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A chemo- and stereoselective reduction of cycloalkynes to (*E*)-cycloalkenes

Alois Fürstner* and Karin Radkowski
Max-Planck-Institut für Kohlenforschung, D-45470 Mülheim/Ruhr, Germany.
E-mail: fuerstner@mpi-muelheim.mpg.de; Fax: +49 208 306 2994; Tel: +49 208 306 2342

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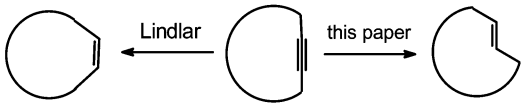
A stereoselective entry into (*E*)-cycloalkenes is described, comprising the ring closing alkyne metathesis (RCAM) of suitable diynes, a ruthenium-catalyzed *trans*-selective hydrosilylation of the cycloalkynes thus formed, followed by a desilylation of the resulting vinylsilanes mediated by AgF.

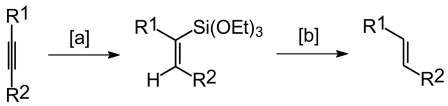
One of the few shortcomings limiting the superb application profile of ring closing olefin metathesis (RCM) is the lack of stereocontrol over the emerging double bond during the formation of macrocyclic rings.[1] The cycloalkenes are usually obtained as (*E*,*Z*)-mixtures, the ratio of which can, at present, be neither controlled nor even accurately predicted. Although this problem may eventually be solved by the development of more selective catalysts and/or the implementation of improved retrosynthetic logic,[2] the use of ring closing alkyne metathesis (RCAM) opens an alternative approach to macrocycles which is devoid of this shortcoming.[3] Thus, RCAM followed by Lindlar reduction of the resulting cycloalkynes constitutes a widely applicable, mild and stereoselective route to (*Z*)-alkenes (Scheme 1) as evident from successful implementations of this methodology into the total synthesis of targets as complex as the epothilones,[4] prostaglandins,[5] glycolipids,[6] alkaloids,[7] perfume ingredients,[8] peptide isosteres[9] and other bioactive compounds.[10]

To increase the relevance of RCAM further, it is desirable to use the cycloalkynes as relays for the corresponding (*E*)-alkenes as well (Scheme 1). Although several methods for the reduction of alkynes to (*E*)-alkenes are known in the literature,[11–13] none of them meets all the criteria of selectivity and functional group tolerance required for applications to advanced organic synthesis. Described below is a two-step protocol which intends to fill this gap. Our disclosure is prompted by a very recent publication of Trost *et al.* reporting a conceptually similar conversion of *acyclic* alkynes into the corresponding (*E*)-alkenes.[14]

Key to success is the hydrosilylation of the cycloalkynes formed by RCAM which proceeds in a highly chemo- and stereoselective manner if catalyzed by the cationic ruthenium complex $[Cp^*Ru(MeCN)_3]PF_6$ (Scheme 2).[15,16] This reaction provides good to excellent yields even with catalyst loadings ⩽1 mol%, it proceeds with high selectivity in favor of the *trans*

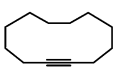
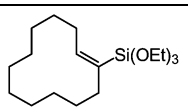
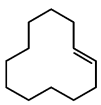
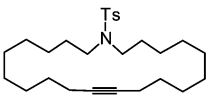
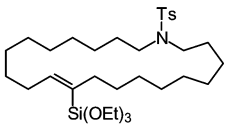
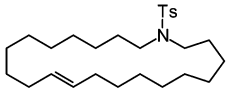
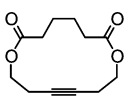
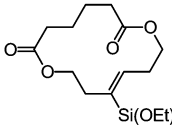
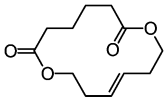
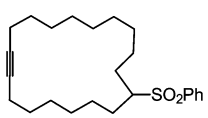
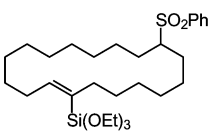
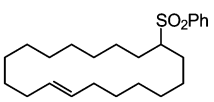
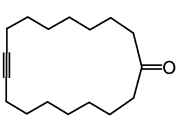
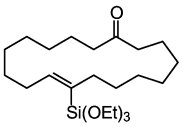
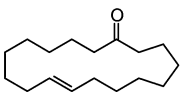


Scheme 1 Cycloalkynes as relays for the preparation of either (*Z*)- or (*E*)-cycloalkenes.



Scheme 2 *Reagents and conditions*: [a] $(EtO)_3SiH$, $[Cp^*Ru(MeCN)_3]PF_6$ (1 mol%), CH_2Cl_2, r.t.; [b] AgF (2 eq.), THF/aq. MeOH, r.t.

Table 1 Reduction of cycloalkynes prepared by RCAM to (*E*)-cycloalkenes *via* the corresponding vinylsiloxanes

Substrate	Vinylsiloxane	Yield (%) (*E*:*Z*)	Cycloalkene	Yield (%) (*E*:*Z*)
		90 (91:9)		84 (90:10)
		86 (>98:2)		85 (>98:2)
		93 (95:5)		92 (95:5)
		92 (>98:2)[a]		88 (>98:2)
		93 (>98:2)		70 (>98:2)

[a] This product is obtained as a 1:1 mixture of regioisomers.

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addition, and is known to be compatible with a host of functional groups. Although various silanes can be used, $(EtO)_3SiH$ turned out to be best suited for the envisaged further elaboration.

Next, the protodesilylation of the vinylsiloxanes thus formed was investigated. Although several methods for this seemingly trivial transformation are known in the literature, none of them is particularly attractive from the application point of view. Specifically, simple protonation with strong mineral acids such as HI suffers from a narrow functional group tolerance and possible problems with the configurational integrity of the double bond.[17] The use of TBAF in various media, on the other hand,[18] requires high temperatures (≥80 °C) and was found to be rather unselective even when applied to the otherwise unfunctionalized cyclododecene derivative depicted in entry 1 (Table 1).

As a consequence, we have carried out a screening of other possible reagents that might effect the desired protodesilylation under sufficiently mild conditions. We were pleased to find that AgF is exquisitely suited for this purpose, meeting the stringent criteria of general applicability and compatibility with sensitive functional groups. Stirring of the vinylsiloxanes with AgF (1.5–2.0 eq.) in THF–aq. MeOH in the dark at ambient temperature effects the rapid, quantitative and selective protodesilylation without noticable isomerization of the alkene interfering; the corresponding (*E*)-alkenes are obtained in good to excellent yields (Table 1).† Although the mode of action of AgF has not yet been elucidated in detail, the fact that it is far more effective than other flouride sources‡ suggests a synergetic action which may result from the specific affinity of the fluoride anion for silicon and that of the silver cation for π-bonds. It is assumed that the fluoride initially leads to a pentacoordinate silicate species,[19] thus facilitating a transmetalation to a transient vinylsilver intermediate that is immediately trapped to give the alkene product.

In summary, a two step protocol for the net conversion of cycloalkynes to (*E*)-cycloalkenes has been developed which is sufficiently mild and selective to serve advanced organic synthesis. It helps to upgrade the now readily available cycloalkynes into versatile relays for the stereoselective formation of either geometrical isomer of the corresponding macrocyclic cycloalkenes. Further studies on this and related reactions are in progress and will be reported in due course.

Notes and references

† *Representative procedure*: To a solution of cycloheptadec-9-yn-1-one (65 mg, 0.262 mmol)[8] and $(EtO)_3SiH$ (51 mg, 0.31 mmol) in CH_2Cl_2 (0.5 mL) was added $[Cp^*Ru(MeCN)_3]PF_6$ (1.3 mg, 1 mol%) and the resulting mixture was stirred for 15 min at ambient temperature. Prior to work-up, $P(CH_2OH)_3$ (5 mg) was added and stirring continued for 30 min. The mixture was filtered through a short pad of silica which was carefully rinsed with Et_2O, and the combined filtrates were evaporated to give (*Z*)-9-[(trisethoxy)silyl]cycloheptadec-9-en-1-one as a colorless syrup (100 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04 (t, *J* 7.4 Hz, 1H), 3.80 (q, *J* 7.0 Hz, 6H), 2.36 (q, *J* 7.1 Hz, 4H), 2.28 (q, *J* 7.1 Hz, 2H), 2.12 (t, *J* 6.3 Hz, 2H), 1.57–1.63 (m, 4H), 1.38–1.43 (m, 4H), 1.26–1.30 (m, 12H), 1.22 (t, *J* 7.0 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.0, 148.7, 132.2, 58.1, 43.1, 42.0, 36.9, 31.4, 29.5, 29.1, 28.7, 28.5, 28.4, 27.9, 27.4, 24.5, 23.6, 18.3; IR: 1712 cm^{-1}; MS (EI) *m*/*z* (rel. intensity): 412 ([M$^+$], 1.5), 366 (100%).

A suspension of AgF (1 M in aq. MeOH, 0.47 mL, 0.47 mmol) was added to a solution of this vinylsiloxane (95 mg, 0.23 mmol) in THF (1.2 mL) and the resulting mixture was stirred in the dark for 3 h. The insoluble residues were filtered off and carefully washed with Et_2O and EtOAc (3 mL each), the combined filtrates were evaporated and the residue purified by flash chromatography (pentane–Et_2O, 8:1) to give (*E*)-cycloheptadec-9-en-1-one as a colorless syrup (40 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.31 (m, 2H), 2.37 (t, *J* 7.1 Hz, 4H), 2.01 (m, 4H), 1.60 (m, 4H), 1.20–1.37 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.0, 131.0, 42.5, 32.0, 28.9, 28.8, 28.4, 27.4, 24.1; IR *ν*/cm^{-1}: 1711 (C=O), 966 ((*E*)-alkene); MS (EI) *m*/*z* (rel. intensity): 250 ([M$^+$], 100%).

‡ Other fluoride sources tested include: HF–pyridine, NaF, KF, CsF, TBAF, $(Bu_4N)(Ph_2SiF_3)$, ZnF_2, FeF_2.

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