One-pot Aminoalkylation of Aldehydes: Diastereoselective Synthesis of Vicinal Diamines with Azaarylmethylamines

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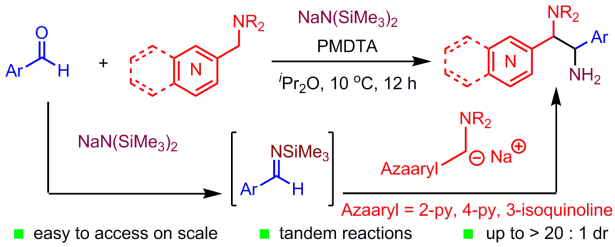
Supporting Information Placeholder



ABSTRACT: A one-pot synthesis of vicinal diamines with azaarylmethylamines and aldehydes is reported. A diverse array of vicinal diamines could be achieved in up to 92% yield with good to excellent diastereoselectivities (up to 20:1). The tandem reaction takes place under mild conditions and provides an alternative strategy for the synthesis of vicinal diamines.

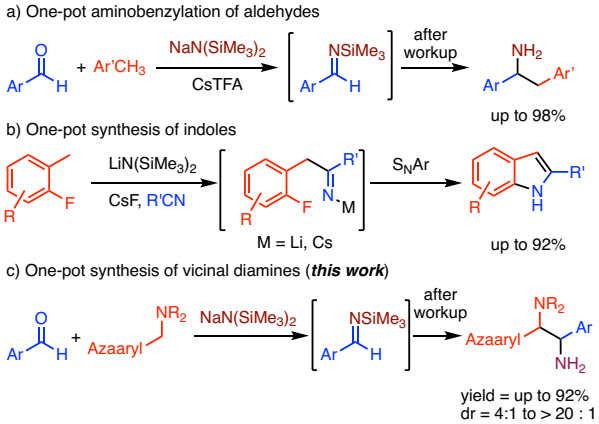
Vicinal diamines constitute an important structural class with broad applications in natural products, chemotherapy, medicinal chemistry, and organic synthesis.[1] Due to their wide applications, their synthesis continues to attract significant attention, where the demand for more diastereoselective and straightforward syntheses still remains high. Furthermore, the rapid introduction of nitrogens into organic structures is a long-standing challenge in medicinal chemistry.[2]

Traditional routes for diamine syntheses generally involve: (1) direct inter- or intra-molecular diamination of unfunctionalized alkenes;[3] (2) addition of organometallic reagents to bisimine derivatives;[4] (3) reductive homocoupling of imines;[5] (4) ring opening of aziridines with nitrogen nucleophiles;[6] and (5) Mannich type reactions employing nitroalkanes followed by reduction of the corresponding nitro groups.[7] These routes have a number of drawbacks. For example, the first three routes are limited to the synthesis of symmetric vicinal diamines whereas the latter two require additional steps to prepare the starting aziridines or use an external reductant to reduce the undesired nitro groups.

The direct addition of α-amino anions to imines is a very important tool to construct a diverse array of vicinal diamines.[8] To the best of our knowledge, however, a one-pot synthesis of vicinal diamines from aldehydes is unknown. Recently, our team developed a one-pot chemoselective C–N and C–C bond forming reaction for the aminobenzylation of aldehydes with toluene derived pronucleophiles (Scheme 1a).[9] More recently, this method has been made catalytic in base.[10]

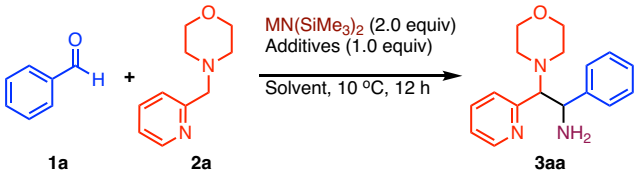
Further adaptation of the chemistry led to a novel one-pot route to 2-arylindoles from readily available 2-fluoro toluenes and benzonitriles (Scheme 1b).[11] We put forth evidence that these reactions are facilitated by formation of a cation-π interactions between the main group metal (Cs^+) and the toluene derivative, facilitating the deprotonation of the benzylic methyl group[9,11-12]. Herein, we advance a straightforward and practical one-pot synthesis of vicinal diamines employing azaarylmethylamines and aldehydes. The tandem reaction provides an alternative strategy for the synthesis of biologically active compounds.[13]

Scheme 1. Tandem synthesis of bioactive fine chemicals.



Based on our previous studies, we began to investigate employing benzaldehyde (**1a**) and 4-(pyridin-2-ylmethyl)morpholine (**2a**) as model substrates (Table 1). We first screened three different bases [$LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and $KN(SiMe_3)_2$] using THF as solvent at 10 °C for 12 h (Table 1, entries 1−3). According to the screening results, $NaN(SiMe_3)_2$ was identified as the best candidate among these three bases, giving **3aa** in 84% AY with 4.5 : 1 dr (entry 2, AY = assay yield determined by ^{1}H NMR integration of the unpurified reaction mixture against an internal standard). It is important to emphasize that $MN(SiMe_3)_2$ (M = Li, Na, K) plays two vital roles: (1) condensation with benzaldehyde and aza-Peterson elimination to in situ generate *N*-(trimethylsilyl)imines; and (2) direct deprotonation of benzylic C−H bonds of 4-(pyridin-2-ylmethyl)morpholine (**2a**) (Scheme 1c). Based on the conditions of entry 2, we next tested five ethereal solvents (^{i}Pr$_2$O, TBME, CPME, DME and Et$_2$O). Based on consideration of diastereomeric ratios and yield, ^{i}Pr$_2$O outperformed other solvents (5.2 : 1 dr, 86% AY, entry 4) and was used going forward. It is noteworthy that TBME also gave good results (90% yield, 4.6 : 1 dr, entry 5). Since amine additives impact the aggregation of silylamide bases,[14] and therefore, their reactivity and selectivity, we examined two commonly used polyamine ligands: *N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine (PMDTA, 1.0 equiv) and TMEDA (1.0 equiv) under the conditions of entry 2. PMDTA improved both the yield and diastereoselectivity, affording the desired product in 95% yield with 6.0 : 1 dr (entry 10). Ultimately, the optimized conditions for this tandem reaction are 1.0 equiv of benzaldehyde, 1.5 equiv of **2a**, 2.0 equiv of $NaN(SiMe_3)_2$, and 1.0 equiv. of PMDTA in ^{i}Pr$_2$O at 10 °C for 12 h. After derivatization of **3aa** by 3,5-dinitrobenzoyl chloride, the corresponding *anti*- and *syn*-diastereomers of **4aa** could be separated. According to ^{1}H NMR of **4aa** (see Supporting Information), the coupling constant between the two protons alpha to the nitrogens of the major isomer of **4aa** is 10.5 Hz whereas the minor component of **4aa** 3.7 Hz, leading to the assignment of the major diastereomer as *anti*-**4aa**.[8h] This spectroscopic difference between the diastereoisomers was used to judge *syn*/*anti* selectivity in the following studies, which show *anti* selectivity in all cases.

Table 1. Optimization of Reaction Conditions[a].



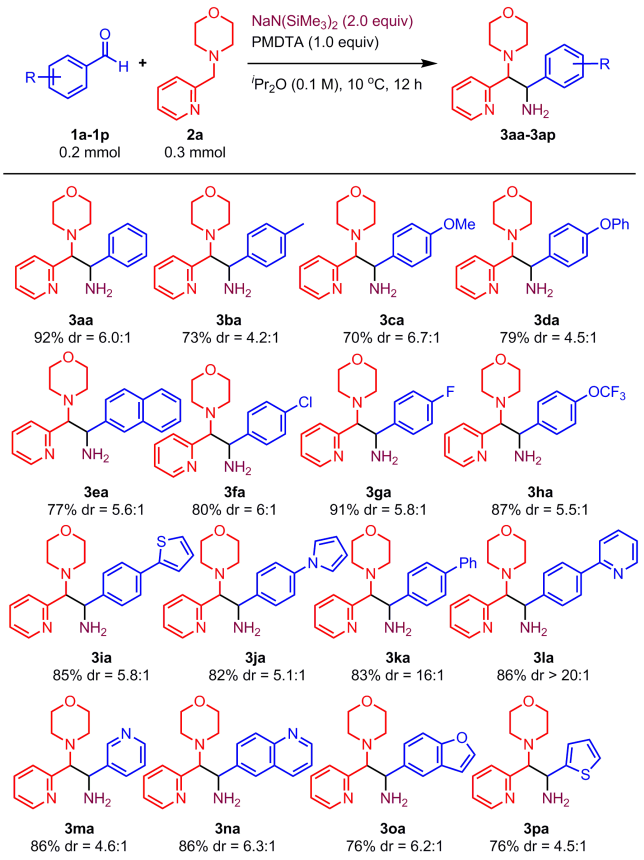
1a + **2a** → **3aa**

entry	base	additive	solvent	AY(%)[b]	dr[c]
1	$LiN(SiMe_3)_2$	--	THF	90	1.6:1
2	$NaN(SiMe_3)_2$	--	THF	84	4.5:1
3	$KN(SiMe_3)_2$	--	THF	Trace	--
4	$NaN(SiMe_3)_2$	--	^{i}Pr$_2$O	86	5.2:1
5	$NaN(SiMe_3)_2$	--	TBME	90	4.6:1
6	$NaN(SiMe_3)_2$	--	CPME	76	5.8:1
7	$NaN(SiMe_3)_2$	--	DME	52	4.3:1
8	$NaN(SiMe_3)_2$	--	Et$_2$O	87	4.4:1
9	$NaN(SiMe_3)_2$	TMEDA	^{i}Pr$_2$O	81	5.5:1
10	$NaN(SiMe_3)_2$	PMDTA	^{i}Pr$_2$O	95	6.0:1

[a]Reactions conducted under argon on 0.1 mmol scale. [b]Yields were determined by ^{1}H NMR analysis of unpurified reaction mixtures with internal standard dimethyl terephthalate. [c]The dr was determined by LC-MS analysis of unpurified reaction mixtures.

With the optimized conditions in hand, the scope of aryl aldehydes was examined (Scheme 2). In general, a diverse array of substituents on the aldehydes was tolerated under the mild conditions. The parent benzaldehyde (**1a**) was successfully transformed to **3aa** in 95% yield with 6.0 : 1 dr. Benzaldehydes substituted by electron donating groups, such as 4-methyl (**1b**), 4-methoxy (**1c**) and 4-phenoxy (**1d**) exhibited good reactivity, giving **3ba**, **3ca** and **3da** in 73%, 70% and 79% yields with similar diastereoselectivities of 4.2 : 1, 6.7 : 1 and 4.5 : 1, respectively. It is interesting that 4-methylbenzaldehyde is a good substrate, given that deprotonation of the relatively acidic methyl group of the aldehyde or imine could be envisioned to be problematic. Substrates containing extended π-systems, such as 2-naphthyl aldehyde (**1e**), furnished the corresponding product **3ea** in 77% yield with 5.6 : 1 dr. Benzaldehydes bearing halogens, such as 4-chlorobenzaldehyde, were also good substrates, as exemplified by the generation of **3fa** (80% yield and 6.0 : 1 dr). This product is primed for further functionalization by cross-coupling methods. Since fluorinated compounds play an extremely important role in medicinal chemistry,[15] we next examined fluorinated benzaldehydes. Both 4-fluoro- (**1g**) and 4-trifluoromethoxy-benzaldehyde (**1h**) were excellent coupling partners, affording **3ga** and **3ha** in 91% (5.8 : 1 dr) and 87% yields (dr = 5.5 : 1) respectively. Benzaldehydes containing aromatic substituents such as 4-(2-thienyl) (**1i**) and 4-(*N*-pyrrolyl) (**1j**) provided products **3ia** and **3ja** in 85% (5.8 : 1 dr) and 82% (5.1 : 1 dr) yields, respectively. To our surprise, 4-phenyl benzaldehyde and 4-(2-pyridyl) benzaldehyde reacted to give the expected products **3ka** and **3la** in very good yields (83% and 86%) with excellent diastereoselectivities (16:1 and > 20:1), respectively. In addition to benzaldehydes, heterocyclic aldehydes such as nicotinaldehyde (**1m**), quinoline-6-carbaldehyde (**1n**), benzofuran-5-carbaldehyde (**1o**) and thiophene-2-carbaldehyde (**1p**) were transformed to their corresponding products in good yields (76−86%) and diastereoselectivities (4.6 : 1 to 6.3 : 1).

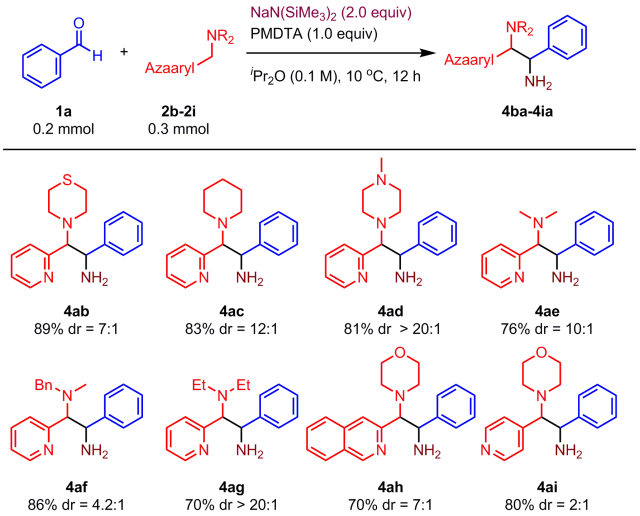
Scheme 2. Substrate Scope of Aldehydes[a]



[a]Reactions conducted under argon on 0.2 mmol scale. Yields are isolated yield. The dr was determined by LC-MS analysis of unpurified reaction mixtures.

Subsequently, the scope of azaarylmethylamines was explored (Scheme 3), beginning with the cyclic amine moiety. When the morpholino group of **2a** was replaced by thiomorpholino (**2b**), piperidine (**2c**) and 1-methylpiperazine (**2d**), the corresponding products **4ab**, **4ac** and **4ad** were obtained in 89%, 83% and 81% yields with dr values of 7 : 1, 12 : 1 and > 20 : 1, respectively. Acyclic amines *N*,*N*-dimethyl- (**2e**), *N*-benzyl-*N*-methyl- (**2f**) and *N*,*N*-diethyl- (**2g**) derivatives were also good coupling partners and their respective products **4ae**, **4af** and **4ag** were recovered in 70−86% yield and with 4.2 : 1 to >20 : 1 dr. To test the azaaryl group, 3-aminomethyl isoquinoline (**2h**) and 4-aminomethhyl pyridine (**2i**) derivatives were examined and the corresponding products (**4ah** and **4ai**) were formed in 70% and 80% yield with 7 : 1 and 2 : 1 dr, respectively. Unfortunately, 3-aminomethyl pyridine derivatives and diphenylmethanes, which are significantly less acidic, did not react under our conditions. To obtain acceptable diastereoselectivity, 2-aminomethyl substituted pyridine derivatives, which can chelate to the main group metal of the base, are required.

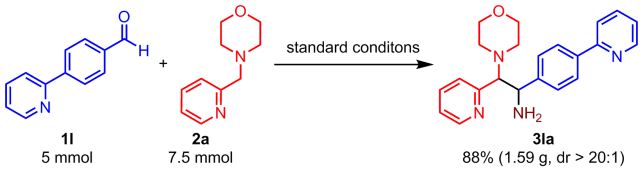
Scheme 3. Substrate Scope of Azaarylmethylamines[a]



[a]Reactions conducted under argon on 0.2 mmol scale. Yields are isolated. The dr was determined by LC-MS analysis of unpurified reaction mixtures.

To investigate the potential scalability (Scheme 4), a 5 mmol scale reaction with **1l** and **2a** was conducted. The desired product **3la** was obtained in 88% yield with greater than 20 : 1 dr. Condensation of **3la** with 3,5-dinitrobenzoyl chloride (1.2 equiv) and triethylamine (1.2 equiv) formed the expected amide, the structure of which was determined to be the *anti*-**4la'** product by X-ray crystallographic analysis (see Supporting Information for details).

Scheme 4. Scale-up to 5 mmol.



In conclusion, we have reported a straightforward and practical one-pot synthesis of vicinal diamines between azaarylmethylamines and aldehydes. The tandem reaction takes place without transition metal catalysts and provides an effective strategy to synthesize biologically active vicinal diamines. A wide range of electron-donating and withdrawing aryl substrates, including heterocycles, are viable substrates in our reaction. The synthetic value and practicality of this method were demonstrated with a highly diastereoselective gram scale reaction. We anticipate that this straightforward avenue to stitch together molecules with 3–4 nitrogen centers from readily available precursors will render it immediately useful to medicinal chemists. Further efforts will focus on the identification of a catalytic asymmetric route to these diamines.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website

Experimental procedures, characterization data, and NMR spectra (PDF)

CIF for compound **4la'** (CIF)

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