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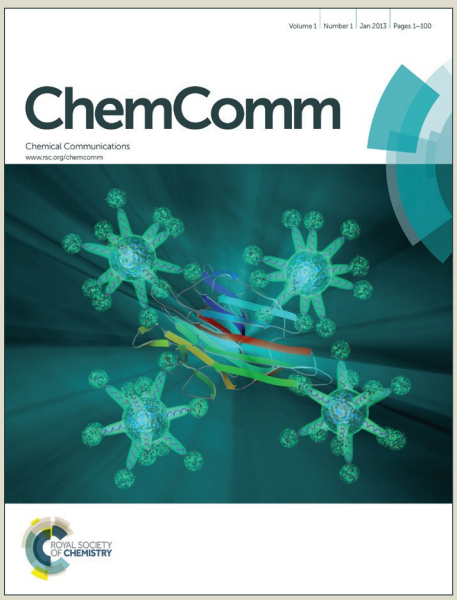

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An annulative transfer hydrogenation strategy enables straightforward access to tetrahydro fused-pyrazine derivatives

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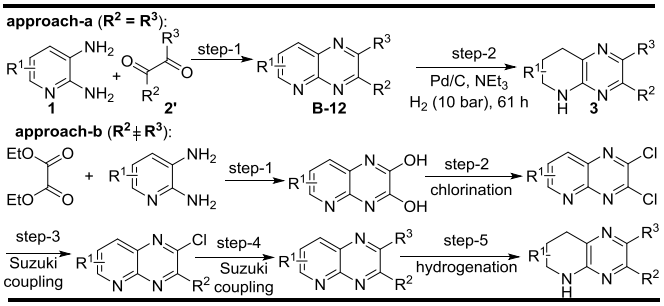
A ruthenium-catalysed annulative transfer hydrogenation strategy, enabling straightforward access to tetrahydron fused-pyrazine derivatives from *N*-heteroaryl diamines and vicinal diols, has been demonstrated for the first time. Such a synthesis proceeds with unprecedented synthetic effectiveness including high step and atom efficiency, generation of water as the sole by-product, short reaction time and no need for external high pressure H_2 gas, offering an important basis for the transformation of vicinal diols, a class of bio-mass derived resource, into functionalized products.

Transfer hydrogenation (TH) is a fundamental tool in obtaining saturated products, which appeals to many synthetic chemists because it does not need for flammable high pressure H_2 gas, offering more convenient and safer production processes. During the past decade, a number of hydrogen donors (i.e. NH_3BH_3,[3] Hantzsch ester,[4] HCO_2H,[5] $NaCO_2H$,[6] diboron reagents with water[7] and NH_2-NH_2·H_2O[8]) have been extensively applied for various synthetic purposes. In general, these protocols produce stoichiometric amount of wastes, their applications to large-scale production are easily restricted.

In recent years, the utilization of abundant and sustainable alcohols for TH reactions has also been elegantly explored. Representative examples mainly involve: (1) borrowing-hydrogen reactions.[9] Via hydrogenation of the *in-situ* formed C-C and C-N double bonds with alcohols, a series of N-alkylation and C-alkylation methodologies have been reported by the leading groups of Beller,[10] Williams,[11] Kempe,[12] Fujita,[13] Bruneau[14] and others[15]. (2) Transfer hydrogenative coupling reactions. In this aspect, the Krische group has demonstrated distinguished contributions on the coupling of alcohols and C-C double/triple bonds.[16] (3) Reduction reactions. In which, alcohols were applied as alternative hydrogen sources to reduce unsaturated chemical bonds with liberation of carbonyl by-products.[17] Despite these important advances, due to the thermodynamic stability and kinetic inertness of heteroaryl systems, the TH of heteroaromatics with alcohols under atmospheric pressure still remains challenging. If such a goal is realistic, the envisaged strategy, employing the *in-situ* formed carbonyls and hydrogen arising from alcohol dehydrogenation for new ring construction and TH of heteroaryl ring, respectively, would shed new light on step- and atom-economic access to saturated fused-heterocycles that are currently inaccessible or challenging to prepare with conventional methods.

Upon a thorough literature investigation, it was found that tetrahydropyrido[2,3-b]pyrazine moiety constitutes the core structure of numerous functionalized molecules, which exhibit diverse biological and therapeutic activities such as potent agonist of the IP receptor, vasodilator, anti-proliferation, anti-thrombosis and etc.[18] However , the preparation of such compounds has to date presented a difficult goal. Generally, it was achieved via the condensation of *N*-heteroaryl 1,2-diamines **1** with 1,2-diketones **2'** followed by hydrogenation with H_2 (Scheme 1, approach-a), or through a multi-step procedure (approach-b). Notably, the synthesis required high pressure H_2 gas, high catalyst loading, long reaction time or complex operations. Therefore, there is a demand for shortcuts to access these valuable compounds.



Scheme 1 Conventional synthetic approaches.

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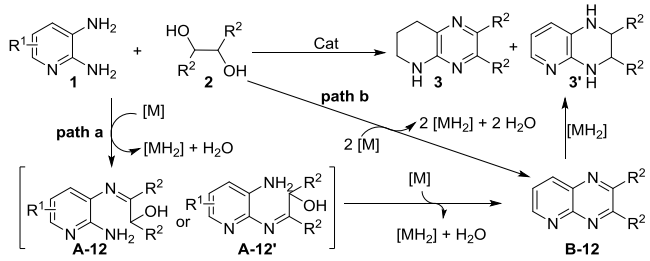
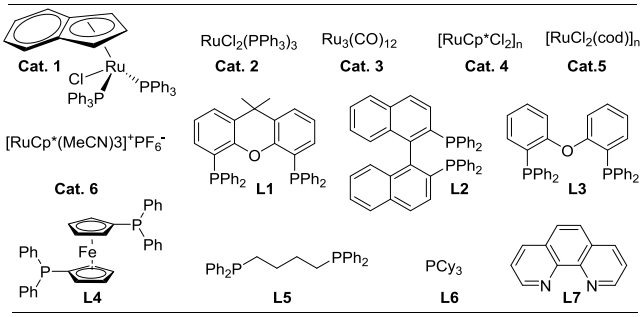
The above-described information led us to envisage an annulative transfer hydrogenation protocol. In which, the reaction initiates with transition metal-catalyzed dehydrogenation of vicinal diols **2** and subsequent condensation with one amino group of N-heteroaryl diamines **1**, resulting in two possible imines **A-12** or **A-12'** and active [MH_2] species[19]. Then the dehydrogenation of **A-12** or **A-12'** followed by a condensation gives the annulation adduct **B-12** (**path a**). Alternatively, a direct dehydrogenation of **2** to di-ketones followed by condensation with diamines **1** also affords **B-12** (**path b**). Finally, the transfer hydrogenation of **B-12** with [MH_2] would afford tetrahydropyridine-fused pyrazine **3** or pyridine-fused tetrahydropyrazine **3'**. Noteworthy, in comparison with the known procedures (Scheme 1), such a protocol would not only offer simple operations, but also produce the products with minimum waste generation.



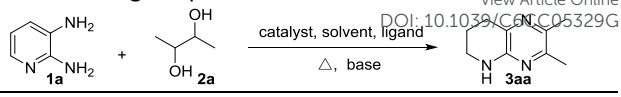
Scheme 2 Envisaged new synthetic strategy.



Scheme 3 Catalysts and ligands tested.

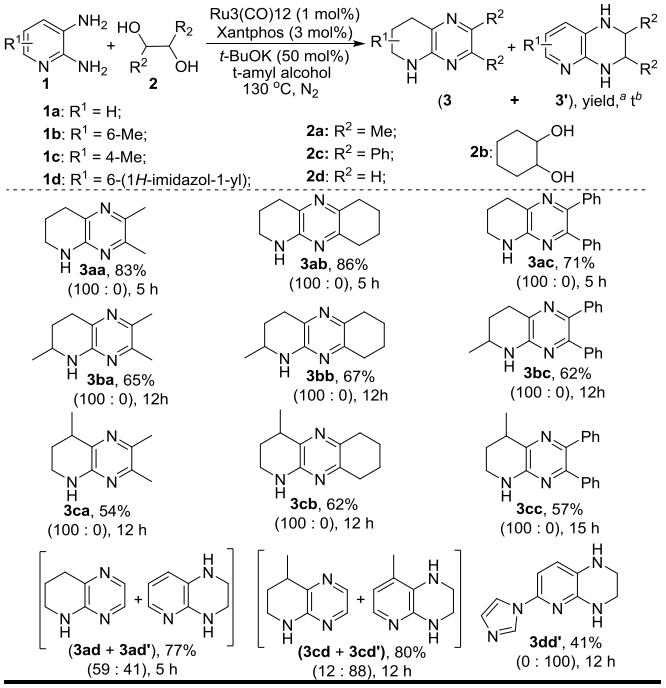
To examine our tentative idea, we performed the reaction of pyridine-2,3-diamine **1a** with butane-2,3-diol **2a** in *t*-amyl alcohol at 130 °C for 5 h under N_2 protection. In consideration of the economic attractiveness of ruthenium catalysis, six catalyst precursors were initially tested by using Xantphos (Scheme 3, **L1**) and *t*-BuOK as the ligand and base, respectively (Table 1, entries 1-6). Gratifyingly, $Ru_3(CO)_{12}$ gave a tetrahydro pyridine-fused pyrazine **3aa** in almost quantitative yield (96%). However, the reaction failed to yield any desired product under catalyst-free conditions (entry 7), indicating that the presence of ruthenium catalysts plays a crucial role in affording the product. Then, other 6 ligands (Scheme 3, **L2**-**L7**) showed to be either less effective or totally ineffective for the transformation as compared to Xantphos (Table 1, entries 8-13). Finally, we checked several other inorganic bases and solvents (entries 14 and 15), but they are inferior to *t*-BuOK and *t*-amyl alcohol, respectively. Thus, the optimal conditions are as described in entry 3 of table 1.

Table 1 Screening of optimal reaction conditions [a]



Entry	Catalyst/mol%	Ligand	Base	**3aa**, Yield%[b]
1	**Cat 1**/3	**L1**	*t*-BuOK	24
2	**Cat 2**/3	**L1**	*t*-BuOK	31
3	**Cat 3**/1	**L1**	*t*-BuOK	96
4	**Cat 4**/3	**L1**	*t*-BuOK	17
5	**Cat 5**/3	**L1**	*t*-BuOK	35
6	**Cat 6**/3	**L1**	*t*-BuOK	trace
7	-	**L1**	*t*-BuOK	-
8	**Cat 3**/1	**L2**	*t*-BuOK	83
9	**Cat 3**/1	**L3**	*t*-BuOK	81
10	**Cat 3**/1	**L4**	*t*-BuOK	75
11	**Cat 3**/1	**L5**	*t*-BuOK	90
12	**Cat 3**/1	**L6**	*t*-BuOK	81
13	**Cat 3**/1	**L7**	*t*-BuOK	trace
14	**Cat 3**/1	**L1**	base	(21, 36, 49)[c]
15	**Cat 3**/1	**L1**	*t*-BuOK	(44, 46, 23)[d]

[a] Unless otherwise stated, the reaction was performed with **1a** (0.5 mmol), **2a** (0.6 mmol), Cat (3 mol%), ligand (3 mol%), base (50 mol%) in *t*-amyl alcohol (1.2 mL) at 130 °C for 5 h under N_2. [b] GC yield of **3aa**. [c] Yields are with respect to use of K_2CO_3, Cs_2CO_3 and $CsOH·H_2O$ as the bases, respectively. [d] Yields are with respect to use of DMSO, DMF, toluene as the solvents, respectively.

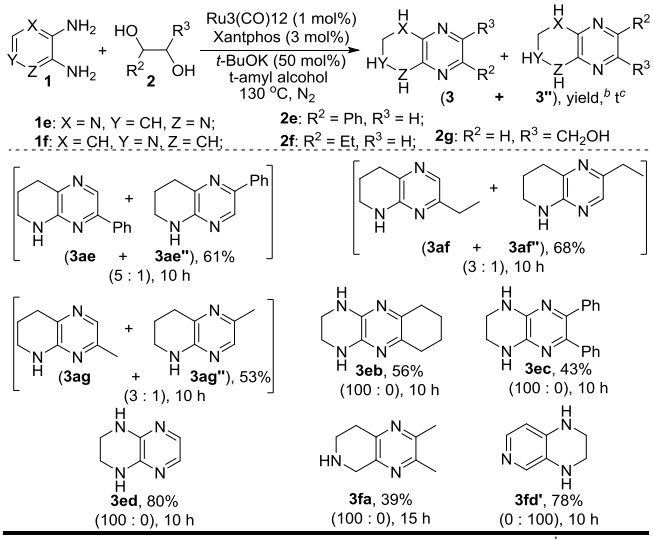


Scheme 4 Synthesis of fused-pyrazines. [a] Isolated yield [b] Reaction time

With the optimal reaction conditions established, we then examined the generality of the synthetic protocol. First, the reactions of pyridine-2,3-diamines (**1a**, **1b** and **1c**) with three symmetrical vicinal diols **2** (**2a**, **2b** and **2c**) were tested. As shown in Scheme 4, all the reactions proceeded smoothly and furnished the products in moderate to excellent yields upon isolation (**3aa**-**3cc**), and the transfer hydrogenation occurred exclusively on the sterically less-hindered pyridyl ring, indicating that the steric factor

plays a crucial role in determining the reduction selectivity. To further prove this conclusion, we performed the reactions of ethylene glycol **2d** with three pyridine-2,3-diamines (**1a**, **1c** and **1d**). The reaction of **1a** gave two region-isomers in near 3 : 2 ratio (**3ad**, **3ad'**), whereas **1c** afforded the isomers in a ratio of 12 : 88 (**3cd**, **3cd'**). As expected, imidazol substituted diamine **1d** yielded a single product **3dd'** in 41% yield, and the transfer hydrogenation occurred only on the newly formed pyrazine ring.

Subsequently, we turned our attention to the utilization of diamines with different substitution patterns in combination with various vicinal diols (Scheme 5). First, the reactions of two unsymmetrical diols (**2e**, **2f**) with **1a** gave two couples of regio-isomers (**3ae** and **3ae''**, **3af** and **3af''**), and the 3-amino group of diamine **1a** is prone to couple with the sterically less-hindered -OH site of vicinal diols. Similar to the results described in Scheme 4, the hydrogen was selectively transfered to the sterically more accessible pyridyl ring. Interestingly, glycerol **2g** could serve as the equivalent of propane-1,2-diol to react with **1a,** giving the regioisomers **3ag** and **3ag''** in a ratio of 3 : 1. Then, pyrazine-2,3-diamine **1e**, also underwent smooth annulative transfer hydrogenation reactions with different diols, affording the desried products in moderate to high yields (**3eb**, **3ec** and **3ed**). Moreover, pyridine-3,4-diamine **1f** could serve as an effective coupling partner to react with diol **2a**, affording a single product **3fa** by reducing the pyridyl ring, whereas the reaction of **1f** and **2d** selectively hydrogenate the newly formed pyrazine ring (**3fd'**).



Scheme 5 Synthesis of various fused-pyrazines. [a] Isolated yield [b] Time

To gain insight into the reaction information, a time-concentration profile of the model reaction under standard conditions was depicted in Figure 1. Diamine **1a** with diol **2a** was converted into **3aa** in a maximum yield (99%) within 5 h. The growth rate of **3aa** and the decreasing rate of **1a** were very fast within the first 2 h and then became slow. During the whole reaction, a coupling adduct 2,3-dimethylpyrido[2,3-b]pyrazine **B-1a2a** was formed rapidly in the first half hour and then was consumed slowly in the remaining 4.5 hours, indicating **B-1a2a** serves as a key reaction intermediate, which is good in agreement with the reaction pathways proposed in Scheme 2, and the reduction of such a coupling adduct is believed to be a rate-determining step.

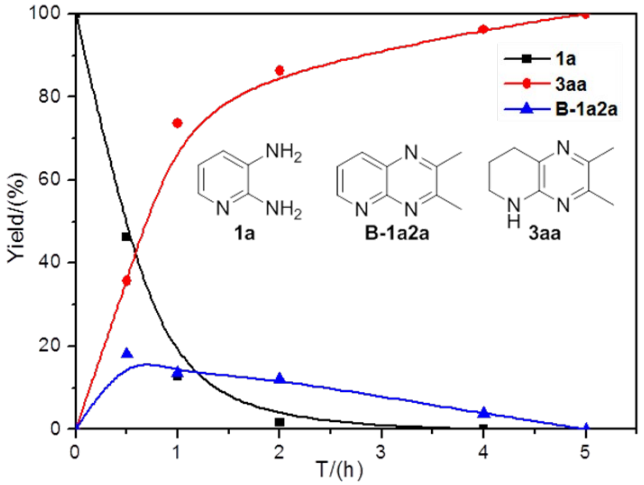
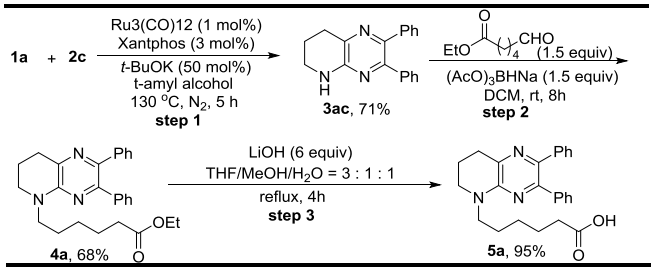


Figure 1 Representative time course of the reaction of **1a** with **2a** to product **3aa** under the standard reaction conditions

Finally, we were interested in applying our synthetic protocol for rapid synthesis of compound **5a**, a highly selective IP receptor agonists used for the treatment of pulmonary fibrosis.[17] As shown in Scheme 6, tetrahydropyrido[2,3-b]pyrazine **3ac** could be efficiently prepared in 71% yield with our synthetic protocol. Then, the *N*-alkylated ester **4a** was synthesized from **3ac** and ethyl 6-oxohexanoate by using $(AcO)_3BHNa$ as a reductant. Ultimately, the ester was converted into carboxylic acid by refluxing **4a** in mixed solvents in the presence of excess LiOH.



Scheme 6 The utility of the new synthetic protocol.

Conclusions

In summary, we have presented a new ruthenium-catalyzed annulative transfer hydrogenation strategy, enabling straightforward access to a wide range of tetrahydro fused-pyrazine derivatives from N-heteroaryl diamines and vicinal diols. Such a synthesis proceeds with unprecedented synthetic effectiveness including high step- and atom-economic efficiency, generation of water as the sole by-product, no need for external high pressure H_2 gas and short reaction time, offering an important basis for the transformation of vicinal diols, a class of bio-mass derived resource, into functionalized products. The application of the method was demonstrated by rapid synthesis of a bioactive molecule.

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