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Simple Brønsted acid catalyzed C–H functionalization: efficient access to poly-substituted pyridines

Shujun Lai [a], Xuwen Ren [a], Jinzhong Zhao [a,*], Zhuo Tang [b,*], Guangxun Li [b,*]

[a] College of Art and Sciences, Shanxi Agricultural University Taigu, Shanxi 030800, China
[b] Natural Products Research Center, Chengdu Institution of Biology, Chinese Academy of Science, Chengdu, Sichuan 610041, China

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ABSTRACT

An exceptionally simple and environmentally friendly methodology has been developed for directly functionalizing the benzylic C–H bond of the poly-substituted pyridines with aromatic imines. Simple Brønsted acid catalysts including salicylic acid and TsOH were successfully employed. Different types of poly-substituted pyridines could be efficiently obtained with moderate yields. Traditional ways to such types of pyridines involved the aromatization of the corresponding Hantzsch 1,4-dihydropyridines, while this method greatly simplified the synthetic procedures.

Introduction

The poly-substituted pyridines with the skeleton **A** were pharmaceutically useful with anti-hypoxic, anti-ischemic, acaricidal, insecticidal, bacterial, and herbicidal activities, (Fig. 1).[1] The existing methods for obtaining such types of skeleton depended on the aromatization of the corresponding Hantzsch 1,4-diydropyridines,[2] which could be obtained through Hantzsch reaction.[3] However, the asymmetric Hantzsch 1,4-dihydropyridines were difficult to obtain, which were involved in the preformed enamines.[4] Therefore, the direct functionalization of the methyl group of the poly-substituted pyridine was interesting and significant. In addition, the obtained poly-substituted pyridines could be reduced to the corresponding Hantzsch 1,4-dihydropyridines, which were pharmaceutically important.[5]

Recently, the direct benzylic C–H bond functionalization of azaarenes has stimulated tremendous research interest. Traditionally ways of the benzylic transformation involved the process of deprotonation-nucleophilic substitution/addition with a strong base such as *n*-BuLi or LDA.[6] However, recent research revealed that a suitable Lewis acid[6b,7] or Brønsted acid[7k,8] could efficiently catalyze this transformation via transforming the alkyl azaarene to its enamine counterpart. This strategy has been successively applied to various nucleophilic additions of benzylic C–H bond of azaarenes for the C–C, C=C, and C–N bond formations. However, in the additions to imines, the substrates employed were mainly *N*-tosylimines[7b,h,9] or N-Boc imines,[10] under metal catalyst, (Scheme 1a and b). However, the ordinary phenyl imines could not work due to the slightly lower reactivity. We herein report a useful method for direct functionalizing the benzylic C–H of the poly-substituted pyridines with simple *N*-aryl imines under mild reaction conditions, (Scheme 1c).

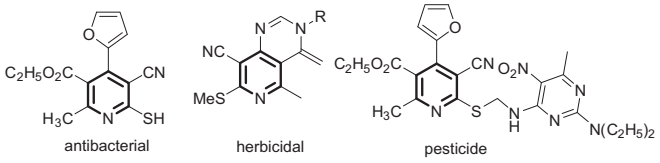

Figure 1. The numerous applications of poly-substituted pyridines.

Result and discussion

Our initial study began with the reaction between the poly-substituted pyridine (**1a**) and aromatic imine (**2a**), (Table 1). The result revealed that the reaction could easily occur to produce the corresponding product **3a** with 36% yield in chloroform with TsOH as catalyst at ambient temperature, (entry 1). Then we began to optimize the reaction conditions through screening of different solvents, (entries 2–7). Acetonitrile was the optimal reaction solvent considering the reaction yield. Then we turned to optimize the

* Corresponding authors.
E-mail addresses: zhaojz@sxau.edu.cn (J. Zhao), tangzhuo@cib.ac.cn (Z. Tang), ligx@cib.ac.cn (G. Li).

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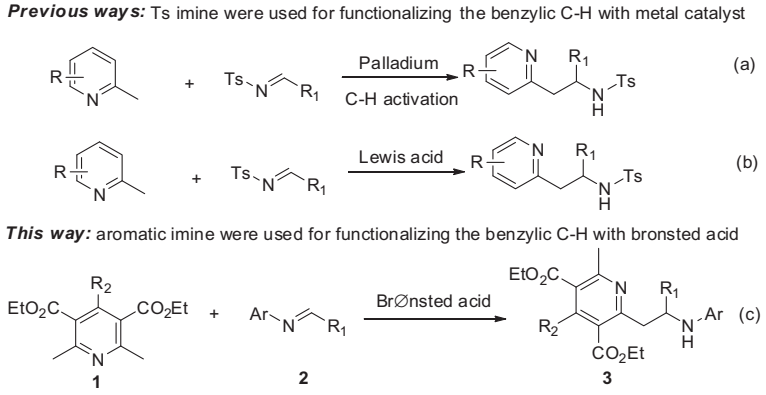
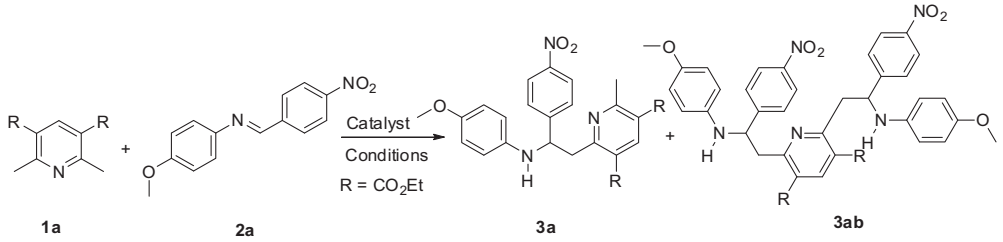


Scheme 1. Benzylic C–H functionalization of azaarenes.

Table 1
Optimization of Reaction Conditions for **3a**[a]



Entry	Solvent	Catalyst	*T* (°C)	Yield (%)[b]	Entry	Solvent	Catalyst	*T* (°C)	Yield (%)[b]
1	$CHCl_3$	TsOH	30	36	14	MeCN	SA	30	60
2	DMF	TsOH	30	17	15	MeCN	AcOH	30	—
3	DMSO	TsOH	30	23	16	MeCN	TFA	30	53
4	DME	TsOH	30	—	17	THF	SA	30	75
5	MeCN	TsOH	30	76	18	$CHCl_3$	SA	30	50
6	THF	TsOH	30	48	19	DMF	SA	30	45
7	MeOH	TsOH	30	55	20	DME	SA	30	<5
8	MeCN	$AlCl_3$	30	54	21	DMSO	SA	30	48
9	MeCN	$FeCl_3$	30	57	22	MeOH	SA	30	20
10	MeCN	$ZrCl_4$	30	48	23	THF	SA	20	65
11	MeCN	$SnCl_2$	30	38	24[c]	THF	SA	40	55(10)
12	MeCN	$InCl_3$	30	47	25[c]	THF	SA	50	47(15)
13	MeCN	$ZnCl_2$	30	<5	26[d]	THF	SA	30	80

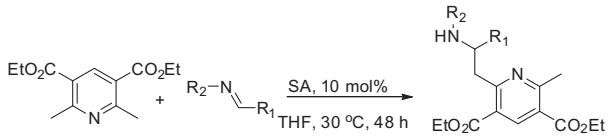
[a] The reaction was run with 0.2 mmol of **1a** and 0.2 mmol of **2a** with 10 mol % of catalyst for 48 h.
[b] The reaction yield was calculated based on purification with fast silicon column.
[c] The yield of **3ab** in the parenthesis.
[d] 1.2 equiv of the imine was used.

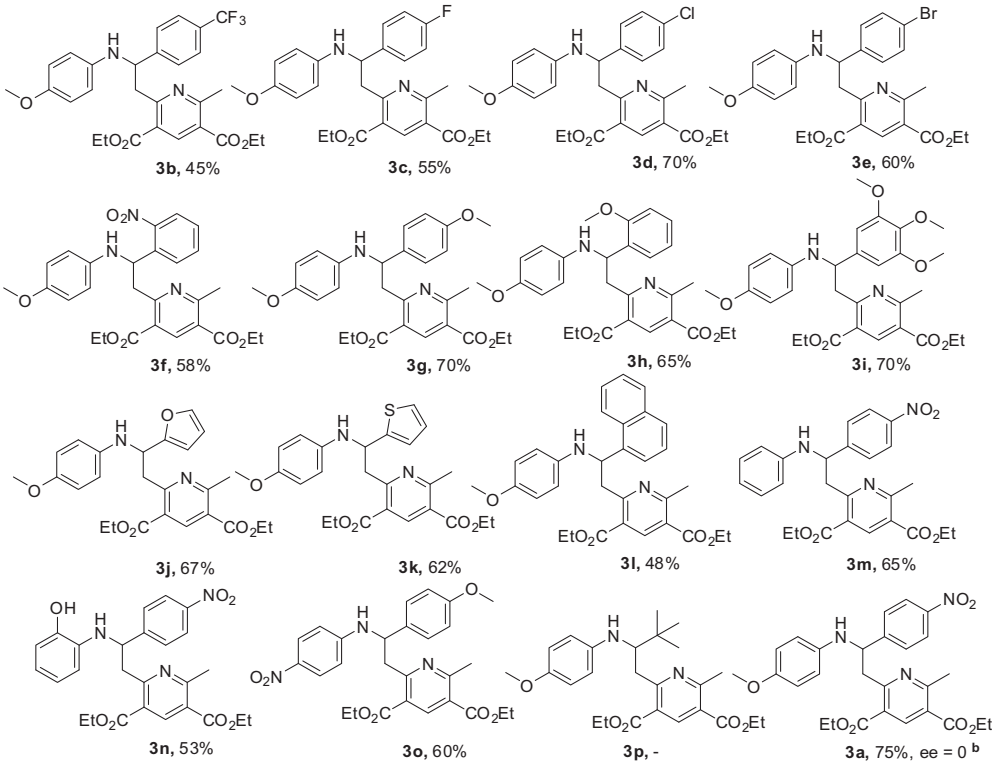
reaction by screening different types of Lewis acid such as $AlCl_3$, $FeCl_3$, $ZnCl_2$, $InCl_3$, etc. and different types of Brønsted acid such as acetic acid, TFA, and salicylic acid (**SA**), etc. Interestingly, **SA** was chosen as the better catalyst in this reaction than other Brønsted acid, and Lewis acid, (entries 8–16). As we know, **SA** was a commonly useful Brønsted acid catalyst.[11] Therefore we screened the reaction solvent again with **SA** as catalyst, which demonstrated that THF was the optimal reaction solvent, (entries 17–22). Meanwhile, the reaction temperature was investigated, which demonstrated that 30 °C was optimal, and the side product **3ab** was found after the raise of the temperature to 40 °C (entries 23–25). Finally, the reaction yield was improved to 80% after 1.2 equiv of imine was used.

Under the optimized reaction conditions, the scopes of the reaction were investigated. As shown in Table 2, various *N*-aryl aldimine **2** were employed in this reaction. Generally, the results demonstrated that aldimines **2** obtained from *p*-anisidine and different aldehydes were easily used to afford the corresponding poly-substituted pyridines **3** with moderate yields, (Table 2, **3b**–**3l**). Meanwhile, imines with heterocyclic rings such as furan and thiophene, imines with naphthalene, were also efficiently used to afford the corresponding product, (**3j**–**3l**). The imines obtained from different types of aromatic amines (with electron withdrawing groups, without substituent or with hydroxyl group) were also investigated, which demonstrated that the corresponding product could be obtained with moderate yield, (**3m**–**3o**). However, when imine obtained from alkyl aldehyde or imine formed with alkyl amine was used as substrate, the resulting products were not obtained, (**3o** and **3p**). In addition, we tried to screen all sorts of BINOL derived phosphoric as catalyst, (Table S2, see Supporting information). However, the resulted products were racemic, (Table 2, **3a**).

The efficiency of the reaction prompted us to extend the reaction to different types of poly-substituted pyridines, which could

Table 2
Substrate scopes of various *N*-aryl aldimines[a]





[a] Reaction conditions: **1a** (0.2 mmol), **2** (1.2 equiv 0.24 mmol), and **SA** (10 mol %) in THF (2 mL) were reacted for 2 d. Then the corresponding products were isolated after fast silicon column chromatography and the yield were calculated based on the isolation.
[b] Used BINOL derived TRIP phosphoric acid as catalyst.

be easily obtained by aromatization of the corresponding Hantzsch 1,4-dihydropyridines. However, the reaction was inefficient under the above optimized reaction conditions. The corresponding product **3n** was obtained with low yields, (<5%). We therefore re-screened the reaction conditions and finally increased the reaction yield to 45% under such reaction condition as following: TsOH 10 mol % in acetonitrile at room temperature for 48 h, (Table S1, see Supporting information).

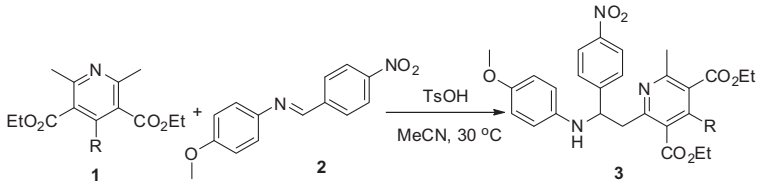
Then we screened the substrates under the optimized reaction conditions. The results revealed that the poly-substituted pyridines with different types of phenyl ring substituted at the C-4 of the pyridine ring, could efficiently be transformed to the corresponding products, (Table 3, **3q**–**3y**). Both electron-withdrawing and electron-donating groups had no obvious effect on the reaction yields. In addition, hetero aromatic substituted pyridine derivatives could be utilized in this protocol to afford the corresponding product with moderate yield (**3x**, **3y**).

Based on the above reaction results and the related references for direct benzylic C–H bond functionalization of azaarenes, the reaction mechanisms were proposed, (Scheme 2). We proposed two reaction mechanisms according to the reaction results. For poly-substituted pyridine without substituent at C-4 of the pyridine ring, the reaction was catalyzed efficiently with **SA**, and the transition state for the activation of the benzylic C–H was **TsA**. However, the activation of the benzylic C–H of poly-substituted pyridine with different aromatic ring substituted at C-4, **SA** were used inefficient which might be ascribed to the slightly lower acidity. Instead, TsOH were efficient due to the higher acidity. And the transition state of the activation of the benzylic C–H bond was **TsB**. Generally, the two catalysts activated the benzylic C–H bond with both the Brønsted acid and Brønsted base functions. The formation of enamine **A** or **B** was important, which could nucleophilically attack the imine substrate to afford the final product.

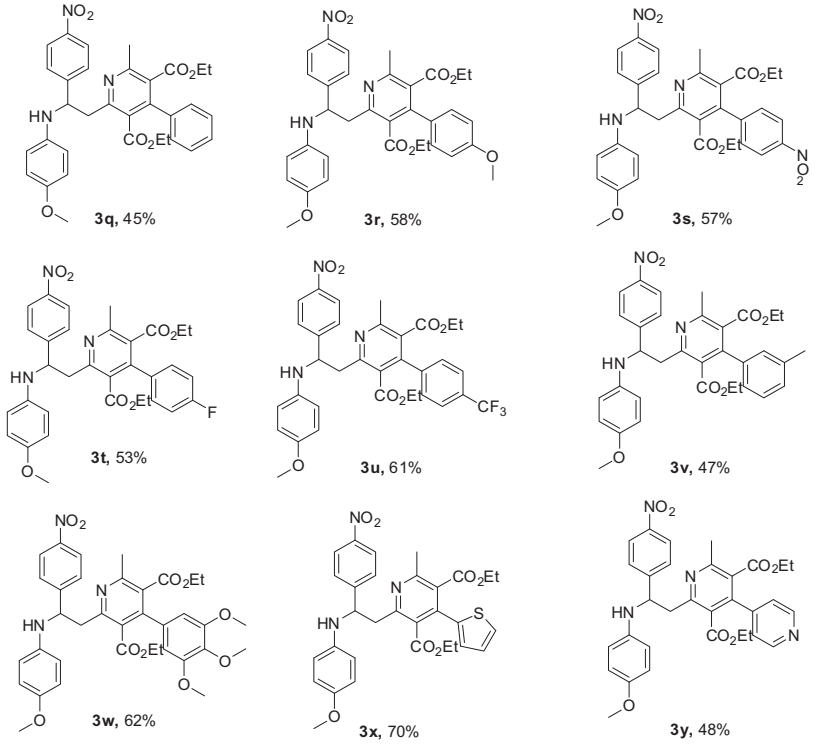
Conclusion

In summary, we have developed an efficient, convenient, and environmentally benign protocol for preparation of various poly-substituted pyridines under mild reaction conditions. Traditional ways depended on the synthesis of the corresponding asymmetric Hantzsch 1, 4-dihydropyridine, and the following aromatization step, while this way simplified the process and greatly improved the synthetic efficiency. The investigations of the Pharmaceutical activity of the obtained product are still under way in our lab.

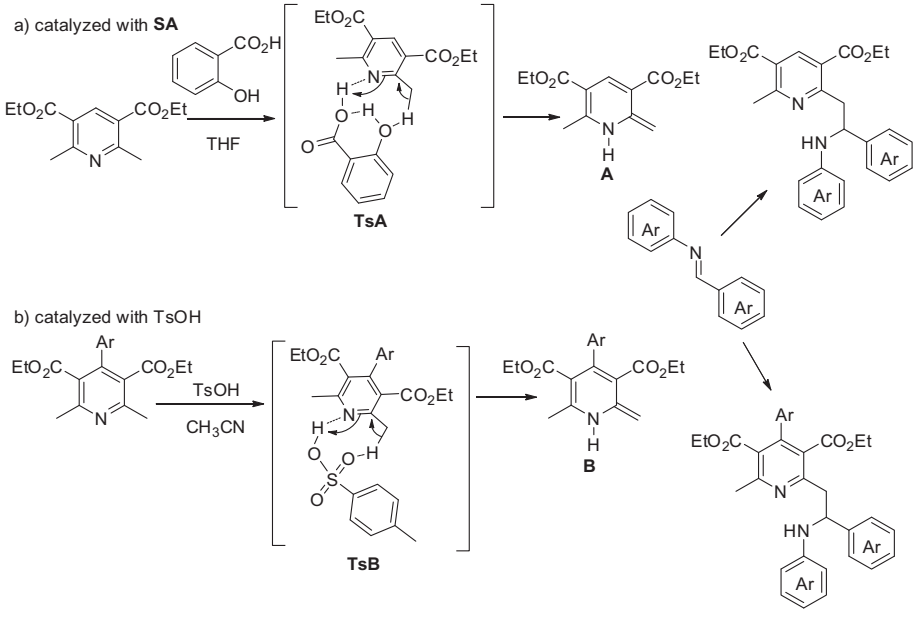
Table 3
Substrates scope of various 4-substituted pyridine derivatives



1 2 3



Reaction conditions: **1** (0.2 mmol), **2** (1.2 equiv 0.24 mmol), and TsOH (10 mmol %) in MeCN (2 mL) were reacted for 2 d. Then the corresponding products were isolated after fast silicon column chromatography and the yield were calculated based on the isolation.



Scheme 2. Proposed reasonable reaction mechanisms.

Acknowledgements

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Supplementary data

Supplementary data (detailed experimental procedure and spectroscopic data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.05.061.

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