Tetrahedron Letters 52 (2011) 7168–7170

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Zinc triflate-catalyzed intermolecular hydroamination of vinylarenes and anilines: scopes and limitations

Gong-Qing Liu, Yue-Ming Li *

College of Pharmacy and Tianjin Key Laboratory of Molecular Drug Research, Nankai University, 94 Weijin Road, Tianjin 300071, People's Republic of China

A R T I C L E I N F O

Article history:
Received 21 August 2011
Revised 12 October 2011
Accepted 21 October 2011
Available online 28 October 2011

Keywords:
Zinc triflate
Styrene
Aniline
Hydroamination
Hydroarylation

A B S T R A C T

Intermolecular hydroamination of vinylarenes and anilines was studied using zinc triflate as catalyst. NMR experiments supported a Lewis acid activation of the C=C double bond. Electronic/steric effect study indicated that Lewis acidity of the catalyst as well as the coordination property of the amine were the governing factors for successful hydroamination of the substrates. More nucleophilic amine would bind more tightly to the central metal, leading to an unproductive coordination. Approach of bulky amine to C=C bond would be hindered, and an alternative electrophilic substitution on benzene ring of the amine would become the major reaction. Electrophilic substitution would become predominant when strong electron-donating group is presented on aniline benzene ring.

Nitrogen-containing compounds have been found extensive application in medicinal chemistry, and significant efforts have been made toward the synthesis of these types of important compounds.[1] Traditional synthesis of nitrogen-containing compounds would involve multistep functional group transformations, and in many cases are proved to be problematic due to the normally harsh reaction conditions involved. Many state-of-the-art methods have been developed for C–N bond formations, and hydroamination of C–C multiple bonds is among the most straightforward and atom economical methods for the construction of C–N bonds and related heterocyclic skeletons.[2]

Due to the electron-rich property of both the substrates and the nucleophiles, hydroamination of unfunctionalized olefins is generally difficult in the absence of a catalyst. An ideal catalyst should bear balanced steric and electronic effects to ensure an effective activation of C=C bond, and also a free amino group which is nucleophilic enough for a meaningful hydroamination reaction.

In addition to their successful application in nucleophilic addition reactions,[3] some zinc related materials such as zinc triflate,[4] zinc-exchanged montmorillonite clay,[5] or aminotroponiminate methyl/ethyl zinc complexes[6,7] were also found effective in hydroamination of different aminoalkenes and aminoalkynes. However, to the best of our knowledge, there is no report on zinc salt-catalyzed homogeneous intermolecular hydroamination of unactivated alkenes with amines. Detailed study is therefore required to fully understand the electronic/steric factors governing the performance of the catalysts.

We are interested in developing efficient and practical method for both intra- and intermolecular hydroamination of unfunctionalized olefins, and it is our first purpose to fully understand the electronic/steric factors which are important for successful hydroamination reactions. In this communication, we wish to report our preliminary results on zinc salts-catalyzed intermolecular hydroamination of vinylalkenes with anilines.

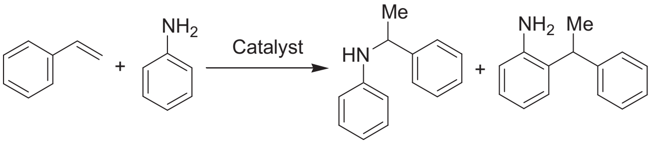
Reaction between styrene and aniline was first chosen as a model reaction to study the effects of Lewis acidity of the zinc salts on the course of reaction, and the results are summarized in Table 1. Reported conditions such as solvent, reaction temperature, catalyst loading, and reaction time were first adopted, and our preliminary results supported a Lewis acid-catalyzed mechanism.[8] Entries 1–7 in Table 1 indicated that relatively higher yields were observed for stronger Lewis acidic catalysts, and zinc dust or zinc hydroxide did not promote any reaction (entries 1 and 2). Zinc triflate was proved to be the most suitable catalyst in the current reaction system, other substrates and anilines were then tested with $Zn(OTf)_2$ under the current conditions. Higher yield was observed at higher catalyst loading (Table 1, entry 8), and coordination solvent such as dioxane was inappropriate for this type of reaction (Table 1, entry 9). Reaction carried out in xylene at higher temperature failed to give a good yield (Table 1, entry 10), possibly due to the deterioration of the substrate at the refluxing temperature. Only trace amounts of product were detected when trifluorosulfonic acid (HOTf) was used as the catalyst (Table 1, entry 11), indicating that zinc triflate was responsible for the hydroamination

---

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

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.10.124

Table 1
Hydroamination of styrene (**1a**) with aniline (**2a**) under different reaction conditions[a]



1a **2a** **3a** **4a**

Entry	Zn source	Catalyst (mol %)	Solvent	T (°C)	Yield **3a**[b] (%)
1	Zn	10	Toluene	130	–
2	$Zn(OH)_2$	10	Toluene	130	–
3	$ZnSO_4·7H_2O$	10	Toluene	130	6
4	$ZnCl_2$	10	Toluene	130	9
5	ZnI_2	10	Toluene	130	15
6	$Zn(OAc)_2$	10	Toluene	130	8
7	$Zn(OTf)_2$	10	Toluene	130	32
8	$Zn(OTf)_2$	20	Toluene	130	46
9	$Zn(OTf)_2$	20	Dioxane	100	12
10	$Zn(OTf)_2$	20	Xylene	160	22
11	HOTf	20	Toluene	130	<2

[a] Reagents and conditions: aniline (1.1 mmol), styrene (1 mmol), catalyst in solvent (1.0 mL), 24 h.

[b] Isolated yield.

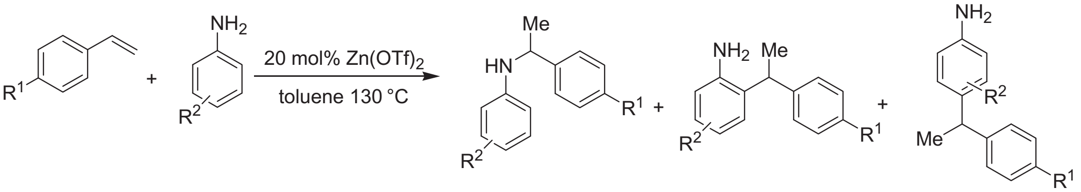
product. This is also in good agreement with the observations made by Schlummer and Hartwig that the intramolecular addition of amines without an electron-withdrawing group did not occur using concentrated sulfuric acid.[9]

Different vinylarenes and anilines were then subjected to intermolecular hydroamination under the optimized conditions, and the results were listed in Table 2.[10] In addition to the expected hydroamination products, hydroarylation (Friedel–Crafts) products were also observed in some cases. For the reactions studied, the selectivity between hydroamination and hydroarylation depended on the nucleophilicity of the aniline nitrogen atom: electron-withdrawing group substituted anilines increased the chemoselectivity and favored the hydroamination products, and electron-donating group substituted aniline increased the amount of hydroarylation of the substrates (entry 1 vs 2–4, entries 2–4 vs 6, and entry 7 vs 11). Substituents on vinylarenes also showed strong effect on the course of the reaction. The reaction proceeded much faster for electron-donating group substituted olefins than for electron-withdrawing group substituted substrates (entries 7 and 8 vs 9), the former produced mainly *para*-substituted hydroarylation product, and *ortho*-substituted hydroarylation products were obtained for the latter (entry 9 vs 8). This is also in agreement with our preliminary calculation of the charge distributions on the benzene ring.[11]

To confirm if the hydroarylation product was formed through an electrophilic process or through Hofmann–Martius rearrangement[12] of the formed hydroamination product, the reaction between styrene and aniline was carried out, and the ratio of **3a** to **4a** was monitored at different stage of the reaction. The result showed that this ratio remained almost unchanged during the course of the reaction, and was not significantly influenced by reaction temperature. This indicated that hydroarylation product was formed through a Friedel–Crafts reaction of the substrate in competition with hydroamination. A control experiment demonstrated that isolated **3a** did not undergo a Hofmann–Martius rearrangement[13] under reaction conditions (Scheme 1). This is in contrast to proton[14] and $TiCl_4$[15] catalyzed reactions where prolonged reaction time favored the formation of hydroarylation products.

NMR experiments were carried out to study the possible interaction between C=C bond and $Zn(OTf)_2$. When equal equivalents of styrene and zinc triflate were mixed in $CDCl_3$, a down field shift of 0.1 ppm was observed for C=C proton signals (δ 7.03, 6.06, 5.55 ppm in the absence of zinc triflate versus δ 7.13, 6.17 and 5.65 ppm in the presence of zinc triflate, respectively), indicating a possible π-coordination of C=C double bond to $Zn(OTf)_2$. Similar down field shifts were also observed in ^{13}C NMR experiments: the chemical shifts for olefin bond: $=CH_2$ 113.93 and $=CH–$ 137.04 ppm without zinc triflate moved to 114.06 and 137.30 ppm, respectively when equal equivalents of zinc triflate were added. Though weak the interaction may be, it is strong enough for a nitrogen atom to undergo a nucleophilic attack on the C=C double bond of the substrate when the electron-donating property of the substituent on aniline is not strong enough to

Table 2
Hydroamination reaction of different vinylarenes and anilines[a]



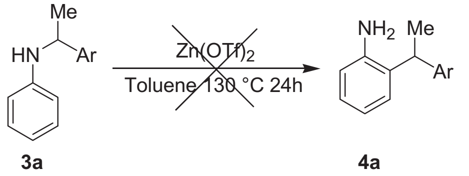
1 **2** **3** **4** **5**

Entry	R^1	R^2	Yield **3**[b] (%)	Yield **4**[b] (%)	Yield **5**[b] (%)	Yield **3** + **4** + **5**[b] (%)
1	H (**1a**)	H (**2a**)	46 (**3a**)	31 (**4a**)	–	77
2	H (**1a**)	*p*-F (**2b**)	28 (**3b**)	15 (**4b**)	–	43
3	H (**1a**)	*p*-Cl (**2c**)	26 (**3c**)	19 (**4c**)	–	45
4	H (**1a**)	*p*-Br (**2d**)	45 (**3d**)	16 (**4d**)	–	61
5	H (**1a**)	*p*-NO_2 (**2e**)	24 (**3e**)	–	–	24
6	H (**1a**)	*p*-OMe (**2f**)	–	57 (**4f**)	–	57
7	F (**1b**)	H (**2a**)	27 (**3g**)	–	–	27
8	Br (**1c**)	H (**2a**)	31 (**3h**)	17 (**4h**)	–	48
9[c]	OMe (**1d**)	H (**2a**)	35 (**3i**)	–	42 (**5i**)	77
10[c]	OMe (**1d**)	*p*-OMe (**2f**)	55 (**3j**)	31 (**4j**)	–	86
11	F (**1b**)	*p*-OMe (**2f**)	20 (**3k**)	53 (**4k**)	–	73

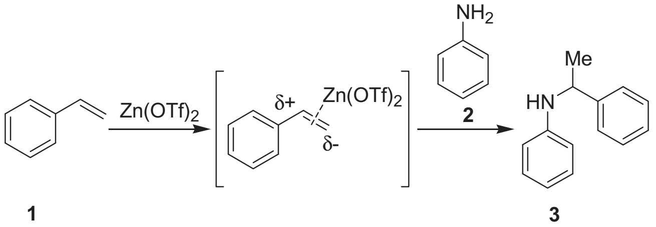
[a] Reaction conditions: aniline (1.1 mmol), styrene (1 mmol), 20 mol % $Zn(OTf)_2$ in solvent (1.0 mL), 24 h.

[b] Isolated yield.

[c] Reaction time 12 h.



Scheme 1. Thermo-stability study of the hydroaminated product **3a**.



Scheme 2. A tentative reaction pathway leading to the hydroamination product.

trigger an electrophilic substitution on the aromatic ring. This also accounts for the Friedel–Crafts products for strong electron-donating group substituted anilines.

When N-substituent was presented in aniline, the reactivity of the nitrogen atom was decreased due to the increased bulkiness, and an electrophilic substitution on aniline could then occur, leading to the formation of by-products **4** and **5**. This process could be strengthened when electron-donating group is presented on the benzene ring of aniline.[16] In these cases, electrophilic substitution overrides the hydroamination and becomes the major reaction. Aliphatic amines such as benzylamine or morpholine failed to undergo hydroamination or hydroarylation reaction possibly due to the strong coordination to the central metal, leading to an unproductive substrate binding as well as the deactivation of the benzene ring for further electrophilic substitution.[17] This was also supported by NMR experiments: NMR signals for aniline were almost unchanged when it was mixed with zinc triflate, while a down field shift was observed when 4-chlorobenzylamine was mixed with zinc triflate.[18] The preliminary NMR experiments indicated that free amino groups were presented in anilines, while aliphatic amines such as benzylamines coordinated more tightly to zinc triflate, rendering the nitrogen atom less nucleophilic for further hydroamination of the C═C bond.

On the basis of these observations, a tentative reaction pathway could be proposed as shown in Scheme 2. The C═C double bond was activated upon zinc coordination, and a subsequent nucleophilic attack of the aniline nitrogen atom gave the expected product **3**. Hydroarylation would become predominant when the aniline benzene ring was further activated by the additional electron-donating groups such as alkoxyl groups.

In summary, $Zn(OTf)_2$ can be used to promote intermolecular hydroamination of unactivated alkenes such as styrenes with anilines, and some functional groups could be tolerated in both substrates and nucleophiles. When strong electron-donating groups are presented, hydroarylation would occur as a competing reaction. This process could be enhanced with secondary amines and the presence of strong electron-donating groups on the aniline benzene ring. Preliminary NMR experiments supported the activation of the C═C double bond by zinc triflate through π-coordination, and a possible reaction pathway could be proposed on the basis of these observations. Further studies on the details of the reaction mechanism and the improvement of the chemoselectivity are in good progress.

Acknowledgment

We acknowledge the financial support from National Natural Science Foundation of China (NSFC 20972072).

References and notes

1. O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446.
2. For leading reviews: (a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892; (b) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367–391; (c) Hong, S.; Marks, T. *J. Acc. Chem. Res.* **2004**, *37*, 673–686; (d) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104–114; (e) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795–813; (f) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675–704; (g) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12–21; (h) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555–4563; (i) Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, *44*, 5105–5118; (j) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199–207.
3. (a) Nakamura, E. In *Organometallics in Synthesis - A Manual*; Schlosser, M., Ed.; John Wiley & Sons Ltd: Chichester, 2002; pp 579–664; (b)*The Chemistry of Organozinc Compounds (Patai Series: The Chemistry of Functional Groups)*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons: Chichester, UK, 2006.
4. (a) Bódis, J.; Müller, T. E.; Lercher, J. A. *Green Chem.* **2003**, *5*, 227–231; (b) Neff, V.; Müller, T. E.; Lercher, J. A. *Chem. Commun.* **2002**, 906–907; (c) Müller, T. E.; Pleier, A.-K. *J. Chem. Soc. Dalton Trans.* **1999**, 583–588; (d) Müller, T. E.; Grosche, M.; Herdtweck, E.; Pleier, A.-K.; Walter, E.; Yan, Y.-K. *Organometallics* **2000**, *19*, 170–183.
5. Shanbang, G. V.; Halligudi, S. B. *J. Mol. Catal. A: Chem.* **2004**, *222*, 223–228.
6. (a) Zulys, A.; Dochnahl, M.; Hollmann, D.; Löhnwitz, K.; Herrmann, J.-S.; Roesky, P. W.; Blechert, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7794–7798; (b) M. Dochnahl, Ph. D. Thesis, Technische Universität Berlin, Germany, 2007.; (c) Meyer, N.; Löhnwitz, K.; Zulys, A.; Roesky, P. W.; Dochnahl, M.; Blechert, S. *Organometallics* **2006**, *25*, 3730–3734.
7. (a) Dochnahl, M.; Löhnwitz, K.; Pissarek, J.-W.; Roesky, P. W.; Blechert, S. *Dalton Trans.* **2008**, 2844–2848; (b) Dochnahl, M.; Pissarek, J.-W.; Blechert, S.; Löhnwitz, K.; Roesky, P. W. *Chem. Commun.* **2006**, 3405–3407; (c) Dochnahl, M.; Löhnwitz, K.; Pissarek, J.-W.; Biyikal, M.; Schulz, S. R.; Schön, S.; Meyer, N.; Roesky, P. W.; Blechert, S. *Chem. Eur. J.* **2007**, *13*, 6654–6666.
8. Burling, S.; Field, L. D.; Messerle, B. A.; Turner, P. *Organometallics* **2004**, *23*, 1714–1721.
9. (a) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471–1474; (b) Talluri, S. K.; Sudalai, A. *Org. Lett.* **2005**, *7*, 855–857.
10. *General procedure of the reaction*: All commercially available products were purchased from Aladdin and used as received. A sealed tube purged with argon was charged dry toluene (1 mL), vinylarene (1.00 mmol) and anilines (1.10 mmol). $Zn(OTf)_2$ (0.20 mmol, 20 mol %) was added, the tube was sealed and the reaction mixture was stirred at 130 °C for 24 h. The reaction mixture was then transferred to a vial and volatile materials were removed *in vacuo* to give an oil which was purified by flash chromatography to give the corresponding product.
11. The calculation was carried out with semi-empirical AM1 method in MOAPC provided by Chem3D.
12. (a) Hofmann, A. W.; Martius, C. A. *Ber.* **1871**, *4*, 742–748; (b) Hofmann, A. W. *Ber.* **1872**, *5*, 720–722.
13. Reilly, J.; Hickinbottom, W. J. *J. Chem. Soc.* **1920**, 103–137.
14. Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542–14543.
15. Kaspar, L. T.; Fingerhut, B.; Ackermann, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 5972–5974.
16. When *N*-benzyl-4-ethoxyaniline was allowed to react with 4-methoxystyrene, the corresponding hydroarylation product was isolated in 63% and only trace amounts hydroamination product was detected.
17. (a) Schaffrath, H.; Keim, W. *J. Mol. Catal. A: Chem.* **2001**, *168*, 9–14; (b) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437–5740; (c) Åkermark, B.; Bäckvall, J. E.; Hegedus, L. S.; Zetterberg, K.; Siirala-Hansén, K.; Sjöberg, K. *J. Organomet. Chem.* **1974**, *72*, 127–138.
18. The interaction between amino groups and zinc triflate was studied by monitoring the ^1H NMR chemical shift of the phenyl group. When equal equivalents of 4-chloroaniline and zinc triflate were mixed in $CDCl_3$, the chemical shift of the phenyl group was almost unchanged (δ 7.12, 6.62 ppm, in the absence of zinc triflate vs δ 7.12, 6.64 ppm in the presence of zinc triflate, respectively). When equal equivalents of 4-chlorobenzylamine and zinc triflate were mixed in $CDCl_3$, a down field shift was observed for phenyl group and methylene proton signals (δ 7.24, 7.19, 3.78 ppm in the absence of zinc triflate versus δ 7.30, 7.24 and 3.84 ppm in the presence of zinc triflate, respectively). These data suggest a stronger coordination between aliphatic amines and zinc triflate than anilines and zinc triflate.