The Catalytic Shapiro Reaction

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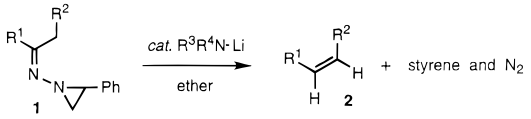
The alkyllithium-mediated decomposition of ketone arenesulfonylhydrazones (*i.e.*, the Shapiro reaction) is certainly one of the most powerful methods for regioselective preparation of alkenes via alkenyllithium reagents.[1] In all cases, however, the procedures require stoichiometric or even excess amounts of the bases to generate the alkenyllithium reagents. Accordingly, development of an efficient catalytic method in the Shapiro reaction constitutes a veritable challenge in organic synthesis. Herein we wish to disclose a first example of excellent regio- and stereoselectivity obtained using the combination of ketone phenylaziridinylhydrazones **1** as arenesulfonylhydrazone equivalents[2,3] with a catalytic amount of lithium amides.

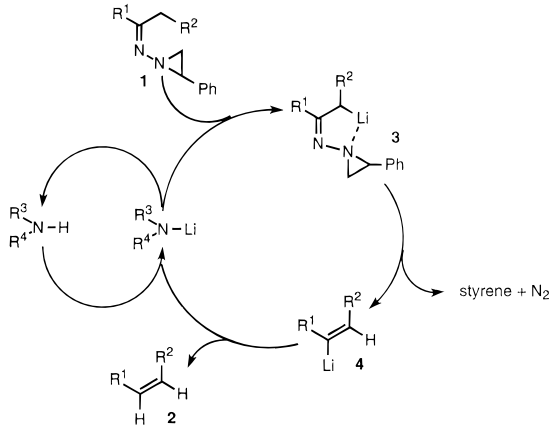
The requisite phenylaziridinylhydrazone **1** (R^1 = pentyl, R^2 = Bu) was prepared from the condensation of 6-undecanone with 1-amino-2-phenylaziridine.[4] Treatment of 6-undecanone phenylaziridinylhydrazone **1** (R^1 = pentyl, R^2 = Bu) in ether with catalytic LDA (0.3 equiv) at −20 °C for 1 h and at 0 °C for 3 h resulted in the smooth extrusion of styrene and nitrogen to furnish 5-undecene **2** (R^1 = pentyl, R^2 = Bu) in 84% yield.



The *cis/trans* ratio was determined to be 99.4:0.6 by capillary GLC analysis after conversion to the corresponding epoxides with MCPBA. The amount of LDA can be decreased to 0.05 equiv without affecting the yield and *cis/trans* ratio of the olefin product in the 30 mmol scale reaction. Lithium 2,2,6,6-tetramethylpiperidide (LiTMP) is equally employable, but use of $LiNEt_2$ and $LiN(SiMe_3)_2$ gave less satisfactory results.

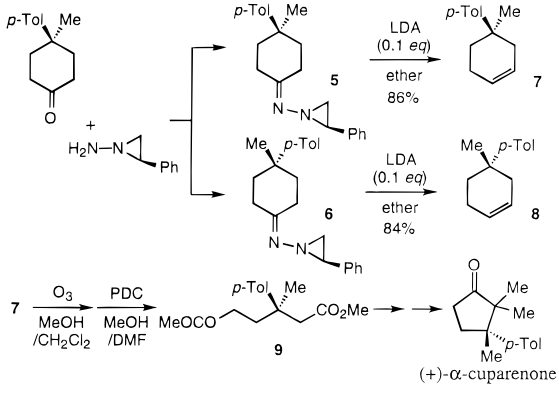
Other selected examples are listed in Table 1. Virtually complete stereoselectivity is observed for butyl cyclohexyl ketone phenylaziridinylhydrazone **1** (R^1 = cyclohexyl, R^2 = Pr) (entry 6). This selectivity is in marked contrast to the normal Shapiro reaction of the corresponding tosylhydrazone with BuLi/TMEDA (*cis/trans* = 75:25). Stereoselective diene synthesis appears feasible (entry 7). In the case of unsymmetrical 3-undecanone, a mixture of (*Z*)-hydrazone **1** (R^1 = Et, R^2 = heptyl) and (*E*)-hydrazone **1** (R^1 = octyl, R^2 = Me) was formed in ∼1:1 ratio, which was easily separated by column chromatography on silica gel.[5] Reaction of the (*Z*)-hydrazone **1** (R^1 = Et, R^2 = heptyl) with catalytic LDA (0.1 equiv) at 0 °C for 1 h yielded *cis*-3-undecene **2** (R^1 = Et, R^2 = heptyl) in 88% yield with exceedingly high regio- and stereoselectivity (entry 8).

Scheme 1



Similarly, the (*E*)-hydrazone **1** (R^1 = octyl, R^2 = Me) was transformed to *cis*-2-undecene (**2**, R^1 = octyl, R^2 = Me) almost exclusively in 98% yield (entry 9). These results clearly support regioselective deprotonation with amide base by preferential abstraction of the α-methylene hydrogen *syn* to the phenylaziridyl moiety in **1** and subsequent decomposition of the resulting **3** to furnish, with extrusion of styrene and nitrogen, alkenyllithium **4**, which abstracts the amine proton, producing alkene product **2** in regeneration of lithium amide for further use in the catalytic cycle for *cis*-alkene formation (Scheme 1). The excellent *cis* selectivity is also explainable by the internal chelation structure **3**.

Utilization of optically active 1-amino-2-phenylaziridine for the present methodology allows the facile synthesis of optically active alkenes. For example, condensation of 4-methyl-4-*p*-tolylcyclohexanone with optically pure 1-amino-2-phenylaziridine (>99% ee),[6] followed by separation of diastereomeric hydrazones by column chromatography, afforded (*R*,*R*)-hydrazone **5** and (*S*,*R*)-hydrazone **6**. Individual treatment of **5** and **6** in ether with catalytic LDA (0.1 equiv) at 0 °C for 1 h gave rise to (*R*)- and (*S*)-3-methyl-3-*p*-tolyl-cyclohexene (**7**, 94% ee, and **8**, 92% ee, respectively) in high yield. Ozonolysis of **7** in $MeOH/CH_2Cl_2$ and further oxidation by PDC in dry DMF in the presence of MeOH gave the known diester **9** in 61% yield, which is a chiral key intermediate of (+)-α-cuparenone.[7]



The application of the present method in natural product synthesis is illustrated in Scheme 2 by a simple route to

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(1) Reviews: (a) Shapiro, R. H. *Org. React.* **1976**, *23*, 405. (b) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55. (c) Chamberlin, A. R.; Bloom, S. H. *Org. React.* **1990**, *39*, 1.

(2) Bamford−Stevens reaction of ketone phenylaziridinylhydrazones: (a) Mohamadi, F.; Collum, D. B. *Tetrahedron Lett.* **1984**, *25*, 271. (b) Sarkar, T. K.; Ghorai, B. K. *J. Chem. Soc., Chem. Commun.* **1992**, 1184.

(3) Shapiro reaction of ketone phenylaziridinylhydrazones with excess base: Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774.

(4) Muller, R. K.; Joos, R.; Felix, D.; Schreiber, J.; Wintner, C.; Eschenmoser, A. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 56.

(5) The regiochemical assignments of (*E*)- and (*Z*)-isomers were made by ^{13}C NMR analysis: Bunnell, C. A.; Fuchs, P. L. *J. Org. Chem.* **1977**, *42*, 2614.

(6) Prepared from optically pure (*R*)-1-phenyl-1,2-ethanediol and purified by recrystallization of 1-amino-2-phenylaziridinium acetate according to the procedure in ref 4.

(7) The enantioselectivity of **7** and **8** was determined by HPLC analysis, and the absolute configuration was correlated to the known diester **9** {70% ee, $[\alpha]_D$ −20.0° (*c* = 1.3, $CHCl_3$)}: Honda, T.; Kimura, N.; Tsubuki, M. *Tetrahedron*: *Asymmetry* **1993**, *4*, 21.

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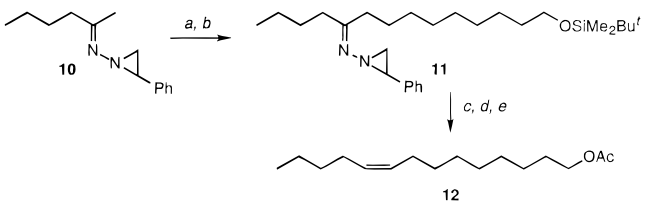
Table 1. Selective *cis*-Alkene Synthesis by the Catalytic Shapiro Reaction[a]

	substrate, **1**					isomeric ratios	
entry	R^1	R^2	lithium amide (equiv)	condition (°C, h)	yield[b] (%)	regio[c]	*cis*/*trans*[d]
1	pentyl	butyl	LDA (0.3)	−20, 1; 0, 3	84		99.4:0.6
2			LDA (0.05)	0, 4	93		99.4:0.6
3			LiTMP (0.3)	0, 1	88		99.1:0.9
4			$LiNEt_2$ (0.3)	0, 1	68		98:2
5			$LiN(TMS)_2$ (0.3)	25, 20	25		96:4
6	cyclohexyl	propyl	LDA (0.1)	−20, 1; 0, 1	89	100:0	99.94:0.06[c] [75:25][f]
7	(*E*)-1-methyl-1-propyl	heptyl	LDA (0.3)	0, 2; 25, 3	85	100:0	96:4[c] [34:66][f]
8	ethyl	heptyl	LDA (0.1)	0, 1	88	98:2	99.6:0.4
9	octyl	methyl	LDA (0.1)	0, 1	98	99.5:0.5	99.6:0.4

[a] The ketone hydrazone **1** was treated with a catalytic amount of lithium amide in ether under the given reaction conditions. [b] Isolated yield. [c] Determined by capillary GLC. [d] Determined by capillary GLC after conversion to their epoxides with MCPBA. [e] Determined by capillary GLC. [f] Ratios by the Shapiro reaction of the corresponding tosylhydrazones with BuLi/TMEDA. The stereochemical assignments were made by ^{13}C NMR spectroscopy.

Scheme 2[a]



[a] (a) LDA, ether; (b) $Br(CH_2)_8OSiMe_2Bu^t$; (c) catalytic LDA, ether; (d) AcOH, THF, H_2O; (e) Ac_2O, pyridine, catalytic DMAP, CH_2Cl_2.

(*Z*)-9-tetradecenyl acetate (**12**), a component of the sex pheromone of the summer fruit tortrix moth (*Adoxophyes orana*).[8] Thus, selective lithiation of 2-hexanone phenylaziridinyl-(*E*)-hydrazone (**10**) with LDA (1.5 equiv) in THF at −78 °C for 1 h and subsequent alkylation with 8(*tert*-butyldimethylsiloxy)-octyl bromide at −45 °C for 2 h gave (*Z*)-hydrazone **11** in 64% yield. The LDA-catalyzed (0.1 equiv) selective decomposition[9] of the (*Z*)-hydrazone **11** in ether at 0 °C for 1 h, followed by hydrolysis of the silyl ether with AcOH in aqueous THF at 25 °C for 3 h, yielded (*Z*)-9-tetradecen-1-ol, which was acetylated with Ac_2O and pyridine in CH_2Cl_2 in the presence of catalytic DMAP at 25 °C for 1 h to afford the target compound **12** in 79% yield (*cis*/*trans* = 99.6:0.4, *regio* = 100:0).[10]

Supporting Information Available: Text describing the experimental procedure and spectral data for all compounds (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(8) Minks, A. K.; Voerman, S. *Entomol. Exp. Appl.* **1973**, *16*, 541.

(9) Decomposition of (*Z*)-hydrazone **11** with catalytic LDA proceeds regioselectively due to *syn*-directing effect: Augeri, D. J.; Chamberlin, A. R. *Tetrahedron Lett.* **1994**, *35*, 5599.

(10) The isomeric purity of **12** was determined by capillry GLC analysis after conversion to the epoxide with MCPBA. The authentic sample of **12** was prepared from 9-tetradecyn-1-ol by hydrogenation over P2−Ni with subsequent acetylation of (*Z*)-enol (*cis*-selectivity = 98.8%): Hoskovec, M.; Saman, D.; Koutek, B. *Collect. Czech. Chem. Commun.* **1990**, *55*, 2270.