ChemPubSoc Europe

DOI: 10.1002/cssc.201403154

CHEMSUSCHEM Full Papers

Lewis Acid Activation of Pyridines for Nucleophilic Aromatic Substitution and Conjugate Addition

Sarah Abou-Shehada,[a] Matthew C. Teasdale,[b] Steven D. Bull,[b] Charles E. Wade,[c] and Jonathan M. J. Williams*[b]

A clean, mild and sustainable method for the functionalization of pyridines and their analogues is reported. A zinc-based Lewis acid is used to activate pyridine and its analogues towards nucleophilic aromatic substitution, conjugate addition, and cyclization reactions by binding to the nitrogen on the pyridine ring and activating the pyridine ring core towards further functionalization.

Introduction

Pyridines are an important class of heterocycles that are found in a wide variety of important molecules ranging from pharmaceuticals and agrochemicals to functional materials.[1] Traditional methods for their functionalization include nucleophilic aromatic substitutions (S_NAr) on substrates that are appropriately activated. However, the substrate scope is limited and the reactions tend to require forcing conditions. The Buchwald–Hartwig amination reaction using palladium-catalyzed *N*-arylation reactions has facilitated a wide range of aryl functionalization which can be readily applied to the elaboration of halopyridines and their derivatives.[2] However, the application of these reactions can have limitations due to the high cost of the catalysts and their associated air and moisture-sensitive ligands.[3]

As a result, Ullmann-type reactions modified for use with copper catalysts have become the favored alternative on an industrial scale, in the case of the most successful adaptations, ligands are still required.[4] In some cases, the methodology may require stoichiometric amounts of the copper catalyst and base as well as high reaction temperatures. A recent noteworthy development in Ullmann-type reactions is the work by Zhang et al., which involves the use of tetraethylenepentamine in conjunction with the copper catalyst in water; the coupling is reported to proceed cleanly with good yields for a broad scope of functional groups.[5]

Avoiding the use of precious-metal catalysts in the functionalization of pyridines and its analogues has been reported in the recent work by Hartwig et al. using a nickel-based complex to achieve a methodology of varied scope in incoming nucleophile, and has been used on a wide variety of aryl and pyridine analogues. However this methodology still suffers from the need for an air- and moisture-free environment and use of a stoichiometric amount of base.[6] Methodologies that use cheap transition metals include a zinc-catalyzed, base-assisted amination of chloropyrimidines,[7] or copper-catalyzed amination of heteroaryl halides which, depending on the nature of amine, may require microwave assistance.[8] The development of efficient methodology using cheaper and more abundant metals as catalysts, is a valuable approach from an environmental standpoint.

In a recent publication by Moody et al., they argue that pyridine analogues which are activated enough to undergo standard S_NAr reactions such as pyrimidinyl halides are still being subjected to the more costly transformations, although greener alternatives that harness the substrate's innate reactivity could be developed and used.[9] In this work we wanted to consider approaches to arene coupling reactions that did not involve direct metal-catalyzed activation of the aryl halide bond, and specifically to apply this to the functionalization of pyridines via remote catalytic activation of the halide.

With this in mind we considered pyridine *N*-oxides, which are orders of magnitude more reactive towards nucleophilic substitution than pyridines,[10] we anticipated that the use of a Lewis acid in a similar manner to that of the oxygen in pyridine *N*-oxides would activate the pyridine ring towards S_NAr catalytically. Equally, Brønsted acids such as HCl are also used as the standard stoichiometric method for S_NAr reactions of halopyridines; by virtue of the pyridinium salt, which activates the pyridine ring, however these systems tend to require forcing conditions (150 °C) and give mitigated yields due to degra-

[a] S. Abou-Shehada
Centre for Doctoral training at the Centre for Sustainable Chemical Technologies
Department of Chemistry
University of Bath
Bath, BA2 7AY (UK)

[b] M. C. Teasdale, Dr. S. D. Bull, Prof. J. M. J. Williams
Department of Chemistry
University of Bath
Bath, BA2 7AY (UK)
E-mail: j.m.j.williams@bath.ac.uk

[c] Dr. C. E. Wade
GSK, Medicines Research Centre
Gunnels Wood Road,
Stevenage, SG1 2NY (UK)

Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/cssc.201403154.

dation of the chloropyridine as a result of the acidity of the reaction conditions.[11]

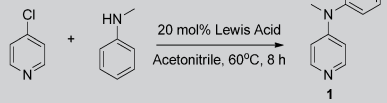
In this work, we report the activation of chloropyridine and analogues towards nucleophilic aromatic substitutions and vinylpyridines towards conjugate additions and cyclization reactions using a cheap metal based Lewis acid catalyst.

Results and Discussion

In an initial investigation, we examined the Lewis-acid-catalyzed amination of 4-chloropyridine with *N*-methylaniline to give the aminopyridine product **1.**

The highest conversions into the amination product were observed using zirconium acetoacetonate and zinc nitrate as the Lewis acids (entries 2 and 9 respectively, Table 1). Whilst the zirconium catalyst offers the higher conversion, it is also significantly more expensive than the zinc catalyst. In a drive towards developing a greener more sustainable methodology we chose to focus our efforts on the zinc-based catalyst. The reaction was optimized to achieve the formation of product **1** in 100% conversion (99% yield) using 2.5 mol% catalyst loading in zinc nitrate, 75 °C and a reaction time of 24 h.

Table 1. Lewis acid screen.



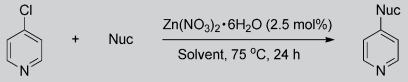
Entry	Lewis acid	Conversion into **1** [%][b]
1	$Sc(OTf)_3$	66
2	$Zr(acac)_4$	81
3	$Zr(Cp)_2Cl_2$	65
4	$Hf(Cp)_2Cl_2$	42
5	$Fe(SO_4)\cdot 7H_2O$	41
6	$[Rh(nbd)Cl]_2$	52
7	$RhCl_3$	36
8	$Pd(acac)_2$	32
9	$Zn(NO_3)_2\cdot 6H_2O$	71
10	ZnI_2	50
11	control	–

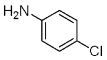
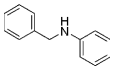
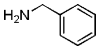
[a] Details of full screen can be found in the supporting information. [b] Conversion determined by analysis of the ^{1}H NMR spectra.

If the benzylamine is indeed binding strongly to the Lewis acid, it effectively poisons the catalyst towards further binding to, and activation of, the chloropyridine. We tested this idea by running the parent reaction with *N*-methylaniline in the presence of 0.5 equivalents of benzylamine, and indeed the reaction yielded complete return of starting materials

Reactions with cyclic amines gave good-to-excellent yields, for pyrrolidine (entry 7, Table 2) as well as indoline (entry 12, Table 2). Piperidine and its analogues also gave good-to-excellent yields (entries 8, 11 and 13, Table 2). Aromatic heterocycles such as imidazole (entry 14, Table 2) were tolerated in this methodology, and gave the product in reasonable yield (56%). Interestingly, acyclic secondary amines such as diethylamine were not successful nucleophiles in this methodology; the argument for higher nucleophilicity of the primary amines poisoning the catalyst cannot be applied here, as cyclic amines tend to be more nucleophilic than their acyclic counterpart. In a similar vein, we looked to investigate this occurrence by running the reaction of chloropyridine with piperidine in the presence of 1 equivalent of diethylamine; the result of which gave entirely the product of the piperidine substitution. The reason for the success of the cyclic amines is presumably due to the beneficial steric effect of having the alkyl groups pinned back

Table 2. Range of amines used in nucleophilic aromatic substitution in 4-chloropyridine.



Entry	Nucleophile (NucH)	Solvent	Conv.[a] [%]	Yield [%]
1		MeCN	100	99
2		THF	80	65
3		THF	100	91
4		THF	100	95
5		THF	93	87
6		THF	89	75
7		MeCN	100	89
8		MeCN	80	71
9		MeCN	69	56
10		MeCN	80	69
11		MeCN	100	89
12		MeCN	100	95
13		MeCN	100	95
14		MeCN	69	56
15		MeCN	–	–
16		MeCN	–	–
17		MeCN	71	–
18[c]	MeCN	MeCN	59	53
19[c]	EtOH	EtOH	66	57
20[c]	^{n}PrOH	^{n}PrOH	60	56

[a] Conversion determined by analysis of the ^{1}H NMR spectra. [b] Reactions run for 4 h. [c] Reaction run with 2 equiv of K_2CO_3 for 8 h.

to facilitate nucleophilic addition on the chloropyridine substrate.

Oxygen-based nucleophiles such as alcohols were also tested and it was found the reaction proceeded well when the incoming group was used as solvent, in the presence of a base. The base was required to neutralize the acid generated during the course of the reaction, which tended to degrade the chloropyridine starting material at these temperatures. Investigations into the optimization of the methodology to use the incoming alcohol group in one equivalent were investigated; however the results were not competitive with the use of alcohol as the solvent.

The methodology tolerates a variety of anilines (entries 1–6, Table 2), cyclic amines (entries 7–13, Table 2), phenyl hydrazine (entry 17, Table 2), and alcohols (entries 18–20). Interestingly when primary amines other than anilines were screened for this transformation, no reaction was observed (benzylamine entry 15, Table 2); this is believed to be as a result of competitive binding with the primary amine to the zinc catalyst.

The scope in substrates for nucleophilic substitution was also investigated (Table 3), particularly 2-chloropyridine which has the same activity towards nucleophilic substitution in pyridine *N*-oxides as the 4-chloropyridine.[10] However, when the reaction was run using this substrate, no product was observed (Table 3, entry 2); we assumed that this is due to steric bulk of the chlorine preventing the approach of the zinc-based Lewis acid to the pyridine nitrogen to activate the ring. Indeed, the same reaction with 2,4-dichloropyridine (entry 3, Table 3) was run, for which conversion into the substitution product at either site was not observed. This result also suggests that the mechanism of the reaction proceeds by activation of the aromatic ring through the binding of zinc to the pyridine nitrogen, rather than a more conventional cross coupling, which would have proceeded at either site. To elucidate the mechanism further and eliminate the possibility of this transformation being achieved via a cross coupling mechanism, the reactions were run with 3-chloropyridine (entry 1, Table 3); an unreactive substrate towards substitution reactions as is also found for its *N*-oxide analogue.[10] With the chlorine further from the nitrogen on the pyridine ring, it should not interfere with the approach of the catalyst; and, indeed, if a coupling mechanism was taking place, conversion into the product should be observed. However, the reaction gave complete return of starting materials which further supports the idea of activation of the pyridine to facilitate a nucleophilic aromatic substitution mechanism. An alternative explanation for the lack of activity of the 2-chloropyridine was the reduced electron density on the nitrogen as the result of such an electron-withdrawing substitute adjacent to it, thus the reaction was carried out using 2-chloro-4-methoxy pyridine (entry 4, Table 3), which also showed no activity towards nucleophilic substitution. This further confirms the steric hindrance of the chlorine in the 2-position; even with an electron-enriched pyridine-nitrogen, no reaction had taken place.

Table 3. Scope in pyridine analogues for nucleophilic aromatic substitution.

Entry	Substrate	Solvent	NucH	*t* [h]	Conv.[a] [%]	Yield [%]
1		MeCN		24	–	–
2		MeCN		24	–	–
3		MeCN		24	–	–
4		MeCN		24	–	–
5		MeCN		2	100	89
6[b]		MeCN		4	100	93
7		MeCN		8	80	71
8		MeCN		8	70	63
9		MeCN		8	74	61

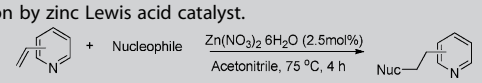
[a] Conversion determined by analysis of the ^{1}H NMR spectra. [b] Reaction run at 60 °C.

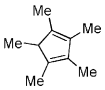
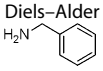
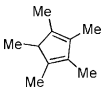
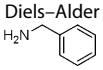
Smaller groups such as the C–H unit of an adjacent fused ring in the case of 4-chloroquinline (entry 6, Table 3) are tolerated in this methodology and still allow for the approach of zinc Lewis acid to the nitrogen of the pyridine unit, allowing the reaction to proceed in high yield (93%).

Interestingly 4-bromopyridine exhibited a much higher reactivity than 4-chloropyridine, yielding the aromatic substitution product in a much shorter reaction time of only 2 h (entry 5, Table 3). Similarly, 2-chloropyrimidine proceeds to the substitution product in 8 h under Lewis-acid-catalyzed reaction conditions, from which some of the amines from the nucleophile screen were also run with good yields in product (entries 7–9, Table 3).

With the success of the zinc catalyst at activating chloropyridine towards nucleophilic substitution, we anticipated that it may also be able to activate vinylic pyridines to conjugate addition and Diels–Alder cyclization reactions. We were pleased to observe that the reaction proceeds with our parent nucleophile in high yields (entries 1 and 7, Table 4) for both the 2-vinyl and 4-vinyl pyridines. The reaction was tested for tolerance of incoming group; the catalytic system tolerates a variety of *N*- and *S*-based nucloephiles (Table 4); however, due to the higher reactivity of the vinyl pyridines, the reactions in most cases require less time and heat, especially in the case of the thiol which only requires a maximum reaction time of 10 min and room temperature (entry 3, Table 4). As with the substitution reactions, primary amines poisoned the catalyst and no addition products were observed, the dialkyl amines also yielded no product due to their diminished reactivity. It should be

Table 4. Conjugate addition of nucleophiles to vinylic pyridines through activation by zinc Lewis acid catalyst.



Entry	Substrate	NucH	*t* [h]	*T* [°C]	Catalyst loading [mol %]	Conv [%][a]	Yield [%]
1			24	90	15	89	87
2			24	25	5	94	94
3			12	60	5	100	95
4			10 min	25	2.5	95	92
5			4	40	2.5	79	78 (90:10 *dr*[b])
		Diels–Alder					
6			24	75	5	–	–
7			24	75	5	–	–
8			24	90	10	86	85
9			12	25	5	100	99
10			4	40	5	90	87
11			10 min	25	2.5	99	96
12			8	40	5	79	78 (89:11 *dr*[b])
		Diels–Alder					
13			24	75	5	–	–
14			24	75	5	–	–

[a] Conversions determined by ^{1}H NMR spectroscopy. [b] Diastereomeric ratio.

noted that there have been many examples of zinc-catalyzed hydroaminations in recent literature; however in the majority of these cases the reactions are air and moisture sensitive, and use benzene as a solvent.[12–14] Two examples that do not require air- and moisture-free conditions use a zinc triflate Lewis acid; however, they proceed under higher reaction temperatures (120–130 °C),[15,16] and, in one case, yield a combination of Markovnikov and conjugate addition products.[14] By comparison, our methodology proceeds using a simpler practical method, with a cheap reagent at lower temperatures and yields purely the conjugate addition products.

The Diels–Alder cyclization with pentamethyl cyclopentadiene (Cp*H) (entries 5 and 12, Table 4) yielded isomeric products. In both instances, the *endo* product containing the methyl group on the bridge pointing towards the alkene bond, was the major isomer. A tentative assignment of the minor isomer is also an *endo* product; however, the bridge methyl group is pointing towards the pyridine; a reasonable explanation for this minor product would be the zinc Lewis acid coordinating to and bringing the thermodynamically unfavored Cp* face in close proximity to the vinyl pyridine thus producing this minor product.

Conclusions

In conclusion, a novel catalytic methodology has been developed for the functionalization of pyridines. The mechanism operates through activation of the pyridine ring, which can lend itself to nucleophilic aromatic substitution, conjugate addition, and Diels–Alder reaction subject to the substrate used. This methodology offers an alternative simple, cheap, and greener catalytic method for the functionalization of pyridines and their analogues.

Experimental Section

The appropriate amine (2 mmol, Table 2) and $Zn(NO_3)_2{\cdot}6H_2O$ (2.5 mol %) were added to an oven dried Radleys carousel tube, followed by acetonitrile (2 mL) and 4-chloropyridine (2 mmol). The tube was sealed before the reaction mixture was heated to 75 °C for the appropriate time (Table 2). After being allowed to cool to room temperature, the solvent was removed in vacuo on a rotary evaporator and then analyzed by their ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry data. Purification by column chromatography was carried out as necessary.

Acknowledgements

S.A.-S. is funded by the EPSRC through the Doctoral Training Center in Sustainable Chemical Technologies (Grant No. EP/G03768X/1).

Keywords: amination · conjugate addition · lewis acid · pyridine · S_NAr

[1] a) C. M. Richardson, R. J. Gillespie, D. S. Williamson, A. M. Jordan, A. Fink, A. R. Knight, D. M. Sellwood, A. Misra, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5993–5997; b) R. Fioravanti, M. Biava, G. C. Porretta, C. Landolfi, N. Simonetti, A. Villa, E. Conte, A. Porta-Puglia, *Eur. J. Med. Chem.* **1995**, *30*, 123–132; c) N. Lah, R. Clérac, *Polyhedron* **2009**, *28*, 2466–2472; d) M. Yoshida, N. Koumura, Y. Misawa, N. Tamaoki, H. Matsumoto, H. Kawanami, S. Kazaoui, N. Minami, *J. Am. Chem. Soc.* **2007**, *129*, 11039–11041.

[2] D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361; *Angew. Chem.* **2008**, *120*, 6438–6461.

[3] S. L. Buchwald, C. Mauger, G. Mignani, U. Scholz, *Adv. Synth. Catal.* **2006**, *348*, 23–39.

[4] F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971; *Angew. Chem.* **2009**, *121*, 7088–7105.

[5] Q. Yang, Y. Wang, L. Yang, M. Zhang, *Tetrahedron* **2013**, *69*, 6230–6233.

[6] S. Ge, R. A. Green, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 1617–1627.

[7] L. B. Delvos, J.-M. Begouin, C. Gosmini, *Synlett* **2011**, *16*, 2325–2328.

[8] a) Z.-J. Liu, J.-P. Vors, E. R. F. Gesing, C. Bolm, *Adv. Synth. Catal.* **2010**, *352*, 3158–3162; b) Z.-J. Liu, J.-P. Vors, E. R. F. Gesing, C. Bolm, *Green Chem.* **2011**, *13*, 42–45.

[9] K. Walsh, H. F. Sneddon, C. J. Moody, *ChemSusChem* **2013**, *6*, 1455–1460.

[10] J. A. Joule, K. Mills in *Heterocyclic Chemistry, 5th ed.*, Wiley-Blackwell, **2010**, pp. 19–33.

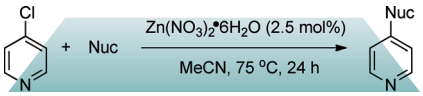
[11] J. M. Campos, M. C. Núñez, R. M. Sánchez, J. A. Gómez-Vidal, A. Rodríguez-González, M. Báñez, M. A. Gallo, J. Lacal, A. Espinosa, *Bioorg. Med. Chem.* **2002**, *10*, 2215 – 2231.
[12] J.-W. Pissarek, D. Schlesiger, P. W. Roesky, S. Blechert, *Adv. Synth. Catal.* **2009**, *351*, 2081 – 2085.
[13] A. Mukherjee, T. K. Sen, P. Kr. Ghorai, P. P. Samuel, C. Schulzke, S. K. Mandal, *Chem. Eur. J.* **2012**, *18*, 10530 – 10545.
[14] J. Jenter, A. Lühl, P. W. Roesky, S. Blechert, *J. Organomet. Chem.* **2011**, *696*, 406 – 418.
[15] G.-Q. Liu, Y.-M. Li, *Tetrahedron Lett.* **2011**, *52*, 7168 – 7170.
[16] K. Alex, A. Tillack, N. Schwarz, M. Beller, *ChemSusChem* **2008**, *1*, 333 – 338.

Received: October 21, 2014
Revised: November 27, 2014
Published online on ■■ ■■, 0000

*S. Abou-Shehada, M. C. Teasdale, S. D. Bull, C. E. Wade, J. M. J. Williams**

■■ – ■■

Lewis Acid Activation of Pyridines for Nucleophilic Aromatic Substitution and Conjugate Addition



Pyridine gets active: For the first time, the catalytic activation of the pyridine ring towards nucleophilic aromatic substitution, conjugate addition, and Diels–Alder reactions is reported. The method utilizes a cheap, non-toxic zinc-based Lewis acid, which binds to the nitrogen of the pyridine ring and activates it towards nucleophilic aromatic substitution. The reaction tolerates a variety of incoming groups and proceeds cleanly and under mild reaction conditions.