DOI: 10.1002/ejoc.200900009

Base-Catalysed Intramolecular Hydroamination of Vinyl Sulfides

Coralie Quinet,[a] Laetitia Sampoux,[a] and István E. Markó*[a]

Dedicated to Professor Alain Krief

Keywords: Heterocycles / Alkaloids / Hydroamination / Sulfur

Small amounts of *n*-butyllithium catalyse the highly efficient hydroamination of a large variety of vinyl sulfides. This novel methodology offers an easy access to a wide range of nitrogen heterocycles, including simple pyrrolidines and piperidines, as well as more complex bicyclic compounds. Subsequent transformations of the sulfur group led to the formation of functionalised alkaloid-like substructures.

Introduction

The hydroamination of alkenes, the addition of an N–H bond across a carbon–carbon double or triple bond, is a highly atom economical method for the preparation of substituted amines. These are attractive targets for organic synthesis and for the pharmaceutical industry. Though the hydroamination reaction is generally a thermodynamic process at room temperature,[1] it is plagued by a high activation barrier due to electronic repulsions between the electron-rich substrate and the amine nucleophile. Moreover, this reaction also displays a highly negative entropy, making it unfavourable at high temperatures. Consequently, catalysis is a prerequisite for this transformation to proceed.[2]

Substantial efforts have resulted in the development of catalytic systems able to promote the hydroamination of *nonactivated* alkenes. Whilst stoichiometric quantities of transition-metal complexes were initially required,[3] exciting breakthroughs have recently been reported on the inter- and intramolecular hydroamination of alkenes using alkali metals,[4] lanthanides[5] and late-transition metals.[6] However, many of these catalysts suffer from a number of shortcomings (air sensitivity, difficult preparation and/or high cost). Moreover, the efficiency of these organometallic species often applies to substrates benefiting from the Thorpe–Ingold effect and, hence, already primed to undergo ring closure, or to specific nitrogen nucleophiles.

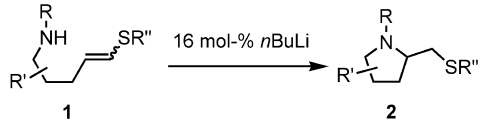
Whereas elevated temperatures (up to 180 °C) and high pressures (up to 800 bar) have been employed with alkali metals,[7] milder conditions have only enabled the inter-[8] and intramolecular[9] addition of amines to somewhat activated substrates such as alkynes,[10] vinyl arenes and dienes.[11] These initial results, employing "activated" acceptors have undergone dramatic improvements over the years. Nowadays, the base-catalysed hydroamination of myrcene forms the basis of an important industrial process: the menthol synthesis by Takasago.[12] In stark contrast, the *base-catalysed intramolecular hydroamination of nonactivated* alkenes has received considerably less attention.[2k] An early contribution to this area was due to Evans and coworkers, who described the preparation of various bridgehead-substituted dibenzo[*a*,*d*]cycloalkenimines by transannular addition of amines to olefins in the presence of catalytic amounts of *n*BuLi or LDA.[13] However, the observed regioselectivity, coupled with the special structure of their substrates, led them to suggest a radical transfer mechanism. To the best of our knowledge, the first report of a "true", *base-catalysed intramolecular* addition of an amine to a *nonactivated* alkene was due to Suginome and coworkers.[9a] In 1992, among several examples of intramolecular hydroamination of styrene derivatives, they described the addition of a secondary lithium amide to a terminal olefin. Unfortunately, this reaction proceeded with moderate yields and went essentially unnoticed.

In 2003, our laboratory accidentally rediscovered the *n*BuLi-catalysed *intramolecular hydroamination of nonactivated olefins* and developed it into a simple and efficient method for the transformation of several ω-unsaturated amines into the corresponding pyrrolidines and piperidines in moderate to good yields.[14] This methodology has subsequently been applied as a key step in several synthetic ventures by various research groups[15] and enantioselective variants have also been published.[16] More recently, we have improved on our initial protocol and devised optimal conditions to enable the competent synthesis of cyclic

[a] Université catholique de Louvain, Département de Chimie, Place Louis Pasteur 1, 1348 Louvain-la-Neuve, Belgium
Fax: +32-10-472788
E-mail: istvan.marko@uclouvain.be

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

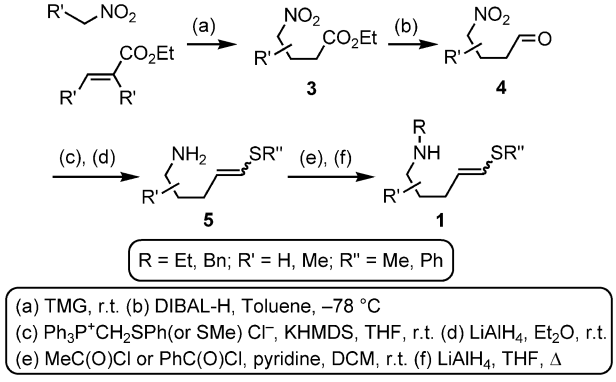
amines, its application to the assembly of more complex bicyclic amines and the synthesis of alkaloid-like natural products.[17] Unfortunately, all these hydroamination reactions only generate the corresponding nitrogen heterocycles bearing an α-methyl substituent. As was the case previously in radical chemistry, the cyclic adduct is less functionalised than the substrate. In order to raise this stringent limitation, we wondered if the hydroamination of vinyl sulfides such as **1**, using our base-catalysed protocol, would lead to the desired sulfur-containing ring system **2**. In this article, we wish to report some of our results on the successful implementation of this novel approach towards functionalised five- and six-membered nitrogen heterocycles (Scheme 1).



Scheme 1. Proposed hydroamination of vinyl sulfides.

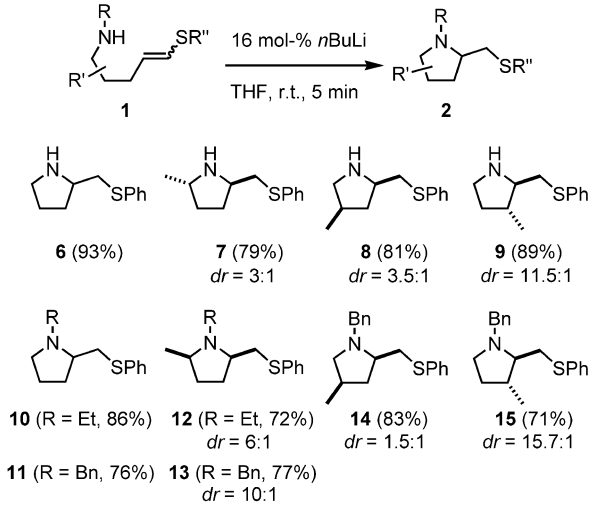
Results and Discussion

At the onset of our work, several amine-containing vinyl sulfides had to be assembled. An efficient and flexible method for their preparation is displayed in Scheme 2. Thus, addition of various nitro compounds to the appropriate acrylates provided nitroester adducts **3**. Chemoselective reduction of the ester function to the corresponding aldehyde **4**, followed by a Wittig reaction with methylthio- or phenylthiomethylene triphenylphosphorane led to the desired vinyl sulfides **5** as mixtures of *E*/*Z* isomers (up to 2.6:1). Subsequent reduction of the nitro function completed the efficient formation of primary amines **1** (R = H). Acetylation or benzoylation of these primary amines, followed by $LiAlH_4$ treatment of the intermediate amides, provided the corresponding secondary amines **1** in good yields.



Scheme 2. Synthesis of the sulfur-containing substrates.

With a variety of vinyl sulfides in hand, the study of their reactivity in the presence of *n*BuLi (16 mol-%), in THF at room temperature, was undertaken.[18] Gratifyingly, under these mild conditions, quantitative formation of the desired adducts **2** was achieved in only 5 min in every case (Scheme 3). Pyrrolidines **6**–**15** were obtained in good to excellent yields and diastereoisomeric ratios. Only the major diastereoisomer is presented in Scheme 3.



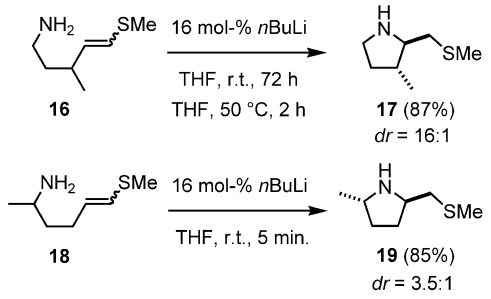
Scheme 3. Efficient preparation of pyrrolidines.

As can be seen in Scheme 3, the intramolecular hydroamination of vinyl sulfides offers one of the easiest accesses to the synthesis of functionalised pyrrolidines. Moreover, this methodology is well suited to a large variety of primary and secondary substrates and tolerates substituents at every position in the starting material. It is interesting to note that the use of a secondary amine leads sometimes to the corresponding pyrrolidine with opposite stereochemical control (compare structures **7** and **12**, **13**). In all cases except one (i.e., **14**), the addition of the secondary amines on the carbon–carbon double bond is always more diastereoselective than the primary amines. Moreover, the Thorpe–Ingold effect is no longer indispensable for these hydroamination reactions to be successful. It thus transpires that phenyl vinyl sulfides appear to be particularly attractive substrates for the efficient synthesis of pyrrolidines by base-catalysed intramolecular hydroamination.

The initial hydroamination reactions employed sulfides **1** as mixtures of *E*/*Z* isomers. In order to delineate the role played by each olefinic isomer in the establishment of the *cis*/*trans* ratio of stereoadducts, the *E*/*Z* isomers of substrate **1** (R = H, R′ = 2-Me, R′′ = Ph) were separated. Unfortunately, the *Z* isomer proved to be unstable and its *E* counterpart provided **7** in a ratio similar to that observed when an *E*/*Z* mixture was employed.

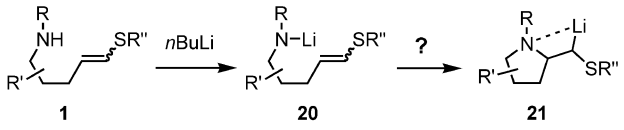
In order to broaden the scope of this methodology and to delineate the key role played by the phenyl sulfide substituent, it was decided to explore the reactivity of two methyl vinyl sulfides **16** and **18**. In the presence of a catalytic amount of *n*BuLi, both **16** and **18** smoothly cyclised, providing the corresponding pyrrolidines **17** and **19** in high yields (Scheme 4). Though the rate of cyclisation of **18** did not differ too much from that of its –SPh counterpart, **16**

underwent hydroamination much more slowly, requiring up to 72 h to reach completion. Interestingly, the ring closure of vinyl sulfide **16** proved to be more diastereoselective (compare **9** and **17**).



Scheme 4. Influence of the sulfur substituent.

It thus transpires that a phenyl substituent on the sulfur atom of the vinyl sulfide substrates probably exerts an electron-withdrawing effect that might help in stabilising a putative carbanionic intermediate. In this regard, the role played by the sulfur group on the rate enhancement of these hydroamination reactions (as compared with the corresponding terminal olefins[14,17]) is less than obvious. Indeed, due to the electron-donating ability of the sulfur atom, the carbon–carbon double bond of a vinyl sulfide is more electron-rich than that of a terminal alkene.[19] Therefore, the presence of sulfur should considerably slow down the addition of lithiated amide **20** (Scheme 5). However, a sulfur atom is also polarisable and well known to stabilise a carbanion at the α position.[20] Even though the initial approach of the negatively charged nitrogen atom on the vinyl sulfide double bond should be significantly disfavoured, the capability of the sulfur substituent to stabilise the developing negative charge in the transition state should lower the energy of activation of the hydroamination process, thereby increasing the rate of addition.[21]

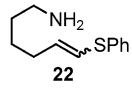
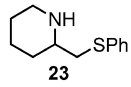
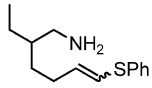
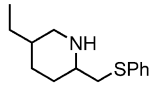
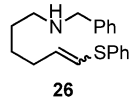
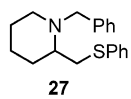


Scheme 5. Possible mechanistic hypothesis.

Though at this stage, an intermediate such as **21** might look plausible, we have not yet been able to substantiate its existence. Moreover, and quite unexpectedly, full metallation of **1** with quantitative generation of **20** does not lead to cyclic derivative **21** (Scheme 5).[14,17] Instead, either no reaction took place or complete decomposition was observed.[22]

The exciting results obtained in the assembly of pyrrolidines by intramolecular hydroamination of the precursors vinyl sulfides prompted us to study the application of this new methodology to the synthesis of the homologous six-membered ring heterocycles. Accordingly, vinyl sulfides **22**, **24** and **26** were readily assembled and then submitted to the *n*BuLi-catalysed hydroamination protocol (Table 1). Much to our pleasure, the corresponding piperidines **23**, **25** and **27** were obtained in excellent yields, either at room temperature or at 50 °C (Table 1). Even though the reaction times were longer (1–10 h at 25 °C) than those required for the synthesis of pyrrolidines (5 min), gentle heating provided the desired piperidines in 5 min or less. Finally, it is interesting to note that secondary amines, such as **26**, are significantly more reactive than their primary counterparts, such as **22**.

Table 1. Efficient synthesis of piperidines.

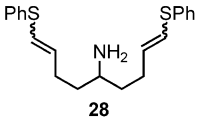
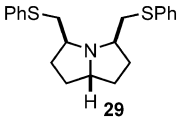
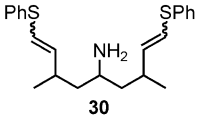
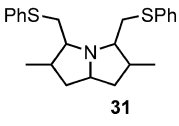
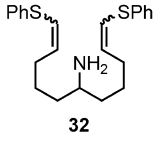
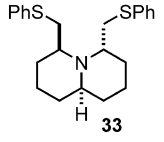
Substrate	Product	*T* [°C]	Time	Yield[a] [%]
 **22**	 **23**	25 50	10 h 5 min	 83
 **24**	 **25**	25	1 h	94[b]
 **26**	 **27**	25 50	2 h 5 min	87 90

[a] All yields are for pure, isolated compounds. All the conversions were quantitative and the reactions were performed by using *n*BuLi (1.6 M in hexanes, 16 mol-%) in THF (0.5 M solutions). [b] *dr* = 1:1.

With a rapid and efficient access to both five- and six-membered nitrogen heterocycles in hand, the assembly of bicyclic structures akin to the pyrrolizidine, indolizidine and quinolizidine alkaloids, using this novel hydroamination protocol, was next investigated. As can be seen from Table 2, divinyl sulfides **28** and **30** underwent smooth cyclisation in the presence of catalytic quantities of *n*BuLi in THF, affording fused bicyclic adducts **29** and **31** in excellent yields. As for the synthesis of pyrrolidines, only 5 min were required to reach full conversion at room temperature. These results stand in sharp contrast to the hydroamination of the corresponding sulfur-free terminal alkenes, which required prolonged reaction times at elevated temperature (110 °C, THP/toluene, 24–48 h).[14,17] Such dramatic differences clearly highlight the importance of the sulfur substituent. Much more surprising was the successful cascade hydroamination of amine **32**, which, upon exposure to small amounts of *n*BuLi, exclusively produced quinolizidine derivative **33** in good yield. This double cyclisation proved to be one of the most difficult to realise and required up to 8 h at 50 °C to reach full completion.[23] Interestingly, pyrrolizidine **31** was obtained as a mixture of only two diastereoisomers, suggesting an excellent stereocontrol during the double ring-closure process.

The intramolecular hydroamination of vinyl sulfides has provided us with a variety of adducts bearing a sulfur substituent that can readily be converted into a range of useful functionalities. Initially though, the reductive cleavage of the C–S bond to obtain the corresponding methyl-substi-

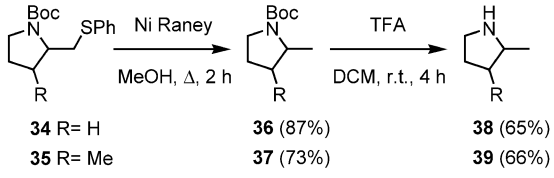
Table 2. Tandem hydroaminations.

Substrate	Product	*T* [°C]	Time	Yield[a] [%]
 **28**	 **29**	25	5 min	92[b]
 **30**	 **31**	25	5 min	93
 **32**	 **33**	25 50	24 h 8 h	78[b]

[a] All yields are for pure, isolated compounds. All the conversions were quantitative and the reactions were performed by using *n*BuLi (1.6 M in hexanes, 16 mol-%) in THF (0.5 M solutions). [b] A single diastereoisomer was obtained.

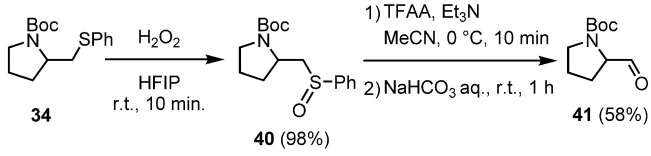
tuted pyrrolidines was investigated. Indeed, simple nitrogen heterocycles, such as pyrrolidines **38** and **39**, are difficult to access by the intramolecular hydroamination of terminal olefins, and the combination of hydroamination of vinyl sulfides followed by desulfurisation might prove to be an expedient and reliable alternative. Moreover, the generation of **38** (a known compound) from **34** will help us in the structural assignment of adduct **34**.

At the onset, Raney nickel desulfurisation was attempted on amines **6** and **9**, alas to no avail. Whilst the starting material was consumed quite readily, only trace amounts of pyrrolidines **38** and **39** could be obtained, even after extensive processing of the catalyst. It soon became evident that these basic nitrogen heterocycles remain strongly adsorbed on the Raney nickel and our efforts to isolate them in good yields proved to be fruitless. Recourse to a protecting group became mandatory and Boc-substituted **34** and **35** were prepared by standard procedures. The reductive cleavage of the C–S bond of **34** and **35** occurred smoothly in refluxing methanol, affording pyrrolidines **36** and **37** in good yields. Finally, the protecting group was removed under acidic conditions (TFA), leading to amines **38** and **39**, identical in all respects to previously prepared authentic samples (Scheme 6).



Scheme 6. Removal of the sulfur substituent.

Further functionalisation of these nitrogen heterocycles by transformation of the sulfur group into an aldehyde moiety was next investigated (Scheme 7). After several attempts, it was found that oxidation of the sulfur atom of compound **34**, by treatment with an aqueous solution of hydrogen peroxide in hexafluoro-2-propanol (HFIP),[24] quantitatively afforded the desired sulfoxide **40**, with no trace of the corresponding sulfone, even in the presence of an excess amount of hydrogen peroxide. Pummerer reaction then produced Boc-protected prolinal **41** in good overall yields.



Scheme 7. Pummerer reaction of sulfur-containing pyrrolidine.

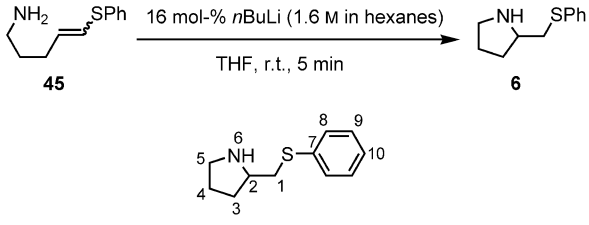
Conclusions

In summary, the base-catalysed hydroamination of vinyl sulfides opens up new vistas for the efficient and concise synthesis of a variety of nitrogen-containing substructures present in numerous natural products. Compared with the hydroamination of terminal olefins, this methodology requires much milder conditions and needs far shorter reaction times. Our method provides an efficient access to a large variety of substituted pyrrolidines and piperidines, as well as to a range of fused bicyclic amine derivatives akin to the pyrrolizidine and quinolizidine alkaloid families. These cascade hydroamination reactions occur smoothly and proceed generally with excellent levels of diastereocontrol. The hydroamination of vinyl sulfides also offers an efficient access to a large variety of functionalised nitrogen heterocycles. Indeed, subsequent transformation of the sulfur group of the final adducts, for example through a Pummerer reaction, provided the corresponding aldehyde from which a range of other structural modifications can be envisioned. Ongoing efforts are now aimed at broadening the scope of this methodology, applying it to the efficient synthesis of several relevant natural products and understanding its mechanism in its most intimate details.

Experimental Section

Representative Procedure for the Hydroamination Reaction. Preparation of 2-[(phenylthio)methyl]pyrrolidine (6): To a stirred solution of vinyl sulfide **45** (400 mg, 2.07 mmol, 1 equiv.) dissolved in tetrahydrofuran (4 mL, 0.5 M) in a Schlenk tube maintained under an argon atmosphere was added *n*BuLi (1.6 M in hexanes, 210 μL, 16 mol-%). The solution was stirred at room temperature for 5 min. Diethyl ether (5 mL) and water (5 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2×). The pooled organic extracts were washed with water and then with brine. After drying with $MgSO_4$, the solid was filtered and the solvent was removed in vacuo. Bulb-to-bulb distillation under reduced pressure (110 °C, turbo pump 3×10^{-3} mbar) afforded pure

6 (374 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.13 (m, 5 H, Ph), 3.28 [quint (tt), J = 6.8 Hz, 1 H, 2-H], 3.09–2.96 (m, 3 H, 1-H and 5a-H), 2.96–2.82 (m, 1 H, 5b-H), 2.01–1.88 (m, 1 H, 3a-H), 1.88–1.67 (m, 3 H, 4-H and 6-H), 1.55–1.40 (m, 1 H, 3b-H) ppm. ^{13}C NMR (75 MHz, APT, $CDCl_3$): δ = 136.8 (–, C-7), 129.4 and 129.1 (+, C-8 and C-9), 126.1 (+, C-10), 57.8 (+, C-2), 46.6 (–, C-5), 40.3 (–, C-1), 31.3 (–, C-3), 25.5 (–, C-4) ppm. MS (APCI, 70 eV): *m/z* (%) = 194 (59) [M + 1], 177 (10), 149 (15), 135 (11), 123 (66), 116 (11), 96 (10), 84 (100) [M + 1 – PhSH]. IR (film): $\tilde{\nu}$ = 3333 (w, N–H); 3055 (w, =C–H); 2961–2868 (s, C–H); 1620 (w), 1583 (m, C=C); 1479 (s), 1437 (s), 1393 (s), 1339 (m, C–N); 1088 (s), 1024 (s), 812 (m), 737 (s), 691 (s, C–S) cm^{-1}. CAS: [106865–52–5].



Supporting Information (see footnote on the first page of this article): Full experimental details and spectroscopic data.

Acknowledgments

Financial support for this work by the Université catholique de Louvain and Merck Sharp and Dohme (Merck Academic Development Program Award to IEM) is gratefully acknowledged.

[1] a) R. Taube, *Applied Homogenous Catalysis with Organometallic Compounds*, Wiley-VCH, Weinheim, **1996**, vol. 1, p. 507; b) D. Steinborn, R. Taube, *Z. Chem.* **1986**, *26*, 349.

[2] For general references on hydroamination, see: a) M. B. Gasc, A. Lattes, J. J. Perie, *Tetrahedron* **1983**, *39*, 703; b) J. J. Brunet, D. Neibecker, F. Niedercorn, *J. Mol. Catal.* **1989**, *49*, 235; c) D. M. Roundhill, *Chem. Rev.* **1992**, *92*, 1; d) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675; e) J.-J. Brunet, D. Neibecker, *Catalytic Heterofunctionalisation* (Eds.: A. Togni, H. Grützmacher), Wiley-VCH, **2001**, ch. 4, p. 91; f) J. Seayad, A. Tillack, C. G. Hartung, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 795; g) G. A. Molander, J. A. C. Romero, *Chem. Rev.* **2002**, *102*, 2161; h) F. Pohlki, S. Doye, *Chem. Soc. Rev.* **2003**, *32*, 104; i) J. F. Hartwig, *Pure Appl. Chem.* **2004**, *76*, 507; j) S. Hong, T. J. Marks, *Acc. Chem. Res.* **2004**, *37*, 673; k) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795.

[3] For intermolecular hydroamination of alkenes mediated by transition metals, see: a) E. W. Stern, M. L. Spector, *Proc. Chem. Soc. London* **1961**, 370; b) A. Panunzi, R. De Renzi, G. Palumbo, G. Paiaro, *J. Am. Chem. Soc.* **1969**, *91*, 3879; c) D. R. Coulson, *Tetrahedron Lett.* **1971**, *12*, 429; d) B. Akermark, J. E. Bäckvall, L. S. Hegedus, K. Zetterberg, K. Siirala-Hansen, K. Sjöberg, *J. Organomet. Chem.* **1974**, *72*, 127; e) M. B. Gasc, A. Lattes, J. J. Perie, *Tetrahedron* **1978**, *34*, 1943; f) see ref.[2a]; g) J.-J. Brunet, D. Neibecker, K. Philippot, *Tetrahedron Lett.* **1993**, *34*, 3877.

[4] For intramolecular hydroamination of alkenes mediated by alkali metals, see: a) M. R. Crimmins, I. J. Casely, M. S. Hill, *J. Am. Chem. Soc.* **2005**, *127*, 2042; b) P. Horrillo-Martinez, K. C. Hultzsch, F. Hampel, *Chem. Commun.* **2006**, 2221; c) S. Datta, P. W. Roesky, S. Blechert, *Organometallics* **2007**, *26*, 4392.

[5] For selected references on lanthanide- and actinide-catalysed hydroaminations, see: with metallocene Ln catalysts: a) M. R. Gagné, C. L. Stern, T. J. Marks, *J. Am. Chem. Soc.* **1992**, *114*, 275; b) Y. Li, T. J. Marks, *J. Am. Chem. Soc.* **1996**, *118*, 707; c) Y. Li, T. J. Marks, *J. Am. Chem. Soc.* **1998**, *120*, 1757; d) S. Tian, V. M. Arredondo, C. L. Stern, T. J. Marks, *Organometallics* **1999**, *18*, 2568; e) G. A. Molander, E. D. Dowdy, S. K. Pack, *J. Org. Chem.* **2001**, *66*, 4344; f) G. A. Molander, S. K. Pack, *J. Org. Chem.* **2003**, *68*, 9214; g) A. Motta, G. Lanza, I. L. Fragala, T. J. Marks, *Organometallics* **2004**, *23*, 4097; h) A. Motta, I. L. Fragala, T. J. Marks, *Organometallics* **2006**, *25*, 5533; i) B. D. Stubbert, T. J. Marks, *J. Am. Chem. Soc.* **2007**, *129*, 4253; j) H. F. Yuen, T. J. Marks, *Organometallics* **2008**, *27*, 155; with biphenolate and binaphtholate Ln catalysts: k) D. V. Gribkov, K. C. Hultzsch, *Chem. Commun.* **2004**, 730; l) D. V. Gribkov, F. Hampel, K. C. Hultzsch, *J. Organomet. Chem.* **2005**, *690*, 4441; m) D. V. Gribkov, K. C. Hultzsch, F. Hampel, *J. Am. Chem. Soc.* **2006**, *128*, 3748; n) X. Yu, T. J. Marks, *Organometallics* **2007**, *26*, 365; with diamine/diamide Ln catalysts: o) Y. K. Kim, T. Livinghouse, J. E. Bercaw, *Tetrahedron Lett.* **2001**, *42*, 2933; p) Y. K. Kim, T. Livinghouse, *Angew. Chem. Int. Ed.* **2002**, *41*, 3645; q) Y. K. Kim, T. Livinghouse, *Org. Lett.* **2005**, *7*, 1737; r) D. Riegert, J. Collin, A. Meddour, E. Schultz, A. Trifonov, *J. Org. Chem.* **2006**, *71*, 2514; s) N. Meyer, A. Zulys, P. W. Roesky, *Organometallics* **2006**, *25*, 4179; t) M. Rastätter, A. Zulys, P. W. Roesky, *Chem. Commun.* **2006**, 874; u) M. Rastätter, A. Zulys, P. W. Roesky, *Chem. Eur. J.* **2007**, *13*, 3606; v) I. Aillaud, J. Collin, J. Hannedouche, E. Schulz, *Dalton Trans.* **2007**, 5105; w) S. Datta, M. T. Gamer, P. W. Roesky, *Organometallics* **2008**, *27*, 1207.

[6] For intramolecular hydroamination of alkenes mediated by transition metals, see: a) D. V. Gribkov, K. C. Hultzsch, *Angew. Chem. Int. Ed.* **2004**, *43*, 5542; b) J. Y. Kim, T. Livinghouse, *Org. Lett.* **2005**, *7*, 4391; c) C. F. Bender, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2005**, *127*, 1070; d) X. Han, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2006**, *45*, 1747; e) J. A. Bexrud, J. D. Beard, D. C. Leitch, L. L. Schafer, *Org. Lett.* **2005**, *7*, 1959; f) F. E. Michael, B. M. Cochran, *J. Am. Chem. Soc.* **2006**, *128*, 4246; g) J. Zhang, C.-G. Yang, C. He, *J. Am. Chem. Soc.* **2006**, *128*, 1798; h) C. Müller, C. Loos, N. Schulenberg, S. Doye, *Eur. J. Org. Chem.* **2006**, 2499; i) R. K. Thomson, J. A. Bexrud, L. L. Schafer, *Organometallics* **2006**, *25*, 4069; j) Z. Liu, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 1570.

[7] For intermolecular hydroamination of alkenes mediated by alkali metals, see: a) B. W. Howk, E. L. Little, S. L. Scott, G. M. Whitman, *J. Am. Chem. Soc.* **1954**, *76*, 1899; b) H. Lehmkuhl, D. Reinehr, *J. Organomet. Chem.* **1973**, *55*, 215; c) G. P. Pez, J. E. Gall, *Pure Appl. Chem.* **1985**, *57*, 1917; d) D. Steinborn, B. Thies, I. Wagner, R. Taube, *Z. Chem.* **1989**, *29*, 333; e) V. Khedkar, A. Tillack, C. Benisch, J.-P. Melder, M. Beller, *J. Mol. Catal. A* **2005**, *241*, 175.

[8] a) N. Imai, T. Narita, T. Tsuruta, *Tetrahedron Lett.* **1971**, *12*, 3517; b) R. J. Schlott, J. C. Falk, K. W. Narducy, *J. Org. Chem.* **1972**, *37*, 4243; c) M. Beller, C. Breindl, *Tetrahedron* **1998**, *54*, 6359; d) M. Beller, C. Breindl, T. H. Riermeier, M. Eichberger, H. Trauthwein, *Angew. Chem. Int. Ed.* **1998**, *37*, 3389; e) C. G. Hartung, C. Breindl, A. Tillack, M. Beller, *Tetrahedron* **2000**, *56*, 5157; f) M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 9546; O. Löber, M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 4366; g) U. Nettekoven, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 1166; h) J.-S. Ryu, G. Yanwu Li, T. J. Marks, *J. Am. Chem. Soc.* **2003**, *125*, 12584; i) see ref.[2i]; j) A. M. Johns, M. Utsunomiya, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 1828.

[9] a) H. Fujita, M. Tokuda, M. Nitta, H. Suginome, *Tetrahedron Lett.* **1992**, *33*, 6359; b) V. M. Arredondo, F. E. McDonald, T. J. Marks, *J. Am. Chem. Soc.* **1998**, *120*, 4871; c) V. M. Arredondo, S. Tian, F. E. McDonald, T. J. Marks, *J. Am. Chem. Soc.* **1999**, *121*, 3633; d) B. M. Trost, W. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 14542; e) S. Hong, T. J. Marks, *J. Am. Chem.*

Soc. **2002**, *124*, 7886; f) N. T. Patil, L. M. Lutete, N. Nishina, Y. Yamamoto, *Tetrahedron Lett.* **2006**, *47*, 4749; g) R. A. Widenhoefer, X. Han, *Eur. J. Org. Chem.* **2006**, 4555.

[10] a) M. Tokuda, H. Fujita, H. Suginome, *Tetrahedron Lett.* **1990**, *31*, 5353; b) M. Tokuda, T. Myamoto, H. Fujita, H. Suginome, *Tetrahedron* **1991**, *47*, 747.

[11] a) T. Narita, N. Imai, T. Tsuruta, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1242; b) T. Narita, T. Yamaguchi, T. Tsuruta, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3825; c) H. Hamana, F. Iwasaki, H. Nagashima, K. Hattori, T. Hagiwara, T. Marita, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1109; d) D. Tzalis, C. Koradin, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 6193; e) M. Beller, C. Breindl, T. H. Rierrmeier, A. Tillack, *J. Org. Chem.* **2001**, *66*, 1403; f) K. Kumar, D. Michalik, I. G. Castro, A. Tillack, A. Zapf, M. Arlt, T. Heinrich, H. Böttcher, M. Beller, *Chem. Eur. J.* **2004**, *10*, 746; g) P. Horrillo-Martinez, K. C. Hultzsch, A. Gil, V. Branchadell, *Eur. J. Org. Chem.* **2007**, 3311.

[12] a) K. Takabe, T. Katagiri, J. Tanaka, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 222; b) R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008.

[13] B. E. Evans, P. S. Anderson, M. E. Christy, C. D. Colton, D. C. Remy, K. E. Rittle, E. L. Engelhardt, *J. Org. Chem.* **1979**, *44*, 3127.

[14] A. Ates, C. Quinet, *Eur. J. Org. Chem.* **2003**, 1623.

[15] a) W. A. L. van Otterlo, R. Pathak, C. B. de Koning, M. A. Fernandes, *Tetrahedron Lett.* **2004**, *45*, 9561; b) R. Lebeuf, F. Robert, Y. Landais, *Org. Lett.* **2005**, *7*, 4557; c) R. Lebeuf, F. Robert, K. Schenk, Y. Landais, *Org. Lett.* **2006**, *8*, 4755; d) R. Pathak, P. Naicker, W. A. Thompson, M. A. Fernandes, C. B. de Koning, W. A. L. van Otterlo, *Eur. J. Org. Chem.* **2007**, 5337; e) T. Ogata, A. Ujihara, S. Tsuchida, T. Shimizu, A. Kaneshige, K. Tomioka, *Tetrahedron Lett.* **2007**, *48*, 6648; f) W. Zhang, J. B. Werness, W. Tang, *Org. Lett.* **2008**, *10*, 2023.

[16] a) P. Horrillo-Martinez, K. C. Hultzsch, F. Hampel, *Chem. Commun.* **2006**, 2221; b) R. Nadano, Y. Iwai, T. Mori, T. Ichikawa, *J. Org. Chem.* **2006**, *71*, 8748; c) T. Ogata, A. Ujihara, S. Tsuchida, T. Shimizu, A. Kaneshige, K. Tomioka, *Tetrahedron Lett.* **2007**, *48*, 6648. For a short survey on enantioselective metal-catalysed hydroamination reactions, see: P. W. Roesky, T. E. Müller, *Angew. Chem. Int. Ed.* **2003**, *42*, 2708 and references cited therein. For a full survey, see ref.[2k]

[17] C. Quinet, P. Jourdain, C. Hermans, A. Ates, I. Lucas, I. E. Markó, *Tetrahedron* **2008**, *64*, 1077.

[18] Lower amounts of *n*BuLi can also be successfully employed in this reaction. However, for reasons of simplicity, we routinely selected to use 16 mol-% of *n*BuLi, as its commercial concentration is 1.6 M.

[19] a) C. C. Price, J. Zomlefer, *J. Am. Chem. Soc.* **1950**, *72*, 14; b) J. T. Aplin, N. L. Bauld, *J. Chem. Soc. Perkin Trans. 2* **1997**, 853.

[20] C. F. Bernasconi, K. W. Kittredge, *J. Org. Chem.* **1998**, *63*, 1944.

[21] Theoretical calculations are currently underway to determine the importance of the anion-stabilising contribution offered by the sulfur moiety.

[22] The involvement of a true carbanion in the hydroamination of terminal, *nonactivated* alkenes appears rather improbable in view of the enormous difference in pKa values between the N-centred and C-centred anion. This is reflected by the inability to capture such a putative carbanion by using a variety of electrophiles (see also ref.[9a]). Such is not the case for the intramolecular addition of an amide onto an "activated" styrene-type olefin. The stabilisation provided by the aromatic nucleus leads to the generation of a "true" carbanion, which can be intercepted intramolecularly (S. Tsuchida, A. Kaneshige, T. Ogata, H. Baba, Y. Yamamoto, K. Tomioka, *Org. Lett.* **2008**, *10*, 3635). The situation of the vinyl sulfides is far from being clear-cut, as the pKa value of amide **20** is rather close to that of carbanion **21**. That no reaction took place when stoichiometric quantities of *n*BuLi were used tends to suggest the noninvolvement of a "real" carbanion. More work is needed to shed light on this important mechanistic problem.

[23] Despite numerous attempts, quinolizidine synthesis by double hydroamination of the sulfur-free analogue of **32** never afforded even a trace amount of the desired bicyclic nitrogen derivative. C. Quinet, I. E. Markó, unpublished observation.

[24] K. S. Ravikumar, Y. M. Zhang, J.-P. Bégué, D. Bonnet-Delpon, *Eur. J. Org. Chem.* **1998**, 2937.

Received: January 7, 2009
Published Online: February 26, 2008

