Enantioselective Organocatalysis

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Enantioselective Intramolecular Hydroacylation of Unactivated Alkenes: An NHC-Catalyzed Robust and Versatile Formation of Cyclic Chiral Ketones**

*Daniel Janssen-Müller, Michael Schedler, Mirco Fleige, Constantin G. Daniliuc, and Frank Glorius**

Abstract: *A highly enantioselective intramolecular N-heterocyclic carbene (NHC)-catalyzed hydroacylation reaction gives access to a range of cyclic ketones from unactivated olefin-substituted aldehydes (up to 99% ee). Remarkably, aliphatic aldehydes were also transformed efficiently in an NHC-catalyzed hydroacylation reaction for the first time.*

Hydroacylation, the formal insertion of unsaturated functionalities such as olefins into the C–H bond of an aldehyde, is a useful method for the formation of carbon–carbon bonds since both starting materials are abundant and important functional groups in organic chemistry. Catalysis of this transformation has been achieved with transition metals, including rhodium, ruthenium, and cobalt, as well as with N-heterocyclic carbenes (NHCs)[1] as organocatalysts.[2] Transition-metal-catalyzed hydroacylation reactions often suffer from decarbonylation of the acyl metal species, thereby resulting in catalytically inactive carbonyl complexes, and they therefore require an additional coordinating group on one of the substrates. While there are some approaches to prevent decarbonylation of non-chelating substrates, this deactivation pathway remains a general challenge in the field of hydroacylation.[2c,3]

The use of NHCs as organocatalysts for hydroacylation avoids this issue but is still underdeveloped.[2d] Additionally, the NHC-catalyzed intramolecular hydroacylation reaction is complementary to the metal-catalyzed variant, providing *exo*-cyclized products where the transition-metal-catalyzed transformation usually affords *endo*-cyclization.[4] The NHC-catalyzed reaction therefore often efficiently offers access to a quaternary stereocenter, the synthesis of which is generally considered challenging owing to the steric repulsion in the C–C bond forming step.[5]

NHCs have been used to catalytically transform electrophilic aldehydes into nucleophilic species, thereby enabling their reaction with various electrophiles.[6] The Stetter reaction, the NHC-catalyzed addition of an aldehyde to a Michael acceptor,[6b–c,e–g,l,7] is formally a hydroacylation of an electron-deficient C=C bond. While the Stetter reaction is limited to electron-deficient olefins, several hydroacylation reactions of electron-neutral olefins have been discovered and these make the NHC-catalyzed hydroacylation synthetically more versatile and widely applicable.[8–10] The resulting α-functionalized ketones are structurally important motifs in biologically active molecules, such as the loop diuretic drug Indacrinone[11] and the antidepressant drug Nafenodone[12] (Figure 1).

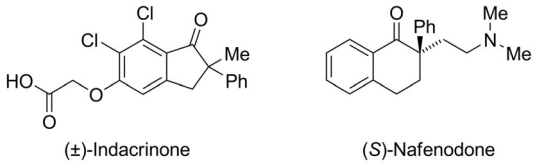
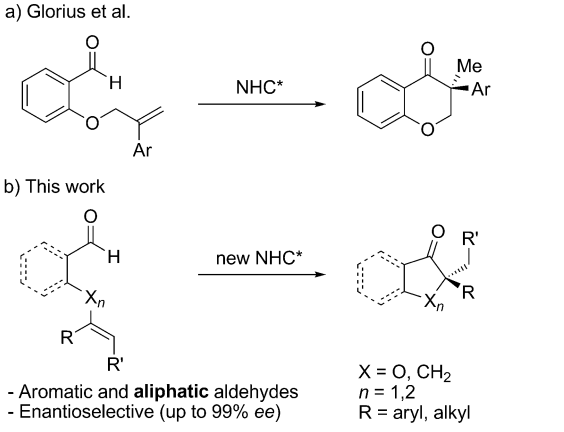


Figure 1. Two biologically active α-chiral ketones.

In 2009, our group reported the intramolecular NHC-catalyzed hydroacylation of electroneutral olefins with the cyclization of *O*-allylated salicylaldehydes to afford chromanones (Scheme 1).[8a,9] We then developed a highly enantioselective variant of this reaction in 2011, however, the



Scheme 1. Intramolecular enantioselective NHC-catalyzed hydroacylation.

[*] D. Janssen-Müller, Dr. M. Schedler, M. Fleige, Dr. C. G. Daniliuc, Prof. Dr. F. Glorius
Westfälische Wilhelms-Universität Münster
Organisch-Chemisches Institut
Corrensstrasse 40, 48149 Münster (Germany)
E-mail: glorius@uni-muenster.de
Homepage: http://www.uni-muenster.de/Chemie.oc/glorius/

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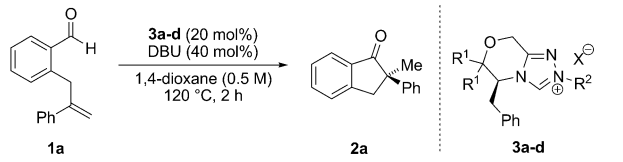
substrates are limited to salicylaldehyde derivatives.[8b] As a result, this potentially useful transformation was restricted to aromatic aldehydes, the formation of heterocycles, and monoaryl-substituted olefins. Motivated by our recent successful development of the intermolecular hydroacylation of cyclopropenes and styrenes,[10] we wanted to reexamine the intramolecular hydroacylation in more detail. Herein, we report the use of a *N*-2,6-dimethoxyphenyl-substituted NHC as an organocatalyst in an intramolecular enantioselective hydroacylation reaction for the construction of a variety of cyclic α-chiral ketones. This reaction is general and remarkably robust, and even the more challenging aliphatic aldehydes can be used.

Since all known substrates for NHC-catalyzed intramolecular hydroacylation contain a heteroatom bridge between the aromatic aldehyde and the olefin, we commenced our studies by exploring whether this constraint could be removed (**1a**) to allow the synthesis of 5-membered carbocycles, such as **2a** (Table 1).

Table 1: Screening of chiral NHC catalysts.[a]



Precat.	R^1	R^2	X	Yield [%][b]	*ee* [%][c]
3a	H	Mes	Cl	100	93
3b	Me	Mes	BF_4	4	n.d.
3c	H	2,6-$(MeO)_2C_6H_3$	BF_4	100	98
3d	Me	2,6-$(MeO)_2C_6H_3$	Cl	95	62
3c[d]	H	2,6-$(MeO)_2C_6H_3$	BF_4	100	98
3c[e]	H	2,6-$(MeO)_2C_6H_3$	BF_4	100	98
3c[f]	**H**	**2,6-$(MeO)_2C_6H_3$**	**BF_4**	**100**	**98**
3a[g]	H	Mes	Cl	100	98
3c[g]	H	2,6-$(MeO)_2C_6H_3$	BF_4	100	98

[a] Conditions: **1a** (0.1 mmol), chiral precatalyst (20 mol%), base (40 mol%), 1,4-dioxane (0.5 M), 120°C, 2 h. [b] The yield of **2a** was determined by ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard. [c] The *ee* value was determined by HPLC using a chiral stationary phase. DBU = 1,8-diazabicyclo [5.4.0]undec-7-ene, n.d. = not determined. [d] Temperature 0°C. [e] Temperature 140°C. [f] Chiral precatalyst (5 mol%) and DBU (10 mol%), 80°C. [g] With aliphatic substrate **1q** instead of **1a**.

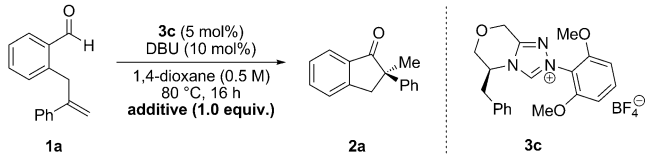
Chiral catalyst **3a**, which bears a mesityl substituent at the triazole core and a benzyl group as the stereo-inducing unit, gave full conversion to the product with high enantioselectivity (93% *ee*).[8a] The more sterically demanding catalyst **3b** was found to be less reactive, giving only 4% conversion. Moving from **3a** to **3c** by simply changing the mesityl substituent to the 2,6-dimethoxyphenyl substituent improved the *ee* to 98%. This confirms the previously reported tendency of improved selectivity with these new 2,6-dimethoxyphenyl-substituted triazolium salts.[10c,d,13] Catalyst **3d**, the *gem*-dimethyl derivative of catalyst **3c**, exhibited high activity for the reaction but a reduced enantioselectivity of 62% *ee*. When using catalyst **3c**, temperatures between 0°C and 140°C were tolerated for this reaction, but 80°C proved to be optimal for most substrates. The catalyst loading could be reduced to 5 mol%.

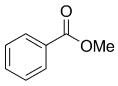
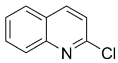
With these conditions in hand, an additive-based robustness screen[14] was performed to test the functional group tolerance of this reaction. Gratifyingly, nearly all of the tested additives, including the standard set of functional groups (entries A1–10) and heterocycles (entries B1–10), did not affect the hydroacylation (Table 2). Moreover, the additives did not decompose under the reaction conditions, thus suggesting that the reaction is well suited for the use of highly functionalized substrates. Only the additives dodecylamine, *N*-pivaloylpyrrol, and 2-chloroquinoline (see Table 2, entries A9, B7, and B10) reduced the yield of the product slightly, but even in the presence of these highly reactive functional groups, hydroacylation was possible, which probably makes this reaction the most robust reaction examined with this robustness screen to date.[14,15] Furthermore, none of the additives had any significant influence on the enantioselectivity.

To demonstrate the scalability of this transformation, we performed the reaction on a 2 g scale. This allowed us to decrease the amount of precatalyst **3c** at room temperature to 2 mol%. The yield of isolated product even increased to 99% and the *ee* was unaffected by the scale-up, remaining at 98%. Having established the high functional-group tolerance of this reaction, we went on to study the substrate scope, focusing especially on the influence of the ring size and the necessity of the aromatic rings. We started investigating different aromatic aldehydes including **1b**, a substrate that bears an electron-rich enol ether rather than an electro-neutral olefin. This substrate was previously used in a non-enantioselective transformation by She et al.[9] Pleasingly, we were able to isolate the product **2b** with good yield and enantioselectivity (Table 3). This methodology could also be extended to the formation of 6-membered carbocycles (**2c**) with excellent enantioselectivity. Next, replacement of the olefin substituent R, which had previously only tolerated aryl substituents, with an ethyl group was explored and ketone **2d** was formed with good yield and selectivity. The introduction of a fluorine atom to the aromatic aldehyde (**1e**) resulted in a 99% yield and an even higher *ee* of 99%.

We also investigated whether heteroaromatic aldehydes are tolerated in this reaction and hence we performed hydroacylation with the two nitrogen-containing heteroaromatic compounds **1f** and **1g**. Hydroacylation of **1f** provided an efficient and highly enantioselective route to pyrrolizine **2f**, an import structural motif found in alkaloids and drugs.[16] The structure and absolute configuration of hydroacylation product **2g** was confirmed by single-crystal X-ray diffraction analysis (see Table 3).[17] The reaction was found to tolerate both electron-donating (**1h**, **1i**, and **1j**) and electron-withdrawing (**1l** and **1m**) substituents on the phenyl ring of the olefin, as well as pyridyl substituents (**1k**), in all cases providing the product with 97% *ee* or higher. The trisubstituted olefin substrates **1n** and **1o** gave products **2n** and **2o** in 77% and 14% yield and with 97% and 88% *ee*, respectively. 1,3-Diene containing substrate **1p** gave the

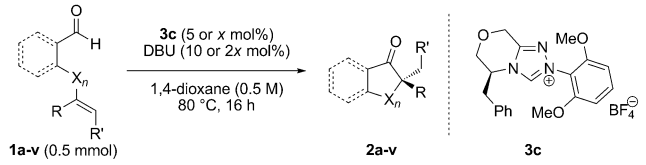
Table 2: Results of the robustness screen.[a]

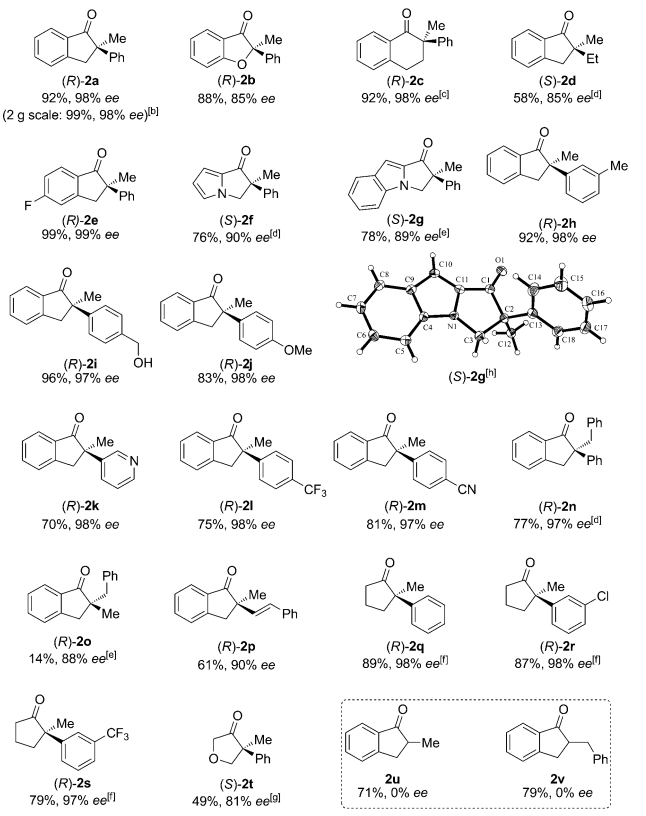


Entry	Additive	Yield of **2a** [%][b]	*ee* of **2a** [%][c]	Additive remaining [%][b]	**1a** remaining [%][b]
A0	none	>95	98	–	0
A1		92	98	95	0
A2		82	98	95	0
A3		92	98	>95	0
A4		>95	98	>95	0
A5		>95	98	>95	0
A6		>95	97	76	0
A7		92	98	91	0
A8		92	98	>95	0
A9		60	97	95	0
A10		93	98	>95	0
B1		>95	97	>95	0
B2		>95	98	>95	0
B3		94	98	89	0
B4		91	98	92	0
B5		95	98	>95	0
B6		>95	98	94	0
B7		61	98	92	21
B8		92	98	>95	0
B9		>95	98	>95	0
B10		77	98	>95	12

[a] The standard reaction (conditions: **1a** (0.1 mmol), **3c** (5 mol%), DBU (10 mol%), 1,4-dioxane (0.5 M), 80°C, 16 h) is undertaken in the presence of one molar equivalent of the given additive. [b] The yield of **2a** and the amounts of additive and starting material **1a** remaining after reaction were determined by GC. [c] The *ee* value was determined by HPLC using a chiral stationary phase.

Table 3: Substrate scope of the enantioselective hydroacylation.[a]





[a] 0.5 mmol of aldehyde was stirred at 80°C for 16 h in 1.0 mL 1,4-dioxane with 5 or *x* mol% triazolium salt **3c** and 10 or 2*x* mol% DBU. Yields given are yields of isolated product after column chromatography. The *ee* was determined by HPLC with a chiral stationary phase. [b] $x=2$. [c] $x=20$ and reaction-time 48 h. [d] $x=20$. [e] $x=20$ and reaction at 140°C. [f] $x=10$. [g] $x=10$, reaction at room temperature. [h] Molecular structure of **2g**.

product **2p** in a slightly lowered yield of 61%, while maintaining a high (90%) *ee*. We also investigated the use of aliphatic aldehydes, which have not yet been previously reported as substrates for intramolecular hydroacylation and which represent the biggest known restriction in this class of NHC-catalyzed transformation. Gratifyingly, the subjection of substrate **1q** to the reaction conditions resulted in the formation of the desired product **2q** in 89% yield with an outstanding enantioselectivity of 98% *ee*. Once again, we investigated whether different substituents on the phenyl ring had an influence on the reaction and found they were well tolerated (**2r–s**). Upon incorporation of an oxygen atom into the aliphatic bridge (**1t**), the furanone **2t** was produced with a lower *ee* of 81% and in a much lower yield of 19% as the result of an NHC-catalyzed side reaction (see the Supporting Information). This side reaction can be reduced by lowering the temperature to room temperature, which allowed the product **2t** to be obtained in 49% yield compared to 19% yield compared to 19% yield at 80°C.

A limitation of this method is the construction of stable ternary stereocenters (**2u** and **2v**), since this stereocenter is prone to racemization under basic conditions. By adding deuterated methanol to the reaction mixture containing substrate **1u**, we observed the incorporation of deuterium atom at the stereogenic center, thus suggesting that the ketone formed is in equilibrium with its enolate. As a result, racemic hydroacylation products were formed.

In order to study the influence of the aromatic backbone of substrate **1a** compared to the aliphatic aldehyde **1q**, we measured time-dependent NMR spectra for both reactions. At 80 °C in deuterated toluene[18] and in the presence of 10 mol % **3c** and 20 mol % DBU, the aliphatic aldehyde **1q** reacted slowly to give the corresponding hydroacylation product **2q** (Figure 2, left). When the reaction was repeated

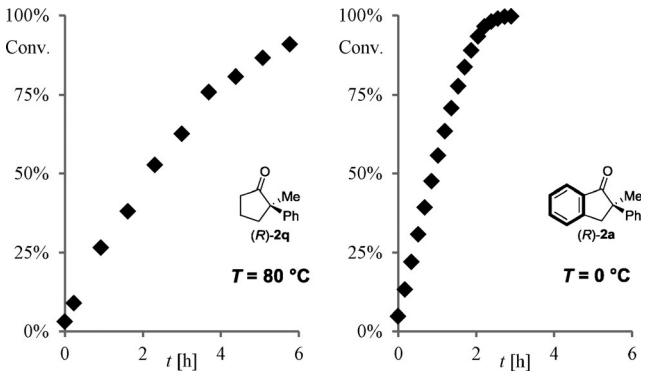


Figure 2. Acceleration by the aromatic backbone: Formation of products **2q** (left) and **2a** (right). Conditions: 10 mol % **3c**, 20 mol % DBU, [D_8]toluene (0.13 M).

with aromatic aldehyde **1a**, the temperature was reduced to 0 °C and the resulting clean conversion of the starting material **1a** into the product **2a** was still 2.0 times faster than the reaction of **1q** at 80 °C (Figure 2 right). Taking the elevated temperature into account, the aromatic substrate **1a** would react about 500 times faster than **1q** if using the same temperature for both substrates.[19] This shows that aliphatic aldehydes are much more challenging substrates for NHC-catalyzed hydroacylation than aromatic ones.

In conclusion, we have shown that intramolecular NHC-catalyzed hydroacylation is a robust and versatile method for the synthesis of α-chiral cyclic ketones bearing quarternary stereocenters. Both 6- and 5-membered rings can be synthesized, as well as aromatic and aliphatic ketones. The robustness screen showed a very high tolerance of this reaction to a diverse range of functional groups.

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

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[17] CCDC 1040461 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
[18] The reaction also takes place in toluene or THF, therefore we used toluene for our kinetic studies.
[19] A Q_{10} coefficient of 2.0 is assumed..

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