Enantioselective Synthesis of Cyclohexenylalkenes by Asymmetric Deprotonation of 4-*tert*-Butylcyclohexanone Followed by *O*-Nonaflation and Heck Couplings

Ilya M. Lyapkalo,[a] Matthias Webel,[b] Hans-Ulrich Reissig*[a]

[a] Freie Universität Berlin, Institut für Chemie − Organische Chemie, Takustr. 3, 14195 Berlin, Germany
[b] Institut für Organische Chemie der Technischen Universität Dresden, 01062 Dresden, Germany
Fax +49-(0)30/8385-5367, E-mail: hans.reissig@chemie.fu-berlin.de

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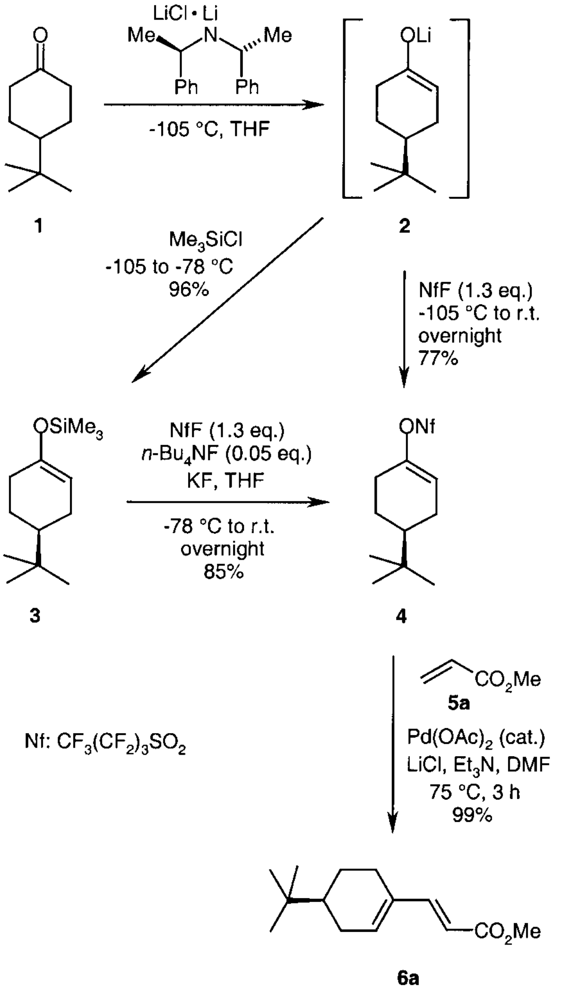
Abstract: Formation of (*S*)-4-*tert*-butylcyclohex-1-enyl nonaflate **4** by reaction with nonafluorobutanesulfonyl fluoride was found to be highly enantioselective both from (*S*)-4-*tert*-butyl-1-(trimethylsiloxy)cyclohexene **3** and from the corresponding lithium enolate **2**. The latter was generated by kinetic deprotonation of 4-*tert*-butylcyclohexanone **1** with lithium (*R,R'*)-bis(1-phenylethyl)amide as enantiopure base. A number of functionalized 2-(4-*tert*-butylcyclohex-1-enyl)alkenes **6** were prepared with roughly 90% enantiomeric excess from trimethylsilyl enol ether **3** using a one-pot nonaflation/Heck reaction sequence.

Key words: enantioselective deprotonation, silyl enol ethers, alkenyl nonaflates, Heck reaction, 1,3-dienes

Desymmetrizing transformation of enantiotopic groups in plane-symmetrical substrates under the action of chiral reagents or catalysts is an elegant trick permitting straightforward access to enantiomerically pure or enriched compounds. Since Koga's discovery of desymmetrization of 4-substituted cyclohexanones[1] by enantioselective kinetically controlled deprotonation with enantiopure lithium amides this reaction was broadly extended[2] and adapted as a key step in syntheses of a number of natural products.[3] The most popular protocol implies a fixation of the initially formed chiral lithium enolate as trialkylsilyl enol ether;[4] in far most cases, the following transformations exploit the reactivity of the enolate C,C-double bond.[2a,3d,e]

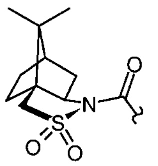
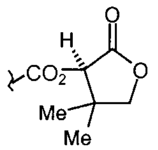
We recently found that model substrate 4-*tert*-butylcyclohexanone **1** could be smoothly transformed into enantiomerically highly enriched (*S*)-4-*tert*-butylcyclohex-1-enyl nonaflate **4**[5] when known silyl enol ether **3** was subjected to our fluoride catalysed *O*-nonaflation procedure.[6] The enantiomerically enriched trimethylsilyl enol ether **3** was prepared from 4-*tert*-butylcyclohexanone **1** (Scheme 1) according to a modified Koga protocol[7] using commercially available (*R,R'*)-bis(1-phenylethyl)ammonium chloride and isolated after cautious acidic (pH = 2) aqueous workup[8] by vacuum kugelrohr distillation in 96% yield.[9] Treatment of a mixture of **3** and tetra-*n*-butylammonium fluoride (5 mol%) with nonafluorobutanesulfonyl fluoride (NfF) afforded target compound **4** in 85% yield after column chromatography (silica gel, hexane).[10] Alternatively, this product was prepared by direct trapping of lithium enolate **2** with the *O*-sulfonylating agent NfF[11] which furnished **4** in 77% yield and almost identical optical purity ($[\alpha]_{365}$ = -101.6 (c = 1.73) versus $[\alpha]_{365}$ = -104.0 (c = 1.82), both measurements in C_6H_6).

The following Heck reactions[12] of both samples of the enantiomerically enriched nonaflate **4** with methyl acrylate **5a** (Scheme 1) resulted in high yields of enantiomerically enriched methyl (*E*)-3-[(*S*)-4-*tert*-butylcyclohex-1-enyl]propenoate **6a**.[5,13]



Scheme 1

Table Synthesis of 1,3-Dienes **6a**-**f**.

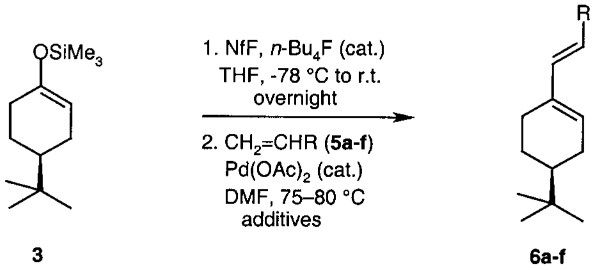
Reaction conditions		Product				
Additives	Time (h)		R	Yield (%)	m.p. (°C)	$[\alpha]_D$ (c, $CHCl_3$)
LiCl, Et_3N	3	**6a**	CO_2Me	85	43–46	-109.3 (1.18)
LiCl, Et_3N	5	**6b**	CN	86[a]	62–79	-117 (1.05)
LiCl, Et_3N	5	**6c**	C(O)Me	85	79–81	-107 (1.18)
KOAc, K_2CO_3	24	**6d**	Ph	78	41–45	-90.5 (0.64)
KOAc, K_2CO_3	6	**6e**		70	170–175	-142 (0.37)
KOAc, K_2CO_3	6	**6f**		87	122–124	-70.4 (0.47)

[a] A mixture of *E*/*Z*-isomers (9: 1); in the presence of KOAc/K_2CO_3 in place of LiCl/Et_3N, the reaction of **4** with acrylonitrile gives only 44% conversion of the starting material with the *E*/*Z*-ratio of the product **6b** being 4: 1.

As nonaflation reaction and Heck coupling imply intermediacy of highly reactive species (ionic enolate and alkenyl palladium, respectively) which may suffer proton/hydrogen migrations resulting in eventual erosion of enantiomeric purity, we aimed to carefully establish the enantiomeric excess of product **6a**. After several unsuccessful attempts,[14] we found that GC-analysis of the *rac*-**6a** on a fused silica capillary column [*Macherey-Nagel* heptakis-(6-*O*-*tert*-butyl-2,3-di-*O*-methyl)-β-cyclodextrin] provides clean separation of both enantiomers allowing reliable integration of the peaks. The following analysis of enantiomerically enriched sample of **6a** showed a 94.5: 5.5 ratio of the enantiomers. Thus, the enantiomeric excess of 89% as generated by the asymmetric deprotonation is fully transferred to nonaflate **4** and subsequently to coupling product **6a**.

Having established the stepwise sequence as described above, we applied the one-pot nonaflation-Heck coupling procedure previously reported by us for achiral substrates[15] to synthesize the enantiomerically enriched functionalized 1,3-dienes **6** from (*S*)-4-*tert*-butyl-1-(trimethylsiloxy)cyclohexene **3** (Scheme 2, Table). For this purpose the required components for the second step were simply added to the reaction mixture containing intermediate nonaflate **4**.[16] The Heck coupling step proceeds smoothly at 75–80 °C to give the desired 1,3-dienes in good yields. With exception of nitrile **6b** (*E*/*Z* = 9:1), the products obtained were isolated as pure *E*-isomers.

Heck couplings with enantiopure acrylate derivatives **5e** and **5f** were performed to investigate the enantioselectivity of the overall reaction sequence (Scheme 2), which would be deduced from the diastereomeric excess of the products **6e** and **6f**. However, in both cases no signal splitting could be observed in the NMR spectra probably because the two chiral units are too much separated. As mentioned above we could solve this problem by applying GC-analysis to **6a**. We assume that all dienes **6** presented in this report have an enantiomeric excess in the range of 89% like precursor silyl enol ether **3**.



Scheme 2

In conclusion, we have found that enantioselective deprotonation of 4-*tert*-butylcyclohexanone (**1**) followed by nonaflation with the industrial product nonafluorobutanesulfonyl fluoride gives (*S*)-4-*tert*-butylcyclohex-1-enyl nonaflate **4** in high yield and with excellent enantioselectivity. The reaction is proven to work equally well in both direct kinetic *O*-nonaflation of the lithium enolate **2** and via the respective trimethylsilyl enol ether **3**, thus constituting two complementary options. In the latter case, reaction was successfully adapted to the synthesis of chiral functionalized dienes **6** using one-pot nonaflation-Heck coupling protocol. We currently investigate whether the described method is generally applicable to plane-symmetrical cyclic ketones. The resulting enantiomerically highly enriched dienes should be very useful chiral building blocks for cycloadditions, Michael reactions or other additions to the 1,3-diene system.

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References and Notes

(1) R. Shirai, M. Tanaka, K. Koga, *J. Am. Chem. Soc.* **1986**, *108*, 543−545.

(2) Reviews: (a) P. J. Cox, N. S. Simpkins, *Tetrahedron: Asymmetry* **1991**, *2*, 1−25. (b) K. Koga, *Pure Appl. Chem.* **1994**, *66*, 1487−1492. (c) P. O'Brien, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439−1457 and references cited therein.

(3) (a) H. Izawa, R. Shirai, H. Kawasaki, H.-d. Kim, K. Koga, *Tetrahedron Lett.* **1989**, *30*, 7221−7224. (b) J. Leonard, D. Ouali, S. K. Rahman, *Tetrahedron Lett.* **1990**, *31*, 739−742. (c) M. Majewski, R. Lazhny, *Tetrahedron Lett.* **1994**, *35*, 3653−3656. (d) T. Momose, M. Toshima, N. Toyooka, Y. Hirai, C. H. Eugster, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1307−1313. (e) I. Vaulont, H.-J. Gais, N. Reuter, E. Schmitz, R. K. L. Ossenkamp, *Eur. J. Org. Chem.* **1998**, 805−826.

(4) The reaction was successfully developed in both internal[1,3a,d] and successive[3e] quenching modes, most commonly with R_3SiCl.

(5) The configuration of the stereogenic center was assigned as (*S*) by analogy with the silyl enol ether **3** whose absolute configuration was strictly determined to be (*S*), see Ref.[1]

(6) E. Hirsch, S. Hünig, H.-U. Reissig, *Chem. Ber* **1982**, *115*, 3687−3696. Also see Ref.[15]

(7) K. Sugasawa, M. Shindo, H. Noguchi, K. Koga, *Tetrahedron Lett.* **1996**, *37*, 7377−7380. A successive quenching with Me_3SiCl as described in Ref.[3e] was applied.

(8) This workup results in clean separation of (*R,R'*)-bis(1-phenylethyl)amine from the silyl enol ether **3**. An addition of excess of KOH to the aqueous phase followed by extraction with hexane allows quantitative recovery of the enantiopure amine.

(9) Optical rotation: $[\alpha]_{365}$ = -209.6, $[\alpha]_D$ = -65.7 (c = 1.22 in C_6H_6), 89% ee. There is some divergence between optical rotatory power magnitudes reported for enantiomerically pure **3**, for details see Ref.[1] and C. M. Cain, R. P. C. Cousins, G. Coumbarides, N. S. Simpkins, *Tetrahedron* **1990**, *46*, 523−544. As a chiral induction in nonaflation or Heck-coupling step seems to be very unlikely, we infer the enantiomeric excess of **3** (at least 89%) from that of the product **6a**.

(10) The quality of n-Bu_4NF is essential to achieve good yields in the transformation of trimethylsilyl enol ethers into enol nonaflates. To this end, we applied drying of the commercially available solutions with freshly activated molecular sieves 4 Å (M. Webel, *Dissertation*, Technische Universität Dresden **2000**) or used n-Bu_4NF solution in the presence of thoroughly dried KF powder (I. M. Lyapkalo, H.-U. Reissig, M. Webel, *Eur. J. Org. Chem.* **2001**, submitted for publication).

(11) The kinetic deprotonation was performed as described in Ref.[3e] followed by addition of the neat NfF at -105 °C for 10 min and gradual warming up to ambient temperature overnight.

(12) Enol nonaflates have occasionally been shown to be very efficient components in Heck coupling reactions, for example, see: (a) S. Bräse, A. de Meijere, *Angew. Chem.* **1995**, *107*, 2741−2743; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2545. (b) S. Bräse, *Synlett* **1999**, 1654−1656. We applied the conditions as described previously by us (Ref.[10])

(13) A good consistency in the optical rotatory power magnitudes of both samples was observed: $[\alpha]_D$ = -111.2 and -109.5 (both c = 1.20, $CHCl_3$).

(14) We failed to observe separate NMR signals of the diastereomers prepared by $LiAlH_4$ reduction of enantiomerically enriched **6a** followed by acylation of the resultant alcohol with *Mosher's* chloride.

(15) M. Webel, H.-U. Reissig, *Synlett* **1997**, 1141−1142.

(16) Typical procedure **3** → **6a**: Thoroughly ground potassium fluoride (0.100 g, 1.72 mmol) was dried at 210−220 ºC (0.03 mbar) for 1 h (kugelrohr apparatus), allowed to cool to r.t., and THF (0.50 ml) and 1.05 M n-Bu_4NF in THF (0.05 mL, 0.05 mmol) were subsequently added (see Ref.[10]). The resulting suspension was vigorously stirred at r.t. for 20 min under Ar-atmosphere before cooling to -78 ºC. (*S*)-**3** (0.226 g, 1.00 mmol, 89% ee) and NfF (0.363 g, 1.20 mmol) were subsequently added at -78 ºC. The mixture was then gradually warmed up to r.t. and stirred overnight (15−17 h). To the resulting solution containing (*S*)-**4**, were subsequently added LiCl (0.15 g, 3.50 mmol), Et_3N (0.36 g, 3.50 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), DMF (1.5 mL) and methyl acrylate (0.129 g, 1.50 mmol). The reaction flask was then flushed with argon for 2−3 min, tightly closed again and heated with vigorous stirring at 73−75 ºC (bath temperature) for 3 h. Aqueous workup, hexane extraction followed by column chromatography (gradient elution: hexane → hexane/Et_2O 20:1) provided (*S*)-**6a** (189 mg, 85**%** yield. 89% ee) as colourless crystals, mp 43−46 °C, $[\alpha]_D$ = -109.3 (c = 1.18, $CHCl_3$) (*cf.* Ref.[13]). For analytical data of *rac*-**6a** see: W. J. Scott, M. R. Peña, K. Swärd, S. J. Stoessel, J. K. Stille, *J. Org. Chem.* **1985**, *50*, 2302−2308.

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