



Communication

Ruthenium catalyzed amination cyclization of 1,2,4-butanetriol with primary amines: A borrowing hydrogen strategy for 3-pyrrolidinol synthesis



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ABSTRACT

A ruthenium based catalytic system ([Ru(p-cymene)Cl₂]₂/XantPhos with substoichiometric Cs₂CO₃) has been established to effectively achieve the first direct amination cyclization of 1,2,4-butanetriol with primary aromatic amines. The product of this sustainable hydrogen autotransfer process is valuable N-aryl-3-pyrrolidinol.

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Alcohol amination through the concept of borrowing hydrogen (BH) or hydrogen autotransfer (HA) mediated by homogenous metal catalysis [1], pioneered by Grigg [2] and Watanabe [3] groups, advanced by the groups of Beller [4], Fujita and Yamaguchi [5], Williams [6], Yus [7], Kempe [8], Milstein [9], Deng [10], Xu [11], Shi [12] and others [13], is emerging as an invaluable strategy because it provides a clean and atom economic access [14] to aliphatic amines, a class of important bulky chemicals. This overall redox-neutral process begins with hydrogen transfer from alcohol to metal catalyst [M] to generate related carbonyl compound and metal-hydride complex [MH], condensation of the nascent aldehyde or ketone RCOR' with primary amine R''NH₂ gives imine intermediate which is reduced to alkylated amine by the previously formed metal-hydride [MH] to complete a catalytic circle with water as the sole byproduct (Scheme 1). The almost ideal green methodology has drawn great attention from industry and swiftly found elegant application in pharmaceutical manufacture [15].

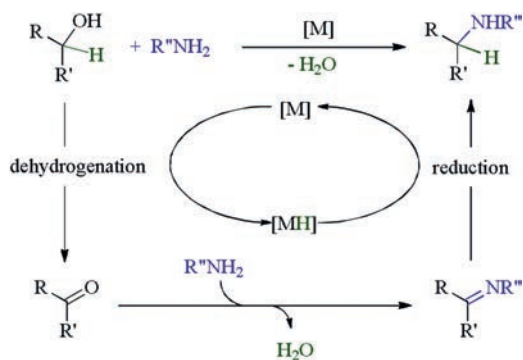
Simple N-heterocycles can also be made from primary amines through two fold hydrogen autotransfer amination of appropriate diols (Scheme 2a). Butanediol, pentanediol, hexanediol and even

heptanediol were all reported for this purpose to achieve corresponding pyrrolidines, piperidines, azepanes and azocanes in various catalytic systems [16]. N-Substituted morpholine and piperazine were accomplished from related diols and primary amines as well [6b,17]. Notably, the formation of 2-methyl pyrrolidine/piperidine **3** demonstrates that diols bearing one secondary OH group can also participate in this BH process [18]. Based on these precedents, we envisioned it would be remarkable if triols are feasible for this reaction, because precious aliphatic N-heterocycles hydroxylated on the saturated ring would be directly formed. The additional free hydroxyl group could cause huge challenge as it might also involve in and therefore complicate the reaction. Here we would like to report our initial findings at this direction (Scheme 2b).

3-Pyrrolidinol is a privileged N-heterocycle that finds significant applications in pharmaceutical industry [19]. Its preparation involves multiple-step transformations and/or hazard reagents [20], and an efficient and clean process is highly appreciated. We therefore set out to explore the BH alkylation cyclization of primary amine with 1,2,4-butanetriol, which would leading to N-substituted 3-pyrrolidinol derivatives. Realizing that transition metal catalyst plays a key role in hydrogen autotransfer reactions, we started this research with catalyst evaluation. A mixture of aniline **5a** with 2 equiv. butanetriol **6a** in reflux toluene was used as model reaction to evaluate metal complexes easily accessible in our laboratory in catalytic amount (5 mol%) (Table 1, for

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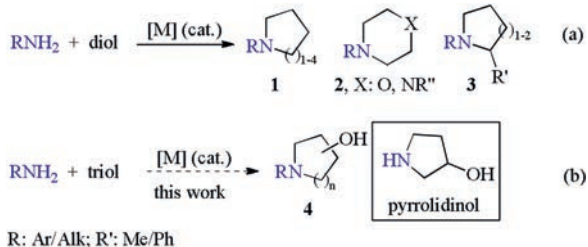
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Scheme 1. Redox-neutral amination via borrowing hydrogen or hydrogen autotransfer protocol.

experimental details please see Supporting information). Iridium complex [IrCp*Cl₂]₂, [Ir(cod)Cl₂]₂ and IrCp*Pro [16e] exhibited no catalytic activity as no consumption of starting aniline occurred (entries 1–3). Although iron cyclone complex FeCyn(CO)₃, upon activation by oxidant Me₃NO, catalyzed the BH amination of aniline with benzyl alcohol efficiently [21], the same catalyst combination lost its activity completely in current triol amination (entry 4). [RuCp*Cl₂]₂ and Ru(bby)₃Cl₂/dppf also failed to promote the desired double *N*-alkylation (entries 5 and 6). To our delight, catalytic amount of RuHCl(CO)(PPh₃)₃/XantPhos combination was able to realize the target reaction in the presence of 20 mol% Cs₂CO₃ and cyclic aminoalcohol **4a** was achieved in 58% isolated yield after 48 h reaction and [Ru(*p*-cymene)Cl₂]₂ delivered similar outcomes with K₂CO₃ as the base (entries 7 and 8). Bidentate phosphorines dppf, BINAP and dppbz were much inferior to XantPhos as ligand for [Ru(*p*-cymene)Cl₂]₂ (entries 9–11), and monophosphine ligands XPhos and DavePhos behaved even worse (entries 12 and 13). These observations underline the importance of ligand effect on this reaction. Using Et₃N or *t*-BuOK as the base instead resulted in decreased yields (entries 14 and 15), whereas Cs₂CO₃ improve the yield of **4a** to 81% under the identical conditions (entry 16). Introduction of 10 mol% AgNO₃ as additive did not improve but unexpectedly ruined the reaction (entry 17). Dioxane as reaction medium worked similarly well as toluene (entry 18). It was found that both 1.5 equiv. and 2.5 equiv. butanetriol provided lower yield than 2.0 equiv. triol could provide (entries 19–20). A slower reaction accompanied by a lower yield (53%) was observed when the catalyst load was decreased to 2 mol% (entry 21). It was worthy to note that in most cases where low yields were obtained, the starting aniline was not consumed completely. Obviously, the conditions used in entry 16 were the optimal ones and were set as the standard for next studies.

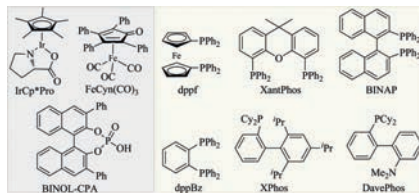
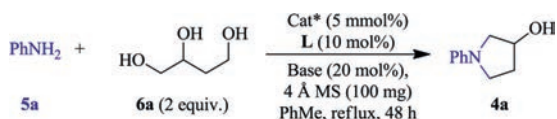
With the optimal and standard conditions in hand, the reaction of a variety of aryl amines with butanetriols **6a** were carried out (Scheme 3). *N*-Aryl-3-pyrrolidinols **4b–4e** were produced in mediate to high yields from the two fold *N*-alkylation reaction of



R: Ar/Alk; R': Me/Ph

Scheme 2. Borrowing hydrogen strategy for the synthesis of (a) *N*-heterocycles from diols and (b) hydroxylated *N*-heterocycles from triols.

Table 1
Conditions optimization.^a



Entry	Cat*	Ligand	Base	Yield (%) ^b
1	[IrCp*Cl ₂] ₂	–	NaHCO ₃	0
2 ^c	[Ir(cod)Cl ₂] ₂	BINOL-CPA	–	0
3	IrCp*Pro	–	–	0
4 ^d	FeCyn(CO) ₃	–	–	0
5	[RuCp*Cl ₂] ₂	–	NaHCO ₃	0
6	Ru(bby) ₃ Cl ₂	dppf	K ₂ CO ₃	0
7	RuHCl(CO)(PPh ₃) ₃	XantPhos	Cs ₂ CO ₃	58
8	[Ru(<i>p</i> -cymene)Cl ₂] ₂	XantPhos	K ₂ CO ₃	60
9	[Ru(<i>p</i> -cymene)Cl ₂] ₂	dppf	K ₂ CO ₃	17
10	[Ru(<i>p</i> -cymene)Cl ₂] ₂	BINAP	K ₂ CO ₃	17
11	[Ru(<i>p</i> -cymene)Cl ₂] ₂	dppbz	K ₂ CO ₃	26
12	[Ru(<i>p</i> -cymene)Cl ₂] ₂	XPhos	K ₂ CO ₃	0
13	[Ru(<i>p</i> -cymene)Cl ₂] ₂	DavePhos	K ₂ CO ₃	5
14	[Ru(<i>p</i> -cymene)Cl ₂] ₂	XantPhos	Et ₃ N	35
15	[Ru(<i>p</i> -cymene)Cl ₂] ₂	XantPhos	<i>t</i> -BuOK	40
16	[Ru(<i>p</i> -cymene)Cl ₂] ₂	XantPhos	Cs ₂ CO ₃	81
17 ^e	[Ru(<i>p</i> -cymene)Cl ₂] ₂	XantPhos	Cs ₂ CO ₃	34
18 ^f	[Ru(<i>p</i> -cymene)Cl ₂] ₂	XantPhos	Cs ₂ CO ₃	74
19 ^g	[Ru(<i>p</i> -cymene)Cl ₂] ₂	XantPhos	Cs ₂ CO ₃	34
20 ^h	[Ru(<i>p</i> -cymene)Cl ₂] ₂	XantPhos	Cs ₂ CO ₃	65
21 ⁱ	[Ru(<i>p</i> -cymene)Cl ₂] ₂	XantPhos	Cs ₂ CO ₃	53

^a Conditions: **5a** (0.5 mmol), **6a** (1.0 mmol), Cat* (5 mol%), ligand (10 mol%), base (20 mol%), toluene (2.0 mL), 4 Å MS (100 mg), N₂, reflux, sealed tube, 48 h.

^b Isolated yield.

^c BINOL-CPA (5 mol%) as co-catalyst.

^d Me₃NO (10 mol%) as additive.

^e AgNO₃ (10 mol%) as additive.

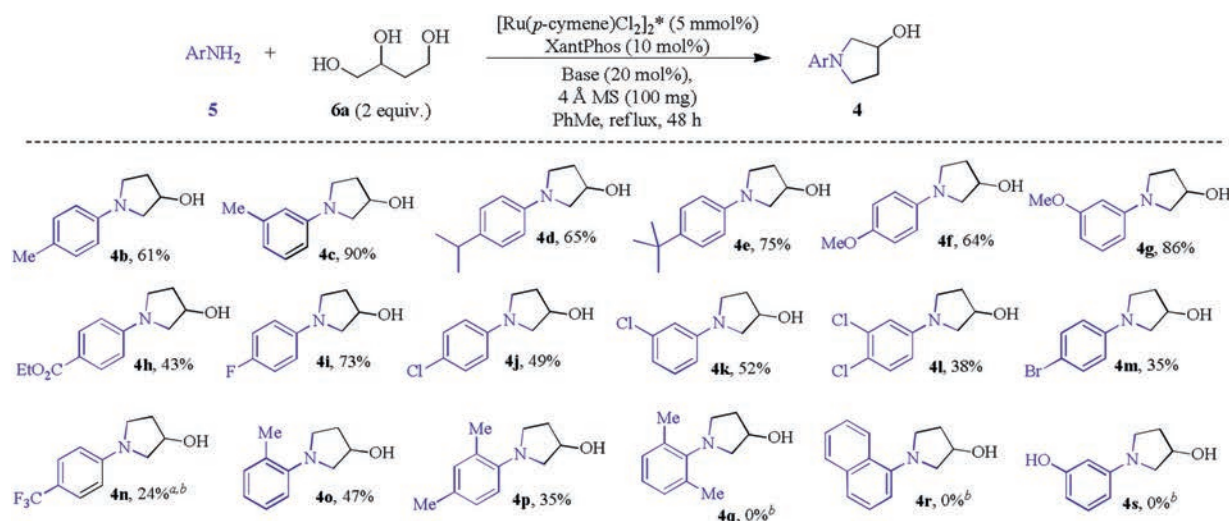
^f dioxane instead of toluene as solvent.

^g 1.5 equiv. triol was used.

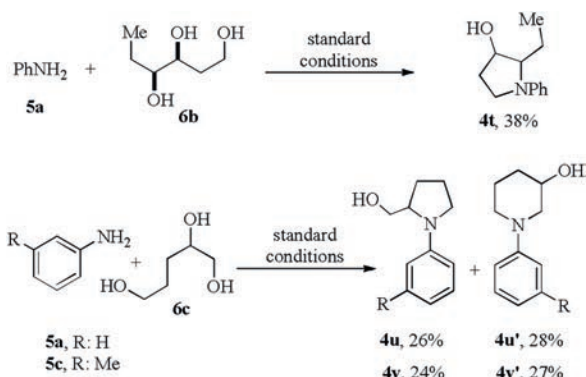
^h 2.5 equiv. triol was used.

ⁱ 2 mol% catalyst was used instead.

corresponding *para* or *meta* alkyl anilines. *para* and *meta* methoxyl anilines were smoothly transformed into **4f** and **4g** in 64% and 86% yield respectively with complete conversion in 48 h. *p*-CO₂Et aniline was also feasible substrate and was successfully converted to **4h**, albeit in a slightly decreased yield of 43%. The reaction of 4-F aniline proceeded smoothly to provide pyrrolidinol **4i** in 73% yield. *N*-Aryl-3-pyrrolidinols **4j–4m** with Cl or Br substitution were also achieved in moderate yields indicating that these two venerable halide substitutions on the aniline are compatible with this transition metal catalyzed process in reflux toluene although relative complicated reaction mixtures were observed. Interestingly, *p*-CF₃ **5n** aniline was partially transformed into **4n** (24% yield) with ca. 70% recovery of starting aniline even after 3 days reaction. The reactions to form **4o** and **4p** were pretty slower than previous ones and significant amount of starting anilines **5o** and **5p** remained after 48 h. It can reasonably be attributed to the steric effects and was further confirmed by the entire failure of reactions of the triol with 2,6-dimethylaniline **5q** and 1-naphylamine **5r**. *m*-OH aniline **5s** was also inert for this reaction, apparently the phenolic OH deactivated the catalytic system.



Scheme 3. Amination of 1,2,4-butanetriol with primary arylamines. Reaction conditions: **5b–q** (0.5 mmol), **6a** (1.0 mmol), [Ru(*p*-cymene)Cl₂]₂ (5 mol%), XantPhos (10 mol%), C₂S₂O₃ (20 mol%), toluene (2.0 mL), 4 Å MS (100 mg), N₂, reflux, sealed tube, 48 h. Isolated yield. ^a72 h. ^bStarting anilines was recovered.



Scheme 4. Amination cyclization of other two triols.

Next, to further test the potential of this catalytic system, 1,3,4-hexanetriol **6b** was submitted to the standard conditions with aniline **5a** as the alkylation acceptor. Pleasingly, 2-ethyl pyrrolidinol **4t** was also produced, albeit in only 38% yield (Scheme 4, top). When 1,2,5-pentanetriol **6c** was used as the alkylating agent, the same reaction with aniline **5a** gave rise to a pyrrolidine/piperidine pair **4u/4u'** in good combined yield and equal selectivity. Analogous results were obtained for *m*-Me aniline **5c** (Scheme 4, bottom). Related experiment details, characteristics of compounds, copies of NMR spectra can be found in Supporting information for this article.

In summary, a ruthenium catalyzed hydrogen autotransfer amination of triols has been developed for 3-pyrrolidinol synthesis. This catalytic system is proved to be compatible with the additional free hydroxyl group. A variety of substituted anilines are successfully transferred into highly valuable 3-pyrrolidinol derivatives from abundant and cheap 1,2,4-butanetriol with high efficiency. This extremely environmental benign and low-cost protocol would stimulate further investigations.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ccl.2019.05.027>.

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