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Base-Catalyzed Intramolecular Hydroamination of Conjugated Enynes

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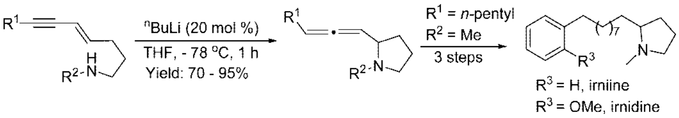
ABSTRACT



A de novo intramolecular hydroamination of conjugated enynes was developed using commercially available *n*-BuLi as a precatalyst. This hydroamination reaction successfully afforded allenyl-substituted pyrrolidines with up to 95% yield. One of the resulting allenyl pyrrolidines was converted to the natural products irniine and irnidine in three steps.

New methods for producing nitrogen heterocycles in a catalytic manner are of fundamental importance in organic chemistry and pharmaceutical sciences. Intramolecular hydroamination of alkenes[1] would be, in terms of an optimum material balance, a superior atom-economical process.[2] Impressive progress has been made recently for transition metal catalyzed intramolecular additions of amides and sulfonamides to alkenes, allenes, and dienes.[3] The addition of unprotected amines to alkenes, arguably the most important donors and acceptors,[4] has been studied in very limited systems. The intramolecular addition of unprotected amines to monosubstituted alkenes has been tested in a number of catalytic systems based on rare earth metals,[5] titanium and zirconium,[6,7] zinc,[8] alkali metals,[9,10] and late transition metals.[11] A few catalysts were developed for the intramolecular addition of unprotected amines to 1,1-disubstituted alkenes[12,13] and 1,2-disubstituted alkenes.[14] To extend the scope of olefin substrates for the preparation of nitrogen

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(1) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, 1579. Mueller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

(2) Trost, B. M. *Science* **1991**, *254*, 1471. Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259.

(3) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 1611. Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938. Zhang, Z. B.; Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 14148. Han, X. Q.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747. Bender, C. F.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 4143. Zhang, J. L.; Yang, C. G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. Liu, X. Y.; LiC. H.; Che, C. M. *Org. Lett.* **2006**, *8*, 2707. LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. Zhang, Z. B.; Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 2887.

(4) Ritter, S. *Chem. Eng. News* **2008**, *86*, 12.

(5) Gagne, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108. Kim, Y. K.; Livinghouse, T.; Bercaw, J. E. *Tetrahedron Lett.* **2001**, *42*, 2933. Kim, Y. K.; Livinghouse, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3645. Gribkov, D. V.; Hultzsch, K. C.; Hampell, F. *Chem. Eur. J.* **2003**, *9*, 4796. O'Shaughnessy, P. N.; Knight, P. D.; Morton, C.; Gillespie, K. M.; Scott, P. *Chem. Commun.* **2003**, 1770. Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. Lauterwasser, F.; Hayes, P. G.; Brase, S.; Piers, W. E.; Schafer, L. L. *Organometallics* **2004**, *23*, 2234. Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737. Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748.

(6) Knight, P. D.; Munslow, I.; O'Shaughnessy, P. N.; Scott, P. *Chem. Commun.* **2004**, 894. Gribkov, D. V.; Hultzsch, K. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5542. Muller, C.; Loos, C.; Schulenberg, N.; Doye, S. *Eur. J. Org. Chem.* **2006**, 2499. Marcsekova, K.; Loos, C.; Rominger, F.; Doye, S. *Synlett* **2007**, 2564. Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 354. Ackermann, L.; Kaspar, L. T.; Althammer, A. *Org. Biomol. Chem.* **2007**, *5*, 1975.

(7) Bexrud, J. A.; Beard, J. D.; Leitch, D. C.; Schafer, L. L. *Org. Lett.* **2005**, *7*, 1959.

(8) Zulys, A.; Dochnahl, M.; Hollmann, D.; Lohnwitz, K.; Herrmann, J. S.; Roesky, P. W.; Blechert, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7794. Dochnahl, M.; Lohnwitz, K.; Pissarek, J. W.; Biyikal, M.; Schulz, S. R.; Schon, S.; Meyer, N.; Roesky, P. W.; Blechert, S. *Chem. Eur. J.* **2007**, *13*, 6654.

(9) Fujita, H.; Tokuda, M.; Nitta, M.; Suginome, H. *Tetrahedron Lett.* **1992**, *33*, 6359.

(10) Ates, A.; Quinet, C. *Eur. J. Org. Chem.* **2003**, 1623. Martinez, P. H.; Hultzsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221.

(11) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070.

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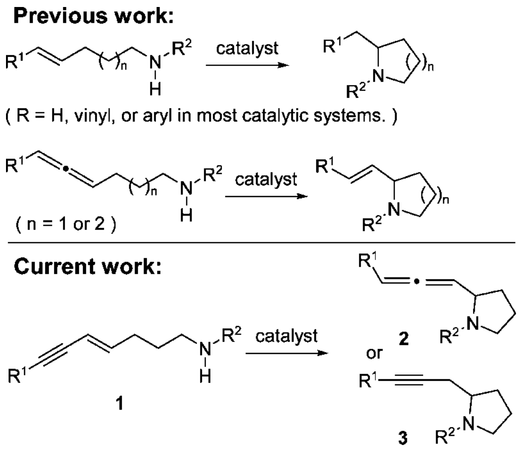
heterocycles bearing key substituents present in naturally occurring compounds, conjugated amino dienes,[15,16] vinyl arenes,[7,9,17] and highly reactive aminoallenes[18] have been used to prepare substituted nitrogen heterocycles via intramolecular hydroamination.

Despite impressive progress on the hydroamination of carbon−carbon multiple bonds, the intramolecular hydroamination of conjugated enynes has never been explored (Scheme 1).[19] An interesting question arises because two potential hydroamination products can be formed—allenyl amine **2** and homopropargyl amine **3** as shown in Scheme 1. Herein, we report the first intramolecular hydroamination of conjugated enyne **1**, which selectively affords allenyl amine **2**.

Scheme 1. Intramolecular Hydroamination of Alkenes



Alkali metals have been used to catalyze the addition of amines to monosubstituted alkenes,[9,10] 1,1-disubstituted alkenes,[12] 1,3-butadienes,[16,20] and conjugated vinyl arenes[9,21] including electron-rich vinylarenes[22] via deprotonation of the amine followed by addition to the double bonds.[23] In an effort to develop a catalyst that is cost-effective and readily accessible, we decided to explore the potential of alkali metals for the intramolecular hydroamination of conjugated enynes.

When we first treated aminoenyne **1a**[24] with 120 mol % of *n*-BuLi at −78 °C in THF, compound **1a** was completely cycloisomerized to allenyl pyrrolidine **2a** with a 1.8:1 diastereomeric ratio after 1 h. We then reduced the amount of *n*-BuLi to 20 mol % and increased the concentration of the aminoenyne to 0.4 M in THF. A 100% conversion was achieved at −78 °C with a 1.6:1 diastereomeric ratio after 1 h. No homopropargyl amine **3** was observed under these conditions.

We then investigated the scope of the hydroamination of conjugated aminoenynes using 20 mol % of *n*-BuLi as a precatalyst (Table 1). Amino enynes with different substituents on the amino group all worked well under optimal conditions with no significant changes of the yields and diastereomeric ratios. Surprisingly, increasing the steric bulk of the alkyne improved the diastereomeric ratio from 2:1 to 5:1 (Table 1, entries 3 and 7). It is worth mentioning that amines with a removable benzyl group worked well (Table 1, entries 6 and 8). A phenyl substituted enyne also provided a high yield of the hydroamination product (Table 1, entry 9). Substituted pyrroldine **2j** was obtained as a mixture of two diastereomers, which yielded only the cis-1,2-disubstituted pyrrolidine upon hydrogenation (Table 1, entry 10). Efforts toward the formation of six-membered-ring heterocycles via hydroamination of enynes were not successful (Table 1, entry 11).

The proposed mechanism for the base catalyzed hydroamination of XXenynes is shown in Scheme 2.[23] The

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(12) Evans, B. E.; Anderson, P. S.; Christy, M. E.; Colton, C. D.; Remy, D. C.; Rittle, K. E.; Engelhardt, E. L. *J. Org. Chem.* **1979**, *44*, 3127.

(13) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1998**, *63*, 8983. Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1999**, *64*, 6515. Molander, G. A.; Pack, S. K. *J. Org. Chem.* **2003**, *68*, 9214. Kim, H.; Lee, P. H.; Livinghouse, T. *Chem. Commun.* **2005**, 5205. Dochnahl, M.; Pissarek, J. W.; Blechert, S.; Lohnwitz, K.; Roesky, P. W. *Chem. Commun.* **2006**, 3405.

(14) Ryu, J.-S.; Marks, T. J.; McDonald, F. E. *Org. Lett.* **2001**, *3*, 3091. Kim, Y. K.; Livinghouse, T.; Horino, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9560. Ryu, J.-S.; Marks, T. J.; McDonald, F. E. *J. Org. Chem.* **2004**, *69*, 1038. Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 4253. Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570.

(15) Hong, S.; Marks, T. J. *J. Am. Chem. Soc.* **2002**, *124*, 7886. Hong, S.; Kawaoka, A. M.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 15878. Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 8134. Tobisch, S. *Chem. Eur. J.* **2007**, *13*, 9127.

(16) Lebeuf, R.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2006**, *8*, 4755.

(17) Thomson, R. K.; Bexrud, J. A.; Schafer, L. L. *Organometallics* **2006**, *25*, 4069. Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 6042. Kaspar, L. T.; Fingerhut, B.; Ackermann, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 5972.

(18) Arredondo, V. M.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 4871. Arredondo, V. M.; McDonald, F. E.; Marks, T. J. *Organometallics* **1999**, *18*, 1949. Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633. Sweeney, Z. K.; Salsman, J. L.; Andersen, R. A.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 2339. Straub, B. F.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4632. Shi, Y.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 3967. Ackermann, L.; Bergman, R. G. *Org. Lett.* **2002**, *4*, 1475. Ackermann, L.; Bergman, R. G.; Loy, R. N. *J. Am. Chem. Soc.* **2003**, *125*, 11956. Ackermann, L. *Organometallics* **2003**, *22*, 4367. Michael, F. E.; Duncan, A. P.; Sweeney, Z. K.; Bergman, R. G. *J. Am. Chem. Soc.* **2003**, *125*, 7184. Hoover, J. M.; Petersen, J. R.; Pikul, J. H.; Johnson, A. R. *Organometallics* **2004**, *23*, 4614. Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421. Patil, N. T.; Lutete, L. M.; Nishina, N.; Yamamoto, Y. *Tetrahedron Lett.* **2006**, *47*, 4749.

(19) A Pd-catalyzed intermolecular hydroamination of conjugated enynes yielded 1,4-diaminoalkenes via π-allyl palladium complexes: Radhakrishnan, U.; Al-Masum, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 1037.

(20) Takabe, K.; Katagiri, T.; Tanaka, J.; Fujita, T.; Watanabe, S.; Suga, K. *Org. Synth.* **1989**, *67*, 44. Inoue, S.; Takaya, H.; Tani, K.; Otsuka, S.; Sato, T.; Noyori, R. *J. Am. Chem. Soc.* **1990**, *112*, 4897. Lebeuf, R.; Robert, F.; Landals, Y. *Org. Lett.* **2005**, *7*, 4557.

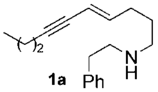
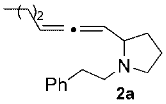
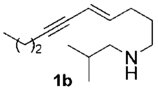
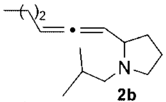
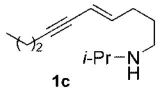
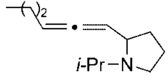
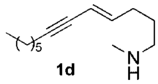
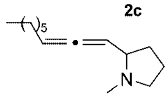
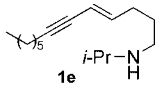
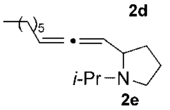
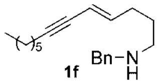
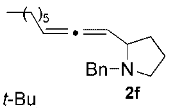
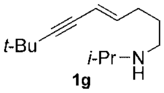
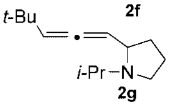
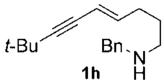
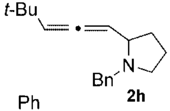
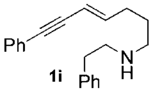
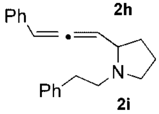
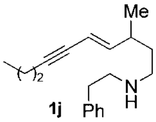
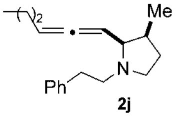
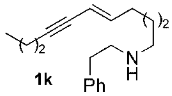
(21) Beller, M.; Breindl, C.; Riermeier, T. H.; Eichberger, M.; Trauthwein, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 3389. Beller, M.; Thiel, O. R.; Trauthwein, H.; Hartung, C. G. *Chem. Eur. J.* **2000**, *6*, 2513. Barry, C. S.; Simpkins, N. S. *Tetrahedron Lett.* **2007**, *48*, 8192. Kumar, K.; Michalik, D.; Castro, I. G.; Tillack, A.; Zapf, A.; Arlt, M.; Heinrich, T.; Bottcher, H.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 746. Ogata, T.; Ujihara, A.; Tsuchida, S.; Shimizu, T.; Kaneshige, A.; Tomioka, K. *Tetrahedron Lett.* **2007**, *48*, 6648.

(22) Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2003**, *125*, 8744. Pathak, R.; Naicker, P.; Thompson, W. A.; Fernandes, M. A.; de Koning, C. B.; van Otterlo, W. A. L. *Eur. J. Org. Chem.* **2007**, 5337. van Otterlo, W. A. L.; Pathak, R.; de Koning, C. B.; Fernandes, M. A. *Tetrahedron Lett.* **2004**, *45*, 9561.

(23) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795.

(24) The aminoenynes can be prepared in two to four steps from commercially available materials. See the Supporting Informationfor details.

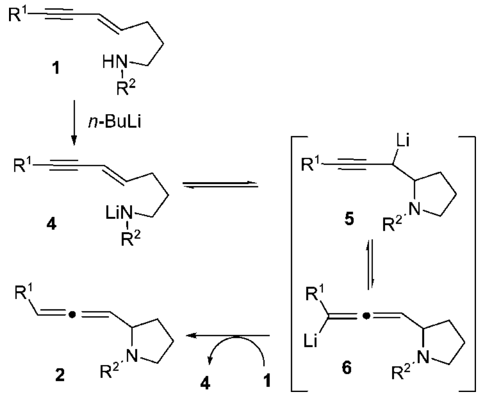
Table 1. Hydroamination of Conjugated Enynes[a]

entry	enyne	product	yield (%)	dr[b]
1	 **1a**	 **2a**	93	1.6:1
2	 **1b**	 **2b**	79	2.1:1
3	 **1c**	 **2c**	83	2.0:1
4	 **1d**	 **2d**	95	1.8:1
5	 **1e**	 **2e**	80	1.8:1
6	 **1f**	 **2f**	70	2.1:1
7	 **1g**	 **2g**	73	5.0:1
8	 **1h**	 **2h**	72	1.7:1
9	 **1i**	 **2i**	78	1.0:1
10	 **1j**	 **2j**	88	1.3:1
11	 **1k**	complex mixture		

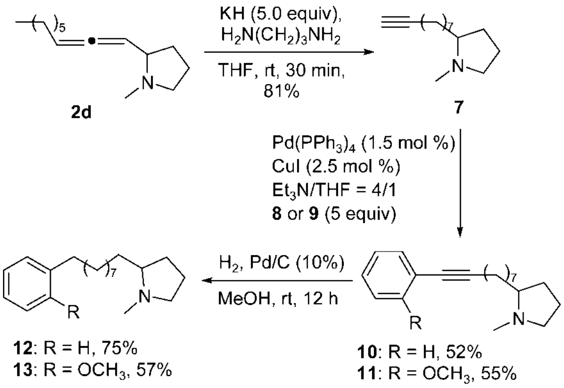
[a] All reactions were performed at −78 °C with *n*-BuLi (20 mol %) in THF (0.4 M). [b] Ratios were determined using NMR in CD_3COCD_3.

amine N−H was first deprotonated by *n*-BuLi to form lithium amide **4** which presumably served as the catalytic species. A 5-*exo-trig* cyclization could generate propargyllithium **5** and/or allenyllithium **6**,[25] which could then be protonated by amino enyne **1** to give allenylamine **2** and catalyst **4**.

Scheme 2. A Proposed Mechanism



Scheme 3. Short Syntheses of Irniine and Irnidine



8: iodobenzene, **9**: 1-iodo-2-methoxybenzene

Substituted pyrrolidines exist in numerous natural products and pharmaceutical agents and display a broad spectrum of biological activities.[26] For example, irniine **12** (Scheme 3) was isolated from the tubers of *Arisarum vulgare*, a toxic amceae responsible for human and animal poisonings in Morocco.[27] Irniine[28] displayed significant antibacterial and antimycotic activity[29] and a strong binding affinity for DNA.[30] From the same natural source, derivatives of irniine such as irnidine **13** have also been isolated.[31] We envisioned that an alkyne-zipper reaction[32] could convert the allene functional group next to the pyrrolidine ring in **2a**−**f** to a terminal alkyne, which can then be further transformed to a desired functionality. Indeed, treatment of hydroamination product **2d** with excess potassium hydride in a solution of 1,3-diaminopropane completely isomerized allene **2d** to terminal alkyne **7**. Sonogashira cross-coupling reactions[33] between alkyne **7** and iodobenzene **8** or 1-iodo-2-methoxybenzene **9** provided penultimate intermediates **10** and **11**. Palladium catalyzed hydrogenation of alkyne **10** and **11** then cleanly afforded natural products irniine **12** and its congener irnidine **13**.

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(25) Reich, H. J.; Holladay, J. E.; Mason, J. D.; Sikorski, W. H. *J. Am. Chem. Soc.* **1995**, *117*, 12137.

(26) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.

(27) Melhaoui, A.; Jossang, A.; Bodo, B. *J. Nat. Prod.* **1992**, *55*, 950.

(28) Takahata, H.; Ihara, K.; Kubota, M.; Momose, T. *Heterocycles* **1997**, *46*, 349. Jossang, A.; Melhaoui, A.; Bodo, B. *Heterocycles* **1996**, *43*, 755.

(29) Rakba, N.; Melhaoui, A.; Rissel, M.; Morel, I.; Loyer, P.; Lescoat, G. *Toxicon* **2000**, *38*, 1389.

(30) Melhaoui, A.; Belouali, H. *J. Ethnopharmacol.* **1998**, *62*, 67.

(31) Melhaoui, A. *Planta Med.* **1998**, *64*, 476.

(32) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891.

(33) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

In summary, we report the first intramolecular hydroamination of conjugated enynes. The reaction was catalyzed by lithium amide to yield allenylpyrrolidines in up to 95% yield. A stereogenic center and an axial chiral allene were generated in this cycloisomerization reaction, and a diastereomeric ratio of up to 5:1 was achieved. The resulting allene could be further functionalized[34] as demonstrated in the divergent synthesis of the natural products irniine and irnidine. The sequential enyne-hydroamination followed by alkyne-zipper reaction should be applicable to the synthesis of other pyrrolidines with remote functional groups, such as the family of broussonetine iminosugars.[26] The low cost of commercially available *n*-BuLi precatalyst and the mild conditions make this hydroamination feasible for industrial production of substituted pyrrolidines. The current results also encourage further development of a catalytic, diastereo-, and enantioselective hydroamination method for conjugated enynes.

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

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(34) Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; Vols. 1 and 2. Brandsma, L. *Acetylenes, allenes and cumulenes*; Elsevier: Amsterdam, 2005. Tracey, M. R.; Hsung, R. P.; Antoline, J. A.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. Houben-Weyl Methods of Molecular Transformations. In *Science of Synthesis*; Weinreb, S. M., Ed.; Georg Thieme Verlag KG: Stuttgart, 2005; Chapter 21.4. MaS., *Chem. Rev.* **2005**, *105*, 2829.