Direct synthesis of functionalized 3-pyrrolidines and 4-piperidines using the borrowing hydrogen methodology

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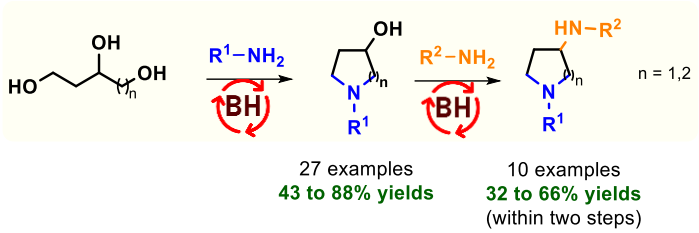
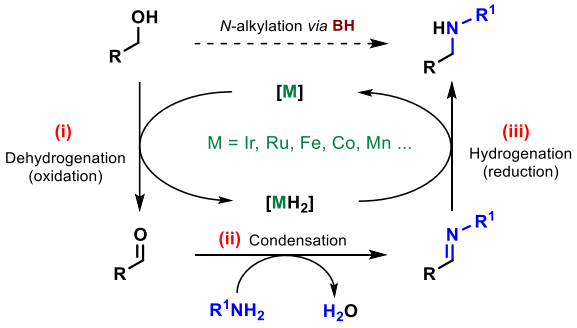


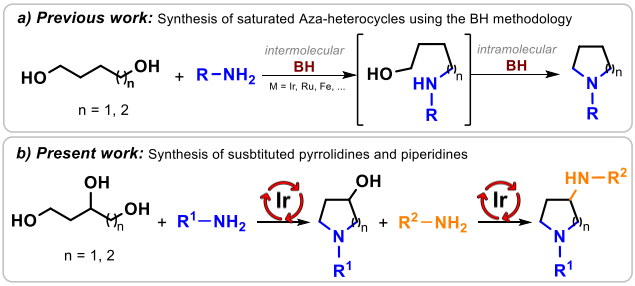
ABSTRACT: The Ir(III)-catalyzed synthesis of 3-pyrrolidinols and 4-piperidinols combining 1,2,4-butanetriol or 1,3,5-pentanetriol with primary amines was carried out. This borrowing hydrogen methodology (BH) was further extended to the sequential diamination of triols leading to aza-pyrrolidines and aza-piperidines.

Saturated aza-heterocycles are identified as key molecules and found in several top-selling small molecule pharmaceuticals and natural alkaloids.[1–5] Among them, piperidines and pyrrolidines are respectively the 6-membered and 5-membered most prevalent nitrogen rings system in U.S. FDA approved drugs.[6] Their preparation from acyclic precursors often involve multi step synthesis,[7] but over the recent years, borrowing hydrogen methodology[8–13] has emerged as a powerful tool for the synthesis of saturated aza-heterocycles from primary amines and diols. The general mechanism of this atom-efficient method is an *in situ* process organized through three different steps: (i) catalytic dehydrogenation of an unreactive alcohol to form the corresponding carbonyl compound (ii) condensation of the so-formed carbonyl compound with an amine to generate *in situ* the corresponding imine (iii) hydrogenation of the imine using the hydrogen stored by the metal catalyst (Scheme 1).



Scheme 1. General mechanism for the amination of alcohol using the BH methodology

The reaction of a primary amine with a diol proceeds through a repeated BH reaction leading to the saturated aza-heterocycle: a first intermolecular process followed by a second intramolecular one (Scheme 2a). Depending on the nature and pattern of the diol, this strategy provided excellent results for the preparation of aza-heterocycles such as piperidines and pyrrolidines. Regarding the transition metal classically used for this transformation, Ir[14–24] and Ru[24–30] are often used as catalyst but Feringa and Barta also showed efficiency of Fe for this reaction.[31] Heterogeneous catalysis using either $NiCuFeO_x$[32] or bimetallic $Pt\text{-}Sn/\gamma Al_2O_3$[33,34] has also been reported.



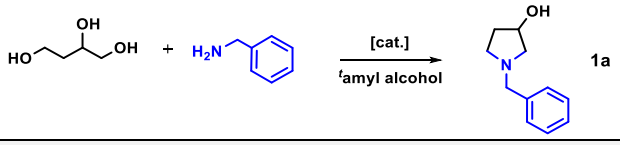
Scheme 2. Previous work and our strategy for the sequential synthesis of substituted pyrrolidines and piperidines using the BH methodology

Switching from diols to triols such as the 1,2,4-butanetriol could allow the straightforward synthesis of 3-pyrrolidinol derivatives which are interesting scaffolds found in bioactive alkaloids[35] and used as intermediates for the synthesis of drugs such as Barnidipine.[36] The reported synthetic strategies often involved two steps either from malic acid,[37–40] *cis*-1,4-dichlorobutene,[35] *N*-substituted 3-pyrroline[41] or natural (–) vasicine.[42] Reaction of dimethylsulfoxonium methylide with epoxysulfonamides[43] as well as enzymatic hydroxylation of *N*-substituted pyrrolidines were also reported.[44] The BH strategy appeared to us as an interesting alternative for the preparation of 3-pyrrolidinols. Considering the enhanced reactivity of primary alcohols in comparison with secondary alcohols, the BH reaction is expected in theory to be chemoselective. Moreover, the unreactive hydroxyl group could then be promoted in a second BH reaction

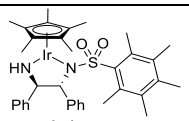
to afford aza-pyrrolidines also used for pharmaceutical purposes.[45–47] Our aims at the outset were twofold: (i) to first investigate the direct synthesis of hydroxy aza-heterocycles using a large scope of amines (ii) to take advantage of the remaining hydroxyl group for further functionalization to form novel CN bonds. Depending of the length of the triol, 3-substituted pyrrolidines along with 4-substituted piperidines could be targeted (Scheme 2b).

We initiated our study by investigating the direct synthesis of 3-pyrrolidinol **1a** using 1,2,4-butanetriol and benzylamine as a model substrate (Table 1). Very recently, Xu and Shen reported the synthesis of 3-pyrrolidinols using the borrowing hydrogen methodology using anilines and an excess of 1,2,4-butanetriol.[48] The first attempt was thus conducted reproducing these reaction conditions (entry 1) using [Ru(*p*-cymene)Cl_2]$_2$, Xantphos and Cs_2CO_3 in toluene with 3Å MS at 120 °C. After 48 h, 25% of the benzylamine was consumed but the expected 3-pyrrolidinol was only observed as trace. When switching to the Knölker complex (entry 2), despite a full consumption of the benzylamine, no product was formed. The dimeric iridium complex [Cp*IrCl_2]$_2$, often used in cooperation with $NaHCO_3$ for the amination of alcohol conducted to the formation of the desired compound **1a** but with a poor yield of 15% (entry 3). Based on our recent publications on the amination of secondary alcohol,[49,50] a cooperative catalysis between an iridium catalyst (5 mol%) and a Brønsted acid (5 mol%) was envisioned. Despite a complete conversion after 24 h, the formation of the product did not exceed 30% (entry 4). Switching the iridium source from [Cp*Ir(*R*,*R*)-(Ts*-dpen)] **Ir-1** to an achiral neutral chloride iridium complex **Ir-2**, the yield increased to 54% (entry 5).

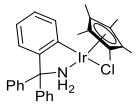
Table 1. Optimization of the aza-heterocyclization of 1,2,4-butanetriol



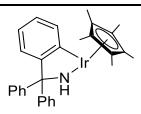
Entry	eq. $BnNH_2$ / Triol	catalyst (mol%) + additive (mol%)	T, t	Yield % - **1a** [a]
1[b,c]	1 : 2	[Ru(*p*-cymene)Cl_2]$_2$ (5) + Xantphos (10) + Cs_2CO_3 (20)	120 °C, 48 h	**<10**
2	1 : 2	Fe Knölker (10) + $MeNO_3$ (20)	100 °C, 24 h	**nr**
3[b,d]	1 : 2	[Cp*IrCl_2]$_2$ (2.5) + $NaHCO_3$ (5)	110 °C, 24 h	**15**
4[c]	1 : 2	**Ir-1** (5) + $(PhO)_2P(O)OH$ (5)	100 °C, 24 h	**29**
5[c]	1 : 2	**Ir-2** (5) + $(PhO)_2P(O)OH$ (5)	100 °C, 24 h	**54**
6[c]	1 : 2	**Ir-2** (5) + KOH (20)	100 °C, 24 h	**66**
7	1 : 2	**Ir-2** (5) + KOH (20)	100 °C, 24 h	**82 (61%)**
8	1 : 2	**Ir-2** (5)	100 °C, 24 h	**62**
9	1 : 2	**Ir-3** (5)	100 °C, 24 h	**80 (80%)**
10[d]	1 : 2	**Ir-3** (5)	100 °C, 24 h	**84**
11[d]	1 : 1.5	**Ir-3** (5)	100 °C, 24 h	**79 (74%)**
12[d]	1 : 1.2	**Ir-3** (5)	100 °C, 24 h	**60**
13[d]	1 : 1.2	**Ir-3** (2)	100 °C, 24 h	**72 (69%)**
14[d]	1 : 1.2	**Ir-2** (2) + ^{t}BuOK (2)	100 °C, 24 h	**84 (78%)**
15[d]	1 : 1.2	**Ir-2** (2) + ^{t}BuOK (2)	100 °C, 7 h	**80**



Ir-1



Ir-2

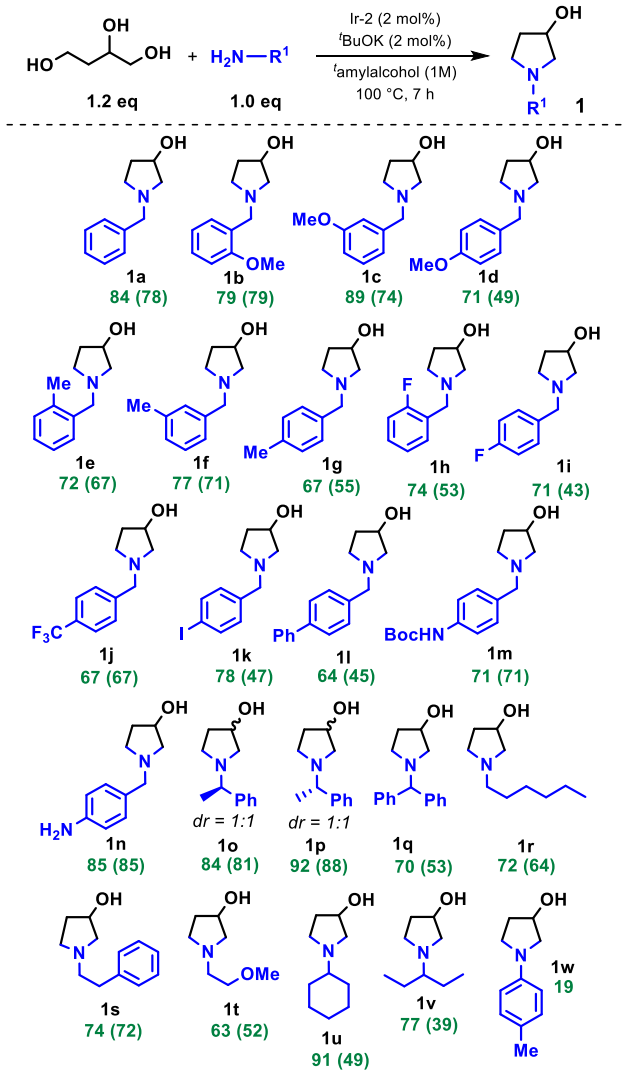


Ir-3

Reaction conditions: 1,2,4-butanetriol, benzylamine, catalyst, additive, ^{t}amyl alcohol [0.3M]. Reactions were performed on 0.4 mmol scale. a) NMR yields were determined by ^{1}H NMR of the crude mixture using 1,3,5-trimethoxybenzene as internal standard. Isolated yields in parenthesis. b) toluene used as solvent. c) 3Å MS were added. d) solvent [1M]. **nr**: no reaction

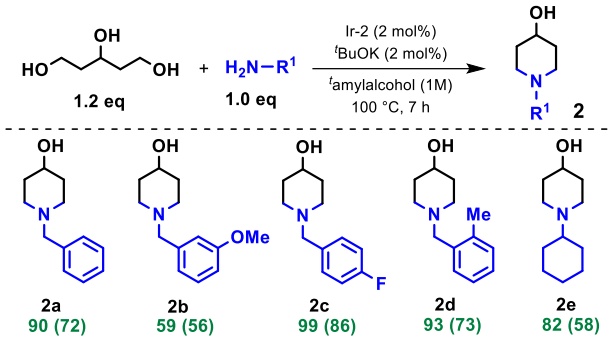
Iridacycle **Ir-2** has also been reported to be efficient for the amination of secondary alcohol in the presence of KOH.[51] We thus performed the reaction using 2 eq. of 1,2,4-butanetriol, 1 eq. of benzylamine, 5 mol% of **Ir-2** and 20 mol% of KOH at 100 °C in ^{t}amyl alcohol in presence of 3Å MS and were delighted to observe the formation of **1a** in 66% yield (entry 6). Moreover, when removing the molecular sieves from the reaction medium, the NMR yield reached 82% (entry 7). In order to understand the importance of the base, the reaction was investigated either using **Ir-2** without any base or using directly the activated 16-electron Iridium complex **Ir-3**.[52] While a lower yield of 62% was obtained using **Ir-2** without any base (entry 8), **Ir-3** led to the formation of the desired product within 80%. We thus assumed that the role of the base was solely to activate the neutral chloride iridium complex **Ir-2** (entry 9). Interestingly, concentration medium could be increased to 1.0 M without any loss of selectivity (entry 10). The main drawback of the reaction remained the use of a large excess (2 eq.) of 1,2,4-butanetriol. Reducing the amount of triol to 1.5 eq. and 1.2 eq. led to the formation of the product within respectively 79 and 60% yields (entries 11 and 12). But, very pleasingly, when decreasing the catalyst loading to 2 mol%, **1a** could be obtained within 72% yield using only a slight excess of triol (1.2 eq. - entry 13). For practical reasons, the active 16-electron complex **Ir-3** was generated *in situ* using **Ir-2** (2 mol%) and ^{t}BuOK (2 mol%) without any loss of reactivity. Indeed, **1a** was formed within 84% NMR yield and isolated in 78% yield (entry 14). Finally, after monitoring the reaction, we noticed that the reaction was completed within 7 hours only (entry 15).

Dioxane, xylene, anisole or 2-MeTHF were also tested as solvent but did not bring better results than ᵗamyl alcohol.



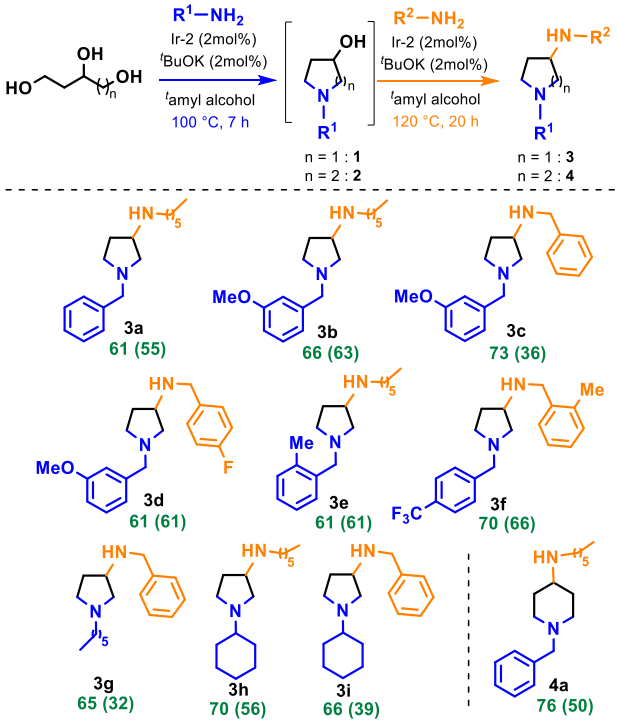
Scheme 1. Preparation of 3-pyrrolidinols 1 from 1,2,4-butanetriol. Isolated yields in parenthesis

With the optimized conditions in hand, the scope of the reaction was first studied with various benzylic amines (scheme 3). The nature of the substituent had no significant impact on their reactivities. Corresponding 3-pyrrolidinols **1a-l** were formed within 64 to 89% NMR yields. The same conclusion was delivered regarding the ortho/meta or para position of the substituent on benzylamine, either with methoxy or methyl substituent. Interestingly, the reaction was also compatible with other amino groups. 4-(Boc-amino) and 4-amino-benzylamines conducted to the formation of **1m** and 1**n** within excellent yields of 71 and 85% respectively. No amination of the aromatic amino group was observed in the crude ^{1}H NMR. This observation was in accordance with the poor reactivity of *p*-toluidine: **1w** was formed within less than 20% NMR yield. More hindered benzylamines such as α-methylbenzylamines (*R* and *S*) and benzhydrylamine were also investigated without a significant drop on the reactivity. Primary aliphatic amines could also be condensed efficiently affording **1r-v** within 63 to 91% NMR yields. Lower isolated yields could often be explained by difficulties addressed during the purification. A slight modification was considered, switching the 1,2,4-butanetriol to 1,3,5-pentanetriol, offering the possibility to prepare 4-piperidinols. The methodology was easily transferable and compounds **2a-e** were formed in 59 to 99% NMR yields and isolated within 56 to 86% yields (Scheme 4).



Scheme 4. Preparation of 4-piperidinols 2 from 1,3,5-pentanetriol. Isolated yields in parenthesis

Inspired by our first results, we next envisioned the further functionalization of the remaining hydroxyl group *via* a second BH reaction leading to novel aza-heterocycles. In the literature, Takacs *et al.* reported the sequential diamination of diols only after prior isolation of the amino alcohol intermediate.[30] We thus decided to tackle independently the amination of pure 1-benzylpyrrolidin-3-ol **1a** as a model reaction. Compound **1a** was subjected to reaction with *n*-hexylamine using 5 mol% of **Ir-2** and 5 mol% of ᵗBuOK at 120 °C in ᵗamyl alcohol for 20 h affording the desired *N*-hexyl-1-benzylpyrrolidin-3-amine **3a** within 81% NMR yield. Decreasing the catalyst loading to 2 mol% provided similar results: **3a** was obtained in 88% NMR yield. Showing the feasibility of the amination reaction of **1a**, the sequential reaction without purification of the intermediate was thus undertaken and **3a** was isolated within 55% yield (Scheme 5).



Scheme 5. Scope of few 3-azapyrrolidines in the optimized sequential sequence. Isolated yield under brackets

Sequential diamination reactions, combining independently and alternatively benzylic and aliphatic amines either in the first or second step were investigated (Scheme 5). 3-Azapyrrolidines **3a-i** were obtained in yields ranging from 61 to 73% over two steps. This methodology was also successfully applied to the synthesis of the 4-azapiperidine **4a** using benzylamine, 1,3,5-pentanetriol and hexylamine.

In summary, we developed an efficient iridium(III) catalyzed amination of triols with various benzylic and aliphatic amines. A family of 22 pyrrolidinols (**1a-v**) and 5 piperidinols (**2a-e**) were synthesized with yields ranging from 39 to 88%. Taking advantage of the third hydroxyl group, the methodology was further extended to the sequential diamination of triols leading to novel aza-pyrrolidines (**3a-i**) and aza-piperidine (**4a**).

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