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Asymmetrical synthesis of fluorinated 2-(pyridin-2-yl) alkylamine from fluoromethyl sulfinyl imines and 2-alkylpyridines

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ABSTRACT

A novel strategy was developed to synthesize fluorinated 2-(pyridin-2-yl) alkylamines via condensation of 2-alkylpyridines and chiral fluoromethyl *N*-*tert*-butyl sulfinyl imines with good diastereo-control and good chemical yields. The chiral *N*-*tert*-butyl sulfinyl auxiliary can be easily removed under mild acidic condition at room temperature. The application of this strategy was demonstrated in the synthesis of a fluorine-containing pesticide candidate.

Introduction

2-(Pyridin-2-yl) alkylamines are versatile precursors for the synthesis of drugs and materials. They have been used in the synthesis of neurological drugs,[1] polymers with magnetic carrier function,[2] detection of pathogenic cells,[3] and as ligands of metal catalysts.[4] Conventional methods to synthesize 2-(pyridin-2-yl) alkylamines include addition of acetylene silane to 2-chloropyridine, followed by reduction using ammonia or hydrazine, or reduction of 2-(pyridin-2-yl) alkylamide by $NaBH_4$.[5] Although these methods give 2-(pyridin-2-yl) alkylamines in good yields, they need complicated reaction conditions and are difficult to be implemented for synthesis of optical pure products.

As the fluorine atom has similar radius to the hydrogen atom, strong electronegativity, and low polarizability, fluorinated compounds often exhibit special chemical and biological properties.[6] Over the last decades, fluorinated compounds have been widely used in agrochemicals, pharmaceuticals, and materials.[6h] To the best of our knowledge, no synthetic method is available for the synthesis of fluoromethyl substituted 2-(pyridin-2-yl) alkylamines so far. Recently, Shaikh and co-workers reported the triflic acid-catalyzed C_{sp3}–H functionalization of 2-methyl azaarenes with a α-trifluoromethyl imino ester.[7] Inspired by Shaikh's work, we are glad to report herein the asymmetric synthesis of fluoromethyl substituted 2-(pyridin-2-yl) alkylamines from condensation of chiral fluoromethyl sulfinyl imines and 2-alkyl pyridines.

Results and discussion

Chiral α-fluoroalkyl amines were synthesized successfully via asymmetric addition of silyl dienolates to fluorinated chiral sulfinyl imine **1** in our laboratory in 2013.[8] **1** is a very electrophilic imine, which is often used in the preparation of optically pure fluorine-containing amines.[9] Directed by the chiral *N*-*tert*-butyl sulfinyl auxiliary, these reactions usually give good diastereoselectivity.[10] We envisaged that fluoromethyl substituted 2-(pyridin-2-yl) alkylamines **3** could be prepared from nucleophilic addition of α-alkyl pyridine to **1** in the presence of a strong base such as *n*-BuLi. The condensation of 2-methylpyridine and **1a** was chosen as our model system to optimize the reaction condition (Table 1). According to the literature Letter,[11] the sp^3 hybridized α-H in 2-alkylpyridine can be deprotonated by *n*-BuLi at low temperature (−50 to −20 °C), and the generated anion is stable at low temperature (<−20 °C). Our first trial gave the desired product **3a** in moderate yield and diastereoselectivity (43% yield, dr = 90:10, Table 1, entry 1) using *n*-BuLi as a base. Addition of a basic additive (potassium *tert*-butoxide) gave a much worse yield (Table 1, entry 2). To our delight, Lewis acidic additive $Ti(O^iPr)_4$ (1 equiv)[12] improved chemical yield significantly (80%), and the diastereomeric ratio also increased (Table 1, entry 3). However, less amount of $Ti(O^iPr)_4$ led

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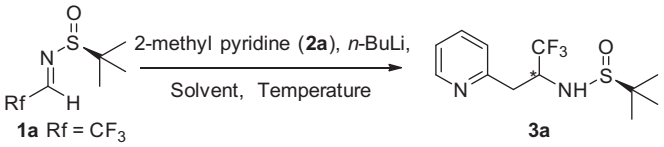
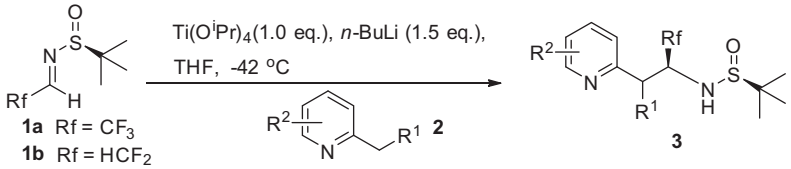
Table 1
Optimization of *n*-BuLi mediated condensation of 2-methyl pyridine and sulfinyl imine **1a**[a]

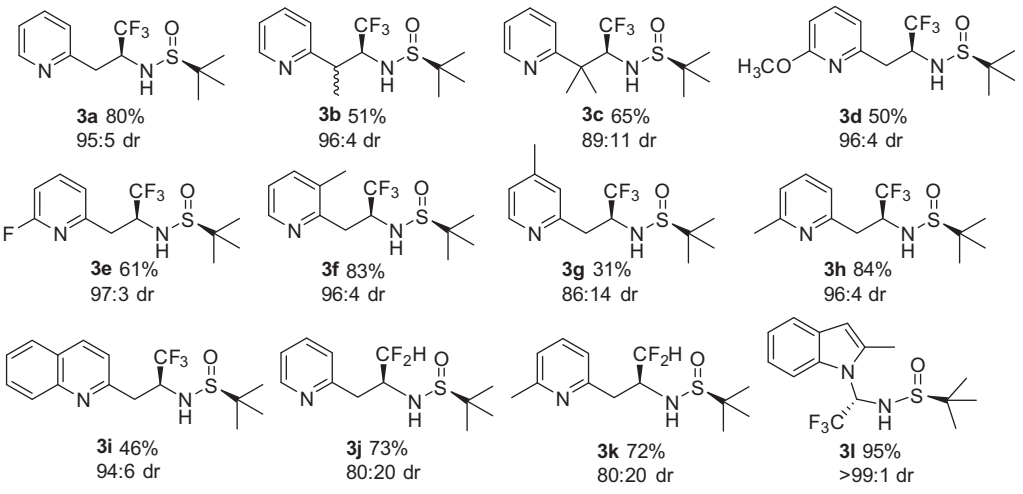


Entry	**2a** (equiv)	*n*-BuLi (equiv)	Additive (equiv)	Solvent	Temp (°C)	Yield[b] (%)	(dr)[c]
1	1.5	1.76	—	THF	−42	43	90:10
2	1.5	0.75	*t*-BuOK (1.0)	THF	−42	5	—[d]
3	1.5	1.76	$Ti(O^iPr)_4$ (1.0)	THF	−42	80	96:4
4	1.5	1.76	$Ti(O^iPr)_4$ (0.5)	THF	−42	81	92:8
5	1.5	1.76	$Ti(O^iPr)_4$ (0.1)	THF	−42	63	86:14
6	1.5	1.76	$Ti(O^iPr)_4$ (1.0)	Et_2O	−42	14	—[d]
7	1.5	1.76	$Ti(O^iPr)_4$ (1.0)	Hexane	−42	Trace	—[d]
8	3.0	3.3	$Ti(O^iPr)_4$ (1.0)	THF	−42	80	96:4
9	2.0	2.2	$Ti(O^iPr)_4$ (1.0)	THF	−42	79	96:4
10	1.0	1.1	$Ti(O^iPr)_4$ (1.0)	THF	−42	67	94:6
11	1.5	1.76	$Ti(O^iPr)_4$ (1.0)	THF	−60	64	94:6
12	1.5	1.76	$Ti(O^iPr)_4$ (1.0)	THF	−78	82	85:15

[a] Reaction condition: **2a**, *n*-BuLi, **1a** (1.0 equiv) in THF, 4 h.
[b] Isolated yield.
[c] Determined by ^{19}F NMR analysis of the reaction mixture.
[d] Not determined.

Table 2
Condensation of 2-alkyl pyridines and fluoromethyl sulfinyl imines [a,b,c]





[a] General conditions: **2** (1.5 mmol), **1** (1.0 equiv), $Ti(OiPr)_4$ (1.0 equiv), *n*-BuLi (1.76 mmol, 2.5 M in hexane), THF (10 mL), −42 °C, 4–8 h.
[b] **3a**–**3i** were prepared from **1a**, **3j** and **3k** were prepared from **1b**.
[c] Isolated yields, dr was determined by ^{19}F NMR.

to low diastereomeric ratio (Table 1, entries 3–5). We proposed that $Ti(O^iPr)_4$ might act as a water-scavenger as well as an imine stabilizer. Meanwhile, lithium–titanium exchange between pyridinylmethyl lithium and $Ti(O^iPr)_4$ might occur resulting in pyridinylmethyl titanium which in turn reacts with fluoromethyl sulfonyl imines to provide addition reaction products.[13] Then the solvent effect was investigated. Both Et_2O and hexane were not good solvents for this reaction (Table 1, entries 6 and 7) compared to THF. On the other hand, the yield and selectivity of **3a** did not change much when the amount of 2-methylpyridine was increased from 1.5 equiv to 2 equiv and 3 equiv (Table 1, entries 8 and 9). But when 1 equiv of 2-methylpyridine was used, both the yield and dr decreased significantly (Table 1, entry 10). Usually lowering the reaction temperature would give better stereoselectivity, however, this did not happen in this case (Table 1, entries 11 and 12).

With the optimized condition (Table 1, entry 3) in hand, we proceeded to explore the substrate scope (Table 2).[14] In general, when Rf = CF_3–, the diastereomeric ratio of **3** was generally good (Table 2,