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Diastereoselectivity in the McLafferty Rearrangement of Photoionized 3-Methyl Valeramide

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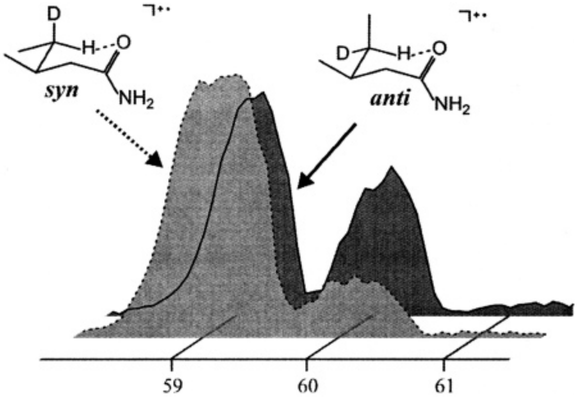

The McLafferty rearrangement of photoionized 3-methyl valeramide proceeds quasi-barrierless and with high regioselectivity. The mass spectra of the stereospecifically labeled syn- and anti-[4-D$_1$]-diastereomers reveal a strong preference for activation of the γ-hydrogen/deuterium in anti-position relative to the methyl group at C(3), which serves as a steric marker. Quantitative analysis of the fragmentation patterns of other photoionized isotopomers permits the determination of primary and secondary kinetic isotope effects (KIEs), the branching ratios of competing McLafferty reactions, and the steric effect (SE) associated with transfer of the diastereotopic H(D) atoms at C(4). While the associated KIEs of the title reaction are negligible, the steric effect (SE = 2.9) is remarkably large for the otherwise flexible, monofunctional compound. The findings can be explained by a preferentially chairlike transition structure for the initial γ-H atom transfer.

Beside regiospecificity, aspects of stereoselectivity are an important feature of organic reactions, which, however, are not easy to probe by mass spectrometric means.[1] Steric effects (SEs) provide complementary information to the insights provided by kinetic isotope effects (KIEs) of decisive C−H bond activation steps. While the KIEs depend on intrinsic structural details of the C−H bond cleavage, the SE is sensitive to conformational aspects such as, for example, the accessibility of a reactive conformation from the precursor molecule.[2] While numerous examples exist for steric effects in the gas-phase fragmentation of ionized cyclic or otherwise rigid molecules,[3] the stereoselectivity of flexible systems[4−6] is usually quite small because of the high degree of freedom for the backbone. Nonetheless, reactions that yield products of different thermochemical stability[7] or proceed through highly ordered transition structures may generate a fleeting rigidity, and the presence of a stereogenic center could possibly evoke large SEs.

Arguably, the most prominent rearrangement process of ionized organic molecules is the McLafferty reaction.[8,9] A particularly large regioselectivity, advantageous for an "unperturbed" analysis of stereochemical effects, is observed for the McLafferty reaction of carboxamides.[10] Valeramide, the simplest system with secondary γ-hydrogens, is a convenient model for larger carboxamides[11] and has itself been studied thoroughly.[12−15] Introduction of a methyl group as a steric marker in the vicinity of the γ-C atom combined with diastereospecific [D$_1$]-labeling of the γ-C position allows us to investigate the diastereotopic aspects of the McLafferty reaction. Thus, 3-methyl valeramide (**1**) and some isotopomers (**1a**−**e**, Chart 1)[16] relevant for a comprehensive analysis of the regio- and diastereoselectivity were prepared and investigated by photoionization mass spectrometry.

The McLafferty (McL) reaction of $\mathbf{1}^{+\bullet}$ (Scheme 1) yields the enol form of ionized acetamide ($[H_2C{=}C(OH)NH_2]^{+\bullet}$, *m/z* = 59) via an initial [1,5]-H shift of a γ-hydrogen to the carbonyl oxygen ($\mathbf{1}^{+\bullet} \rightarrow \mathbf{2}^{+\bullet}$) followed by C(2)−C(3) bond cleavage to expel butene ($\mathbf{2}^{+\bullet} \rightarrow \mathbf{3}^{+\bullet} + C_4H_8$). This process dominates the dissociation behavior of photoionized **1** and bears a low appearance energy, AE(McL)

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[14] Schröder, D.; Loos, J.; Semialjac, M.; Weiske, T.; Schwarz, H.; Höhne, G.; Thissen, R.; Dutuit, O. *Int. J. Mass Spectrom.* **2002**, *214*, 155.

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[16] Note that the synthesis of **1a** and **1b** affords racemic mixtures of diastereomerically pure compounds (>98% de). Thus, **1a** corresponds to a 1:1 mixture of (3*R*,4*S*)-3-methyl-[4-D$_1$]-valeramide and (3*S*,4*R*)-3-methyl-[4-D$_1$]-valeramide. Likewise, **1b** is a mixture of (3*R*,4*R*)-3-methyl-[4-D$_1$]-valeramide and (3*S*,4*S*)-3-methyl-[4-D$_1$]-valeramide. For the sake of simplicity, only one of the two enantiomers is shown. Similarly, **1** and **1c**−**e** were studied as racemic mixtures. Because we are probing only diastereomeric effects, this has no consequences for the data analysis.

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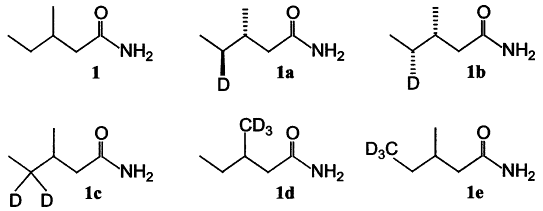
CHART 1



SCHEME 1

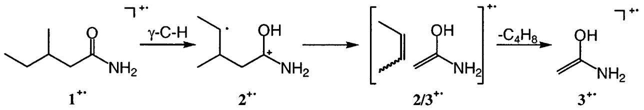


TABLE 1. Ion Masses (*m/z* in amu) and Normalized Intensities[a,b] of the McLafferty Related Processes of the Molecular Ion $1^{+\bullet}$ and Its Isotopomers Obtained by Photoionization of the Corresponding Neutral Amides with 11 eV Photons

	experimental data			corrected data[c]	
	59	60	61	59	60
$\mathbf{1}^{+\bullet}$	97	3		100	
$\mathbf{1a}^{+\bullet}$	61	37	2	63	37
$\mathbf{1b}^{+\bullet}$	84	15	1	87	13
$\mathbf{1c}^{+\bullet}$	51	47	2	52	48
$\mathbf{1d}^{+\bullet}$	61	38	1	63	37
$\mathbf{1e}^{+\bullet}$	97	2	0.4	100	
$\mathbf{1x}^{+\bullet d}$				75	25

[a] Normalized to $\Sigma = 100$ after ^{13}C correction. [b] The error bars of the intensities (I) can be described by the empiric function $\Delta I(I) = I \bullet [0.003 + 1/(I + 1)]$. [c] The corrected data is obtained from the experimental data by subtracting the [McLafferty + 1] contributions (given by $I(m/z = 60) = 3$ for $\mathbf{1}^{+\bullet}$) according to $I(m/z = 60)_{\mathrm{corr}} = I(m/z = 60) - [3 - I(m/z = 61)]$. [d] The hypothetical spectrum of $\mathbf{1x}^{+\bullet}$ is the mathematic average of the data of $\mathbf{1a}^{+\bullet}$ and $\mathbf{1b}^{+\bullet}$.

= 9.52 ± 0.02 eV compared to ionization energy IE(**1**) = 9.36 ± 0.04 eV.[17] The isotopomers $\mathbf{1a}^{+\bullet}$–$\mathbf{1e}^{+\bullet}$ (Chart 1) additionally form ions $[\mathrm{H_2C{=}C(OD)NH_2}]^{+\bullet}$ (m/z = 60). Minor signals at m/z = 60 and 61 (Table 1) result from a side reaction, which is addressed further below. The present study is focused on the mass spectra obtained at a photon energy of $E_{h\nu}$ = 11 eV, which proved to be sufficiently above the ionization threshold to ensure a good quality of the spectra, while side reactions are minor. A full article will cover the data obtained at lower photon energies, for which much more extensive and complex modeling is required because of stronger competition of the side reaction.[17]

The anti- and syn-[4-D$_1$]-isotopomers $\mathbf{1a}^{+\bullet}$ and $\mathbf{1b}^{+\bullet}$ show considerably different patterns for the McLafferty-related signals (Figure 1). The differences between the diastereotopic γ-H(D) atoms with respect to branching ratios as well as possibly associated KIEs lead to a pronounced change of ratio of m/z = 59 and m/z = 60, which is ascribed to the operation of a steric effect. Although the ratios of m/z = 59 and m/z = 60 are indeed much lower for $\mathbf{1a}^{+\bullet}$ than for $\mathbf{1b}^{+\bullet}$, it is not completely reversed, as one might suppose for an inversion of configuration. Two factors are to be considered in this respect. At first, a primary KIE associated with the γ-H(D) transfer may disfavor migration of deuterium for either diastereomer. Hence, the KIE attenuates the SE in $\mathbf{1a}^{+\bullet}$, while both effects operate in the same direction for $\mathbf{1b}^{+\bullet}$. Before attempting to determine the magnitude of the SE, a proper assessment of the KIE therefore is mandatory. The second reason the mass spectra of the two diastereomers are not fully complementary to each other is the additional occurrence of a McLafferty reaction involving the C(4′) position of $\mathbf{1}^{+\bullet}$. In fact, the hydrogens at C(4′) can also undergo a [1,5]-H shift to oxygen and may thus initiate a McLafferty process in competition with the one initiated by a [1,5]-H migration from C(4). For a distinction, the latter is referred to as McL$_{\mathrm{I}}$, and the competing process involving a C(4′)-bound hydrogen is termed McL$_{\mathrm{II}}$; likewise, the primary KIEs associated with the respective [1,5]-H shifts are referred to as KIE$_{\mathrm{I}}$ and KIE$_{\mathrm{II}}$. The pronounced formation of ions with m/z = 59 and m/z = 60 from the respectively γ- and γ'-labeled isotopomers $\mathbf{1c}^{+\bullet}$ and $\mathbf{1d}^{+\bullet}$ reveals that McL$_{\mathrm{I}}$ and McL$_{\mathrm{II}}$ compete effectively. Notable H/D-scrambling in the McLafferty processes can be excluded because $\mathbf{1e}^{+\bullet}$ gives almost exclusively ions m/z = 59; the ca. 3% contributions of m/z = 60 and 61 are due to the side reaction addressed next.

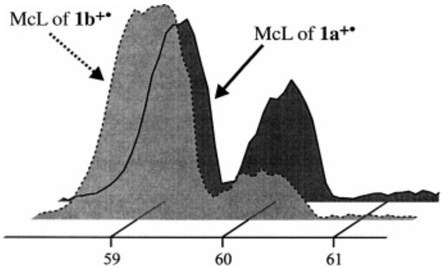


FIGURE 1. McLafferty regions of the anti- and syn-diastereomers ($\mathbf{1a}^{+\bullet}$ and $\mathbf{1b}^{+\bullet}$) at $E_{h\nu}$ = 11 eV. The McL$_{\mathrm{I}}$ reaction proceeding via D-transfer (m/z = 60) is more pronounced in the case of the anti-[4-D$_1$]-diastereomer ($\mathbf{1a}^{+\bullet}$) than in the case of the syn-compound ($\mathbf{1b}^{+\bullet}$), irrespective of the possible operation of KIEs.

Before assessing the branching ratio and the KIEs of the McLafferty processes, which, in turn, allow us to determine the SE for the two diastereomers $\mathbf{1a}^{+\bullet}$ and $\mathbf{1b}^{+\bullet}$, we have to tackle as a minor complication the side reaction mentioned before; a more detailed discussion of the [McLafferty + 1] processes is given in ref 17. Already for unlabeled $\mathbf{1}^{+\bullet}$ a notable signal at m/z = 60 is observed, which can be assigned to the occurrence of a second hydrogen transfer following the McLafferty rearrangement. Such a McLafferty reaction with double hydrogen transfer is known as [McLafferty + 1] reaction.[3,18] For the deuterated isotopomers **1a**–**e**, a second hydrogen/deuterium transfer results in signals at m/z = 60 and 61; m/z = 62 is conceivable, but not observed experimentally. For the present analysis of the SE, it is sufficient to correct the experimental abundances for the [McLafferty + 1] contributions without further analysis of the latter. Such a correction can be achieved by taking the relative intensity of m/z = 60 from unlabeled **1** as a measure for the amount of [McLafferty + 1] products.

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(17) Loos, J.; Schröder, D.; Schwarz, H.; Thissen, R.; Dutuit, O. *Int. J. Mass Spectrom.* **2005**, *240*, 121.

(18) McLafferty, F. W.; Tureček, F. *Interpretation of Mass Spectra*, University Science Books, Sausalito, CA, 1993; p 81.

For the labeled compounds, this amount is shared between fragment ions with $m/z = 60$ and 61. For a deconvolution of single and double hydrogen transfer, identical amounts of double hydrogen transfer for deuterated and nondeuterated ions are assumed, irrespective of possible KIEs (see footnote c of Table 1). Considering the low abundance of the [McLafferty + 1] products, the simplification appears justified. Moreover, the almost equal amounts of [McLafferty + 1] products from $\mathbf{1}^{+\bullet}$ (2.9% for $m/z = 60$) and deuterated $\mathbf{1e}^{+\bullet}$ (2.7% for $m/z = 60$ and 61) suggest that the discrimination of the deuterated [McLafferty + 1] products is indeed negligible compared to the magnitude of the McLafferty processes.

The corrected data (Table 1) form the basis for an analysis of the various parameters by means of kinetic modeling.[12,19] Beside the γ- and γ'-labeled isotopomers $\mathbf{1c}^{+\bullet}$ and $\mathbf{1d}^{+\bullet}$, an arbitrary 1:1 mixture ($\mathbf{1x}^{+\bullet}$) of the diastereomers $\mathbf{1a}^{+\bullet}$ and $\mathbf{1b}^{+\bullet}$ also qualifies for the determination of $\mathrm{KIE_I}$, $\mathrm{KIE_{II}}$, and the branching ratio between $\mathrm{McL_I}$ and $\mathrm{McL_{II}}$. The hypothetical spectrum of $\mathbf{1x}^{+\bullet}$ is obtained by averaging the data of $\mathbf{1a}^{+\bullet}$ and $\mathbf{1b}^{+\bullet}$.

Comparison of the relative intensities from the isotopomers deuterated in the C(4)-position further implies the operation of a moderate secondary kinetic isotope effect ($\mathrm{KIE_{sec}}$) of the H(D) atom remaining at C(4). Thus, fragmentation of $\mathbf{1c}^{+\bullet}$ via the $\mathrm{McL_I}$ reaction results exclusively in ions with $m/z = 60$, whereas the $\mathrm{McL_I}$ dissociation of $\mathbf{1x}^{+\bullet}$ should yield a 1:1 ratio of ions with $m/z = 59$ and 60, modulated by $\mathrm{KIE_I}$, which disfavors the formation of the heavier ion. Accordingly, one would expect the relative intensity of ions $m/z = 60$ from $\mathbf{1x}^{+\bullet}$ to be at best half the magnitude of that from $\mathbf{1c}^{+\bullet}$. However, the amount of $m/z = 60$ from $\mathbf{1x}^{+\bullet}$ is about 1.06 times larger than half the intensity of $m/z = 60$ from $\mathbf{1c}^{+\bullet}$, which implies the operation of a secondary KIE with $\mathrm{KIE_{sec}} \geq 1.06$. The range is in perfect agreement with $\mathrm{KIE_{sec}} = 1.07 \pm 0.10$ derived for the McLafferty reaction of photoionized valeramide.[12] In the kinetic modeling of the data for the title compound, we accordingly adopt $\mathrm{KIE_{sec}} = 1.07$ for both the C(4) and C(4′) positions.

The [McLafferty + 1]-corrected ratios of $m/z = 59$ and $m/z = 60$ for the isotopomers **1c**, **1d**, and **1x** can be expressed by the following kinetic equations:

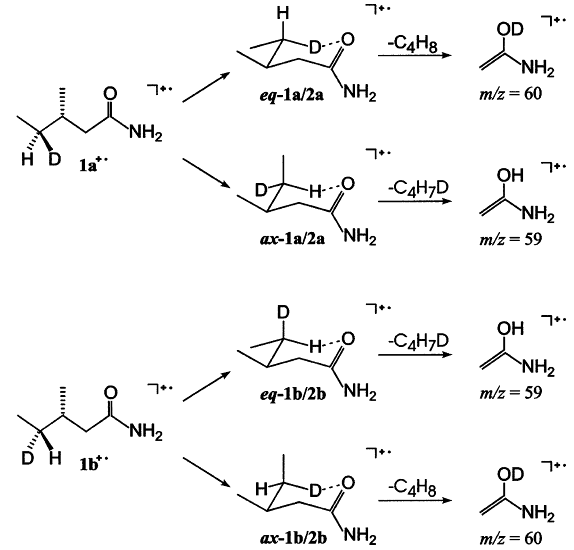
$$c59/c60 = X_{\mathrm{II}}/[X_{\mathrm{I}}/(\mathrm{KIE_I} \bullet \mathrm{KIE_{sec}})] \quad (1)$$

$$d59/d60 = X_{\mathrm{I}}/[X_{\mathrm{II}}/(\mathrm{KIE_{II}} \bullet \mathrm{KIE_{sec}}^2)] \quad (2)$$

$$x59/x60 = (0.5 \bullet X_{\mathrm{I}}/\mathrm{KIE_{sec}} + X_{\mathrm{II}})/(0.5 \bullet X_{\mathrm{I}}/\mathrm{KIE_I}) \quad (3)$$

where X_{I} and X_{II} are the branching ratios of the competing McLafferty reactions with the normalization $\Sigma X_{\mathrm{i}} = 1$. Equations 1−3 permit an explicit calculation of the variables as: $\mathrm{KIE_I} = 1.0$, $\mathrm{KIE_{II}} = 1.6$, $X_{\mathrm{I}} = 0.49$, and $X_{\mathrm{II}} = 0.51$. These findings fit nicely to what is known already about the McLafferty reaction of amides.[11−13] Thus, the γ-H shift from C(4) to oxygen is not the rate-determining step and is therefore not associated with a significant primary KIE. The fact that $\mathrm{KIE_{II}}$ is more pronounced can be attributed to the higher energy demand of a hydrogen/deuterium abstraction from the primary C(4′) in comparison to the secondary C(4),[20] which, because of the competition of both processes, results in a more pronounced apparent KIE compared to the intrinsic one.[21]

SCHEME 2



Having determined the branching ratios and the KIEs, it is possible to calculate the SE for the McLafferty reactions of diastereomers $\mathbf{1a}^{+\bullet}$ and $\mathbf{1b}^{+\bullet}$ from the following kinetic equations:

$$a59/a60 = (X_{\mathrm{A}}/\mathrm{KIE_{sec}} + X_{\mathrm{II}})/(X_{\mathrm{S}}/\mathrm{KIE_I}) \quad (4)$$

$$b59/b60 = (X_{\mathrm{S}}/\mathrm{KIE_{sec}} + X_{\mathrm{II}})/(X_{\mathrm{A}}/\mathrm{KIE_I}) \quad (5)$$

where X_{A} represents the contribution of the $\mathrm{McL_I}$ reaction involving the H/D atom in anti-position to the methyl group at C(3), and X_{S} stands for the contribution from the syn-position (hence, $X_{\mathrm{A}} + X_{\mathrm{S}} = X_{\mathrm{I}}$). With eqs 4 and 5, the steric effect associated with the $\mathrm{McL_I}$ reaction evolves as $\mathrm{SE} = X_{\mathrm{S}}/X_{\mathrm{A}} = 2.9$, which is quite large for an monofunctional compound with a flexible aliphatic chain.[2,6]

A straightforward mechanistic rationale of this steric effect is that the initial step of the McLafferty reaction, the γ-H shift from the C(4) atom to oxygen ($\mathbf{1}^{+\bullet} \rightarrow \mathbf{2}^{+\bullet}$), occurs via a chairlike transition structure (TS; Scheme 2). Thus, the transfer of a γ-hydrogen in $\mathbf{1a}^{+\bullet}$ requires one of the two methyl groups (i.e., C(4′) or C(5), respectively) to adopt an energetically demanding, axial position in the TS (e.g., ***ax*-1a/2a**$^{+\bullet}$). In contrast, a γ-deuterium transfer from $\mathbf{1a}^{+\bullet}$ can proceed via a preferable, double-equatorial conformation (***eq*-1a/2a**$^{+\bullet}$) and is hence sterically more facile than H-transfer. For $\mathbf{1b}^{+\bullet}$, the situation is reversed, in that H-migration can take place via a double-equatorial TS (***eq*-1b/2b**$^{+\bullet}$) and therefore is sterically more favorable than D-transfer.

The fact that the McLafferty reaction of ionized carboxamides is associated with a considerable SE, but negligible KIEs, confirms inter alia our earlier finding

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[19] Also see: Kondrat, R. W.; Morton, T. H. *Org. Mass Spectrom.* **1991**, *26*, 410.

[20] Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; Wiley-Interscience: New York, 2001; p 243.

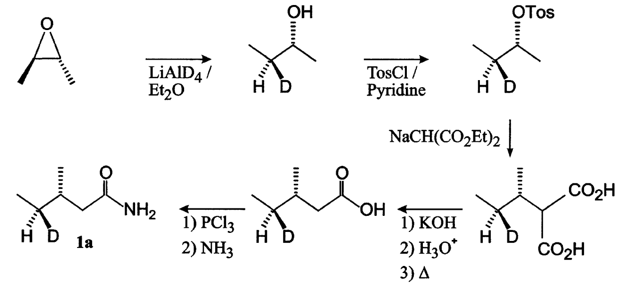
[21] For a good review on this topic, see: Thibblin, A.; Ahlberg, P. *Chem. Soc. Rev.* **1989**, *18*, 209.

that the rate of this reaction is not that much affected by the [1,5]-H shift. Instead, the preceding rotational barriers to adopt a suitable conformation from which hydrogen migration can take place determine the product distribution.[12,13] The proposed chairlike transition structure associated with H-transfer not only can account for the observed steric preferences of the two diastereotopic hydrogen atoms at C(4) in relation to the stereogenic center in 3-methyl valeramide. In addition, the conformational constraints of such a TS also provide a convincing mechanistic rationale for the large sensitivity toward sterical/conformational restrictions despite the high flexibility of the molecule.

Experimental Details

The experiments were performed with the CERISES[22] apparatus mounted to the beamline SA63 of the synchrotron SuperACO at LURE (Orsay, France). The line includes a normal incidence monochromator that provides tunable VUV-light in the range of 7−35 eV. Slits were opened to 1 mm, corresponding to a photon-energy resolution of about 500 (i.e., 20 meV at 10 eV). The accuracy of the photon energy ($E_{h\nu}$) was verified by measuring the ionization threshold of argon within 2 meV of its nominal value. A lithium−fluoride window was inserted at $E_{h\nu} \leq 11.8$ eV to effectively eliminate higher-order photons emerging from the grating of the monochromator. Neutral **1**−**1e** were introduced into the source and ionized by 11 eV photons. The formed cations were extracted from the source by a small electrostatic field of 1 V/cm and transferred into a QOQ system (Q stands for quadrupole and O for octopole), and the product ions were mass-analyzed by Q2. The AE of the McLafferty reaction was determined from $\mathbf{1d}^{+\bullet}$ in single-ion monitoring mode while scanning the photon energy, and it was derived by linear extrapolation of the onset to the baseline without applying any further corrections for temperature, kinetic shifts, etc. The IE of the undeuterated parent molecule was retrieved as the first point with a notable ion signal. For each isotopomer, several mass spectra of the McLafferty-product region (m/z = 59−62) were recorded at $E_{h\nu}$ = 11 eV and averaged.

SCHEME 3



The synthesis of the labeled (>98 atom % D) 3-methyl valeramides (Chart 1) followed previously described strategies.[16,23,24] Briefly, the amides were made by ammonolysis of the corresponding esters or acid chlorides. The 3-methylvaleric acids for the synthesis of **1c**−**e** were prepared by conjugate addition of grignard reagents to the corresponding α,*β*-unsaturated esters (ethylmagnesium bromide and crotonate for **1c** and **1e**, methylmagnesium iodide and pent-2-enoate for **1d**). The diastereoselectively labeled amides **1a** and **1b** were prepared starting from *cis*- and *trans*-butene oxide, respectively, which were then reduced, tosylated, and converted to the desired amides by using well-established synthetic procedures, as shown in Scheme 3 for the synthesis of **1a**.[23b] The final products were purified by recrystallization from chloroform/hexane and fully characterized by ^{1}H NMR and GC−MS.

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[22] Dutuit, O.; Alcaraz, C.; Gerlich, D.; Guyon, P. M. Hepburn, J. W.; Metayer-Zeitoun, C.; Ozenne, J. B.; Weng, T. *Chem. Phys.* **1996**, *209*, 177.

[23] (a) Schröder, D.; Schwarz, H. *J. Am. Chem. Soc.* **1990**, *112*, 5947. (b) Hornung, G. Regio- and Stereochemistry in the Transition Metal Mediated Remote Functionalisation in the Gas Phase. Ph.D. Thesis, Technische Universität, Berlin, Germany, 1998; http://www.dissertation.de/.

[24] Hornung, G.; Schröder, D.; Schwarz, H. *J. Am. Chem. Soc.* **1995**, *117*, 8192.