C–H Acidity

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Estimation of the Kinetic Acidity from Substrate Conformation—Stereochemical Course of the Deprotonation of Cyclohexenyl Carbamates**

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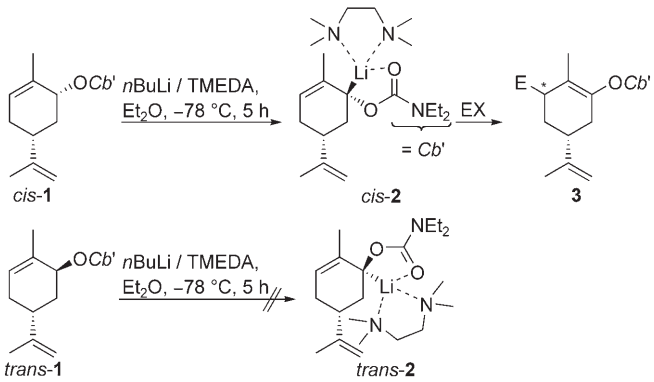
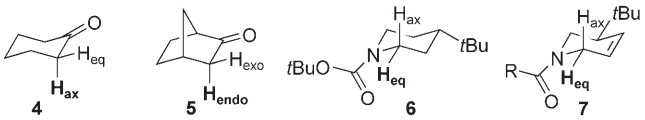
Dedicated to Professor Gerhard Erker on the occasion of his 60th birthday

Chiral lithiated 2-alkenyl carbamates are valuable intermediates for enantioselective homoaldol reactions.[1] These can be prepared by using enantiotopos-differentiating α deprotonation of achiral primary 2-alkenyl carbamates mediated by (−)-sparteine,[2] γ deprotonation of 1-alkenyl carbamates,[3] or by stereospecific deprotonation of enantioenriched secondary 2-alkenyl carbamates.[4] As we recently observed, *cis*-carveyl *N*,*N*-diethylcarbamate (**1**) is smoothly deprotonated by *n*-butyllithium/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in diethyl ether to form the expected lithium compound *cis*-**2**, which was trapped with electrophiles to form the γ-addition products **3** (Scheme 1).[5] However, under the same conditions, the *trans* diastereomer *trans*-**1** was not lithiated.[6] We suspected that an insufficient kinetic acidity of the allylic α proton which arises from minor stabilization of the developing negative charge by the adjacent double bond might be the origin.



Scheme 1. Deprotonation of carveyl *N*,*N*-diethylcarbamates. *Cb*′ = C(O)NEt$_2$, E = electrophile.

Pioneering investigations by Corey and Sneen and later Ireland et al had shown that stereoelectronic effects have a great influence on the acidity of cyclic carbonyl compounds.[7,8] The transition states of the deprotonation of cyclohexanones are stabilized by a σ–π* delocalization of the cleaved C–H bond and the carbonyl double bond. As a result of better orbital overlap, the axial proton is preferentially removed (Scheme 2). The energy difference between axial and equatorial deprotonation of cyclohexanone (**4**) and norcamphor (**5**) is close to 3 kcal mol^{-1}, as estimated by DFT calculations.[9]



Scheme 2. Enhanced acidity in cyclic compounds through stereoelectronic effects.

Interestingly, deprotonation of piperidine carbamate **6** and addition of a carbonyl compound gave exclusively *syn* equatorial substitution.[10] The amide conjugation in the transition state (TS) and the conformation of the *N*-*tert*-butoxycarbonyl (*N*-Boc) group direct the base to remove an equatorial proton.[11] The ratio between pseudoequatorial and pseudoaxial deprotonation in the conformationally fixed Δ^3-piperidinyl amide **7** is only 2.4 to 1, and hence the activation by the olefinic π system here is relatively small.[12] The question arose: to what extent do stereoelectronic effects between the α proton and the adjacent double bond influence the acidity of cyclohexenyl carbamates of type **8**?

We have undertaken a detailed deprotonation study with a selection of substituted cyclohex-2-enyl *N*,*N*-diisopropylcarbamates **8** (Scheme 3), calculated their preferred conformations, and found that the ease of lithiation is predictable from the conformational analysis of the substrates **8**. This simple and synthetically applicable prediction was also investigated and proven by comparison of the DFT calculations of the energetics for the deprotonation step of both diastereomers, *cis*-**8c** and *trans*-**8c**. In addition, the stereo-

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[+] X-ray crystal structure analyses.

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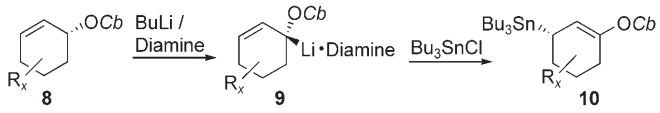
Supporting Information for this article, including experimental procedures for the substitution reactions and density functional calculations, is available on the WWW under http://www.angewandte.org or from the author.



Scheme 3. Stereochemical course of the stannylation reactions. *Cb* = C(O)N*i*Pr$_2$.

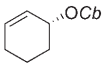
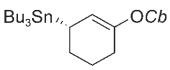
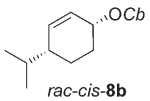
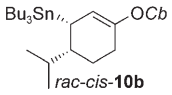
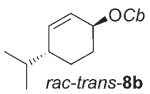
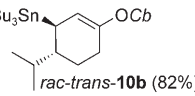
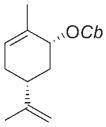
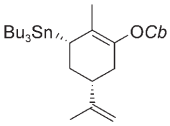
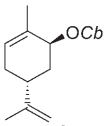
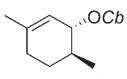
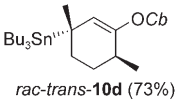
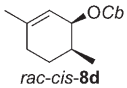
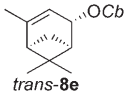
chemical course of the stannylation reaction of some lithium compounds was determined.

The *N*,*N*-diisopropylcarbamates **8** were deprotonated under one of the following conditions with reaction times from two to six hours in diethyl ether at −78 °C: A) *s*BuLi and TMEDA, B) *s*BuLi and *rac-trans*-1,2-bis(dimethylamino)cyclohexane (TMCDA), C) *n*BuLi and TMEDA, or D) *n*BuLi and TMCDA. The intermediate lithium compound **9** was trapped with excess tributyltin chloride to yield the stannanes **10** (Scheme 3, Table 1).[13] Only the cyclohexenes *rac*-**8a**, *rac-cis*-**8b**, *rac-trans*-**8b**, *cis*-**8c**, and *rac-trans*-**8d** afforded the stannanes **10**, thus indicating that only these substrates give stable lithium intermediates **9**. Compounds *trans*-**8c**, *rac-cis*-**8d** and *trans*-**8e** either underwent decomposition reactions or were not lithiated (Table 1).[14,15]

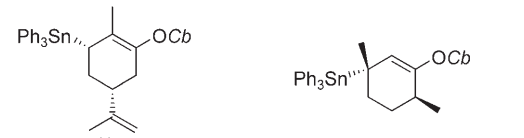
Although the stannylation of lithiated allyl carbamates is accepted to proceed as an *anti* S_E' process,[16,3a] *cis*-**8b** afforded a 2:1 mixture of stannanes *cis*-**10b** and *trans*-**10b**, which were separated by chromatography. Evidently, the stereochemically favored *anti* attack on *cis*-**9b** is hindered by the vicinal isopropyl group on the same face, and thus some *syn*-S_E' attack takes place.

The configuration of the allylic stannanes was clarified by reaction of the intermediates *cis*-**9c** and *rac-trans*-**9d** with triphenyltin chloride in toluene, which led to crystalline products *cis*-**11c** and *rac-trans*-**11d** (Scheme 4). The absolute configuration of *cis*-**11c** and the relative configuration of *rac-trans*-**11d** were determined by X-ray analysis.[17–19]

Table 1: Results from the stannylation reactions.

Substrate	Product (yield)	Method, *t* [h]	Φ[a]
 *rac*-**8a**	 *rac*-**10a** (75%)	D, 4	105.3° (135.6°)[b]
 *rac-cis*-**8b**	 *rac-cis*-**10b** (42% + 20% *rac-trans*-**10b**)	D, 6	135.0° (100.2°)[c]
 *rac-trans*-**8b**	 *rac-trans*-**10b** (82%)	A, 2	106.1°
 *cis*-**8c**	 *cis*-**10c** (85%)	A, 2	108.6°
 *trans*-**8c**	(*trans*-**10c**) (–)	A, 2	133.9°
 *rac-trans*-**8d**	 *rac-trans*-**10d** (73%)	B, 2	110.2°
 *rac-cis*-**8d**	(*rac-cis*-**10d**) (–)	B, 2	138.7°
 *trans*-**8e**	(*trans*-**10e**) (–)	C, 5	118.7°[d]

[a] Torsion angles Φ (see Figure 1) of the energetically favored conformers (B3LYP/6-31G*). [b] Conformer **B**. [c] Conformer **F**. [d] X-ray analysis of *trans*-**8e** showed the Φ to be 118° in the solid state.[20]

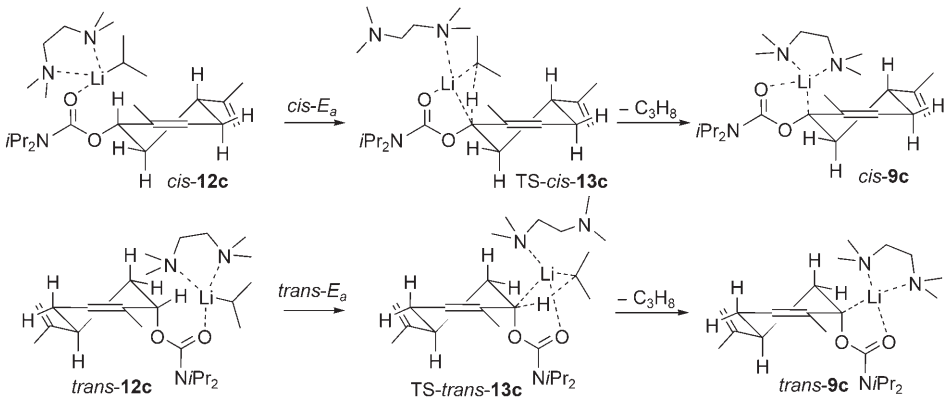


cis-**11c** (59%, d.r. >98:2) *rac-trans*-**11d** (40%, d.r. >98:2)

Scheme 4. Relative configurations of the triphenyltin adducts.

The activation energies (E_a) for the deprotonation of the ternary precomplexes from *cis*-**12c** to TS-*cis*-**13c** and from *trans*-**12c** to TS-*trans*-**13c** were calculated by full geometry optimizations at the DFT level, which included corrections for intramolecular van der Waals interactions (DFT-D-PBE/TZVP,[21] Turbomole[22]) and were found to be 12.4 kcal mol^{-1} and 16.2 kcal mol^{-1}, respectively.[23,24] Thus, the E_a for the deprotonation of *cis*-**12c** is 3.8 kcal mol^{-1} less than for the deprotonation of *trans*-**12c** (Scheme 5). Interestingly, according to the calculations, TMEDA serves as a monodentate ligand in the TS.[25] The resulting lithium complex *cis*-**9c** is 3.9 kcal mol^{-1} lower in energy than *trans*-**9c**, which indicates that the negative charge is better stabilized by the adjacent double bond in *cis*-**9c**.

The similarity of the calculated three-dimensional structures of the ground states **8c**, precomplexes **12c**, and the transition states **13c** demonstrates that the ring conformation is not significantly altered along the reaction pathway. Moreover, the similarity indicates that the stereoelectronic preferences in the deprotonation step are not large enough to override the conformational bias of the substituted cyclohexene rings **8**. Thus, the value of the dihedral angle Φ[26] between the α proton and the adjacent π system in the preferred conformations of the starting carbamates **8** might be a more accessible indicator of the kinetic acidity than the activation energies. The energies and geometries were calculated and fully optimized at the DFT level (B3LYP/6-31G*[27] Gaussian 03[28]). The best interactions of the orbitals and therefore the lowest E_a values are achieved when the α-C–H bond is orthogonal to the plane of the double bond ($\Phi = 90°$, Figure 1, Table 1). Thus, when the torsion angle Φ is less than 110°, kinetic acidity is sufficient for



Scheme 5. Deprotonation of carveyl carbamates *cis*-**12c** and *trans*-**12c**; Activation energies: *cis*-$E_a = 12.4$, *trans*-$E_a = 16.2$ kcal mol^{-1}, $\Delta E_a = 3.8$ kcal mol^{-1}. Complex *cis*-**9c** is 3.9 kcal mol^{-1} lower in energy than *trans*-**9c**.

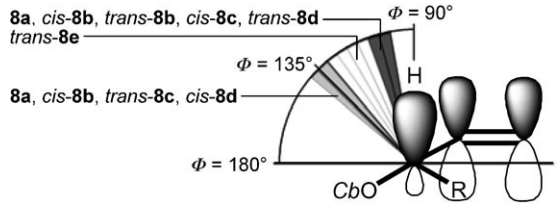
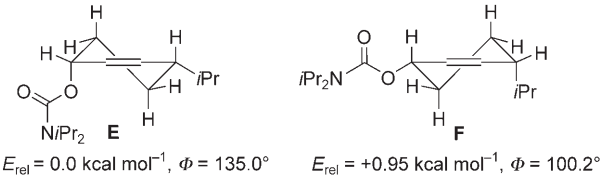


Figure 1. Correlation between the torsion angles Φ[26] in the carbamates **8** and their kinetic acidity. Dark gray: α lithiation is possible, light gray (pseudoequatorial α proton), white: low α-C–H acidity.

deprotonation. At angles equal or greater than $\Phi = 119°$ (as in *cis*-**8e**), no intermediate lithium complex **9** is formed.

For **8a**, four conformational minima **A**–**D** were located (Scheme 6).[29] The lowest energy conformer **A** bears a pseudoequatorial O*Cb* group and a pseudoaxial α-C–H bond,[30] and the torsion angle Φ of 105.3° allows rapid deprotonation. However, the conformer **B** with an inverted cyclohexene ring also has a low energy, but contains a pseudoequatorial α-C–H bond with a Φ of 135.6°, which does not permit efficient overlap of the developing lone pair of electrons with the π system of the double bond. In all substrates **8** and in the precomplexes *cis*-**12c** and *trans*-**12c**, *syn* orientation of the carbonyl oxygen to the α proton is most energetically favored. In addition to the increased acidification upon precomplexation with the base (complex-induced proximity effect, CIPE),[11] a directed lithiation is permitted without requiring a change in the conformational bias of the chelating carbamoyl group. Here, the stereoelectronic effects of the carbamoyloxy group seem to be of minor importance, in contrast to the investigations of piperidines **6** and **7** (Scheme 2) where the conformation of the amide group dominates the kinetic acidification.

For *cis*-4-isopropylcyclohex-2-enyl carbamate *cis*-**8b** there are two competing conformations: **E** ($E_{rel} = 0.0$ kcal mol^{-1}, $\Phi = 135.0°$) and **F** ($E_{rel} = +0.95$ kcal mol^{-1}, $\Phi = 100.2°$; Scheme 7). Both conformers were detected by using temperature-dependent ^{1}H NMR spectroscopy. The energy barrier $\Delta\Delta G^{\neq}$ of the cyclohexene ring inversion at −80 °C in toluene was determined by line-shape analysis. The values of $\Delta\Delta G^{\neq} = (9.5 \pm 0.1)$ and (10.1 ± 0.1) kcal mol^{-1} indicate that steady delivery of the reactive conformer **F** over the course of the reaction, even at −78 °C, is allowed.



Scheme 7. Low-energy conformations of *cis*-**8b**.

We have demonstrated that the cyclohex-2-enyl carbamates **8** smoothly undergo deprotonation to form configurationally stable lithium complexes **9** if the orbital interactions between the α-C–H bond and the π system of the double bond are sufficient. A qualitative prediction of the kinetic acidity of allylic carbamates is possible through simple conformational analysis. This prediction should also be applicable to more complicated C–H acids such as medium-sized cycloalkenyl compounds.[31] Moreover, this approach may prove useful for interpreting other reactions, such as with allylamides **7** (Scheme 2), where the removal of a proton is an essential feature.[12,32]

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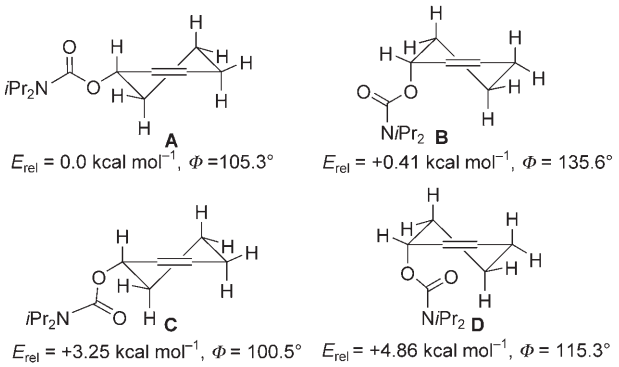

Scheme 6. Low-energy conformations of **8a**.

Keywords: asymmetric synthesis · C–H acidity · carbanions · conformational analysis · density functional calculations

[1] For reviews, see: a) D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282; b) H. Ahlbrecht, U. Beyer, *Synthesis* **1999**, 365; c) D. Hoppe, F. Marr, M. Brüggemann, *Top. Organomet. Chem.* **2003**, *6*, 61; d) P. Beak, T. A. Johnson, D. D. Kim, S. H. Lim, *Top. Organomet. Chem.* **2003**, *6*, 134; e) D. Hoppe, G. Christoph in *The Chemistry of Organolithium Compounds* (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2004**, p. 1055.

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[6] The starting material *trans*-**1** was re-isolated.

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[13] Conditions A–D were tested to optimize the yield of the reaction, but the results were in principle identical.

[14] The use of *s*BuLi/diamine at −78 °C led to rapid (1 h) decomposition of the starting materials **8** with loss of the carbamoyloxy group. With *n*BuLi/diamine, no reaction was observed after a short time (TLC, GC, MS), but decomposition arose with longer reaction times.

[15] The reactions were performed with diastereomerically pure carbamates with the exception of *rac-trans*-**8d** and *rac-cis*-**8d**, which were found to be inseparable by flash chromatography, HPLC, or fractional distillation. However, on deprotonation, the minor diastereomer *rac-cis*-**8d** decomposed, and thus the diastereomerically pure allylstannane *rac-trans*-**10d** could be obtained.

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[17] Crystal data for *cis*-**11c**: $C_{35}H_{43}NO_2Sn$, $M = 628.39$, colorless crystal $0.30 \times 0.25 \times 0.15$ mm, $a = 11.832(1)$, $b = 11.953(1)$, $c = 22.935(1)$ Å, $V = 3243.6(4)$ Å^3, $\rho_{calcd} = 1.287$ g cm^{-3}, $\mu = 0.817$ mm^{-1}, empirical absorption correction ($0.792 \le T \le 0.887$), $Z = 4$, orthorhombic, space group $P2_12_12_1$ (No. 19), $\lambda = 0.71073$ Å, $T = 198$ K, ω and ϕ scans, 17411 reflections collected ($\pm h, \pm k, \pm l$), $[(\sin\theta)/\lambda] = 0.66$ Å^{-1}, 7495 independent ($R_{int} = 0.039$) and 6327 observed reflections [$I \ge 2\sigma(I)$], 358 refined parameters, $R = 0.038$, $wR^2 = 0.087$, Flack parameter −0.04(2), max. residual electron density 0.61 (−0.93) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.

[18] Crystal data for *rac-trans*-**11d**: $C_{33}H_{41}NO_2Sn$, $M = 602.36$, colorless crystal $0.35 \times 0.20 \times 0.10$ mm, $a = 10.127(1)$, $b = 11.259(1)$, $c = 13.926(1)$ Å, $\alpha = 96.94(1)$, $\beta = 100.81(1)$, $\gamma = 102.87(1)°$, $V = 1498.4(2)$ Å^3, $\rho_{calcd} = 1.335$ g cm^{-3}, $\mu = 0.881$ mm^{-1}, empirical absorption correction ($0.748 \le T \le 0.917$), $Z = 2$, triclinic, space group $P\bar{1}$ (No. 2), $\lambda = 0.71073$ Å, $T = 198$ K, ω and ϕ scans, 13806 reflections collected ($\pm h, \pm k, \pm l$), $[(\sin\theta)/\lambda] = 0.67$ Å^{-1}, 7160 independent ($R_{int} = 0.032$) and 6493 observed reflections [$I \ge 2\sigma(I)$], 340 refined parameters, $R = 0.027$, $wR^2 = 0.066$, max. residual electron density 0.73 (−0.75) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.

[19] Data sets were collected with Nonius KappaCCD diffractometers, (Mo radiation, rotating anode). Programs used: for data collection, COLLECT (Nonius B. V., **1998**); for data reduction, Denzo-SMN (Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307); for absorption correction SORTAV(R. H. Blessing, *Acta Crystallogr. Sect. A* **1995**, *51*, 33, R. H. Blessing, *J. Appl. Crystallogr.* **1997**, *30*, 421), and Denzo (Z. Otwinowski, D. Borek, W. Majewski, W. Minor, *Acta Crystallogr. Sect. A* **2003**, *59*, 228); for structure solution, SHELXS-97 (G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467); for structure refinement, SHELXL-97 (G. M. Sheldrick, Universität Göttingen, **1997**); for graphics, SCHAKAL (E. Keller, Universität Freiburg, **1997**). CCDC-616268–616270 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[20] Crystal data for *trans*-**8e**: $C_{17}H_{29}NO_2$, $M = 279.41$, colorless crystal $0.45 \times 0.30 \times 0.30$ mm, $a = 11.016(1)$, $b = 11.932(1)$, $c = 13.227(1)$ Å, $V = 1738.6(3)$ Å^3, $\rho_{calcd} = 1.067$ g cm^{-3}, $\mu = 0.536$ mm^{-1}, empirical absorption correction ($0.795 \le T \le 0.856$), $Z = 4$, orthorhombic, space group $P2_12_12_1$ (No. 19), $\lambda = 1.54178$ Å, $T = 223$ K, ω and ϕ scans, 7631 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.60$ Å^{-1}, 2943 independent ($R_{int} = 0.030$) and 2814 observed reflections [$I \ge 2\sigma(I)$], 188 refined parameters, $R = 0.044$, $wR^2 = 0.121$, Flack parameter 0.1(3), max. residual electron density 0.18 (−0.13) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.

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