 21.4 kJ mol^{-1} rotational barrier between the two conformers was obtained for **11a** as the difference of the total energies calculated at the B3LYP/6-31G(d) level, corrected for the zero-point, and thermal correction at 298 K. A relaxed 10° stepwise scan around the C−N bond was performed in order to locate the transition-state geometry. The highest energy structure was then fully optimized to obtain the transition-state geometry, which was confirmed by frequency and IRC calculations.

(22) (a) Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem.* **1996**, *100*, 16098. (b) The CPCM model led to results quite similar to the SCIPCM model C−Hα BDE = 308.1 kJ mol^{-1} for **11a**, C−Hγ BDE = 352.2 kJ mol^{-1} for **11b**. The PCM model led to completely divergent data.

Table 4. Solvent Effects on the Computed BDEs at 298 K Using the SCIPCM Model with the 6-31+G(d) Basis Set on Geometries Optimized at the UB3LYP/6-31+G(d,p) Level

compound	solvent	
	benzene	acetonitrile
TolS-H	302.2[a]	301.7
10a C−Hα	304.6	
10b C−Hγ	323.7	
11a C−Hα	300.2	299.1
11b C−Hγ	339.7	337.3

[a] S−H BDE = 312.1 kJ mol^{-1} at the UB3LYP/6-31+G(d,p) level of theory.

benzene and the delocalized reactive species. It is largely admitted that the solvent has little influence on radical reactions. Our results demonstrated that the reaction can work in a solvent more polar than benzene, like acetonitrile (cf. Table 1). The calculations in Table 4 show that the BDEs are not significantly modified by changing the nature of the solvent (it is known from the literature that the experimental value of C−Hα BDE in triethylamine is identical whether it is measured in benzene or in acetonitrile).[20b]

Table 3 contains several points to be discussed. The C−Hα BDE is sightly less sensitive to the nature of the substituent at the terminal carbon of the double bond than the C−Hγ BDE. It varies in a rather narrow range (318.8−333.6 kJ mol^{-1} at 298 K). The calculated values for the *N*-allylamine **11a** and for the *N*-prenylamine **10a** are rather similar: their difference is about 4 kJ mol^{-1}. The comparison of **10a** to **13a** shows that the additional methyl group at nitrogen in **10a** does not have a significant influence either. This observation is consistent with the data recently reported for saturated aliphatic amines.[20] The BDE is only slightly lowered in the cinnamyl derivative **12a**. Conversely, the delocalization of the lone pair due to the presence of a phenyl group (**14a**), or to the electron-withdrawing methoxycarbonyl group (**15a**), results in an increase in the C−Hα BDE by 3.0 or 5.1 kJ mol^{-1}, respectively.

Regarding the C−Hγ BDE, it varies within a larger range (327.7−356.0 kJ mol^{-1}). The influence of the substituent at Cγ is predominant. The tertiary C−Hγ BDE is weaker than the primary one by 15.4 kJ mol^{-1} (cf. **10b** and **11b**). The phenyl group in **12b** results in the weakening of the C−Hγ BDE by 12.9 kJ mol^{-1} compared to that in **10b**. Comparatively, the phenyl group in **14b**, like the methoxycarbonyl group in **15b**, has nearly no effect on the C−Hγ BDE with respect to the same reference.

The substitution affects the overall exothermicity of the isomerization process (Table 3). It can be noted that, according to the calculations, if the reactions were thermodynamically controlled, all the isomerizations in the series should be total except for that of ether **16a**.

Additional information is given by the comparison of the C−H bond dissociation energies to the S−H bond dissociation energies. As exemplified by amines **10a** and **13a**, which are tertiary and secondary amines, the calculations indicate that the corresponding enamines are more stable than the parents amines by 21.0 and 22.3 kJ mol^{-1}, respectively. According to the calculated values in Tables 2 and 3, *p*-TolS$^{\bullet}$ is able to abstract Hα, and the subsequent return hydrogen transfer leads irreversibly to the enamine (the first step is far more exothermic than the second step, which is nearly thermoneutral according to gaseous-phase calculations).[23] Thus, a catalytic amount of thiol is formally sufficient for the isomerization to proceed with complete conversion, which was confirmed experimentally. If the solvent effects were taken into account, one would expect the first hydrogen abstraction to be slowed, and the second one to be accelerated.

Table 5. Hyperconjugative Effects Affecting the C−Hα Bond, and Bond Lengths Determined by the NBO Method for the Lowest Energy Conformers Calculated at the UB3LYP/6-311++G(3df,3pd)//UB3LYP/6-31+G(d,p) Level

model compound		$n \rightarrow \sigma^*_{C-H}$[a]	$\pi_{C=C} \rightarrow \sigma^*_{C-H}$[a]	d_{C-H}[b]
10a		34.3	<2	1.109
11a		36.1	10.3	1.112
12a		35.9	10	1.112
13a		30.3	<2	1.107
14a	H_α	6.5	13.3	1.096
	$H_{\alpha'}$	11.6	<2	1.095
15a	H_α	12.1	8.6	1.098
	$H_{\alpha'}$	3.2	<2	1.089
16a	n_1	24	11.5	1.105
	n_2	3.3		
5d	H_a	34.1	13.4	1.113
	H_b	32.2	<2	1.109
25a		<2	<2	1.097
26a		36.4	<2	1.110
27		29.0	14.8	1.112

[a] Stabilization energies in kJ mol^{-1}. [b] In Å.

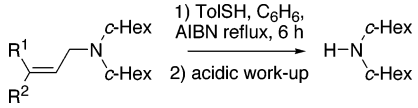
The data in Table 3 also corroborate the observed influence of the nature of the thiol. According to G3MP2 calculations, the S−H BDE in the alkanethiol (*n*-OctylSH) is about 20.3 kJ mol^{-1} stronger than the C−Hγ bond in **10b**. Step **a** should be accelerated but, conversely, step **c** should be slowed; the enthalpic effect plays in favor of the backward step (**d**) (cf. Scheme 2). This would account for the slower conversion of **5a** reported in Table 2 for the stoichiometric reaction. The rate of step **c** would be too slow in the presence of a catalytic amount of *n*-OctylSH.

The optimized preferred conformations of model compounds were analyzed with the natural bond orbitals method,[7b] included in the Gaussian-98 package (NBO 3.1), to determine the incidence of stereoelectronic effects on the abstraction of Hα. Results are given in Table 5.

The approach to the reactivity through the localized orbitals model corroborates quite well the C−Hα BDEs determined through the DFT calculations at the UB3LYP/6-311++G(3df,3pd)//UB3LYP/6-31+G(d,p) level. The lowest energy conformers are stabilized mainly by two orbital overlaps, i.e., the overlap between the nitrogen lone pair and the σ^*_{C-H} orbitals, and the overlap between the $\pi_{C=C}$ and the σ^*_{C-H} orbitals. Both effects play a major role in the weakening of the C−Hα bond. The failure to cleave the allylic C−H bond in **5d** (Figure 2) is also consistent with the theoretical calculations. In this case the benzylic bond (C−Ha) is slightly weaker than the allylic bond (C−Hb) (C−Ha BDE = 302.3 kJ mol^{-1}, C−Hb BDE = 305.5 kJ mol^{-1} at the UB3LYP/6-311++G(3df,3pd)//UB3LYP/6-31+G(d,p) level). The abstraction of Ha is favored, because this transfer benefits from particularly favorable stereoelectronic effects, the axial hydrogen atom to be abstracted being ideally predisposed in space. As shown in Table 5, the

(23) Heating at 80 °C has little incidence. At 353 K, the C−Hα BDE in **10a** is 301.3 kJ mol^{-1}, the C−Hγ BDE is 322.2 kJ mol^{-1} (at the UB3LYP/6-311++G (3df, 3pd) level), and the S−H BDE in *p*-thiocresol is changed by less than 1 kJ mol^{-1}.

Table 6. Influence of the Structure of the Allylic Group



substrate		product	yield (%)
17a	$R^1 = H$ $R^2 = H$	**6a**	63[a] 76[b]
18a	$R^1 = H$ $R^2 = Me$	**6a**	95[a]
19a	$R^1 = H$ $R^2 = Ph$	**6a**	70[a]

[a] TolSH, 1.2 equiv. [b] TolSH, 0.15 equiv.

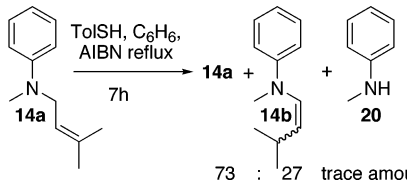
delocalization of the lone pair in the σ^*_{C-Ha} localized orbital stabilizes the system by 34.1 kJ mol^{-1}. Furthermore, the delocalization of the adjacent double bond in the aromatic ring induces an additional stabilization by 13.4 kJ mol^{-1}. Stereoelectronic factors are less favorable to the abstraction of Hb. The observed degradation of **5d** might arise from the oxidation of the benzylic radical resulting from the abstraction of Ha.

The efficient deprenylation of **5c**, which as compared to **5d** is also a benzylic amine but an open-chain one, might appear surprising in the light of the above comments. However, it is known from the literature[11] that benzylic stabilization of α-amino radicals (from tertiary amines) results in an unfavorable interaction between the *ortho*-phenyl hydrogens and the syn substituent at nitrogen. Steric strain is relieved by rotation around the N−C$^\bullet$ or the C_{Ph}−C$^\bullet$ bond which, as a consequence, diminishes the radical stabilization and increases slightly the α-C−H BDE (calculations at the UHF/6-31+G* level performed on the benzylic radical derived from benzyl dimethylamine have shown that the aromatic ring is fully conjugated with the radical center while the lone pair is nearly orthogonal).[11] Therefore, the experimental results reported for **5c** and **5d** are not contradictory. These results are rather consistent with the regioselectivity in the photochemical addition of acyclic and cyclic benzylic amines to stilbene.[24]

(d) Influence of the Nature of the Allylic Chain. Additional experiments were carried out on amines **17a**−**19a** in order to determine if the cleavage could occur with other allylic chains. These isomerizations were performed with *p*-TolSH as mediator. The results are given in Table 6.

In agreement with the calculations, the *N*-allyl derivative **17a** behaved similarly to the prenyl derivative **5a** (Table 1) under both stoichiometric and catalytic conditions. However, it can be underlined that longer reaction times were needed to reach completion (6 h compared to 4 h for **5a**) and the unoptimized yields were lower. This statement is rather surprising in light of the calculations performed on **10a**−**c** and **11a**−**c**. The crotyl derivative **18a** led to **6a** in high yield. The *N*-cinnamyldicyclohexylamine (**19a**) led to slightly lower yields. This is in agreement with the calculations performed on **12a**−**c**, since the second hydrogen transfer, which in this particular case would be slightly endothermic, is likely to slow the chain process.

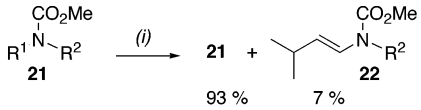
(e) Influence of the Substituents at Nitrogen. The result obtained with the aniline derivative **14a** (eq 4) is somewhat puzzling with respect to the calculated BDEs. After a 7 h run under stoichiometric conditions, the analysis of the crude mixture by ^{1}H NMR allowed us to determine a 73:27 ratio of **14a**:**14b**. The aniline **20** was detected in a trace amount.[25] Longer reaction times did not improve the conversion.



(4)

The C−Hα BDE in **14a** is 331.5 kJ mol^{-1}. It is stronger than any of the C−Hα BDEs in the amines **10a**−**13a**, and it is only slightly weaker than in that carbamate **15a** (cf. Table 3). This can be rationalized by looking at the preferred conformation of **14a**, which shows that none of the allylic protons benefit from favorable overlaps with the lone pair and the double bond simultaneously (cf. Table 5). Furthermore, the preferred conformation of radical **14c** shows that, owing to steric interactions, the phenyl ring is twisted and brings little additional stabilization to the radical (there is a 26.5° dihedral angle between the plane of the delocalized radical and the aromatic ring). Both hydrogen transfers (steps **a** and **c**) would be too slow for the isomerization to proceed efficiently. In addition, it can be emphasized that the basicity of the enamine is also weaker, and this would prevent its consumption through the addition of *p*-thiocresol.

The influence of an electron-withdrawing substituent was then investigated. As exemplified in eq 5, when carbamate **21** was reacted with *p*-thiocresol in the presence of AIBN, 93% of the substrate remained unchanged and only 7% of the corresponding enamide **22** was formed.[26] The related BOC-protected amine remained totally unchanged under the same experimental conditions.



(5)

R^1 = -$CH_2CH{=}C(Me)_2$; R^2 = -$(CH_2)_2Ph$

(i) TolSH (1.2 equiv.), C_6H_6, AIBN reflux, 7 h.

According to the calculations performed on carbamate **15a**, the C−Hα bond is strengthened (BDE = 333.6 kJ mol^{-1}).[27] Again, both hydrogen transfers would be too slow for the isomerization to occur. This would explain why the thiophenol-mediated cyclizations of related 3-aza-1,6-dienes (analogous to **1**) bearing an electron-withdrawing substituent at nitrogen were successful.[28]

(f) Rationalization of the Chemoselectivity. As stated in the Introduction, this study was undertaken after the fortuitous discovery of the cleavage of **1a**,**b**. It must be placed in the

(24) Lewis, F. D.; Ho, T.-I.; Simpson, T. *J. Am. Chem. Soc.* **1982**, *104*, 1924.

(25) **14b** is a mixture of two isomers characterized by the signals of the corresponding vinylic protons β to nitrogen at 5.30 ppm (dd, J = 9.2 and 5.2 Hz) and 5.80 ppm (dd, J = 8.9 and 3.0 Hz), respectively.

(26) Yields were determined from the ^{1}H NMR spectra of the crude mixture, using pentamethylbenzene as internal standard. They are based on the signals of vinylic protons at 5.13 ppm (br t) and at 4.95 ppm (dd, J = 14.2 and 7.4 Hz), assigned to **21** and **22**, respectively.

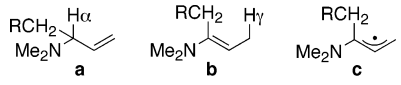
(27) The strengthening of adjacent bonds due to the influence of electron-withdrawing substituents has been reported for thiophenols (ref 10a) and phenols, see: (a) Bordwell, F. G.; Zhang, X.-M.; Satish, A. V.; Cheng, J.-P. *J. Am. Chem. Soc.* **1994**, *116*, 6605. (b) Brigati, G.; Lucarini, M.; Mugnaini, V.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 4828. For toluenes and fluorenes, see: (c) Cheng, J.-P.; Liu, B.; Zhao, Y.; Wen, Z.; Sun, Y. *J. Am. Chem. Soc.* **2000**, *122*, 9987.

(28) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 6199.

Table 7. Calculated Total Energies (*E*) for **25a**,**b** and **26a**,**b**, and the Corresponding Radicals; ΔH and ΔG at 298 K; C−Hα and C−Hβ BDEs (ZPE-Corrected)

	UB3LYP/6-31+G(d,p)				UB3LYP/6-311++G(3df,3pd)//UB3LYP/6-31+G(d,p)				
structure	E^a	$BDE_{298}{}^b$	$\Delta H_{298}{}^b$	$\Delta G_{298}{}^b$	E^a	$BDE_{298}{}^b$	$\Delta H_{298}{}^b$	$\Delta G_{298}{}^b$	$BDE_{298}^{corr\ b,c}$
25a	−366.42828	321.6	−17.8	−19.4	−366.53322	313.6	−19.4	−21.2	340.9
25b	−366.43509	339.4			−366.54064	333.0			351.4
25c	−365.79527				−365.90129				
26a	−291.20787	310.2	−27.9	−30.5	−291.28599	303.3	−29.5	−32.1	330.6
26b	−291.21889	338.1			−291.29763	332.8			351.2
26c	−290.57931				−290.65809				

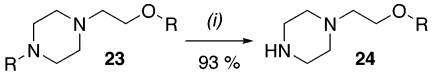
[a] In hartrees. [b] In kJ mol^{-1}. [c] Isodesmic correction.



25 : R = OH; **26** : R = H

Figure 4.

context of the pioneering work of Roberts and co-workers concerning the use of thiols as polarity reversal catalysts.[16] In particular, it is interesting to compare our results to the data reported by this author which concern the isomerization of allylic silyl ethers into silylenol ethers.[29] It is worth noting that, in the case of ethers, the migration of the double bond requires the mediation of C_6F_5SH. We have verified that *p*-thiocresol was inefficient in the case of a simple alkyl prenyl ether. This is not surprising in the light of the calculated C−Hα and C−Hγ BDEs in **16a** and **16b**. The first step is too endothermic to occur, unless a thiyl radical like $C_6F_5S^{\bullet}$, giving rise to a much stronger S−H bond, is used.[29] The overall process is only very slightly exothermic (it is noteworthy that the isodesmic corrections designed for *N*-allylamines and the corresponding enamines are not perfectly adapted to ethers); therefore, under the mediation of *p*-thiocresol, the exothermicity of the second hydrogen transfer would not compensate the endothermicity of the first one. Thus, it is possible to cleave selectively an allylic amine in the presence of an allylic ether, as exemplified by the reaction that was carried out on **23** (eq 6).



(6)

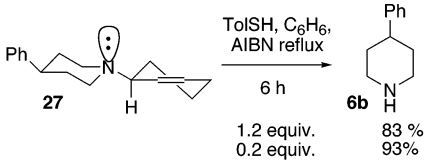
R = -$CH_2CH{=}C(Me)_2$

(i) TolSH (1.2 equiv.), C_6H_6, AIBN reflux, 6 h

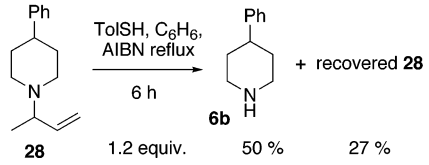
Additional investigations into the effect of branching at the α position were undertaken in order to rationalize the selective cleavage **1a**,**b**. DFT calculations were performed on **25a**−**c** and **26a**−**c** (Figure 4, Table 7). The results show that the substitution at the α-carbon results in the strenghtening of the C−Hα bond (by 16.7 and 6.4 kJ mol^{-1} for **25a** and **26a**, respectively, compared to **11a**). Branching at the α-carbon does not weaken significantly the C−Hγ BDE compared to **11b**. Thus, the α-substitution should prevent the migration of the double bond by increasing the barrier to the abstraction of Hα. The β-oxygen was found experimentally to lower the α-C−H BDE in saturated aliphatic amines by less than 8.4 kJ mol^{-1}, which was considered as negligible.[20b] The important effect observed in **25a** is likely to be due to intramolecular hydrogen bonding, which locks the conformation around the C−N bond. This results in an increase of the C−Hα BDE owing to the absence of hyperconjugative effects, as confirmed by NBO calculations (cf. Table 5).

In all likelihood, a conformational effect is also responsible for the slight strengthening of the C−Hα BDE in **26a**, where the hydroxymethyl group is replaced by a methyl group (taken as a model for a CH_2OR group). As confirmed by NBO calculations, the C−Hα bond suffers no weakening from the delocalization of the vicinal π electrons. The preferred conformation of the *N*,*N*-dimethyl-α-methallylamine (**26a**) is controlled by the minimization of the allylic 1,3-strain. The C−H bond lies in the plane of the double bond. However, according to NBO calculations, the overlap of the σ^*_{C-H} localized orbital with the lone pair stabilizes the system by 36.4 kJ mol^{-1}.

As reported in eqs 7 and 8, comparative experiments have been performed on amines **27** and **28**.



(7)



(8)

The cleavage is far less efficient in the case of the α-methallyl derivative **28** than with **27**. This is quite consistent with the calculations performed on **26a**. The C−Hα BDE reaches a critical value (330.6 kJ mol^{-1}) that was noted previously as an upper limit for the abstraction to have an acceptable rate (cf. **14a**), even though, owing to the exothermicity, the second hydrogen transfer might compensate the first one. This applies to **28**.

Conversely, in the case of **27**, there is a conjunction of favorable stereoelectronic factors, since the σ^*_{C-H} orbital benefits from a maximum overlap with both the lone pair and the double-bond π system (Table 5). Thus, a rather small conformational effect would be responsible for the kinetically controlled chemoselective cleavage of **1a**,**b**.

(g) Reaction Profiles for Hydrogen Transfers from 10a and 11a to *p*-TolS$^{\bullet}$. The last part of this study was devoted to the modeling of the reaction profile for the initial hydrogen abstraction step by *p*-TolS$^{\bullet}$. The calculations were performed on both **10a** and **11a** in order to determine the order of magnitude of the corresponding rate constants. It must be noted

(29) (a) Fielding, A. J.; Roberts, B. P. *Tetrahedron Lett.* **2001**, *42*, 4061. (b) For a closely related method, see: Markovic, D.; Vogel, P. *Org. Lett.* **2004**, *6*, 2693.

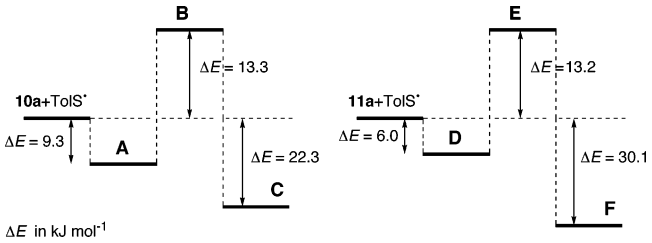


Figure 5. Reaction profiles for TolS•-mediated hydrogen abstractions from **10a** and **11a**.

Table 8. Geometrical Parameters of Stationary Points (Precomplexes, **A** and **D**; Transition States, **B** and **E**; and Products, **C** and **F**)[a]

stationary point	*d*(C–Hα)	*d*(S–H)	∠CHαS	Δ*q*	*L*
A	1.109				
B	1.436	1.598	177	−0.312	1.334
C		1.353			
D	1.112				
E	1.424	1.600	172	−0.305	1.263
F		1.353			

[a] Bond lengths in Å; bond angles in degrees. Charge transfer according to the CHelpG scheme in e⁻.

that the calculations were performed starting from the anti-parallel conformer of **11a**, since as previously stated the rotation around the allylic C−N bond is very fast. After having located the transition states, the relevant activation barriers at 298 K were determined from IRC calculations (vide infra computational details).[30] The energy differences between ZPE-corrected total energies of the optimized stationary points at 298 K are given in Figure 5.[31] The effective activation energies are quite similar for the two model reactions.The geometrical parameters of the stationary points **A**−**F** are given in Table 8. Additional assessment of the reactant- or product-like character of the transition states was made by calculating the parameter *L* (eq 9).[32]

$$L = \frac{r(\mathrm{C{-}H\alpha})^{\mathrm{TS}} - r(\mathrm{C{-}H\alpha})^{\mathrm{pre{-}comp.}}}{r(\mathrm{S{-}H})^{\mathrm{TS}} - r(\mathrm{S{-}H})^{\mathrm{product}}} \qquad (9)$$

In both cases there is a quasi linear arrangement of the three atoms C−H−S in the transition-state structure. The transition state is slightly earlier in the case of **11a**, which is not surprising with regard to the enthalpic effect. The S−H bonds in the TSs are about 0.25 Å longer than in *p*-TolSH, while the C−Hα bond is 0.31−0.32 Å longer than in the amine. The net atomic charges were calculated according to the CHelpG scheme.[33] The noticeable amount of charge transferred from the subtrate to the *p*-TolS• radical is in agreement with the electrophilic behavior of the sulfur-centered radical in the process. However, the charge transfer is almost the same for **11a** and **10a**. One cannot consider that the polar contribution is significantly

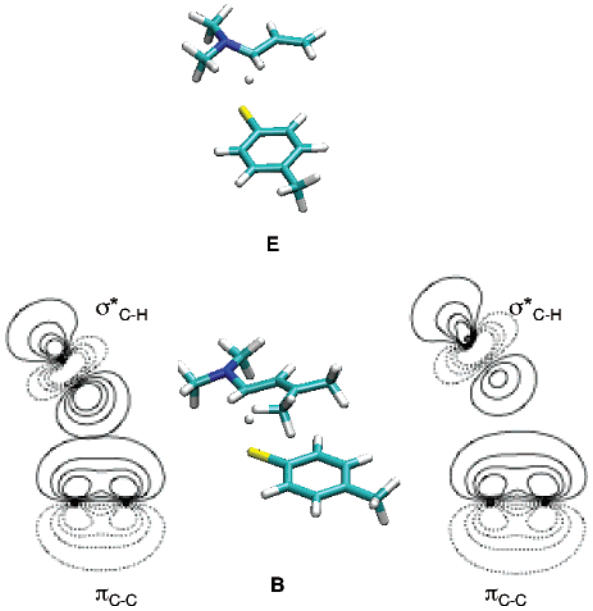


Figure 6. Overlaps between the σ^*_{C-H} orbitals of the *C*-methyl groups and the localized aromatic C=C bonds in transition state **B**.

increased by the presence of two additional methyl groups on the double bond.

Conversely, as shown in Figure 6, there is a dramatic change in the geometry of the transition structure between the two model substrates. This gives evidence for an overlap between the σ^*_{C-H} orbitals of the two methyl fragments and the π orbitals of the aromatic ring localized C=C bonds in the transition structure **B**, which makes it strikingly different from **E**. This overlap was analyzed by the NBO method. The structures of **B** and **E**, and the relevant overlaps in **B**, are shown in Figure 6. It can be noted that, in the latter, the spatial arrangement is not exactly symmetrical with respect to the two $=CCH_2-H$ bonds.

However, the transition state **B** is stabilized by only 1.5 kJ mol^{-1} throughout these interactions. Even though this additional stabilization energy is weak,[34] it accounts for the geometry difference between the transition structures **B** and **E**. We have verified that a geometrical arrangement similar to that of **E** does not correspond to a stationary point for the reaction of *p*-TolS• with **10a**. This interaction might provide a rationale for the slightly faster isomerization of **5a** compared to **17a**.[35]

The calculations allowed us to estimate the rate constants. Assuming $A = 2 \times 10^{10}$ M^{-1} s^{-1} for the abstraction of hydrogen by thiyl radical[31a] would lead to $k_{298} = 9.4 \times 10^7$ M^{-1} s^{-1} (E_a = 13.3 kJ mol^{-1} from Figure 5) for the bimolecular abstraction from **10a**, and $k_{298} = 9.7 \times 10^7$ M^{-1} s^{-1} (E_a = 13.2 kJ mol^{-1}) for the bimolecular abstraction from **11a**. The rate constants for the addition of thiyl radicals to terminal olefins at 298 K range from 4×10^4 M^{-1} s^{-1} (for PhS•) up to 1.9×10^6 M^{-1} s^{-1} (for *t*-BuS•).[36] Even though they might be overestimated, the rate constants for the hydrogen abstraction from allylic amines are quite consistent with the absence of products

(30) (a) Fukui, K. *J. Chem. Phys.* **1970**, *74*, 4161. (b) Heidrich, D. *Understanding Chemical Reactivity; The Reaction Path in Chemistry: Current Approaches and Perspective*; Heidrich, D., Ed; Kluwer Academic Publishers: Dordrecht, 1995; Vol. 16, pp 2−10.
(31) For recent theoretical calculations on hydrogen abstractions by RS•, see: (a) Reid, D. L.; Armstrong, D. A.; Rauk, A.; Von Sonntag, C. *Phys. Chem. Chem. Phys.* **2003**, *5*, 3994. (b) Zipse, H. *Org. Biomol. Chem.* **2003**, *1*, 692.
(32) For calculations referring to hydrogen abstraction by imide-*N*-oxyl radicals, see: Arnaud, R.; Milet, A.; Adamo, C.; Einhorn, C.; Einhorn, J. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1967 and references therein.
(33) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361.
(34) For general reviews on C−H/π interactions, see: (a) Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi Y. *Tetrahedron* **1995**, *51*, 8665. (b) Nishio, M.; Hirota, M. *Tetrahedron* **1989**, *45*, 7201.
(35) In support to the possible impact of C−H/π interactions, when the relative reactivity of **5a** and **17a** was investigated with respect to thioglycolic methyl ester, after 4 h at reflux under standard conditions, the conversion of **5a** to dicylohexylamine was 78%, whereas the conversion of **17a** was total. Prenyl ethers are more rapidly cleaved than allyl ethers in the closely related reaction involving tosyl radicals reported in ref 29b.

resulting from the addition/cyclization sequence in the reaction of *p*-TolS$^{\bullet}$ with diene **1a**,**b** (cf. eq 1).

Conclusion

Thiyl radicals mediate the isomerization of allylic amines into enamines. This reaction provides a new selective methodology to cleave the allylic C−N bonds in the presence of either a stoichiometric or a catalytic amount of thiol. The process involves two subsequent hydrogen tranfers. As supported by DFT calculations of the C−Hα BDE in the starting amine and of the C−Hγ BDE in the resulting enamine, and their comparison to the S−H BDE, a balance must be respected between the three BDEs. In an ideal situation, the S−H bond should be stronger than the C−Hα bond but weaker than the C−Hγ bond. The incidence of the structure of the allylic chain, of the nature of the substituents at nitrogen, and of the nature of the thiol demonstrates that slight effects could have a significant impact on the reactivity. The results were interpreted in terms of enthalpic and stereoelectronic effects.

Experimental Section

General Procedure. A 0.06 M solution of amine (1 equiv), thiol [1.2 equiv (stoichiometric) or 0.2 equiv (catalytic)], and AIBN (0.2 equiv) in degassed benzene was refluxed for 6 h (every 2 h AIBN was added by portions). After evaporation, the residue was diluted with HCl (1 N) and extracted with Et_2O (three times). The aqueous phase was then basified with a solution of Na_2CO_3 and extracted with Et_2O. The organic phase was further washed with water and brine, dried (Na_2SO_4), and concentrated, leading to pure products.

Computational Details. All calculations were performed with the Gaussian-98 molecular orbital package.[7a] The geometry optimizations were carried out without constraints at the UB3LYP/6-31+G(d,p) level of theory. Vibrational frequencies were calculated at the UB3LYP/6-31+G(d,p) level to determine the nature of the located stationary points. The spin contamination was low for all radical species (maximum value for $\langle S^2 \rangle = 0.775$, cf. Supporting Information). In all cases the vibrational frequencies were scaled by a factor of 0.9804 in considering the zero-point energy.[37] The BDE values at 298 K were calculated by standard statistical thermodynamic methods using the above-mentioned frequencies. Single points were calculated at the UB3LYP/6-311++G(3df,3pd) level to obtain more accurate energies. Solution BDEs were calculated with the SCIPCM model at the UB3LYP/6-31+G(d) level on the geometries optimized at the UB3LYP/6-31+G(d,p) level.

For the determination of the reaction profiles for the hydrogen abstraction reactions, the geometries of the reactants, products, and transition states were fully optimized at the UB3LYP/6-31G(d) level. A *p* polarization function was added on the abstracted hydrogen to obtain more accurate results, as suggested by Arnaud and co-workers.[32] Frequency calculations were performed to confirm that the geometry was a minimum or a saddle point (0 or 1 imaginary frequency, respectively). The harmonic frequencies were scaled by 0.9613 to calculate thermodynamic properties. All the transition-state structures were confirmed by IRC calculations. The single-point energies were then calculated at the UB3LYP/6-311++G(3df,3pd) level of theory. It can be noted that spin contamination was also very low for both transition structures ($\langle S^2 \rangle = 0.764$ for **B**, and $\langle S^2 \rangle = 0.763$ for **E**).

Acknowledgment. We thank the Centre National de la Recherche Scientifique for financial support. An allocation of computer time by the IDRIS is gratefully acknowledged.

Supporting Information Available: Detailed experimental procedures and spectral data (^{1}H NMR, ^{13}C NMR, and HRMS) for all new compounds (S1−S13). UB3LYP/6-31+G(d,p) and UB3LYP/6-311++G(3df,3pd) computed total energies, unique imaginary frequency (for TSs), $\langle S^2 \rangle$ for radical species, and Cartesian coordinates for **10a**−**c** through **16a**−**c**; triallylamine **a**−**c**; **5d** (and the corresponding radicals **5da** and **5db**); **25a**−**c**, **26a**−**c**, and **27**; for *p*-thiocresol, methyl thioglycolate, and *n*BuSH; UB3LYP/6-31+G(d,p)//UB3LYP/6-31G(d) stationary points for the reactions of **10a** and **11a** with *p*-TolS$^{\bullet}$; G3MP2 enthalpies at 298 K; and Cartesian coordinates for triallylamine **a**−**c**, *p*-thiocresol, and *n*BuSH (S14−S60). This material is available free of charge via the Internet at http://pubs.acs.org.

JA049859X

(36) (a) Chatgilialoglu, C.; Altieri, A.; Fischer, H. *J. Am. Chem. Soc.* **2002**, *124*, 12816. (b) Ito, O. In *S-Centered Radicals*; Alfassi, Z. B., Ed.; Wiley: Chichester, 1999. (c) McPhee, D. J.; Campredon, M.; Lesage, M.; Griller, D. *J. Am. Chem. Soc.* **1989**, *111*, 7563.

(37) Foresman, J. B.; Frish, A. *Exploring Chemistry with Electronic Structure Methods*, 2nd ed.; Gaussian, Inc.: Pittsburgh, PA, 1996.