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COMMUNICATIONS

Published on Web 02/12/2004

Efficient Stereoselective Alkenylation through a Homolytic Domino Reaction Involving a 1,5 Sulfur-to-Carbon Translocation

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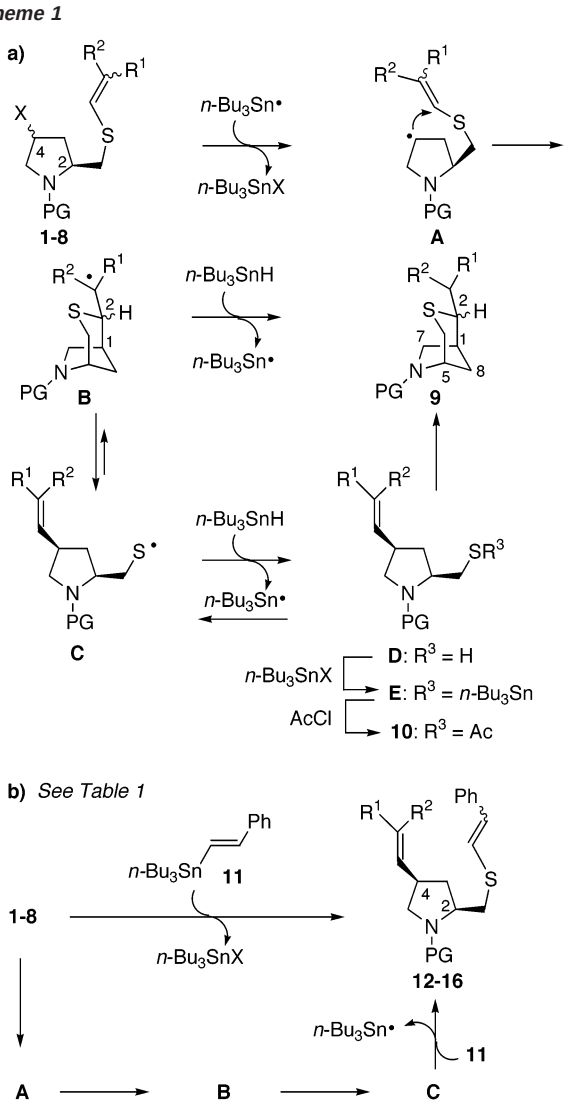
Although being of great power when applied to C(sp^2) electrophiles, transition metal-catalyzed cross-couplings suffer from basic limitations in the case of C(sp^3) electrophiles, especially of those possessing β-hydrogen atoms.[1] Indeed, while encouraging advancements in the cross-coupling of C(sp^2) nucleophiles with primary alkyl electrophiles have been recently described,[1,2] the couplings of less active secondary alkyl halides or sulfonates were unsuccessful,[1] except for a few atypical cases.[3,4] Far better results were obtained by employing homolytic proximal addition−elimination of secondary carbon-centered radicals to stannyl-,[5] sulfonyl-,[5a,6a,b] or sulfinylalkenes.[6c] Methods for intramolecularization via temporary connection can secure stereoselectivity during C−C bond formation.[7] Combination of temporary silicon connection and intramolecular free-radical reactions provided an efficient tool for the stepwise cis-stereoselective attachment of various carbon appendages, including unsaturated ones.[7−10] Of relevance to the present work is a method for the stereocontrolled C−C bond formation using temporary sulfur connection in a process combining homolytic and heterolytic reactions.[11] All homolytic translocations[12] are widely applied for the preparation of biaryls through intramolecular shift of aryl groups[13] but have not been used for stereoselective attachment of alkenyl fragments to sp^3-stereogenic carbon.[14]

Herein we report on a novel efficient method for cis-stereoselective C-alkenylation through a single homolytic domino reaction involving a 1,5 translocation of functionalized alkenyl fragments from divalent sulfur to secondary sp^3 carbon. To test the feasibility of this approach, pyrrolidine derivatives **1**−**8**, bearing a free radical precursor X (Br or I) at C(4) and an alkenylsulfide radical acceptor on the side chain attached to stereogenic center C(2), were designed (Scheme 1a). To minimize secondary reactions due to potentially reactive products, crude reaction products were treated with acetyl chloride/pyridine. An early experiment indicated that heating a benzene solution of iodide **1** ($R^1 = R^2 = CO_2Et$, PG = Ts, X = I) with *n*-Bu_3SnH and a catalytic amount of AIBN, under conditions commonly used in translocation reactions,[12−14] afforded the bridged bicyclic sulfides **9** ($R^1 = R^2 = CO_2Et$, PG = Ts) as a mixture of C(2) epimers in 77% total yield (Scheme 1a). Only traces of translocation product **10** ($R^1 = R^2 = CO_2Et$, PG = Ts) were detected in this experiment. The translocation process was then boosted by increasing the reaction temperature and decreasing the hydrogen donor concentration. Indeed, slow addition (4.5 h) of *n*-Bu_3SnH into a solution of bromide **2** ($R^1 = R^2 = CO_2Et$, PG = Ts, X = Br) in toluene at 110 °C increased the yield of translocation product **10** to 35%, although formation of **9** (56%) still prevailed. Analysis of the reaction mechanism indicates that the incipient carbon-centered radical **A** undergoes a 6-exo-trig cyclization to carbon-centered radical **B**. Due to the bridged-bicyclic nature of radical **B**, it is imperative that a new C(1)−C(2) bond is formed with absolute stereoselectivity. Hydrogen transfer to **B** gives the bicyclic sulfide **9**. In a competing monomolecular step, carbon-centered radical **B** undergoes β-scission of the C(2)−S bond,

Scheme 1



generating the thiyl radical **C**, which is in equilibrium with thiol **D**. The latter could also undergo two competitive polar reactions: cyclization to bicyclic sulfide **9** and stannylation to tin sulfide **E**. Both **D** and **E** are eventually acetylated to 2,4-cis-disubstituted pyrrolidine **10**. Formation of bicycles of type **9** by hydrogen transfer to radical **B** is accelerated as the reaction proceeds due to an increase in the combined concentration of the two potent hydrogen donors: *n*-Bu_3SnH and thiol **D**. Therefore, to sustain the path leading to the desired translocation products on account of that leading to the bridged bicyclic sulfides of type **9**, it is necessary to use a tin mediator which is not a hydrogen donor. Such a mediator should also act as a thiyl radical trap and thus would make redundant the

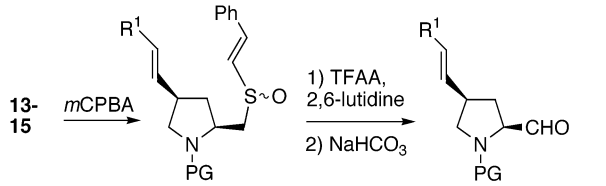
10.1021/ja031766c CCC: $27.50

Table 1. Tri-*n*-butylstyryltin (**11**)-Mediated Homolytic 1,5 S → C Translocation of Alkenyl Groups (Scheme 1)

entry	substrate					time/h[a]	product, yield (%)[b]
		R^1; R^2	(*E* : *Z*)	X	PG		
1	**2**	CO_2Et; CO_2Et		Br	Ts	7	**12**, 89
2	**3**	Ph; H	(2:1)	I	Ts	4	**13**, 82
3	**4**	CO_2Me; H	(2:3)	Br	Boc	7	**14**, 84
4	**5**	CO_2Me; H	(2:3)	I	Boc	4	**14**, 86
5	**6**	CO_2Me; H	(2:3)	Br	Ts	7	**15**, 78
6	**7**	CO_2Me; H	(4:5)	I	Ts	4	**15**, 69
7	**8E**	H; Ts		Br	Boc	7	**16**, 86
8	**8Z**	Ts, H		Br	Boc	7	**16**, 89

[a] A solution of substrate, styryltin **11** (3−4 equiv), and 1,1′-azobis(cyclohexanecarbonitrile) (ACN) (0.1 equiv) in toluene was heated for the indicated time at 105 °C. [b] Isolated yields.

Scheme 2



extra step of sulfur protection. These properties are known to be characteristic for tri-*n*-butylstyryltin (**11**).[15]

Indeed, upon treatment of 4-bromopyrrolidines **2**, **4**, **6**, and **8** or 4-iodopyrrolidines **3**, **5**, and **7** with tri-*n*-butylstyryltin (**11**) (3−4 equiv) and a radical initiator (ACN, 5−10%) in toluene at 105 °C, a smooth reaction took place, furnishing the corresponding 2,4-cis-disubstituted 4-alkenyl-2-(styrylsulfanyl)methylpyrrolidines **12**−**16** in high yields (Scheme 1b, Table 1). In the final products **12**−**16**, the composition and connectivity of alkenyl appendages at C(4) are the same as those in the alkenyl substituent on the sulfur atom of the starting compounds **2**−**8**. Irrespective of the C=C bond geometry in precursors **2**−**8**, migration of the unsaturated appendages resulted in *E*-alkenyl substituents at C(4) of pyrrolidines **12**−**16**. The C=C bond geometry of the C(2)-styrylsulfanylmethyl side chain in **12**−**16** accounts for about 90% of *E*-isomer.

To widen the scope of this methodology, it was proved that the styrylsulfanylmethyl group is a viable synthetic equivalent of the formyl group. Since styrylsulfoxides are vinylogues of phenylsulfoxides, it was expected that they should undergo a similar Pummerer rearrangement to aldehydes. So far, Pummerer-type transformations of alkenylsulfoxides to carbonyl compounds have not been reported. We were pleased to find that selective low-temperature (−30 °C) oxidation of sulfides **13**−**15** to sulfoxides **17**−**19**, followed by treatment of the latter with TFAA and 2,6-lutidine, afforded the aldehydes **20**−**22** in good yields (Scheme 2).

In summary, we have elaborated an effective method for cis-stereoselective attachment of various functionalized alkenyl appendages to an sp^3 carbon atom through a new 1,5 S(II) → C translocation.[16] This method takes advantage of the particular properties of the C−S bond and thiyl radicals. The intramolecular cyclization to the bridged-bicyclic key radical intermediate **B** guaranties an exclusive cis-stereochemistry of the products. Reaction conditions are mild and are tolerated by a variety of functional groups. Facile conversion of the styrylsulfanylmethyl group into an aldehyde function opens an additional avenue for further synthetic applications.

Acknowledgment. This research was supported by the Israel Science Foundation, founded by the Israel Academy of Sciences and Humanities, and by Minerva Science Foundation, Germany. E. E. K. thanks the Israel Ministry of Absorption for Giladi and Kamea fellowships.

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

References

(1) (a) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384−387. (b) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187−3204.
(2) (a) Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718−3719. (b) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910−3912.
(3) Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 6514−6515.
(4) (a) Thottathil, J. K.; Moniot, J. L. *Tetrahedron Lett.* **1986**, *27*, 151−154. (b) Normant, J. F.; Mulamba, T.; Scott, F.; Alexakis, A.; Cahiez, G. *Tetrahedron Lett.* **1978**, *19*, 3711−3712.
(5) (a) Rosenstein, I. J. In *Radicals in Organic Synthesis. Vol. 1: Basic Principles*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; pp 50−71. (b) Baldwin, J. E.; Kelly, D. R. *Chem. Commun.* **1985**, 682−684. (c) Russell, G. A.; Ngoviwatchai, P.; Tashtoush, H. I. *Organometallics* **1988**, *7*, 696−702. (d) An, H.; Wang, T.; Maier, M. A.; Manoharan, M.; Ross, B. S.; Cook, P. D. *J. Org. Chem.* **2001**, *66*, 2789−2801.
(6) (a) Bertrand, F.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1999**, *38*, 1943−1946. (b) Kalai, C.; Tate, E.; Zard, S. Z. *Chem. Commun.* **2002**, 1430−1431. (c) Delouvrié, B.; Fensterbank, L.; Lacôte, E.; Malacria, M. *J. Am. Chem. Soc.* **1999**, *121*, 11395−11401.
(7) (a) Cox, L. R.; Ley, S. V. In *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 2000; pp 276−393. (b) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2238−2289. (c) Fensterbank, L.; Malacria, M.; Sieburth, S. McN. *Synthesis* **1997**, 813−854. (d) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253−1277.
(8) Pearce, A. J.; Mallet, J.-M.; Sinay, P. In *Radicals in Organic Synthesis. Vol. 2: Applications*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; pp 538−577.
(9) (a) Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054−7056. (b) Mazeas, D.; Skrydstrup, T.; Doumeix, O.; Beau, J.-M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1383−1386.
(10) Sugimoto, I.; Shuto, S.; Matsuda, A. *J. Org. Chem.* **1999**, *64*, 7153−7157.
(11) (a) Bachi, M. D.; Bar-Ner, N.; Melman, A. *J. Org. Chem.* **1996**, *61*, 7116−7124. (b) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1997**, *62*, 1896−1898. (c) Bachi, M. D.; Bilokin, Y. V.; Melman, A. *Tetrahedron Lett.* **1998**, *39*, 3035−3038.
(12) Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94−103.
(13) Reviewed in: Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649−9667.
(14) Related examples: (a) low-yielding desulfonylative 1,4 translocation of styryl fragment from S(VI) to a primary sp^3 carbon; Köhler, J. J.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, *18*, 635−638. (b) Desulfonylative 1,4 S(VI) → sp^2 C styryl shift: Godfrey, C. R. A.; Hegarty, P.; Motherwell, W. B.; Uddin, M. K. *Tetrahedron Lett.* **1998**, *39*, 723−726.
(15) Russell, G. A.; Ngoviwatchai, P. *Tetrahedron Lett.* **1985**, *26*, 4975−4978.
(16) For a recent cis-stereoselective 1,4 Si → sp^3 C transfer of some alkenyl fragments through a Heck/sila-Stille sequence, see: Quan, L. G.; Cha, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 12424−12425.

JA031766C