Communication to the Editor

Deprotonative Coupling of Pyridines with Aldehydes Catalyzed by an HMDS-Amide Base Generated *in Situ*

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Herein, the deprotonative functionalization of pyridine derivatives with aldehydes under ambient conditions has been demonstrated using an amide base generated *in situ* from a catalytic amount of CsF and a stoichiometric amount of tris(trimethylsilyl)amine (N(TMS)₃). Pyridine substrates bearing two electron-withdrawing substituents (*i.e.*, fluoro, chloro, bromo, and trifluoromethyl moieties) at the 3- and 5-positions efficiently react at the 4-position with various aldehydes including arylaldehydes, pivalaldehyde, and cyclohexanecarboxaldehyde.

Key words pyridine; deprotonative functionalization; amide base generated *in situ*

Introduction

Pyridine is a key structural motif in pharmaceutical, agrochemical, and materials science. The deprotonative functionalization of pyridines with electrophiles has been widely used to synthesize a variety of pyridine derivatives.^{1–10} Strong Brønsted bases such as *n*-BuLi, *sec*-BuLi, lithium diisopropylamide (LDA), and lithium tetramethylpiperidide (LiTMP) are employed in the deprotonation step to prepare the requisite pyridyl lithium species (Fig. 1a, upper scheme).^{1–6} The reactions are usually performed under cryogenic conditions, which

aim at inhibiting the temperature increase observed during this exothermic process and to restrain any side-reactions involving the lithiated species, such as nucleophilic addition onto an electrophilic substituent as well as the halogen dance reaction and aryne formation in the case of halogenated substrates. Protocols using milder bases, such as magnesium- and zinc-derived reagents, have also been developed, which can be conducted at near ambient conditions with high functional group tolerance (Fig. 1a, lower scheme).^{6,7,11–23} However, the preparation of these reagents requires the use of stoichiometric amounts of several chemical reagents. Hence, further development of an efficient protocol to perform this transformation is still imperative in organic chemistry.

Our group has previously reported the deprotonative functionalization of C–H bonds in pronucleophiles using a hexamethyldisilazide (HMDS)-amide base generated *in situ* using a catalytic amount of a fluoride or alkoxide salt and a stoichiometric amount of tris(trimethylsilyl)amine (N(TMS)₃).^{24–34} The system efficiently catalyzes the reaction of heteroarenes, methyl(hetero)arenes, acetate, and terminal alkynes with electrophiles such as carbonyl and polyfluoroarene compounds. The heteroarenes employed in the reaction include five-membered heterocyclic compounds such as (benzo)thiophene, benzofuran, benzothiazole, and indole derivatives. Herein, we report that this reaction system is applicable toward the transformation of pyridine derivatives; for example, 3,5-dibromopyridines react with a variety of aldehydes (1.1 equiv) under

Table 1. Optimization of the Coupling Reaction between **1a** and **2a**^{a)}

Entry	Fluoride or alkoxide salt	Solvent	Yield (%) ^{b)}
1	KF	DMF	0
2	RbF	DMF	32
3	CsF	DMF	quant.
4	TMAF ^{c)}	DMF	38
5	TBAT ^{d)}	DMF	93
6	NaOEt	DMF	69
7	NaO- <i>t</i> -Bu	DMF	85
8	KO- <i>t</i> -Bu	DMF	81
9	CsCl	DMF	0
10	CsI	DMF	0
11	CsF	DMA	76
12	CsF	DMSO	95
13	CsF	NMP	77
14	CsF	DMI	87
15	CsF	THF	trace
16	CsF	Et ₂ O	0
17	CsF	Toluene	0
18	CsF	DMF	quant. (97) ^{e,f)}

a) Reactions were conducted on a 0.2 mmol scale. b) Yields were determined by ¹H-NMR analysis. c) Tetramethylammonium fluoride. d) Tetrabutylammonium difluorotriphenylsilicate. e) The yield reported in the parenthesis denotes the isolated yield. f) Reaction was conducted using CsF (15 mol%) and N(TMS)₃ (1.5 equiv) for 6 h.

(a) Conventional protocols

(b) This work: *In situ* generated amide base catalysis

Fig. 1. Deprotonative Functionalization of Pyridine Derivatives with Electrophiles

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ambient conditions (Fig. 1b).

Results and Discussion

At the beginning of this research project, the reaction conditions were investigated using 3,5-dibromopyridine (**1a**) and benzaldehyde (**2a**) as model substrates³⁵ (Table 1). Among the fluoride salts examined, CsF was the most effective and formed the desired coupling product (**3aa**) in quantitative yield (entries 1–5). Alkoxide salts including NaOEt, NaO-*t*-Bu, and KO-*t*-Bu can also be used in the reaction, however, they were inferior to CsF (entries 6–8). CsCl and CsI did not give **3aa** (entries 9 and 10). Subsequently, the solvent effect on the reaction was examined (entries 11–17). Using aprotic polar solvents such as *N,N*-dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), 1-methyl-2-pyrrolidone (NMP), and 1,3-dimethyl-2-imidazolidinone (DMI) afforded the target product in good yields, while the reaction did not proceed in tetrahydrofuran (THF), Et₂O, and toluene. Finally, when the reaction was conducted using decreased amounts of CsF (15 mol%) and N(TMS)₃ (1.5 equiv) for a shorter reaction time (6 h), **3aa** was still isolated in a high yield (97%) (entry 18).

With the optimal conditions in hand, the substrate scope of the reaction was investigated using a range of pyridine (**1**) and carbonyl (**2**) compounds (Fig. 2). 3,5-Dichloropyridine (**1b**) and 3,5-difluoropyridine (**1c**) coupled with **2a** to provide the target products in 94 and 74% yields, respectively. 3-Chloro-5-(trifluoromethyl)pyridine (**1d**) also reacted with **2a** to form the desired product in 42% yield. The reactions of **1a** and **1b** with pivalaldehyde (**2b**) furnished **3ab** and **3bb** in 98% and 94% yields, respectively. Mono-halogenated pyridines **1e** and **1f** were also employed in the reaction, however, the target products were produced in low yields (12% and 14%, respectively). Arylaldehydes other than **2a** were also applied in the reaction. *Ortho*- and *para*-methyl-substituted **2c** and **2d** reacted with **1a** to form **3ac** and **3ad** in 98 and 82% yields, respectively. Compounds **2e** and **2f** bearing electron-donating methoxy and dimethylamino groups also underwent the reaction to give their corresponding products in 91% and 80% yields, respectively. Chloro- and bromo-substituents were tolerated in the reaction and gave alcohols **3ag** and **3ah** in 92% and 80% yields, respectively. When employing substrate **2i** bearing an ester moiety in the reaction, product **3ai** was isolated in 45%

Fig. 2. Substrate Scope of the Deprotonative Functionalization Reaction of Pyridine Derivatives^{a,b)}

^{a)} Reactions were conducted on a 0.2 mmol scale. ^{b)} Isolated yields. ^{c)} Reactions were conducted using CsF (20 mol %) and N(TMS)₃ (2.0 equiv).

Fig. 3. Proposed Mechanism for the Deprotonative Functionalization of Pyridine Derivatives

yield. 2-Naphthaldehyde (**2j**) furnished product **3aj** in 92% yield. Reaction of 2,6-dimethylbenzaldehyde (**2k**) also took place in 78% yield. The use of heteroarylaldehydes, 2-formylbenzothiophene (**2l**) and 3-formylpyridine (**2m**), led to the formations of **3al** and **3am** in 47% and 69% yields, respectively. Enolizable cyclohexanecarboxaldehyde (**2n**) was also used in the reaction and resulted in the formation of product **3an** in 73% yield.³⁶⁾

The proposed mechanism for the deprotonative functionalization reaction is shown in Fig. 3. Initially, amide-base **A** is generated *in situ* from CsF and N(TMS)₃,³¹⁾ which performs the deprotonation of **1a** to give pyridyl anion species **B**. Subsequently, **B** couples with **2a** to form alkoxide **C**. Then, the reaction of **C** and N(TMS)₃ occurs to provide silyl ether **D** and regenerate **A** to complete the catalytic cycle.³⁷⁾

In summary, a catalytic system consisting of an amide-base generated *in situ* allows the coupling of a range of pyridine derivatives to be performed under ambient conditions. 3,5-Dihalopyridines and 3-chloro-5-(trifluoromethyl)pyridine react efficiently under these reaction conditions. In addition, a diverse range of aldehydes, which include arylaldehydes bearing a variety of substituents (*i.e.*, methyl, methoxy, dimethylamino, chloro, bromo, and ester moieties) and heteroarylaldehydes as well as pivalaldehyde and cyclohexanecarboxaldehyde, were used in the reaction.

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Conflict of Interest The authors declare no conflict of

interest.

Supplementary Materials The online version of this article contains supplementary materials.

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- 36) Methyl iodide, benzophenone, and methyl benzoate were also employed as electrophiles in the reaction with **1a**, however, which did not give the coupling products (results not shown).
- 37) When the reaction of **1a** and **2a** was carried out in the presence of a radical scavenger of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), **3aa** was obtained in 86% yield (Chart S1). The result suggests that a radical mechanism is not involved in the reaction.