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Ligand acceleration in ZnI₂-catalyzed intramolecular hydroamination of unfunctionalized olefins

Gong-Qing Liu, Wei Li, Yu-Mei Wang, Zhen-Ying Ding, Yue-Ming Li*

College of Pharmacy, State Key Laboratory of Medicinal Chemical Biology and Tianjin Key Laboratory of Molecular Drug Research, Nankai University, Tianjin 300071, People's Republic of China

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ABSTRACT

Zinc halide-promoted hydroamination of 4-penten-1-amine compounds was studied. Preliminary results indicated that both steric and electronic factors are crucial for this Lewis acid-promoted reaction. ZnI_2 gave the most promising results and the reactivity could be further increased upon addition of a suitable ligand. Up to 95% isolated yields were obtained when the reactions were carried out in 1,4-dioxane in the presence of 10 mol % of ZnI_2 and 8-hydroxyquinoline.

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Nitrogen-containing organic compounds are the most important components of biologically active compounds. They constitute the most important part of privileged structures and have played vital roles in drug discovery.¹ To this end, significant efforts have been made toward the formation of C–N bonds as well as the construction of nitrogen-containing skeletons.² Among all the methods studied, hydroamination represents one of the most straightforward and efficient methods for the formation of carbon–nitrogen bonds. In the past decades, both transition metal complex-catalyzed and organo-catalytic hydroamination have been reported for this purpose.³

Comparing to the widespread applications of organozinc reagents as nucleophiles in different organic reactions, the Lewis acid property of zinc compounds is far less pursued.⁴ It is our purpose to develop a facile and easily accessible reaction system for catalytic hydroamination of unfunctionalized olefins, and to use this as a starting point for catalytic asymmetric hydroamination of unfunctionalized olefins. In this communication we wish to report our preliminary results on ligand-accelerated hydroamination of N-substituted 4-penten-1-amines catalyzed by zinc iodide.

Studies on zinc-exchanged zeolite-catalyzed hydroamination of alkynes⁵ and the interaction between C=C double bond and zinc⁶ can be traced back to 1970s. Later, Penzien and Müller reported the hydroamination of several unfunctionalized olefins using zinc ion exchanged β -zeolites as catalysts.⁷ Roesky et al. showed that aminotroponate zinc compounds were effective in hydroamination of a variety of substrates.⁸ Very recently we showed that zinc

triflate was able to promote intermolecular hydroamination of styrenes with aromatic amines.⁹ However, there is still a need to fully understand the steric and electronic factors governing the activity of a catalyst, so that easily accessible catalyst system could be developed for hydroamination of unfunctionalized olefins.

4-Penten-1-amine (1), which was used as a model substrate in many publications, was first tested in zinc salt-promoted hydroamination reactions. However, our first efforts did not give any positive result.



The Thorpe–Ingold or *gem*-dimethyl (more generally dialkyl) effect has been observed in several cyclization reactions including hydroamination reactions.¹⁰ To see if the introduction of substituents in the mainchain of the substrate would increase the reactivity of the substrate, 2,2-diphenyl-4-penten-1-amine (**2**), in which two phenyl groups were introduced at the 2-position of substrate **1**, was then used as another model substrate. Additional advantage of compound **2** was its UV absorption property which made us easy to monitor the reaction with TLC. However, no product could be detected after the reaction mixtures were refluxed in toluene for 48 h.

It is generally acceptable that the choice of an amino group is crucial for successful hydroamination of a substrate. Strongly nucleophilic amines would coordinate tightly to the metal center, leading to the blockage of an essential site for C=C binding and





^{*} Corresponding author. Tel.: +86 22 23506290; fax: +86 22 23507760. *E-mail address*: ymli@nankai.edu.cn (Y.-M. Li).

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the decrease of reactivity of the amino group, and finally resulting in an unproductive substrate binding.¹¹ It is reasonable to assume that the reactivity of an amino group would be resumed if its coordination to zinc could be weakened. Introducing a bulky group to the nitrogen atom would in some extent increase the steric hindrance of the amino group and therefore weaken the coordination of the amino group to the central metal. Introduction of an alkyl group to nitrogen atom could also compensate the loss of nucleophilicity caused by metal coordination. In this context, another substrate **3a**, in which the nitrogen atom was benzylated, was used for a further study. Reported conditions were adopted for the initial study. The substrate and catalyst were mixed in toluene, and the mixture was heated in an oil bath at 130 °C. To our delight, intramolecular hydroamination products were detected for most cases. Some results were listed in Table 1. A sealed tube could be used to avoid the escape of the solvent, but this was not a requisite.

Preliminary studies showed that counter anions and the amount of zinc salts had significant effects on the course of the reaction. Metal zinc was not able to promote the reaction due to the lack of Lewis acidity, zinc hydroxide was also not able to promote the reaction due to the lack of sufficient Lewis acidity, and zinc iodide gave the best results. Balanced Lewis acidity was crucial for successful hydroamination of the substrate. Strong Lewis acid such as zinc triflate failed to give high yield (entry 2) possibly due to the strong coordination of the amino group to the central metal. Reducing the catalyst loading resulted in a drop of yield, and the yield could be regained through prolongation of reaction time.

Results in Table 1 indicated that in order for hydroamination to proceed in a reasonable rate, the promoter must have enough Lewis acidity. However, Lewis acidity alone was not the governing factor for successful hydroamination of the substrates. Zinc chloride was more acidic than zinc iodide but sterically less hindered, and gave lower yield under identical conditions. An ideal promoter should bear balanced Lewis acidity and steric hindrance to ensure enough C=C double bond activation whereas the coordination of amine could be reduced to the minimum extent.

After getting general information about the key factors governing the reactions, efforts were made to find an optimal reaction condition for this easy-to-operate reaction. ZnCl₂ was used as the reaction promoter in order to observe big differences among different conditions, and ZnI₂-promoted reactions were carried out for comparison. Some results are shown in Table 2.

Table 1

Hydroamination of 3a using different zinc salts^a



^a Amount of zinc salt = 1 equiv.

^b Ratios were calculated based on crude NMR analysis of the reaction mixtures.

As these results indicated, toluene or 1,4-dioxane was more suitable for the reaction, and ZnI_2 was superior to $ZnCI_2$ in most cases. ZnI_2 was then used as a reaction promoter for further optimization of the reaction conditions.

One of the important properties for zinc-catalyzed (or -promoted) reaction is its ligand acceleration feature, that is, the reaction rate of an organozinc reagent can be accelerated upon addition of suitable ligands. To see if ligands would have some positive effects on ZnI₂-promoted hydroamination reactions, commercially available mono- and bidentate ligands were tested. We assumed that the ligands should bear balanced bulkiness to ensure the efficient coordination and activation of substrate C=C double bonds, while the strong binding of substrate amino group to the central metal should be avoided so that the nucleophilicity of the amino group would be preserved. Such system would ensure the nucleophilic attack of the amino group on the activated C=C bond, leading to a meaningful hydroamination of the substrate. Figure 1 listed some of the ligands which would accelerate the ZnI₂-promoted hydroamination of substrate **3a**.

Results in Figure 1 indicated that 8-hydroxyquinoline was one of the ligands able to accelerate the hydroamination reaction. While reaction carried out in the presence of 50 mol % of ZnI_2 alone under otherwise identical conditions gave 14% hydroaminated product, 78% yield was observed when 8-hydroxyquinoline was presented in the reaction mixture. Other ligands bearing a similar planar structure could also accelerate the reaction. Monodentate triphenylphosphine gave 70% yield, and bidentate DPPE gave the product in less than 5% yield, possibly due to the lack of enough space for C=C double bond binding, and thus indicating a streeo-demanding feature of the reaction. 8-Hydroxyquinoline was finally chosen as the ligand due to its easy availability.

To see if similar ligand acceleration could be observed for other zinc salts, ZnCl₂, ZnBr₂, and Zn(OTf)₂ in combination with 8-hydroxyquinoline were also tested for hydroamination of **3a**, and the results are summarized in Table 3. As these results indicated, zinc iodide in combination with 8-hydroxyquinoline was the most effective catalyst system in hydroamination of substrate **3a**. Reducing the catalyst loading resulted in a drop of reaction rate, and longer reaction time resulted in a complete conversion of the substrate.

Other substrates were then tested to study the scope of the reaction, and the results are shown in Table 4.¹² The reactions were carried out in 1,4-dioxane at 110 °C for 36 h, 10 mol % of zinc iodide and 10 mol % of 8-hydroxyquinoline were used as catalyst. Both toluene and 1,4-dioxane were suitable for the reaction. The latter was finally chosen as the solvent due to its less toxicity and its ease of removal. Longer reaction time and higher temperature were used to ensure a complete conversion of all the

Table 2			
Hydroamination of N-benzyl	2,2-diphenyl-4-pentenamine	in different	solvents

Entry	Solvent	Reaction temperature (°C)	3a:4a ^b
1	Hexane	80	83:17
2	DCE	80	80:20
3	CH₃CN	80	76:24 (71:29)
4	Benzene	80	89:11 (87:13)
5	Toluene	80	75:25 (80:20)
6	1,4-Dioxane	80	70:30 (67:33)
7	Toluene	130	40:60
8	1,4-Dioxane	120	39:61 (16:84)
9 ^c	Toluene	130	14:86
10 ^d	Toluene	130	39:61

^a Reaction conditions: 100 mol % ZnCl₂, 24 h.

 $^b\,$ Based on crude NMR analysis of the reaction mixtures. Data in parentheses are results from 100 mol $\%\,$ ZnI_2 under identical conditions.

^c Reaction time: 48 h.

d 200 mol % ZnCl2, 48 h.

Znl₂ (no ligand): 20mol%: <5%, 50 mol%: 14% DBU: 20 mol%, 13%, 50 mol%, 64% DABCO: 20 mol% 9%, 50 mol%, 55%



Reaction conditions: benzene, 80 °C, 48 h, ZnI₂:Ligand = 1 : 1

Figure 1. Ligand acceleration in Znl_2 -promoted hydroamination of 3a in the presence of different ligands.

Table 38-Hydroxyquinoline-accelerated hydroamination of 3a with different zinc salts^a

Entry	Catalyst	Catalyst loading (mol %)	Reaction time (h)	3a	:4a ^b
1	ZnI ₂	20	24	7	93
2	ZnCl ₂	20	24	80	20
3	ZnBr ₂	20	24	86	14
4	Zn(OTf)2	20	24	87	13
5	ZnI ₂	20	48	<1	>99
6	ZnI ₂	10	48	<1	>99
7	ZnI ₂	5	48	12	88
8	ZnI ₂	10	24	10	90
9	ZnI_2	10	36	<1	>99

^a Reaction conditions: solvent = 1,4-dioxane, ligand = 8-hydroxyquinoline, temperature = $110 \degree C$ (oil bath temperature).

^b Based on crude NMR analysis of the reaction mixtures.

substrates. The reactions proceeded readily, giving the pyrrolidine product **4** in good to excellent isolated yields. Amides (**3i**–**3k**) or aromatic amine (**3s**) failed to react, possibly due to the low reactivity of the nitrogen atoms (entries 9–11, and entry 19). Sterically less hindered substrates (**3p** and **3r**) also failed to react (entries 16 and 18), possibly due to a tighter coordination between the amino group to central metal and the lack of Thorpe–Ingold effect.

To further test the influence of Thorpe–Ingold effect on the course of the reaction, substrate **5** was also subjected to hydroamination reaction under the same conditions $(10 \text{ mol }\% \text{ Znl}_2 + 10 \text{ mol }\%)$

Table 4

ZnI2-8-hydroxyquinoline-catalyzed hydroamination of unfunctionalized olefins

$$\begin{array}{c} R^{1} R^{1} H \\ 3 \end{array} \xrightarrow{R^{2} 110 \circ C, 36 h} CH_{3} \xrightarrow{R^{1}} CH_{3} \xrightarrow{R^{2}} 4 \end{array}$$

Entry	Substrate	R ¹	R ²	Yield ^a (%)
1	3a	Ph	Bn	95
2	3b	Ph	4-MeBn	86
3	3c	Ph	4-i-PrBn	86
4	3d	Ph	4-MeOBn	84
5	3e	Ph	3-MeOBn	93
6	3f	Ph	4-FBn	91
7	3g	Ph	4-BrBn	95
8	3h	Ph	4-O ₂ NBn	82
9	3i	Ph	Ac	N.R. ^b
10	3j	Ph	Ts	N.R.
11	3k	Ph	Boc	N.R.
12	31	Ph	i-Pr	84
13	3m	Ph	Су	58
14	3n	Ph	<i>i</i> -Bu	92
15	30	Me	Bn	92
16	3р	Н	Bn	N.R.
17	3q	-(CH ₂) ₅ -	Bn	94
		H N-		
18	3r	Bn CH		N.R.
		U⊓ ₃		
10	2-			ND
19	35	L L		N.K.
		∼ NHBn		

^a Isolated yields.

^b N.R. = no reaction.

8-hydroxyquinoline) (Scheme 1). This compound contains two different 4-pentenyl groups, one of which was substituted with two phenyl groups.

Results showed that compound **6** was obtained in 93% isolated yield, and the sterically less hindered product **7** was not observed, indicating the positive effect of *gem*-disubstituents on the activity of the substrate.



In summary, we have shown that both steric and electronic factors played important roles in Zn(II)-catalyzed hydroamination of unfunctionalized olefins. The catalyst should bear balanced Lewis acidity as well as steric hindrance to ensure an efficient C=C bond activation and to avoid an over-strong interaction between the central metal and the amino group. Zinc iodide showed highest activity among all zinc salts studied, and its catalytic activity could



Scheme 1. Thorpe–Ingold effect in ZnI₂-catalyzed hydroamination reaction.

be further increased upon addition of suitable ligands. 8-Hydroxyquinoline and other similar ligands showed prominent results in rate acceleration. Another most important advantage of the current catalyst system is its ease of operation. Both the catalyst and the ligand were easily accessible, and all the operations could be carried out in the open air without any loss of yields. Ligand acceleration and steric demanding features of the current catalyst system may shed light on the design of chiral ligands for stereoselective hydroamination of unfunctionalized olefins.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.033.

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- 12. A general procedure for intramolecular hydroamination reaction: All commercially available starting materials were purchased from Aladdin Reagents (Beijing) and J&K Chemicals (Shanghai) and were used as received. A sealed tube was charged with dry 1,4-dixoane (1 mL), aminoalkene (1.00 mmol). To this tube were added Znl₂ (0.1 mmol, 10 mol %) and 8-hydroxyquinoline (0.1 mmol, 10 mol %). The tube was then sealed and was heated in an oil bath (110 °C). The reaction mixture was stirred at this temperature for 36 h and was then cooled to room temperature. The mixture was transferred to separating funnel with the aid of CH₂Cl₂ (20 mL) (*Caution: care must be taken when opening the sealed tube.*). The reaction mixture was washed with saturated Na₂CO₃ solution, dried (MgSO₄), and concentrated to give an oil which was purified by flash chromatography to give the corresponding product.