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The effect of hydrogen bond on Brønsted acid-catalyzed intramolecular hydroamination of unfunctionalized olefins

Ting-Ting Li [a], Gong-Qing Liu [a], Yu-Mei Wang [a], Bin Cui [a], Hui Sun [a], Yue-Ming Li [a,b,*]

[a] College of Pharmacy and Tianjin Key Laboratory of Molecular Drug Research, Nankai University, Tianjin 300071, People's Republic of China
[b] CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, People's Republic of China

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ABSTRACT

The catalytic activity of benzoic acid could be increased by introducing a hydrogen bond donor group at the *ortho*-position. Preliminary DFT calculation indicated that the activation of C=C double bond was realized by the action of both the carboxyl group and the hydrogen bond donor. The amino group was brought to the activated C=C bond by the interaction between the carboxyl oxygen and amino proton. This interaction also increased the nucleophilicity of the amino group. Thus, in the presence of 20 mol % of 2-(trifluoromethanesulfonamido)benzoic acid, intramolecular hydroamination of unfunctionalized olefins gave the corresponding products in up to 95% isolated yields.

1. Introduction

Nitrogen-containing heterocycles are the privileged structures in medicinal chemistry and have played important roles in drug research and development.[1] As a result, significant efforts have been made to develop new methods for C–N bond formation and for nitrogen-containing heterocycle construction.[2] In addition to conventional functional group transformation reactions,[3] hydroamination reaction should also be one of the most straightforward and efficient methods for the formation of C–N bonds and for the construction of nitrogen-containing heterocycles.[4] In the past decades, progresses have been made in this area, and hydroamination of different types of substrates have been realized both chemo- and stereoselectively using organolanthanides,[5] main group compounds,[6] group IV compounds,[7] noble metal compounds,[8] and other transition metal compounds[9] as catalysts.

In contrast to the achievements in metal-catalyzed hydroamination reactions, Brønsted acid-catalyzed hydroamination of unfunctionalized olefins bearing N-electron rich amino groups was relatively less pursued due to the buffering effect of the amino group.[10] Strong Brønsted acids would first interact with amino groups of the substrates, leading to the formation of ammoniums, which could not further react with free olefins in the absence of additional catalysts. Strong Lewis acids would coordinate more strongly with the amino groups, rendering the latter less reactive.[11] For these obvious reasons, sulfonamide substrates were mostly used in Brønsted acid-catalyzed hydroamination of unfunctionalized olefins to partially reduce the interaction between nitrogen atoms with the catalysts.[12] This approach was generally successful, and good to excellent isolated yields could be obtained in most cases in Brønsted as well as heteropoly acids-catalyzed hydroamination reaction of N-electron deficient substrates.[13] Similar results could also be obtained when different Lewis acids were used as catalysts,[14] but more and more evidences showed that the reactions were promoted by the corresponding Brønsted acids formed during the reaction.[15]

Efforts have been made to develop different Brønsted acids for efficient hydroamination of unfunctionalized olefins bearing N-electron rich amino groups.[16] Using phosphoric acid diesters as organocatalysts, different N-electron rich substrates were converted to the corresponding hydroamination products, and the reactions could proceed stereoselectively in the presence of chiral catalyst.[17] Shapiro et al. showed that dithiophosphoric acid was an efficient organocatalyst for hydroamination of 1,3-diene substrates. The successfulness of the catalyst system relied on the special structure of the 1,3-diene substrates, which could easily be attacked by the catalyst, and the relatively easy leaving group property of the

* Corresponding author. Tel.: +86 22 23504028; fax: +86 22 23507760; e-mail address: ymli@nankai.edu.cn (Y.-M. Li).

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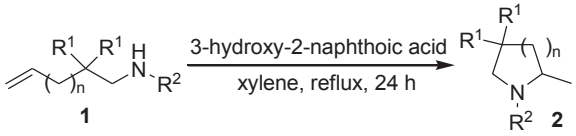
thiol group, which ensured the regeneration of the catalyst to complete catalytic circle.[18]

It is our purpose to understand the rationale for organocatalytic intramolecular hydroamination reactions. In this paper, we wish to report our progress on the design of bifunctional Brønsted acids, and the application of such catalysts in intramolecular hydroamination of N-electron rich olefin substrates.

2. Results and discussion

In our course of developing new methods for intramolecular hydroamination of unfunctionalized olefins bearing electron rich amino groups, we found that the Lewis acid catalysts should bear balanced Lewis acidity such that the C=C double bonds could be activated, and over-coordination of the catalyst to the amino groups should be avoided so that the reactivity of the amino groups could be maintained.[19] Similar trends were also observed for Brønsted acid-catalyzed reactions. While at most half amount of the substrate could be converted when trifluoromethanesulfonic acid or methanesulfonic acid was used, high conversion was observed when trifluoroacetic acid was used under otherwise identical conditions,[20] and Brønsted acid with acidity lower than this point was not successful for the reaction.

Given that intramolecular hydroamination is an entropy unfavorable process,[21] catalysts bearing additional functional groups, which could bring nitrogen atom close to C=C double bond would show some benefit for the reactions. Inspired by this rationale, we tested a variety of bifunctional Brønsted acids, and found that hydroxyarenecarboxylic acids showed higher activity than other catalysts (Scheme 1).[22]

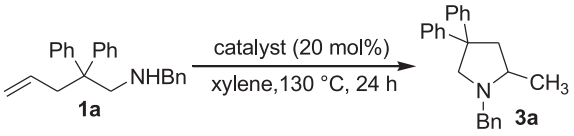


Scheme 1. 3-Hydroxy-2-naphthoic acid-catalyzed intramolecular hydroamination.

To find new organocatalysts suitable for intramolecular hydroamination of N-electron rich substrates, and to further understand the effect of additional functional groups on the catalytic activity of the catalysts, several easily available bifunctional compounds were tested for intramolecular hydroamination of *N*-benzyl-2,2-diphenyl-4-penten-1-amine (**1a**). Previous reaction conditions such as catalyst loading, reaction medium, reaction time, and reaction temperature were adopted,[22] and the results were summarized in Table 1.

As shown in Table 1, carboxyl group was essential for hydroamination of substrate **1a**, and compound lacking of the carboxyl group (**2a**) was unable to promote the reaction and the starting material was recovered (entry 1). *N*-Toluenesulfonyl proline (**2b**) gave 30% with the recovery of starting material yield (entry 2), *N*-toluenesulfonyl phenylalanine (**2c**) and *N*-toluenesulfonyl valine (**2d**) gave 63% and 74% yields, respectively (entries 3 and 4), revealing the important role of the additional functional groups played during the cyclization. Similar result was also observed when mandelic acid (**2e**) was used as catalyst (entry 5). Multifunctional compounds such as tartaric acid (**2f**) or *N*-toluenesulfonyl serine (**2g**) failed to give good results (entries 6 and 7), possibly due to the interference of the additional functional groups on the reaction. 2-Aminobenzoic acids **2h** and **2i** gave poor results, possibly due to the formation of inner salts (entries 8 and 9). The formation of inner salt could be avoided when the amino group was sulfonylated (**2j**), and this led to the increase of reactivity (entry 9 vs entry 10). The tethering group acted as hydrogen bond donor (entry 9 vs entries 11–14), and increasing the hydrogen bond donor ability led to significant increase of the activity of the catalysts (entries 11–14). Stereoselectivity was not observed for **2b** to **2g**-catalyzed reactions, possibly due to the high reaction temperature applied.

Table 1
Intramolecular hydroamination of **1a** in the presence of different bifunctional compounds[a,b]



Entry	Catalyst	Conversion of **1a** (%)
1	*o*-TfNHPhCOOH (**2a**)	NR
2	L-*N*-Ts Pro (**2b**)	30
3	L-*N*-Ts-Phe (**2c**)	63
4	L-*N*-Ts-Val (**2d**)	74
5	Mandelic acid (**2e**)	71
6	(+)-Tartaric acid (**2f**)	35
7	L-*N*-Ts Ser (**2g**)	22
8	*o*-NH_2PhCOOH (**2h**)	<20
9	*o*-MeNHPhCOOH (**2i**)	20
10	*o*-MeTfNPhCOOH (**2j**)	68
11	*o*-AcNHPhCOOH (**2k**)	43
12	*o*-MsNHPhCOOH (**2l**)	76
13	*o*-TsNHPhCOOH (**2m**)	80
14	*o*-TfNHPhCOOH	92

[a] Reactions were carried out in a sealed tube with 0.5 mmol of **1a**, 0.1 mmol of catalyst, and 2 mL of xylene at 130 °C.
[b] Conversions were based on crude NMR analysis of the reaction mixture.

The results in Table 1 showed that compound **2n** (2-(trifluoromethanesulfonamido)benzoic acid) gave the highest yield. This compound was then used as catalyst for further study. To find the most suitable conditions for the intramolecular hydroamination of **1a**, reactions in different solvents were carried out, and the results were summarized in Table 2.

Table 2
Effects of solvents and temperature on the intramolecular hydroamination of **1a**[a]

Entry	Solvent	*T*/°C	**3a**[b] (%)
1	Xylene	130	92
2	DMF	130	46
3	DMSO	130	10
4	Toluene	100	63
5	Dioxane	100	12
6	Benzene	90	29
7	DCE	90	19
8	EtOH	80	Trace
9	$CHCl_3$	80	12
10	THF	70	NR
11	Xylene	rt	NR
12	Xylene	60	NR
13	Xylene	90	6
14	Xylene	100	47
15	Xylene	110	61
16	Xylene	120	83
17[c]	Xylene	130	91
18[d]	Xylene	130	92
19[e]	Xylene	130	92

[a] Reactions were carried out in a sealed tube with 0.5 mmol of **1a**, 0.1 mmol of **2n**, and 2 mL of xylene.
[b] Based on crude NMR analysis of the reaction mixture.
[c] The amount of solvent=0.5 mL.
[d] The amount of solvent=1 mL.
[e] The amount of solvent=4 mL.

As shown in Table 2, high temperature was generally favorable for the intramolecular hydroamination reaction (entry 1 vs entries 11–16), no reaction was observed when the reactions were carried