Organocatalysis

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NHC-Catalyzed Hydroacylation of Styrenes**

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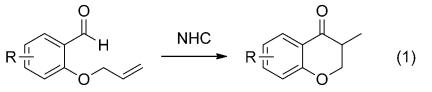
The hydroacylation of multiple bonds is a highly versatile reaction that uses abundant starting materials such as alkenes and aldehydes for the formation of valuable ketone structures.[1] However, the catalytic hydroacylation is an underexplored reaction and has only recently gained considerable interest. Until now, rhodium complexes have been the most common catalysts for olefin hydroacylation. A major problem for these catalyst systems is an undesired decarbonylation step, which often limits suitable substrates to aldehydes bearing additional coordinating groups, such as *ortho*-hydroxybenzaldehydes,[2] although certain substrate combinations[3] or the use of ruthenium catalysts[4] avoid this problem. An alternative approach is the intermediate transformation of aldehydes to imines that bind more strongly to the catalyst preventing decarbonylation.[5]

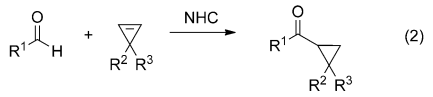
A promising alternative to metal-catalyzed hydroacylations is the use of N-heterocyclic carbenes (NHCs) as organocatalysts.[6] NHCs are versatile catalysts for several umpolung reactions, including the benzoin condensation and the Stetter reaction.[7] While the classical Stetter reaction is limited to the addition of an aldehyde to a polarized C–C double bond such as in nitroolefins, chalcones, and alkylidene malonates, the hydroacylation of less activated multiple bonds would broaden the scope of NHC organocatalysis significantly. To date, the latter type of NHC-catalyzed hydroacylation is limited to intramolecular reactions [Eq. (1)][8] and to compounds with strained multiple bonds [Eq. (2)].[9,10]

Previous Work:
NHC-catalyzed, *intramolecular* hydroacylation of *simple* alkenes[8]



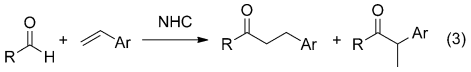
(1)

NHC-catalyzed, *intermolecular* hydroacylation of *strained* olefins[9]



(2)

This work:
NHC-catalyzed, *intermolecular* hydroacylation of *simple* styrenes



(3)

Herein we report the NHC-catalyzed hydroacylation of styrenes [Eq. (3)], the first intermolecular NHC-catalyzed hydroacylation of unstrained, rather electron-neutral alkenes. This transformation is remarkable as the organocatalyzed transformation of electron-neutral alkenes such as styrenes is a long-standing challenge in organocatalysis; only some rare examples of organocatalyzed epoxidations[11] and organocatalyzed brominations,[12] and a few examples relying on radical mechanisms have been reported.[13]

Recently, we designed a family of novel NHCs bearing a 2,6-dimethoxyphenyl moiety.[14] We hypothesized that these electron-rich NHCs would result in increased nucleophilicity of the Breslow intermediate[15,16] and would thus be suitable for the challenging hydroacylation of styrenes. Starting with the slightly activated *p*-cyanostyrene (**2a**) under the conditions employed for the hydroacylation of cyclopropenes,[9b] we were pleased to obtain the linear and branched hydroacylation regioisomers *l*-**3a** and *b*-**3a**, respectively. In addition to the four dimethoxy-NHCs **4a**, **5a**, **6a**, and **7a**, we also tested the commonly used NHCs **4b** and **5b** (Table 1, entries 1–6). As seen previously for intermolecular hydroacylations, the triazolium-derived NHCs were superior to other NHC scaffolds. We were especially happy to see our hypothesis of the higher reactivity of the 2,6-dimethoxy moiety confirmed as **4a** was the best of the NHCs tested (Table 1, entry 1, 50 % yield). While a screening of bases and reaction temperatures[17] did not improve the yield, the solvent had a marked influence on the reaction. Changing the solvent to THF improved the yield to 72 % (Table 1, entry 7). All attempts to further improve the yield in this solvent proved to be futile.[17]

We realized that several different side reactions prevented us from optimizing the reaction to full conversion. Two side reactions were of particular importance: Firstly, the 2,6-dimethoxy NHCs are not only highly reactive catalysts for the desired hydroacylation, but they also catalyze redox reactions of benzoin, an ubiquitous reaction intermediate in NHC-catalyzed umpolung reactions of aldehydes. This side reaction yields deoxybenzoin **8a** and consumes the aldehyde irreversibly (Scheme 1 A).

Secondly, the products **3a** contain an acidic methylene group in α-position to the carbonyl group. Under basic

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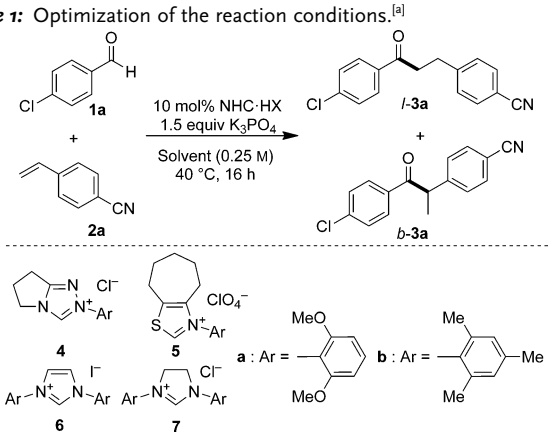
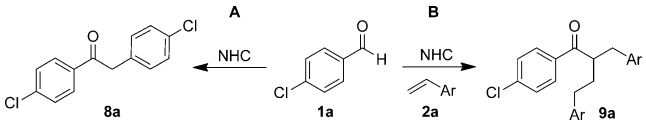
Table 1: Optimization of the reaction conditions.[a]



Entry	NHC·HX	Ratio 1a/2a	Solvent	Yield [%][b]	Ratio *l*/*b*[c]
1	**4a**	1:1.5	1,4-dioxane	50	84:16
2	**4b**	1:1.5	1,4-dioxane	21	75:25
3	**5a**	1:1.5	1,4-dioxane	2	–[g]
4	**5b**	1:1.5	1,4-dioxane	0	–[g]
5	**6a**	1:1.5	1,4-dioxane	27	81:19
6	**7a**	1:1.5	1,4-dioxane	3	–[g]
7	**4a**	1:1.5	THF	72	86:14
8	**4a**	1:1.5	DMF	13[d]	83:17
9[e]	**4a**	1.5:1	DMF	97 (89)[f]	85:15

[a] Standard conditions: 1 equiv ≙ 0.1 mmol, 10 mol% NHC·HX, 1.5 equiv K_3PO_4, solvent (0.25 M), 40 °C, 16 h. [b] Yield (*l*-**3a** + *b*-**3a**) determined by ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard. [c] Ratio of linear and branched product determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Byproduct **9a** (Scheme 1) was formed in 63% yield. [e] 1 equiv **2a** (0.2 mmol) was used. [f] Yield of isolated products (both products together), 1 equiv **2a** (0.5 mmol), 5 mol% **4a**, DMSO as solvent. [g] Only the linear product was detected.

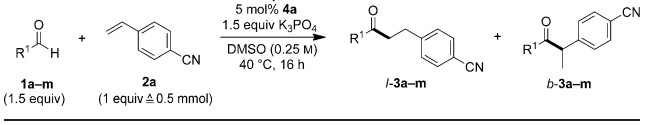


Scheme 1. Undesired side reactions in the hydroacylation of styrenes; Ar = *p*-CN-C_6H_4.

conditions this methylene group can be deprotonated and the resulting enolate can undergo further reaction. In highly polar solvents as DMF this side reaction becomes the main pathway and the desired product **3a** is formed in only 13% yield; **3a** adds to another molecule of styrene, forming byproduct **9a** (Table 1, entry 8; Scheme 1B). By changing the stoichiometry to an excess of aldehyde instead of an excess of styrene we could suppress both problematic side reactions and the product **3a** was formed in 97% yield (NMR yield, Table 1, entry 9). Using less reactive styrenes, we obtained even better results in DMSO.[17] Furthermore, the catalyst loading could be lowered to 5 mol% without decreasing the yield.

With these optimized conditions we tested a broad scope of different aromatic aldehydes. Generally, the linear product was obtained as the main product together with a small, easily separable amount of the branched product. The results with

Table 2: Variation of the aldehyde.



R^1	Ratio linear/branched[a]	Products: linear	Products: branched
p-Cl-C_6H_4	4.7:1	*l*-**3a**, 74%	*b*-**3a**, 15%
m-Cl-C_6H_4	2.9:1	*l*-**3b**, 66%	*b*-**3b**, 23%
p-Br-C_6H_4	5.8:1	*l*-**3c**, 65%	*b*-**3c**, 8%
p-Me-C_6H_4[b]	>20:1	*l*-**3d**, 47%	
2-naphthyl	8.3:1	*l*-**3e**, 50 %	
2-furyl	6.5:1	*l*-**3f**, 78%	*b*-**3f**, 8%
2-pyridyl	2.7:1	*l*-**3g**, 70%	*b*-**3g**, 26%
2-thiophenyl	1:1	*l*-**3h**, 44%	*b*-**3h**, 47%
phenyl	>20:1	*l*-**3i**, 49%	
p-Ph-C_6H_4	>20:1	*l*-**3j**, 52%	
p-CF_3-C_6H_4	2.4:1	*l*-**3k**, 51%	*b*-**3k**, 23%
m-MeO-C_6H_4	>20:1	*l*-**3l**, 46%	
3,4-dichloro-phenyl	1:1.3	*l*-**3m**, 27%	*b*-**3m**, 35%

[a] Ratio of linear to branched product determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] DMF, room temperature, 10 mol% **4a**, 0.5 equiv K_3PO_4.[17]

m-chlorobenzaldehyde were as good as those with *p*-chlorobenzaldehyde, only substitution in *ortho* position was not tolerated.[18] We were also pleased to see that several heteroaromatic aldehydes (Table 2, **1f–h**) gave the hydroacylation products in good to excellent yields. Additionally, we could show that electronically differently substituted aromatic aldehydes were well tolerated in this reaction.

If one compares the regioselectivities observed for this reaction, it can be noted that electron-rich aldehydes yield only the linear product, while electron-poor aldehydes give a mixture of the two products. Generally, the ratio of the two products can be attributed to the electronic character of the

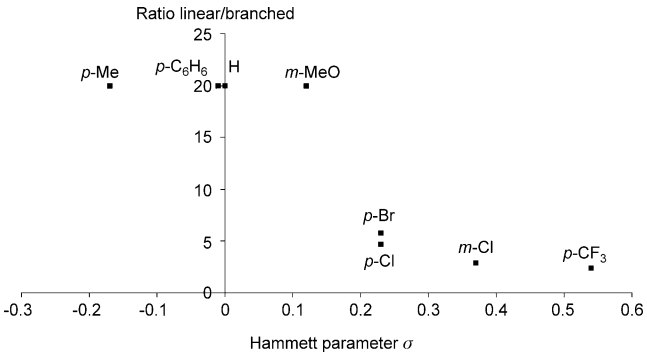


Figure 1. Ratio of *l*-**3** to *b*-**3** as a function of the Hammett parameter σ of the aldehyde.[17]

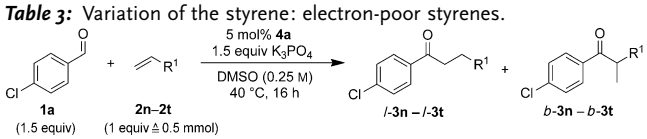
aldehyde, which can be measured by the Hammett parameter σ (Figure 1).[17,19]

We then focused on the variation of styrene **2** and were able to show that several styrenes with electron-withdrawing substituents including ester groups (Table 3, **3p**) and trifluoromethyl groups (Table 3, **3r**, **3s**) gave the targeted ketones in good to excellent yields.

The hydroacylation of unsubstituted styrene is of particular interest not only because styrene is one of the most important bulk chemicals, but also because the reaction is an especially challenging transformation. The successful hydroacylation of styrene would be a big step forward for the field of NHC-catalyzed intermolecular hydroacylations. Using styrene under our optimized conditions yielded promising traces of product; NHC-catalyzed redox chemistry caused the undesired consumption of most of the aldehyde, thus preventing better yields.

In order to accelerate the desired hydroacylation step, the amount of styrene was increased and a 1:1 mixture of styrene and DMSO was found to be optimal.[17] Using the triazolium salt **4b** and aldehyde **1k** yielded the branched hydroacylation product *b*-**3u** in 42% yield (Table 4). Under the same conditions we could even obtain the branched hydroacylation product of the electron-rich styrenes **3v** and **3w** in moderate yields (Table 4).

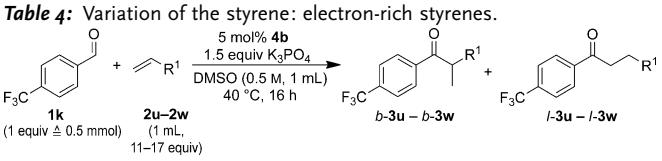
Table 3: Variation of the styrene: electron-poor styrenes.



R^1	Ratio linear/branched[a]	Products linear	branched
2-pyridyl	4.5:1	*l*-**3n**, 52%	*b*-**3n**, 8%
4-pyridyl	7.7:1	*l*-**3o**, 76%	*b*-**3o**, 9%
p-CO_2Me-C_6H_4	3.9:1	*l*-**3p**, 69%	*b*-**3p**, 15%
p-Ph(CO)-C_6H_4	15:1	*l*-**3q**, 57%	
p-CF_3-C_6H_4	1.1:1	*l*-**3r**, 24%	*b*-**3r**, 28%
3,5-bis-(trifluoromethyl)-phenyl	1:1	*l*-**3s**, 33%	*b*-**3s**, 37%
m-CN-C_6H_4	1:1.5	*l*-**3t**, 16%	*b*-**3t**, 33%

[a] Ratio of linear/branched product determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

Table 4: Variation of the styrene: electron-rich styrenes.

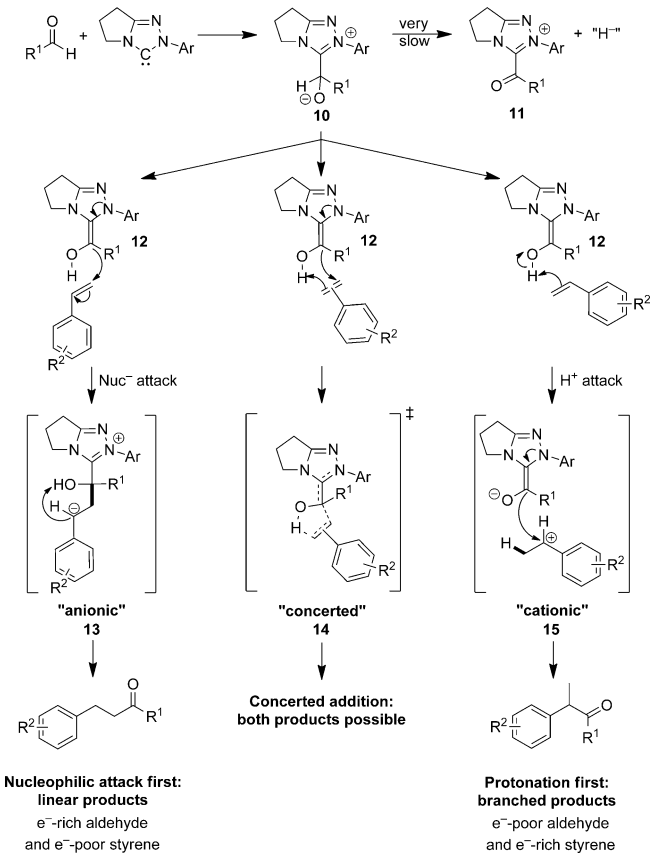


R^1	Ratio linear/branched[a]	Branched product
Ph	1:13	*b*-**3u**, 42%
p-*t*Bu-C_6H_4	<1:20	*b*-**3v**, 39%
p-O*t*Bu-C_6H_4	<1:20	*b*-**3w**, 25%

[a] Ratio of linear to branched product determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

Based on all our results we propose a mechanism for the hydroacylation of styrenes (Scheme 2). The sequence starts with the attack of the NHC on the aldehyde, providing the Breslow intermediate **12** after a formal 1,2 H-shift. This can react in a fast, but reversible way with another aldehyde, yielding benzoin. Hence, when we used 4,4′-dichlorobenzoin instead of the corresponding aldehyde as the starting material we obtained **3a** in 96% yield (81% *l*-**3a**, 15% *b*-**3a**). Instead of the formation of the Breslow intermediate **12**, **10** can also transfer a hydride yielding the poisoned catalyst **11** and reduce benzoin to deoxybenzoin.[20]

The Breslow intermediate is then able to attack the styrene in three possible ways, which is manifested in the two different regioisomers of the product that are formed. Nucleophilic attack of the Breslow intermediate on the styrene should give the linear product. In this case an anionic charge is formed on the benzylic position and proton transfer from the Breslow intermediate to the styrene follows as the second step (Scheme 2, left). After the elimination of the NHC the product is formed and the catalytic cycle is complete. This mechanism resembles the mechanism of the Stetter reaction and is favored by electron-rich aldehydes



Scheme 2. Proposed mechanism for the hydroacylation of styrenes.

(increased nucleophilicity of the Breslow intermediate) and electron-poor styrenes (stabilization of the anionic charge). Alternatively, the Breslow intermediate may first protonate the styrene at the terminal carbon of the double bond leading to a positive charge in the benzylic position (Scheme 2, right). This full protonation mode would arguably correspond to an unprecedented activation mode of the Breslow intermediate and is favored by electron-rich styrenes and electron-poor aldehydes (higher acidity of the OH group of the Breslow intermediate by stabilization of the negative charge in **15**). This mechanism is not related to the Stetter mechanism and the formation of the branched products cannot be explained by the classical mechanism of the Stetter reaction.

In addition to these two mechanisms that describe two extremes (cationic intermediate versus anionic intermediate), a third intermediate mechanism is possible (Scheme 2, middle). This mechanism would be a concerted hydroacylation similar to the addition of a 1,3-dipole to an alkene. A concerted addition could produce both products, depending on steric and electronic properties. In our previous intramolecular hydroacylations, DFT calculations indicated a concerted but highly asynchronous step, with the protonation triggering the sequence.[8b]

In summary, we have presented the NHC-catalyzed hydroacylation of styrenes spanning the whole range from electron-poor and electron-neutral to electron-rich styrene substrates. Many functional groups, such as halides and ethers, different heteroaromatic rings, and even carbonyl groups such as esters, ketones, and nitrile groups are well tolerated and valuable products are formed in good yields from simple and ubiquitous starting materials.

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