ACS Combinatorial Science

Technology Note

pubs.acs.org/acscombsci

A One-Pot Parallel Reductive Amination of Aldehydes with Heteroaromatic Amines

Andrey V. Bogolubsky,[†] Yurii S. Moroz,*[,†,‡] Pavel K. Mykhailiuk,*[,†,§] Dmitriy M. Panov,[†] Sergey E. Pipko,[‡] Anzhelika I. Konovets,[†,∥] and Andrey Tolmachev[†,‡]

[†]Enamine Ltd., 23 Matrosova Street, Kyiv 01103, Ukraine

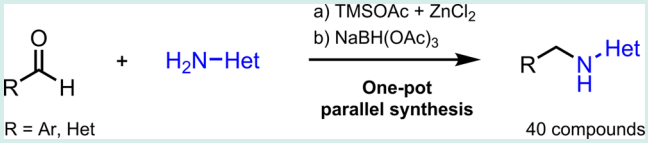
[‡]ChemBioCenter, Kyiv National Taras Shevchenko University, 61 Chervonotkatska Street, Kyiv 02094, Ukraine

[§]Department of Chemistry, Kyiv National Taras Shevchenko University, 64 Volodymyrska Street, Kyiv 01601, Ukraine

[∥]The Institute of High Technologies, Kyiv National Taras Shevchenko University, 4 Glushkov Street, Building 5, Kyiv 03187, Ukraine

Supporting Information

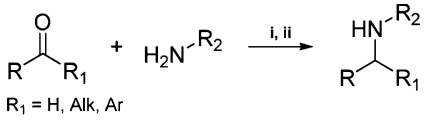
ABSTRACT: A parallel reductive amination of heteroaromatic amines has been performed using a combination of $ZnCl_2$–TMSOAc (activating agents) and $NaBH(OAc)_3$ (reducing agent). A library of diverse secondary amines was easily prepared on a 50–300 mg scale.



KEYWORDS: *heteroaromatic amines, reductive amination, trimethylsilyl acetate, one-pot approach, parallel synthesis*

The reductive amination of carbonyl substrates (aldehydes or ketones)[1,2] has attracted considerable attention among other approaches toward secondary amines.[3−7] The reductive amination reaction consists of (i) formation of an imine from a primary amine and a carbonyl substrate and (ii) reduction of the imine with a suitable hydride source.[8−15] There are two distinct approaches for the reductive amination: the direct approach, which uses the in situ-generated imine (Scheme 1), and the indirect approach, which uses the previously isolated imine. The direct approach allows for the quick generation of sets of amines when the synthesis is conducted in a one-pot fashion and therefore is widely utilized.

Scheme 1. Direct Reductive Amination



One of our projects was to apply the reductive amination approach to a parallel synthesis of secondary amines derived from aldehydes and heteroaromatic amines. The approach must satisfy the following conditions of the parallel synthesis: (a) one-pot procedure with a simple "in vial" setup; (b) stable, compatible reagents that would allow the creation of highly diverse sets of compounds and be easily separated from the product; and (c) addition of the reagents without control of the temperature.

Despite the fact that heteroaromatic amines are common building blocks in the synthesis of drugs and agrochemicals[16] (Figure 1), literature reports on reductive amination with these amines are rare and nonsystematic.[2,17,18] The amino group of heteroaromatic amines, which is generally electron-deficient, often affords poor yields of the intermediate imines in direct reductive amination. Gutierrez et al.[18] proposed a one-pot reductive amination approach employing a combination of a Lewis acid, $TiCl(OiPr)_3$, to facilitate the imine formation and $NaBH(OAc)_3$ as a reducing agent, which satisfies criterion (a) of the parallel synthesis. However, this approach has drawbacks that result in its incompatibility with criteria (b) and (c): an exothermic reaction with gas evolution occurs during the addition of $NaBH(OAc)_3$ because of the interaction of the reductant with a byproduct (HCl), and laborious workup is required because of the amorphous precipitate of titanic acid formed after hydrolysis of $TiCl(OiPr)_3$.

We recently employed trimethylsilyl chloride (TMSCl)[19] as a promoter and a water scavenger in the reductive amination reaction. However, similar to $TiCl(OiPr)_3$, its application in combination with $NaBH(OAc)_3$ to the one-pot parallel synthesis is limited because of the HCl release. We then chose trimethylsilyl acetate (TMSOAc), resulting in AcOH as the byproduct, which is compatible with $NaBH(OAc)_3$. Initial experiments, however, showed poor yields in reactions with some substrates because of the low reactivity of TMSOAc. Therefore, we added $ZnCl_2$ as an additional promoter for the reductive amination.[12] The experimentally established optimal amount of $ZnCl_2$ (0.05 equiv) allowed for the effective imine formation and had no effect on the purity of the final product. Herein we report our results on the use of this combination of reagents, a TMSOAc/$ZnCl_2$ mixture and $NaBH(OAc)_3$, in the parallel reductive amination of aldehydes with heteroaromatic amines.

We selected 10 aldehydes (Figure 2) and 20 amines (Figure 3) from our internal database to test the proposed combination. For

Received: April 8, 2014
Revised: June 16, 2014
Published: June 23, 2014

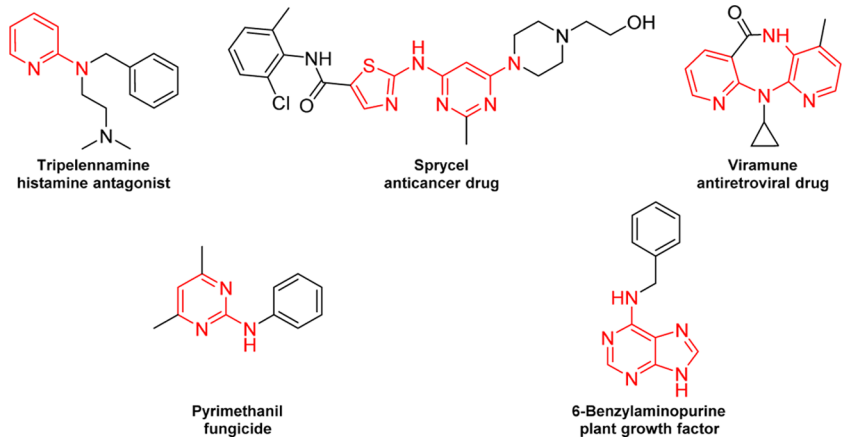


Figure 1. Agrochemicals and drugs bearing heteroaromatic amine moieties.[20,21]

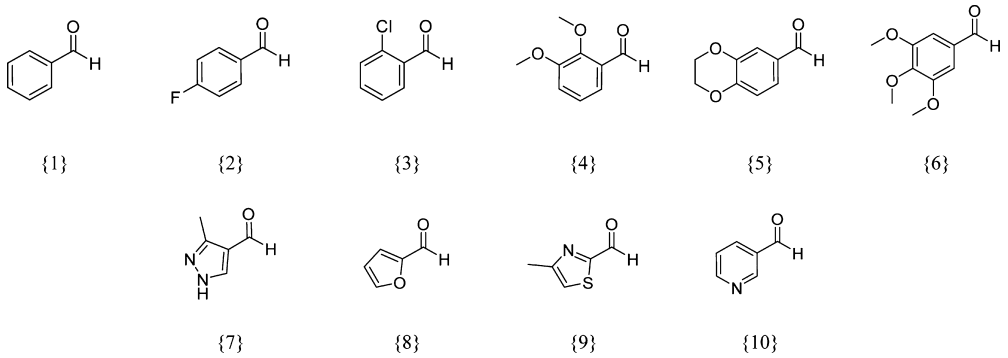


Figure 2. Aldehydes tested in the study (chemset **1**).

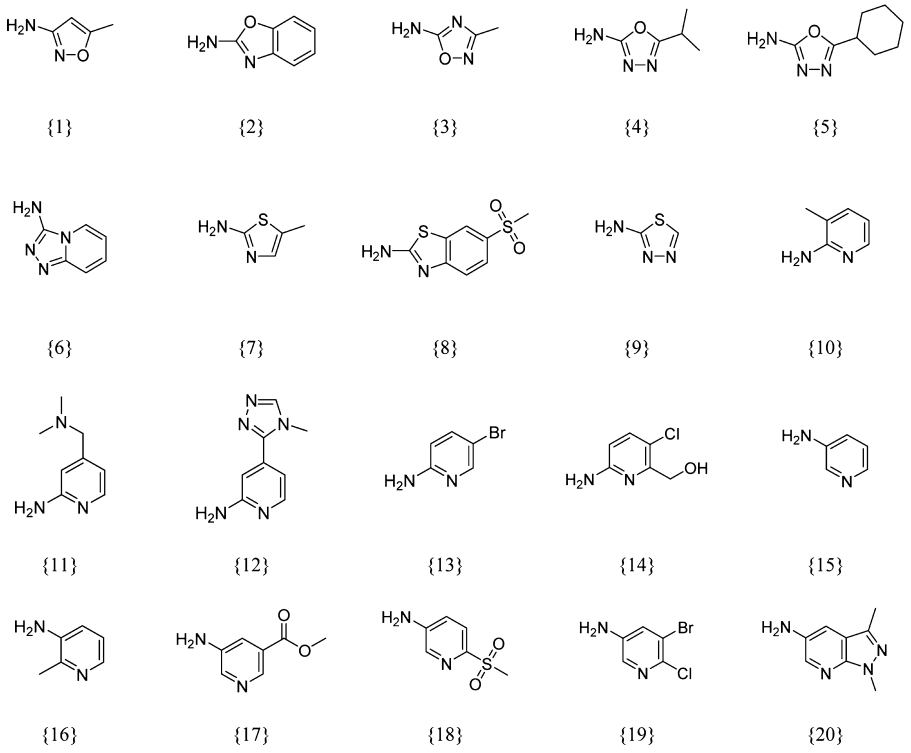
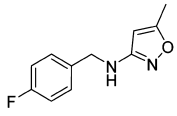
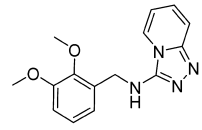
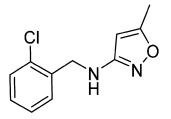
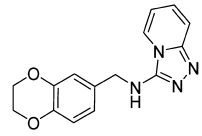
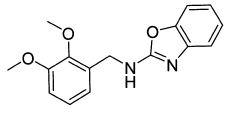
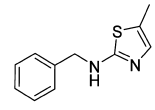
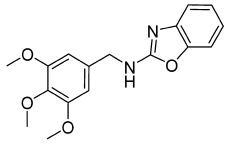
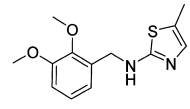
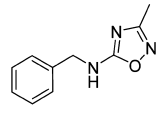
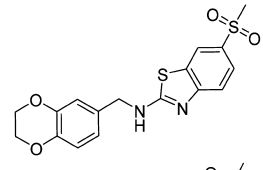
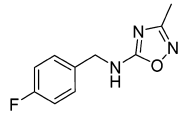
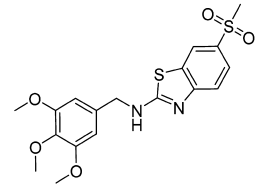
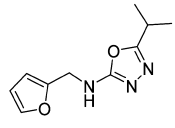
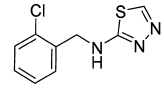
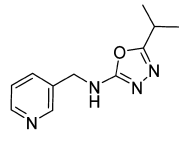
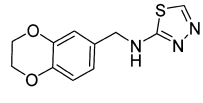
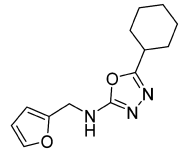
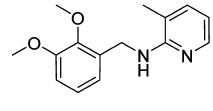
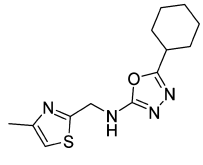
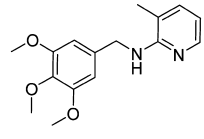


Figure 3. Amines tested in the study (chemset **2**).

the aldehydes, we chose benzaldehyde and five of its derivatives along with four heteroaromatic aldehydes. For the amines, we selected nine five-membered ring and 11 six-membered ring heteroaromatic substrates with electron-donating groups (EDGs) or electron-withdrawing groups (EWGs) on the ring. Then we conducted the parallel reductive amination, preparing a

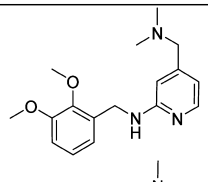
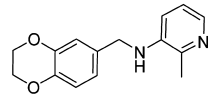
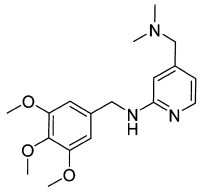
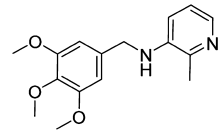
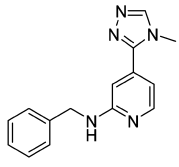
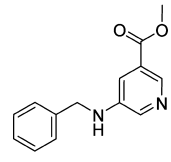
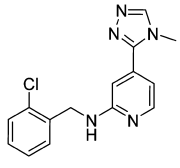
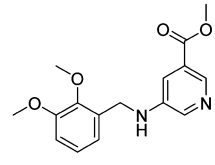
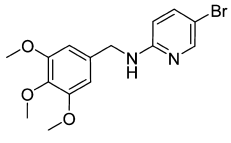
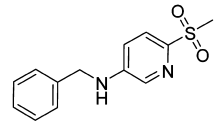
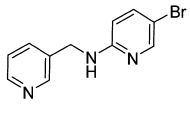
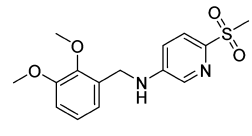
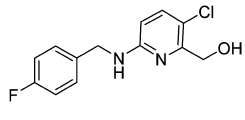
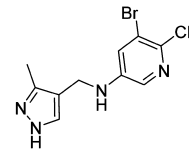
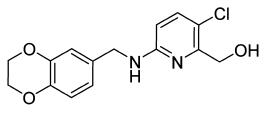
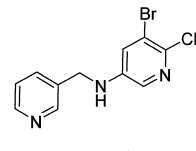
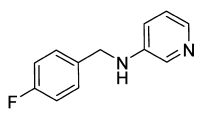
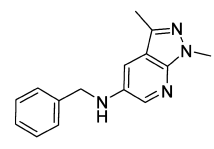
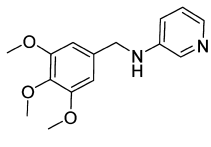
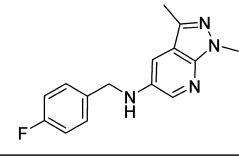
dx.doi.org/10.1021/co5000568 | *ACS Comb. Sci.* 2014, 16, 375−380

Table 1. Synthesized Secondary Amines (Chemset 3)

Entry	Amine **3**		Yield[a] (%)	Entry	Amine **3**		Yield[a] (%)
1	**3**{2,1}		69	11	**3**{4,6}		20
2	**3**{3,1}		23	12	**3**{5,6}		22
3	**3**{4,2}		84	13	**3**{1,7}		79
4	**3**{6,2}		32	14	**3**{4,7}		41
5	**3**{1,3}		60	15	**3**{5,8}		47
6	**3**{2,3}		43	16	**3**{6,8}		42
7	**3**{8,4}		67	17	**3**{3,9}		68
8	**3**{10,4}		54	18	**3**{5,9}		42
9	**3**{8,5}		20	19	**3**{4,10}		32
10	**3**{9,5}		95	20	**3**{6,10}		30

dx.doi.org/10.1021/co5000568 | *ACS Comb. Sci.* 2014, 16, 375−380

Table 1. continued

Entry	Amine **3**	Yield[a] (%)	Entry	Amine **3**	Yield[a] (%)
21	**3**{4,11}		78	31	**3**{5,16}		36
22	**3**{6,11}		95	32	**3**{6,16}		42
23	**3**{1,12}		42	33	**3**{1,17}		73
24	**3**{3,12}		25	34	**3**{4,17}		32
25	**3**{6,13}		93	35	**3**{1,18}		50
26	**3**{10,13}		25	36	**3**{4,18}		50
27	**3**{2,14}		74	37	**3**{7,19}		40
28	**3**{5,14}		23	38	**3**{10,19}		54
29	**3**{2,15}		46	39	**3**{1,20}		20
30	**3**{6,15}		84	40	**3**{2,20}		22

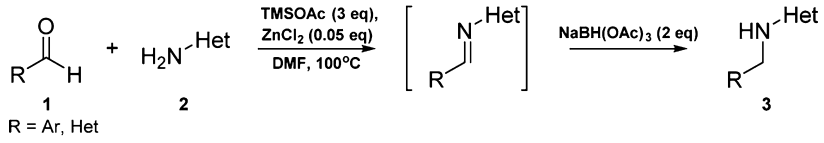
[a]Isolated yields.

40-member library of the secondary amines (Table 1). Our aim was to synthesize a diverse set of amines that completely satisfied the purpose of the work, but not all possible variants.

In the imine formation step, a dimethylformamide solution of aldehyde **1**, amine **2**, and the TMSOAc/$ZnCl_2$ mixture was heated at 100 °C for 8 h (Scheme 2). In the reduction step,

dx.doi.org/10.1021/co5000568 | ACS Comb. Sci. 2014, 16, 375−380

Scheme 2. Parallel Synthesis Approach to the Reductive Amination with Heteroaromatic Amines



$NaBH(OAc)_3$ was added in one portion, and the reaction was conducted at room temperature for 72 h. After the subsequent simple workup, the crude product **3** was isolated and analyzed by LC−MS analysis to check the initial purity (Figures S1−S40 in the Supporting Information). The LC−MS analysis revealed that ∼50% of the samples had purities of >90%, 30% had purities of >80%, and ∼20% had purities of 45−80%. The impurities were identified as starting materials (Figures S2, S9, and S12), intermediate imines (Figures S2, S12, and S19), and products of overalkylation (Figures S24, S31, and S32). Overall, only 50% of the samples required additional purification to obtain compounds with >95% purity; purification was performed by flash chromatography. Final yields of 20−96% were achieved (Table 1). The identities and purities of the obtained secondary amines **3** were confirmed by ^1H and ^{13}C NMR spectroscopy and LC−MS analysis. The experimental data showed that the reaction proceeded in low yields for amines that were deactivated (e.g., [1,2,4]triazolo[4,3-*a*]pyridine-3-amine, entries 11 and 12; 5-methanesulfonyl-1,3-benzothiazol-2-amine, entries 15 and 16; and 1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-amine, entries 39 and 40) or had a sterically hindered amino group (e.g., 3-methylpyridin-2-amine, entries 19 and 20, and 2-methylpyridin-3-amine, entries 31 and 32). The ester functionality of methyl 5-aminopyridine-3-carboxylate (entries 33 and 34) was tolerated under the reaction conditions.

In conclusion, we have demonstrated a highly efficient approach for the parallel reductive amination of aldehydes with heteroaromatic amines utilizing the combination of a TMSOAc/$ZnCl_2$ mixture and $NaBH(OAc)_3$. The approach is based on a simple one-pot procedure and allows for the quick generation of a library of secondary amines in quantities suitable for preliminary biological studies.

EXPERIMENTAL PROCEDURES

General. All of the chemicals and solvents were obtained from commercially available sources (Aldrich, Enamine Ltd.) and used without further purification. Melting points were determined on a Buchi melting point apparatus and are uncorrected. Elemental analysis was done on a Vario MICRO Cube elemental microanalyzer (Elementar). IR spectra were recorded on a PerkinElmer Spectrum BX II spectrometer. ^1H and ^{13}C NMR spectra were acquired on a Bruker Avance DRX 500 spectrometer using DMSO-d_6 as the solvent. The spectra were referenced to the peak of DMSO-d_5. LC−MS data were recorded on an Agilent 1100 HPLC instrument equipped with a diode-matrix and mass-selective detector (Agilent LC-MSD SL) and a Zorbax SB-C18 column (4.6 mm × 15 mm). Eluent A was 95:5 acetonitrile/water with 0.1% TFA, and eluent B was water with 0.1% TFA. The ionization method was atmospheric-pressure chemical ionization (APCI). The purification of the compounds was performed using a Companion Combi-Flash instrument with a UV detector and a reusable LukNova column [eluent A, $CHCl_3$; eluent B, 7:3 (v/v) $CHCl_3$/methanol].

General Procedure for the Parallel Synthesis of Aliphatic Sulfonamides. To a reaction vial containing an amine (0.7 mmol), an aldehyde (0.7 mmol), and TMSOAc (2.1 mmol) was added 0.25 mL of a 2% solution of $ZnCl_2$ in DMF. The vial was heated at 100 °C for 8 h and allowed to cool to room temperature. Then $NaBH(OAc)_3$ (1.4 mmol) was added, and the mixture was kept at room temperature for 72 h with occasional shaking. After subsequent sonication at 50−55 °C, the mixture was treated with 1 mL of 10% KOH solution followed by the addition of 7 mL of water. The product was extracted with 3 mL of $CHCl_3$, and the organic phase was washed with water (2 × 7 mL) and evaporated. Compounds with purity below 95% were subjected to further purification by flash chromatography.

ASSOCIATED CONTENT

Supporting Information

LC−MS data for crude mixtures and spectral data for the selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: ysmoroz@mail.enamine.net.

*E-mail: Pavel.Mykhailiuk@mail.enamine.net; Pavel.Mykhailiuk@gmail.com.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) McGonagle, F. I.; MacMillan, D. S.; Murray, J.; Sneddon, H. F.; Jamieson, C.; Watson, A. J. B. Development of a Solvent Selection Guide for Aldehyde-Based Direct Reductive Amination Processes. *Green Chem.* **2013**, *15*, 1159−1165.

(2) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures. *J. Org. Chem.* **1996**, *61*, 3849−3862.

(3) Das, B. G.; Ghorai, P. The Direct Reductive Amination of Electron-Deficient Amines with Aldehydes: The Unique Reactivity of the Re_2O_7 Catalyst. *Chem. Commun.* **2012**, *48*, 8276−8278.

(4) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. Synthesis of Secondary Amines. *Tetrahedron* **2001**, *57*, 7785−7811.

(5) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. Enantioselective Organocatalytic Reductive Amination. *J. Am. Chem. Soc.* **2006**, *128*, 84−86.

(6) Dang, T. T.; Ramalingam, B.; Shan, S. P.; Seayad, A. M. An Efficient Palladium-Catalyzed N-Alkylation of Amines Using Primary and Secondary Alcohols. *ACS Catal.* **2013**, *3*, 2536−2540.

(7) Agrawal, S.; Lenormand, M.; Martín-Matute, B. Selective Alkylation of (Hetero)Aromatic Amines with Alcohols Catalyzed by a Ruthenium Pincer Complex. *Org. Lett.* **2012**, *14*, 1456−1459.

(8) Borch, R. F.; Bernstein, M. D.; Durst, H. D. Cyanohydridoborate Anion as a Selective Reducing Agent. *J. Am. Chem. Soc.* **1971**, *93*, 2897−2904.

(9) Mićović, I. V.; Ivanović, M. D.; Piatak, D. M.; Bojić, V. D. A Simple Method for Preparation of Secondary Aromatic Amines. *Synthesis* **1991**, 1043−1045.

(10) Lee, O.-Y.; Law, K.-L.; Yang, D. Secondary Amine Formation from Reductive Amination of Carbonyl Compounds Promoted by

Lewis Acid Using the $InCl_3/Et_3SiH$ System. *Org. Lett.* **2009**, *11*, 3302−3305.
(11) Alinezhad, H.; Tajbakhsh, M.; Zamani, R. One-Pot Reductive Amination of Aldehydes and Ketones Using *N*-Methylpiperidine Zinc Borohydride (ZBNMPP) as a New Reducing Agent. *Synlett* **2006**, 431−434.
(12) Bhattacharyya, S.; Chatterjee, A.; Duttachowdhury, S. K. Use of Zinc Borohydride in Reductive Amination: An Efficient and Mild Method for *N*-Methylation of Amines. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1−2.
(13) Sato, S.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. One-Pot Reductive Amination of Aldehydes and Ketones with α-Picoline-Borane in Methanol, in Water, and in Neat Conditions. *Tetrahedron* **2004**, *60*, 7899−7906.
(14) Hiroi, R.; Miyoshi, N.; Wada, M. Solvent-Free One-Pot Reduction of Imines Generated in Situ from Aldehydes and Aniline by Tributyltin Hydride on Silica Gel. *Chem. Lett.* **2002**, *31*, 274−275.
(15) Nguyen, Q. P. B.; Kim, T. H. Solvent- and Catalyst-Free Direct Reductive Amination of Aldehydes and Ketones with Hantzsch Ester: Synthesis of Secondary and Tertiary Amines. *Tetrahedron* **2013**, *69*, 4938−4943.
(16) Lawrence, S. A. *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, U.K., 2004.
(17) Liu, Z. G.; Li, N.; Yang, L.; Liu, Z. L.; Yu, W. $ZrCl_4$/Hantzsch 1,4-Dihydropyridine as a New and Efficient Reagent Combination for the Direct Reductive Amination of Aldehydes and Ketones with Weakly Basic Amines. *Chin. Chem. Lett.* **2007**, *18*, 458−460.
(18) Gutierrez, C. D.; Bavetsias, V.; McDonald, E. $TiCl(OiPr)_3$ and $NaBH(OAc)_3$: An Efficient Reagent Combination for the Reductive Amination of Aldehydes by Electron-Deficient Amines. *Tetrahedron Lett.* **2005**, *46*, 3595−3597.
(19) Ryabukhin, S. V.; Panov, D. M.; Plaskon, A. S.; Chuprina, A.; Pipko, S. E.; Tolmachev, A. A.; Shivanyuk, A. N. Combinatorial Synthesis of Chemical Building Blocks 1. Azomethines. *Mol. Diversity* **2012**, *16*, 625−637.
(20) Gaulton, A.; Bellis, L. J.; Bento, A. P.; Chambers, J.; Davies, M.; Hersey, A.; Light, Y.; McGlinchey, S.; Michalovich, D.; Al-Lazikani, B.; Overington, J. P. ChEMBL: A Large-Scale Bioactivity Database for Drug Discovery. *Nucleic Acids Res.* **2012**, *40*, D1100−D1107.
(21) *Bioactive Heterocyclic Compound Classes: Agrochemicals*; Lamberth, C., Dinges, J., Eds.; Wiley-VCH: Weinheim, Germany, 2012; p 302.