VIP Asymmetric Organocatalysis

DOI: 10.1002/anie.201008081

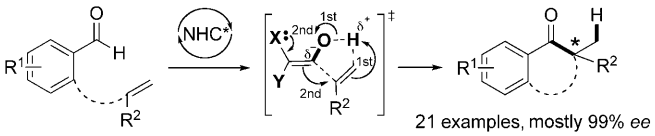
Highly Asymmetric NHC-Catalyzed Hydroacylation of Unactivated Alkenes**

Isabel Piel, Marc Steinmetz, Keiichi Hirano, Roland Fröhlich, Stefan Grimme, and Frank Glorius**

Dedicated to Professor Dieter Enders on the occasion of his 65th birthday

N-Heterocyclic carbene (NHC)-catalyzed umpolung reactions[1] offer an elegant access to several important classes of compounds, such as benzoins[2] or γ-butyrolactones.[3] In addition, Enders et al.[4] and Rovis et al.[5] have pioneered the development of a powerful NHC-catalyzed formation of highly functionalized chromanones by an intramolecular Stetter reaction.[6] Recently, we have reported the NHC-catalyzed hydroacylation of unactivated olefins,[7] a reaction previously only possible with transition-metal catalysts.[8] This intramolecular reaction was also found to be a versatile method for the synthesis of numerous racemic chromanones. However, the mechanism remained unclear.

The highly asymmetric formation of all-carbon quaternary stereocenters is an important challenge in organic synthesis,[9] because this structural motif commonly appears in numerous biologically active compounds.[10] Even though some methods have been developed, the synthetic armory is still rather limited for this task.[9] Herein we report the highly asymmetric hydroacylation of unactivated olefins, resulting in the formation of 21 products mostly with 99% *ee*, each containing a newly formed quaternary (4°) stereocenter (Scheme 1).[6c] In contrast to transition-metal-catalyzed cycloisomerizations, which often suffer from side reactions, the byproduct-free nature of this transformation is attractive.



Scheme 1. NHC-catalyzed hydroacylation of 2-allyloxy benzaldehyde derivatives.

Moreover, based on quantum-chemical calculations, a mechanistic scenario and a mode of stereoinduction are proposed.

We began with the investigation of the enantioselective cyclization of O-allylated *o*-vanillin derivative **1a** (Table 1). Using triazolylidenes derived from L-phenylalaninol good yields were obtained with a catalyst loading of 5–10 mol% even at 60–80°C (compared to 120°C;[7a] Table 1). The carbene generated from triazolium salt **3**[11,12] showed excellent reactivity (Table 1, entry 1). Other established chiral NHCs also showed high, though slightly reduced levels of either reactivity or selectivity; the N-mesityl substituent was found to be especially valuable for reactivity and selectivity. However, higher catalyst loadings of catalyst precursor **6** did not result in significantly higher yields and selectivities. Similarly, lowering the reaction temperature to 60°C led to only a moderate improvement of *ee* value (entries 4–6).

In contrast, 5 mol% of triazolylidene derived from **3** provided the desired chromanone **2a** in an excellent yield even at 60°C (Table 1, entry 9). Moreover, using 10% of catalyst gave a successful reaction even at room temperature (entry 10). In addition, the reaction is insensitive to trace amounts of water (entry 11). Using only 1 mol% of **3** at room temperature still resulted in the formation of 26% of **2a**, together with 36% of benzoin product and 33% residual starting material (entry 12). Based on the isolation of the benzoin product in this reaction, it is reasonable to assume that reversible benzoin formation takes place at room temperature and at higher temperatures. After identifying both the optimal triazolylidene catalyst and conditions, the scope of this reaction using a range of substrates with different substitution patterns of the aromatic ring was examined (Table 2).

Whereas 5 mol% of catalyst were sufficient for the full conversion of substrate **1a**, most of the other substrates **1** required up to 10 mol% of catalyst. Nevertheless, excellent levels of enantioselectivity were observed throughout. Especially substrates with electron-donating substituents at the 2-position showed excellent reactivity (**1a**,**b**),[13] but electron-

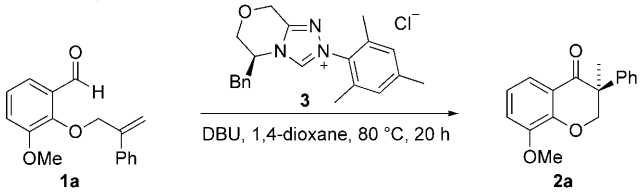
[*] I. Piel, M. Steinmetz, Dr. R. Fröhlich, Prof. Dr. S. Grimme, Prof. Dr. F. Glorius
Westfälische Wilhelms-Universität Münster
Organisch-Chemisches Institut
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 251-83-33202
E-mail: grimmes@uni-muenster.de
glorius@uni-muenster.de
Homepage: http://www.uni-muenster.de/Chemie.oc/glorius/index.html

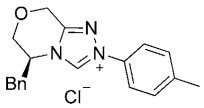
Dr. K. Hirano
Stanford University, Chemistry Department
Stanford, CA 94305-5080 (USA)

[**] We are grateful to Karin Gottschalk for skillful technical assistance. Generous financial support by the Deutsche Forschungsgemeinschaft (SPP 1179 and SFB 858), the Fonds der Chemischen Industrie, AstraZeneca, the International NRW Graduate School of Chemistry (I.P.), and the Deutsche Akademische Austauschdienst (K.H.) is gratefully acknowledged. The research of F.G. was supported by the Alfried Krupp Prize for Young University Teachers of the Alfried Krupp von Bohlen und Halbach Foundation.
NHC = N-Heterocyclic carbene.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201008081.

Table 1: Optimization of the reaction conditions.[a]

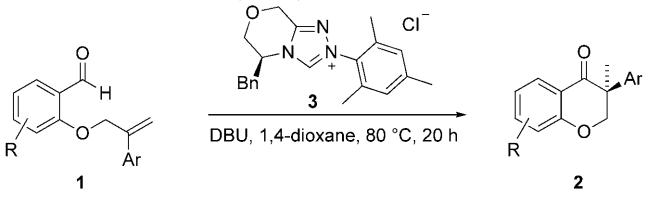


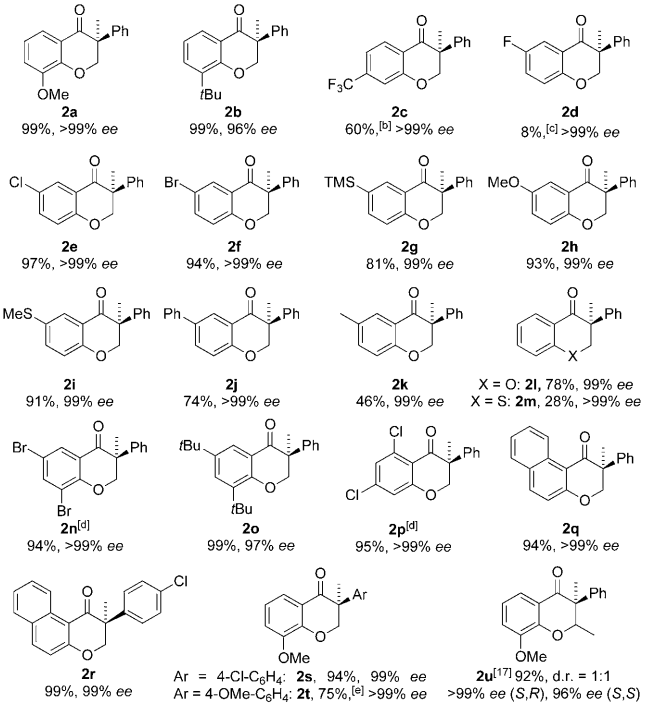


Entry	Variation of the standard conditions[a]	Yield [%][b]	*ee* [%][c]
1	none	97	99
2	10 mol% **4**	30	99
3	10 mol% **5**	92	99[d]
4	20 mol% **6**, 40 mol% DBU	79	86
5	10 mol% **6** at 120°C	63	85
6	20 mol% **6** at 60°C in THF	79	90
7	10 mol% **3** at 60°C in THF	99	99
8	10 mol% **3** at 55°C in MTBE[e]	99	99
9	5 mol% **3** at 60°C in THF	99	99
10	10 mol% **3** at RT in THF	99	>99
11	10 mol% **3**, 60°C, THF, +0.5% H_2O	97	>99
12	1 mol% **3** at RT in THF	26[f]	>99

[a] Standard conditions: **1a** (0.25 mmol), NHC·HX (10 mol%), DBU (20 mol%), 1,4-dioxane (0.5 mL), 80°C, and 20 h. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] Other enantiomer obtained. [e] Non-dried *tert*-butyl methyl ether (MTBE) was used. [f] Together with 33% remaining starting material and 36% of the benzoin product.

Table 2: Enantioselective hydroacylation of unactivated olefins.[a]





[a] General conditions: **1** (0.25 mmol), **3** (10 mol%), DBU (20 mol%), 1,4-dioxane (0.5 mL), 80°C, 20 h. Yields are of isolated product. [b] Using 5 mol% **3**, 10 mol% DBU, THF, 60°C. [c] 8% of **2d** was isolated in an inseparable mixture together with 3% of a by-product. [d] Absolute configuration established by single-crystal X-ray analysis. [e] Determined by ^{1}H NMR spectroscopy; mixture containing 75% of **2t** together with 19% of an inseparable by-product.

withdrawing substituents, such as the trifluoromethyl group (in **1c**), were also tolerated. The transformation of aromatic aldehydes with substituents in the 5-position leads to products **2d**–**k** in good to excellent yields and remarkably high enantioselectivities (99% *ee*) in all cases. Surprisingly, 5-fluoro and 5-methyl derivatives **2d** and **2k**, respectively, were obtained with lower yields, albeit without any loss of enantioselectivity. In addition, the unsubstituted parent system **2l** and its sulfide-tethered analogue, thiochroman-4-one **2m**, were smoothly formed in 99% *ee*. Disubstituted substrates led to the formation of dialkylated or dihalogenated chromanones (**2n**–**p**). The absolute configurations of **2n** and **2p** (as shown in Table 2) were unequivocally determined by single-crystal X-ray diffraction.[14] Based on the very high levels of enantioselectivity generally obtained in the present study, it is reasonable to assume that all the chromananones **2a**–**u** are formed with the same absolute configuration. Finally, naphthaldehydes **1q**,**r** also readily cyclized to the tricyclic dihydronaphthopyran-1-ones (**2q**,**r**). Moreover, the substitution pattern of the olefin could also be varied successfully; electron-withdrawing and electron-donating substituents on the aryl group were tolerated (**2r**–**t**). As most chromanone motifs in natural products or pharmaceutically active compounds are substituted in the position α to the oxygen tether,[15] we prepared substrate **1u**. This undergoes cyclization to the chromanone **2u** in excellent yield and enantiomeric excess, however, with a diastereomeric ratio of 1:1. Preliminary experiments to expand the scope to the formation of dihydroquinolinones or the use of some other olefin substitution patterns have not met with significant success to date.[16]

The investigation of the reaction mechanism of this NHC-catalyzed transformation was informative.[17] First, a simple deuteration experiment allowed us to exclude the direct involvement of the oxygen tether in the reaction mechanism.[18] Second, in a competition experiment, we found that a phenyl substituent on the olefin (R^2 = Ph, Scheme 1) leads to a slightly increased reactivity compared to the unsubstituted olefin (R^2 = H).[19] Furthermore, DFT calculations[19] were

performed to get more insight into the crucial step of the reaction, that is, whether the proton migration or the C–C bond formation occurs first. We investigated substrate **11** together with catalyst generated from **3**. The minima for the open system $\mathbf{1}_{Int}$ (in which the NHC is already added), the ring-closed intermediate $\mathbf{2}_{Int}$, and the corresponding transition state (TS) have been located. Two different dispersion-corrected density functionals were employed which, qualitatively, yield the same picture. In the following only the results including corrections to (relative) reaction enthalpies at the B2PLYP-D/TZVPP/BP86-D/TZVP[20] level are discussed.

In Figure 1 the computed bond lengths and bond orders of the TS are shown for a model system (derived from achiral **7**[18]). The character of the TS is very similar to that obtained

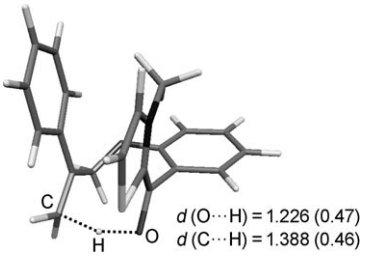


Figure 1. Optimized hydrogen-transfer transition state of a model system (BP86-D/TZVP). The bond lengths are in Å and the Wiberg bond orders are shown in parenthesis.

for the chiral NHC. Starting from the open system $\mathbf{1}_{Int}$, the alkoxy chain first undergoes a conformational rearrangement to bring the reacting parts close together. The TS corresponds to a genuine proton transfer from the hydroxy group to the terminal carbon atom of the double bond. The OH bond is elongated to 1.226 Å and the distance between the H and the C atom is 1.388 Å in the TS. These values and the corresponding bond orders (0.47 and 0.46, respectively) indicate that the OH bond is half broken and the newly created C–H bond is half formed. Note the favorable stacking interaction of the two aromatic rings in the TS. By displacement along the transition mode and further unrestricted geometry optimization, no other intermediate was found implying the direct formation of the C–C bond. Thus, the first important conclusion from these computations is that the reaction mechanism is of a one-step type.

We also considered theoretically the mode of stereoinduction caused by employing a chiral catalyst. We combined mirror images of the substrate with a fixed absolute configuration of **3**. The computed lower barrier of 10 kcal mol^{-1} is compatible with a fast reaction between room temperature and 80 °C. In one of the diastereomeric transition states, steric hindrance between the benzyl group of the catalyst and the substrate causes a large energy difference. The barrier for $\mathbf{2}_{TS2}$ is computed to be 5.5 kcal mol^{-1} higher than for $\mathbf{2}_{TS1}$ (Figure 2). The same trend holds for the relative energies of the intermediates, that is, $\mathbf{2}_{Int2}$ is less stable than the starting material. The basic reason is that in $\mathbf{2}_{Int2}$ the C–C bond (ring) formation is sterically hindered, as shown in Figure 2. Thus even under equilibrium conditions only the intermediate $\mathbf{2}_{Int1}$

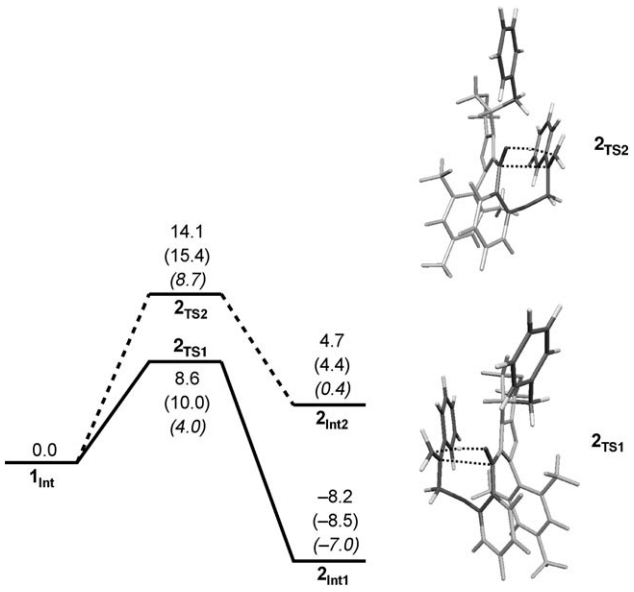


Figure 2. Calculated relative enthalpies at the B2PLYP-D level (relative energies, at the same level, in parenthesis, BP86-D values in italics) for ring-opened intermediate, transition states, and ring-closed intermediates in kcal mol^{-1}. The structures shown represent the diastereomeric TSs ($\mathbf{2}_{TS1}$ and $\mathbf{2}_{TS2}$). The formed C–C and the O–H/C–H bonds involved in the proton transfer are indicated by dotted lines.

is formed, leading to the formation of *S*-configured chromanones, and explaining the high stereoselectivity in the experiments.

In conclusion, we have developed a highly asymmetric NHC-catalyzed intramolecular hydroacylation of unactivated olefins which gives chromanone derivatives containing all-carbon quaternary stereocenters. In addition, quantum-chemical calculations support a concerted but very asynchronous transition state. These results should be helpful for developing related transformations.

Experimental Section

General procedure: the aldehyde (0.25 mmol, 1.0 equiv), the triazolium salt **3** (10 mol %, 0.025 mmol, 9.3 mg), and 1,4-dioxane (0.5 mL) were added to a flame-dried screw-capped test tube equipped with a magnetic stir bar. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added (20 mol %, 0.05 mmol, 7.5 μL) and the resulting mixture was stirred in a pre-heated oil bath at 80 °C for 20 h. The reaction was cooled to ambient temperature, pre-absorbed on silica gel and purified by flash column chromatography on silica gel (typically *n*-pentane/EtOAc = 20/1→5/1).

Received: December 21, 2010
Revised: February 17, 2011
Published online: April 14, 2011

Keywords: enantioselective catalysis · hydroacylation · N-heterocyclic carbenes · organocatalysis · Stetter reaction

[1] For comprehensive Reviews on NHC-organocatalysis, see: a) J. L. Moore, T. Rovis, *Top. Curr. Chem.* **2010**, *291*, 77; b) V. Nair, S. Vellalath, B. Pattoorpadi Babu, *Chem. Soc. Rev.* **2008**, *37*,

2691; c) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; d) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; e) E. M. Phillips, A. Chan, K. A. Scheidt, *Aldrichimica Acta* **2009**, *42*, 55. For Reviews on the alternative application of NHCs as ligands in transition-metal catalysis, see: f) *N-Heterocyclic Carbenes in Synthesis* (Ed.: S. P. Nolan), Wiley-VCH, Weinheim, **2006**; g) *N-Heterocyclic Carbenes in Transition Metal Catalysis* (Ed.: F. Glorius), Springer, Berlin, **2007**; h) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem.* **2007**, *119*, 2824; *Angew. Chem. Int. Ed.* **2007**, *46*, 2768; i) S. Würtz, F. Glorius, *Acc. Chem. Res.* **2008**, *41*, 1523; j) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612. For recent Reviews on physicochemical properties of NHCs, see: k) T. Dröge, F. Glorius, *Angew. Chem.* **2010**, *122*, 7094; *Angew. Chem. Int. Ed.* **2010**, *49*, 6940; l) T. Dröge, F. Glorius, *Nachr. Chem.* **2010**, *58*, 112.

[2] a) D. Enders, A. Grossmann, J. Fronert, G. Raabe, *Chem. Commun.* **2010**, *46*, 6282; b) D. Enders, U. Kalfass, *Angew. Chem.* **2002**, *114*, 1822; *Angew. Chem. Int. Ed.* **2002**, *41*, 1743; in addition, the synthesis of (+)-sappanone B by an aldehyde–ketone crossed-benzoin reaction reported by Suzuki et al. shows the applicability of NHC-organocatalysis in natural-product synthesis: c) H. Takikawa, K. Suzuki, *Org. Lett.* **2007**, *9*, 2713; for related work, see: d) H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, *Angew. Chem.* **2006**, *118*, 3572; *Angew. Chem. Int. Ed.* **2006**, *45*, 3492; e) D. Enders, O. Niemeier, T. Balensiefer, *Angew. Chem.* **2006**, *118*, 1491; *Angew. Chem. Int. Ed.* **2006**, *45*, 1463.

[3] a) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205; b) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370; c) C. Burstein, S. Tschan, X. Xie, F. Glorius, *Synthesis* **2006**, 2418; d) V. Nair, S. Vellalath, M. Poonoth, E. Suresh, S. Viji, *Synthesis* **2007**, 3195; e) K. Hirano, I. Piel, F. Glorius, *Adv. Synth. Catal.* **2008**, *350*, 984. For the formation of lactams, see also: f) M. He, J. W. Bode, *Org. Lett.* **2005**, *7*, 3131; g) N. Duguet, C. D. Campbell, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 1108.

[4] D. Enders, K. Breuer, J. Runsink, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1899.

[5] a) J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 6284; b) S. C. Cullen, T. Rovis, *Org. Lett.* **2008**, *10*, 3141. For a rare (and to our knowledge only) report on a highly asymmetric Stetter reaction leading to the formation of quaternary all-carbon stereocenters, see: c) M. S. Kerr, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 8876.

[6] For a Review on the Stetter reaction, see: a) J. Read de Alaniz, T. Rovis, *Synlett* **2009**, 1189; for recent progress in the intermolecular asymmetric Stetter reaction, see: b) D. Enders, J. Han, A. Henseler, *Chem. Commun.* **2008**, 3989; c) D. Enders, J. Han, *Synthesis* **2008**, 3864; d) Q. Liu, S. Perreault, T. Rovis, *J. Am. Chem. Soc.* **2008**, *130*, 14066; e) Q. Liu, T. Rovis, *Org. Lett.* **2009**, *11*, 2856; f) D. A. DiRocco, K. M. Oberg, D. M. Dalton, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 10872; g) C. Dresen, M. Richter, M. Pohl, S. Lüdeke, M. Müller, *Angew. Chem.* **2010**, *122*, 6750; *Angew. Chem. Int. Ed.* **2010**, *49*, 6600; theoretical investigation of the mechanism: h) K. J. Hawkes, B. F. Yates, *Eur. J. Org. Chem.* **2008**, 5563.

[7] a) K. Hirano, A. T. Biju, I. Piel, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 14190; b) Related work: J. He, S. Tang, J. Liu, Y. Su, X. Pan, X. She, *Tetrahedron* **2008**, *64*, 8797; c) Hydroacylation of unactivated alkynes: A. T. Biju, N. E. Wurz, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 5970; hydroacylation of arynes: d) A. T. Biju, F. Glorius, *Angew. Chem.* **2010**, *122*, 9955; *Angew. Chem. Int. Ed.* **2010**, *49*, 9761; related work: e) N. Kuhl, F. Glorius, *Chem. Commun.* **2011**, *47*, 573; f) R. Lebeuf, K. Hirano, F. Glorius, *Org. Lett.* **2008**, *10*, 4243.

[8] For a Review, see: M. C. Willis, *Chem. Rev.* **2010**, *110*, 725.

[9] For a Review on the formation of all-carbon quaternary stereocenters, see: a) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369; b) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402; *Angew. Chem. Int. Ed.* **1998**, *37*, 388; c) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688; d) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363.

[10] For Reviews, see a) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037; b) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591.

[11] NHC precursor **3** was originally developed by Scheidt et al.: a) E. M. Phillips, M. Wadamoto, K. A. Scheidt, *Synthesis* **2009**, 687; b) M. Wadamoto, E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 10098; synthesis of achiral and chiral triazolium salts: c) M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Org. Chem.* **2005**, *70*, 5725; d) J. R. Struble, J. W. Bode, *Org. Synth.* **2010**, *87*, 362; first applications using N-mesityl substituted NHCs: e) S. S. Sohn, J. W. Bode, *Org. Lett.* **2005**, *7*, 3873; f) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418. NHCs derived from L-phenylalanine: g) R. L. Knight, F. J. Leeper, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1891.

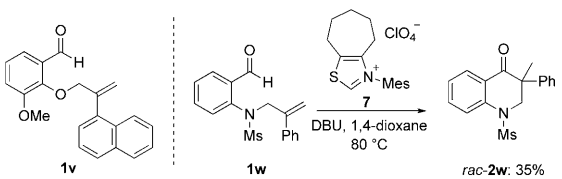
[12] An improved procedure for the synthesis of **3** as well as the, to our knowledge, first single-crystal structural analysis of **3** can be found in the Supporting Information. CCDC 805388 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] For a similar beneficial effect of an *ortho*-alkoxy group on the reactivity, see: K. Mori, T. Kawasaki, S. Sueoka, T. Akiyama, *Org. Lett.* **2010**, *12*, 1732.

[14] Single-crystal structural analysis data of **2n** and **2p** can be found in the Supporting Information. CCDC 805386 and 805387 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.

[15] Selected examples of chromanone derivatives in natural products: a) A. Pontius, A. Krick, S. Kehraus, S. E. Foegen, M. Müller, K. Klimo, C. Gerhäuser, G. M. König, *Chem. Eur. J.* **2008**, *14*, 9860–9863; b) W. Zhang, K. Krohn, Z. Ullah, U. Flörke, G. Pescitelli, L. Di Bari, S. Antus, T. Kurtán, J. Rheinheimer, S. Draeger, B. Schulz, *Chem. Eur. J.* **2008**, *14*, 4913–4923; c) S. Kanokmedhakul, K. Kanomedhakul, N. Phonkerd, K. Soytong, P. Kongsaeree, A. Suksamrarn, *Planta Med.* **2002**, *68*, 834–836.

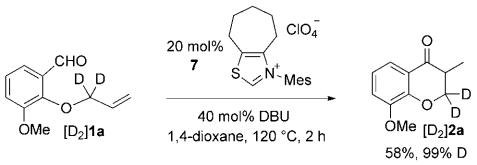
[16] Employing the sterically more demanding 1-naphthyl derivative **1v** provided only trace amounts of product. In addition, using catalyst **3**, the synthesis of dihydroquinolinone **2w** starting from **1w** failed; whereas the use of achiral thiazolylidene precursor **7**[7a] resulted in the formation of some **2w**.



[17] For related uncatalyzed Cope-type hydroaminations proceeding through five-membered transition states see: a) J.-G. Roveda, C. Clavette, A. D. Hunt, S. I. Gorelsky, C. J. Whipp, A. M. Beauchemin, *J. Am. Chem. Soc.* **2009**, *131*, 8740; b) A. M. Beauchemin, J. Moran, M.-E. Lebrun, C. Séguin, E. Dimitrijevic, L. Zhang, S. I. Gorelsky, *Angew. Chem.* **2008**, *120*, 1432; *Angew.*

Chem. Int. Ed. **2008**, *47*, 1410; c) J. Moran, S. I. Gorelsky, E. Dimitrijevic, M.-E. Lebrun, A.-C. Bédard, C. Séguin, A. M. Beauchemin, *J. Am. Chem. Soc.* **2008**, *130*, 17893.

[18] No loss of deuterium was observed, when substrate [D_2]**1a** was converted into the corresponding chromanone [D_2]**2a**,[19] allowing us to rule out the involvement of an intermediate oxonium species:



[19] See Supporting Information for further details.

[20] a) S. Grimme, *J. Comput. Chem.* **2006**, *27*, 1787; b) S. Grimme, *J. Chem. Phys.* **2006**, *124*, 034108; c) T. Schwabe, S. Grimme, *Phys. Chem. Chem. Phys.* **2007**, *9*, 3397; d) A. Schäfer, C. Huber, R. Ahlrichs, *J. Chem. Phys.* **1994**, *100*, 5829; e) F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.

