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# Borrowing Hydrogen C-alkylation with secondary saturated heterocyclic alcohols

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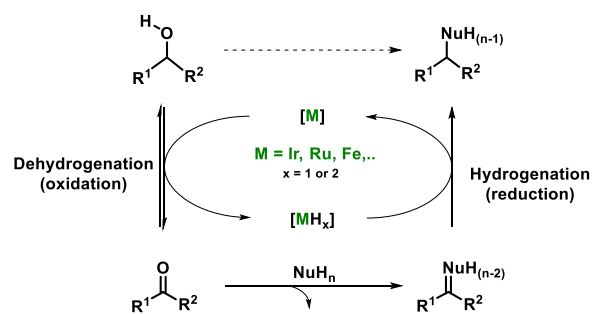
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## Abstract:

The borrowing hydrogen methodology (BH) has emerged as a powerful tool for the rapid construction of C-C bonds, offering a greener alternative to traditional multi-step syntheses. This methodology involves the activation of inactivated alcohols followed by condensation or aldolization, ultimately leading to the regeneration of the saturated product. Herein, we report the C-alkylation of a hindered ketone with challenging secondary saturated heterocyclic alcohols. Our study encompasses the optimization of reaction condition using either iridium or ruthenium catalyst and exploration of substrate scope. We demonstrate the efficient synthesis of substituted pyrrolidines and piperidines directly from a triol precursor, showcasing the versatility of this methodology. Moreover, we illustrate the post-functionalization of BH products, significantly broadening their chemical utility.

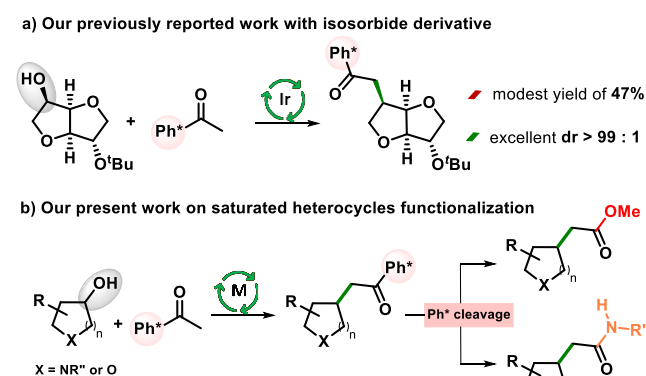
## Introduction:

The facile and rapid construction of C-N or C-C bonds using borrowing hydrogen methodology (BH) has emerged as a powerful tool in recent decades. The versatility of borrowing hydrogen methodology has led to its widespread application across various areas of organic synthesis, including medicinal chemistry, natural product synthesis, and materials science.<sup>1-6</sup> This cascade reaction using inactivated alcohols (primary or secondary) allows the saving of chemicals, solvents, time, gives water as the only by-product and is known as a greener alternative to classical multi-step syntheses. The reaction sequence proceeds as follows: i) Activation of the corresponding alcohol (oxidation to aldehyde or ketone depending on the nature of the alcohol) where the metal catalyst temporarily borrows hydrogens without changing oxidation state (historically ruthenium, rhodium and iridium metal catalysts were used and more recently iron, cobalt or even manganese).<sup>7-12</sup> ii) Condensation or aldolization depending on the nucleophile used where water is released as the only by-product. iii) Finally, the hydrogen borrowed from the dehydrogenation step is given back to generate the saturated product (**Scheme 1**). One of the key advantages of borrowing hydrogen methodology is its atom economy, as it utilizes the substrate as a hydrogen donor in the bond-forming process, leading to reduced waste generation. Additionally, BH reactions often proceed under mild conditions, allowing for the incorporation of sensitive functional groups and enhancing the overall efficiency and selectivity of the synthetic process.



After preliminary investigations on the direct C-alkylation of pentamethyl acetophenone (Ph\* ketone - **1**) with isosorbide,<sup>13</sup> a cyclic diol produced from D-sorbitol, we envisioned to extend this

methodology to a wide range of challenging secondary saturated heterocyclic alcohols. Heterocyclic compounds, especially those containing saturated rings, often pose synthetic challenges due to their structural complexity and the presence of functional groups that can be sensitive to harsh reaction conditions. However, leveraging BH methodology can offer a solution to overcome these challenges and enable the efficient synthesis of such compounds. Despite the general success in  $\alpha$ -alkylation of hindered ketones with primary alcohols<sup>14,15</sup> and secondary alcohols such as 1-phenylethanol, cyclohexanol or even more hindered adamantanol and cholesterol,<sup>16-22</sup> we noticed that secondary saturated heterocycles were yet under-explored. To our knowledge, only two examples are reported in the literature. 1-Benzylpiperidin-4-ol was successfully engaged in C-alkylation reaction using Ph\* ketone in the presence of [Cp\*IrCl<sub>2</sub>]<sub>2</sub> and NaO<sup>t</sup>Bu in toluene at 85 °C for 24 h.<sup>16</sup> BH reaction was also reported with tetrahydro-2H-thiopyran-3-ol and mesityl ketone using a Knölker's iron complex in presence of NaO<sup>t</sup>Bu in reflux of toluene for 24 h.<sup>18</sup> Despite excellent yields of 86% and 83% respectively, in both cases, an excess of secondary alcohol (1.5 eq.) was required. Given the importance of saturated nitrogen<sup>23</sup> and oxygen<sup>24-26</sup> containing heterocycles as bioactive molecules, further investigation of simple and efficient methods for their synthesis and functionalization is warranted. Beyond the functionalization of saturated heterocycles from their corresponding alcohols, we investigated the sequential synthesis of substituted pyrrolidines and piperidines directly from a triol. Finally, we utilized Donohoe's methodology to cleave Ph\* moiety *via* a *retro*-Friedel-Crafts acylation reaction<sup>27</sup> to accede novel ester and amide compounds (**Scheme 2**).



**Scheme 2. Functionalization of heterocyclic scaffolds via the BH methodology**

This approach would provide thus a versatile sequence for the synthesis of valuable molecules with potential applications in drug discovery, functional materials, and beyond.

## Results and discussion:

Ph\* ketone **1** and a simple secondary heterocyclic alcohol, 3-hydroxytetrahydrofuran were chosen for our initial investigations (Table 1). The first attempt was performed under classical BH reaction conditions<sup>16</sup> using alcohol as limiting reagent (entry 1): Ph\* ketone (**1**, 1.1 eq.), 3-hydroxytetrahydrofuran (**2**, 1.0 eq.), [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (5 mol% - i.e. 10% of metal), NaOtBu (2.0 eq.) in toluene at 85 °C. After 24 h, the conversion of **2** reached 91% and C-C product **3a** was obtained within 54% NMR yield (entry 1). Increasing the reaction temperature to 120 °C led to complete conversion of the secondary alcohol and **3a** was isolated in quantitative yield (entry 2). The reaction time was reduced to 6 h but despite an excellent conversion of **2**, the NMR yield decreased to 73% (entry 3). Entry 4 showed that the use of a hindered ketone such as **1** was crucial for preventing self-condensation of the substrate. Indeed, the use of acetophenone under the same reaction conditions led to the formation of the corresponding C-C product within 48% NMR yield and the presence of 1,3-diphenylbutan-1-one was detected as by-product. Given that 10 mol% of Ir metal were used (5 mol% of the dimeric species), the catalyst loading was reduced in entries 5-7 and the best compromise was the use of 3 mol% of [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (i.e. 6 mol% of Ir) where 85% of **3a** was detected by NMR (entry 5). Other catalysts were tested with the same metal catalyst loading (≈ 5 mol%).

**Table 1. Optimization of the C-C coupling with Ph\* ketone **1** and 3-hydroxytetrahydrofuran **2****

Entry	Catalyst (mol%)	T (°C), t	Conv. <b>2</b> (%) <sup>[a]</sup>	yield <b>3a</b> (%) <sup>[a]</sup>
1	[Cp*IrCl <sub>2</sub> ] <sub>2</sub> (5)	85, 24 h	91	54 (30)
2	[Cp*IrCl <sub>2</sub> ] <sub>2</sub> (5)	120, 24 h	100	99 (99)
3	[Cp*IrCl <sub>2</sub> ] <sub>2</sub> (5)	120, 6 h	95	73 (69)
4 <sup>b</sup>	[Cp*IrCl <sub>2</sub> ] <sub>2</sub> (5)	120, 24 h	100	48 (32) <sup>b</sup>
5	[Cp*IrCl <sub>2</sub> ] <sub>2</sub> ( <b>3</b> )	120, 24 h	<b>94</b>	<b>85 (63)</b>
6	[Cp*IrCl <sub>2</sub> ] <sub>2</sub> (2)	120, 24 h	81	74 (64)
7	[Cp*IrCl <sub>2</sub> ] <sub>2</sub> (1)	120, 24 h	80	(70)
8	<b>Ir-1</b> (5)	120, 24 h	<b>100</b>	<b>96 (71)</b>
9	<b>Ir-1</b> (1)	120, 24 h	79	61
10	<b>Ir-2</b> (5)	120, 24 h	100	88
11	<b>Ru-MACHO</b> (5)	120, 24 h	<b>100</b>	<b>84 (66)</b>
12	Mn-MACHO (5)	120, 24 h	100	0

[Cp\*Ir(Ts\*-dpen)](R,R) Ir-1

Iridacycle Ir-2

Ru-MACHO

Mn-MACHO

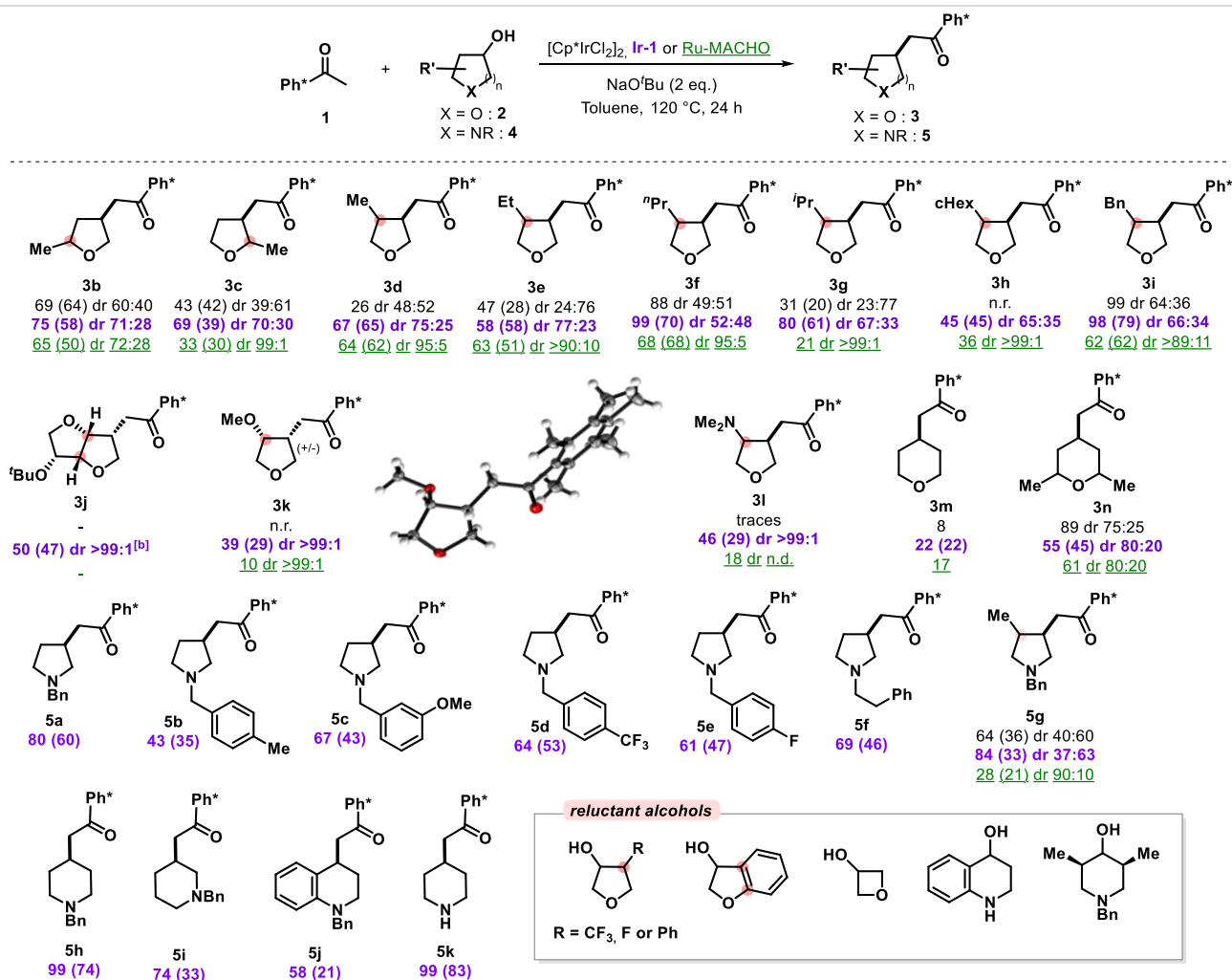
**Reaction conditions:** **1** (1.1 eq.), **2** (1.0 eq.), catalyst, NaOtBu (2 eq.) in toluene [1M] under heating (85 to 120 °C). <sup>a</sup> Conversions and NMR yields were measured with 1,3,5-trimethoxybenzene as internal standard; isolated yields are given under brackets. <sup>b</sup> Reaction performed with acetophenone instead of Ph\* ketone affording the corresponding C-C product.

The use of Noyori's type catalyst **Ir-1** led to the formation of the desired alkylated product within 96% NMR yield and 71% isolated yield (entry 8).

Gratifyingly, the reaction could be carried out on a larger scale (from 0.25 mmol for the optimization to 2.8 mmol) without altering the yield (81% detected by NMR and 71% of **3a** isolated). Reducing the catalyst loading to 1 mol% caused a drop of the conversion to 79% (entry 9). Achiral iridacycle **Ir-2** also proved to be an efficient catalytic system for the BH transformation with complete conversion of **2** and 88% of the product detected by NMR (entry 10). Ruthenium catalysts were also envisioned for this transformation. A complete conversion was observed using a ruthenium complex bearing PNP-ligand (**Ru-MACHO**) and 84% of the desired product **3** was detected by NMR (entry 11). On the contrary, the non-noble Mn-MACHO catalyst did not exhibit any efficiency for BH alkylation. Indeed, despite a full conversion of **2**, no product was formed and only degradation was observed (entry 12). In summary, different reaction conditions proved very effective for this BH transformation (entries 5, 8 and 11 notably). As the excellent reactivity of 3-hydroxyTHF toward alkylation was not altered by the real tuning of metal/ligand, we set out to investigate the scope of the reaction with various saturated heterocycles using these three sets of conditions. The scope of the reaction was first investigated on THF scaffold (**Scheme 3**). Most of the starting materials were synthesized as diastereomerically pure compounds (*trans*-products) (see SI). As previously observed with isosorbide derivatives,<sup>13</sup> substitution on the THF ring could impact either the reactivity and the diastereoselectivity of the reaction. Alkyl substitutions on C2, C4 and/or C5 positions were thus examined. A series of  $\beta$ -alkylated ketones **3b-3f** were isolated in good yields ranging from 39 to 70% (NMR yields: 58 to 99%) using **Ir-1** as catalyst. Whatever the position and the length of the alkyl group, moderate dr ranging from 52:48 to 77:23 were observed. Slightly more hindered groups such as <sup>t</sup>Pr, cyclohexyl and benzyl did not impact the reactivity: **3g**, **3h** and **3i** were obtained within 61, 45 and 79% yield respectively. When [Cp\*IrCl<sub>2</sub>]<sub>2</sub> was used as a catalyst, alkylated ketones **3b-3j** were formed in lower yields and with different diastereoselectivities ranging from 64:36 to 23:77. The results obtained with **Ru-MACHO** catalyst were more surprising. Indeed, despite lower yields (30 to 68%), excellent diastereoselectivities > 90:10 were observed for 3-hydroxyTHF bearing alkyl substituent in C2 and C4 positions. In contrast, reaction with 5-methyltetrahydrofuran-3-ol led to the formation of **3b** in similar NMR yield (50 vs 58%) and dr (≈ 70:30) to those obtained with **Ir-1**. Whatever the catalytic system used, no reaction was observed with 3-hydroxyTHF bearing phenyl substituent on C2 position or with a coumaran derivative. We assume that this may be due more to electronic effects than to steric hindrance of the functional group. The influence of heteroatom substituent was also investigated. *Trans*-4-methoxytetrahydrofuran-3-ol was engaged in BH reaction with Ph\*ketone affording the **3k** in low yield but with an excellent diastereoselectivity dr > 99:1. Indeed, **3k** was formed within 39% NMR yield using **Ir-1** and 10% NMR yield using **Ru-MACHO** (no reaction was observed with [Cp\*IrCl<sub>2</sub>]<sub>2</sub>). The *cis*-configuration, established by single-crystal XRD analysis, is in accordance with our investigations on *exo*-protected isosorbide.<sup>13</sup> The reaction with 4-(dimethylamino)tetrahydrofuran-3-ol supported the idea that the heteroatom could influence the excellent stereoselective BH

reaction. Indeed, **3l** was formed within 46% yield and isolated in 29% yield but with an excellent dr > 99:1 using **Ir-1**. Curiously, when using 3-hydroxyTHF bearing fluorinated substituents, the reaction did not operate. While no conversion was observed with 4-(trifluoromethyl) tetrahydrofuran-3-ol, when 4-fluorotetrahydrofuran-3-ol was subjected to optimized BH reaction conditions using **Ir-1**, **3a** was detected by NMR in 33% yield, evidencing the cleavage of the C-F bond. This observation had already been made by Goldman *et al.* when they disclosed the addition of C(sp<sup>3</sup>)-F bond to iridium *via* initial oxidative addition of a C(sp<sup>3</sup>)-H bond.<sup>28</sup> The influence of the *O*-heterocyclic ring size was then evaluated: simple tetrahydropyran **3m** was formed in low yield (8 to 22%) while more hindered 2,6-

dimethyltetrahydropyran-4-ol led to the formation of the alkylated ketone **3n** in better yield ranging from 55 to 89% depending on the catalyst used. Oxetane, on the other hand, was reluctant due to its self-degradation. Overall, the best balance between reactivity and stereoselectivity was achieved with **Ir-1**. Nevertheless, the importance of substituents in C4 position must be kept in mind. The presence of an alkyl group, regardless of its steric hindrance, has no impact on the reactivity, but led to moderate dr ( $\approx$  70:30). Conversely, the presence of a chelating group (methoxy, amino) leads to a significant drop in yield (30-40%) but induces excellent dr (> 99:1).



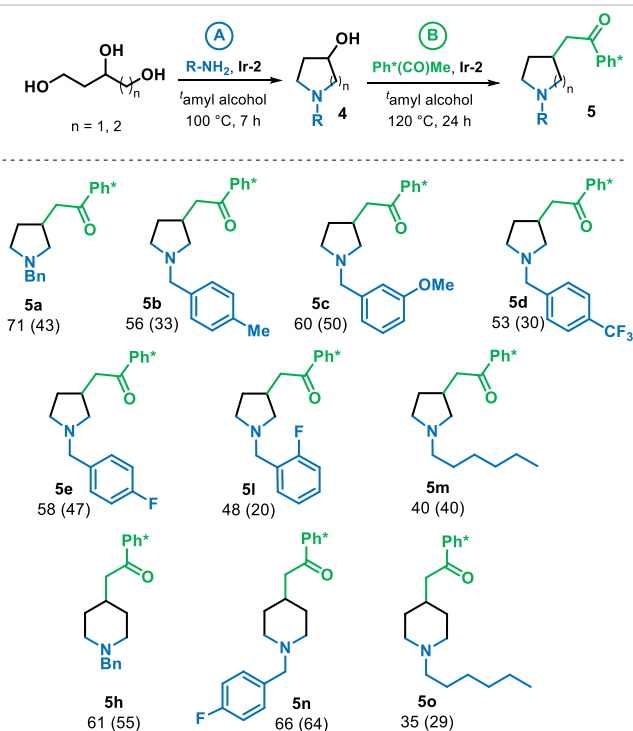
**Scheme 3.** Scope of metal catalyzed borrowing hydrogen C-C coupling with secondary *O*-Heterocyclic alcohols

Reaction conditions: **1** (1.1 eq.), **2** or **4** (1.0 eq.), catalyst (5 mol%), NaOtBu (2 eq.) in toluene [1M] at 120 °C for 24h. NMR yields (%) of **3** are given using 1,3,5-trimethoxybenzene as internal standard and isolated yields (%) are given under brackets.

Gratifyingly, our methodology was successfully extended to *N*-heterocycles using **Ir-1** complex (**Scheme 3**). Various *N*-protected pyrrolidinols were engaged in BH transformation with Ph\* ketone **1** leading to compounds **5a-g** within 43 to 80% NMR yields. The reaction could tolerate benzylic protecting groups bearing either methyl (**5b**), methoxy (**5c**), trifluoromethyl (**5d**) or fluorine (**5e**), as well as alkyl protecting group (**5f**). The diastereoselectivity was addressed with *N*-benzyl-4-methylpyrrolidin-3-ol **4g** using the three optimized catalytic systems. Interestingly, [Cp\*IrCl<sub>2</sub>]<sub>2</sub> and **Ir-1**

exhibited similar reactivities and selectivities: **5g** was formed within 64 to 84% NMR yields<sup>29</sup> and dr around 40:60. And, as observed with THF scaffolds, **Ru-MACHO** led to a drop of reactivity (28% NMR yield) but an improved dr of 90:10. Finally, six-membered ring such as piperidines were targeted and  $\beta$ -alkylated ketones **5h-5j** were obtained in good NMR yields (74 to 99% yield).<sup>29</sup> Pleasingly, unprotected piperidinol could be efficiently used without any by-product formation: **5k** was formed quantitatively and isolated within 83%.

In order to extend the scope of *N*-heterocyclic compounds we took advantage of our recent work on the cyclization of triols (1,2,4-butanetriol and 1,3,5-pentanetriol) with various benzylic and aliphatic amines.<sup>30</sup> By leveraging the cyclization chemistry of triols with benzylic and aliphatic amines, we could efficiently access a diverse range of *N*-heterocycles with tailored structural and functional properties. Indeed, the direct annulation of triols using the BH methodology is a very attractive strategy to accede *N*-protected heterocycles **4** bearing a free hydroxyl group. The sequential triol annulation with amines followed by *C*-alkylation was thus envisioned (**Scheme 4**). The first attempt was carried out under previously reported conditions<sup>30</sup> using benzylamine (1.0 eq.), 1,2,4-butanetriol (1.2 eq.), Ir-2 (2 mol%) and KO<sup>t</sup>Bu (2 mol%) in *t*-amyl alcohol (1 M) at 100 °C for 7 h (**Scheme 4, A**). After removal of the excess of triol by an aqueous workup, the crude was directly engaged in *C*-alkylation reaction using slightly modified reaction conditions: Ph\* ketone (1, 1.1 eq.), Ir-2 (2 mol%), KO<sup>t</sup>Bu (2.0 eq.) in *t*-amyl alcohol at 120 °C. (**Scheme 4, B**). Pleasingly, after 24 h, complete conversion was achieved and **5a** was formed within 71% within 2 steps. Using various benzylic amines, the corresponding ketones (**5b-e**, **5l**) were formed within 48 to 60% NMR yield and isolated in 20 to 50% over two steps. Similar range of yield (40%) was obtained using an aliphatic amine (**5m**). The reaction was successfully applied to the synthesis of piperidines using 1,3,5-pentanetriol: compounds **5n** and **5o** were respectively formed with 66% and 35% overall NMR yields and isolated in 64% and 29% yield.

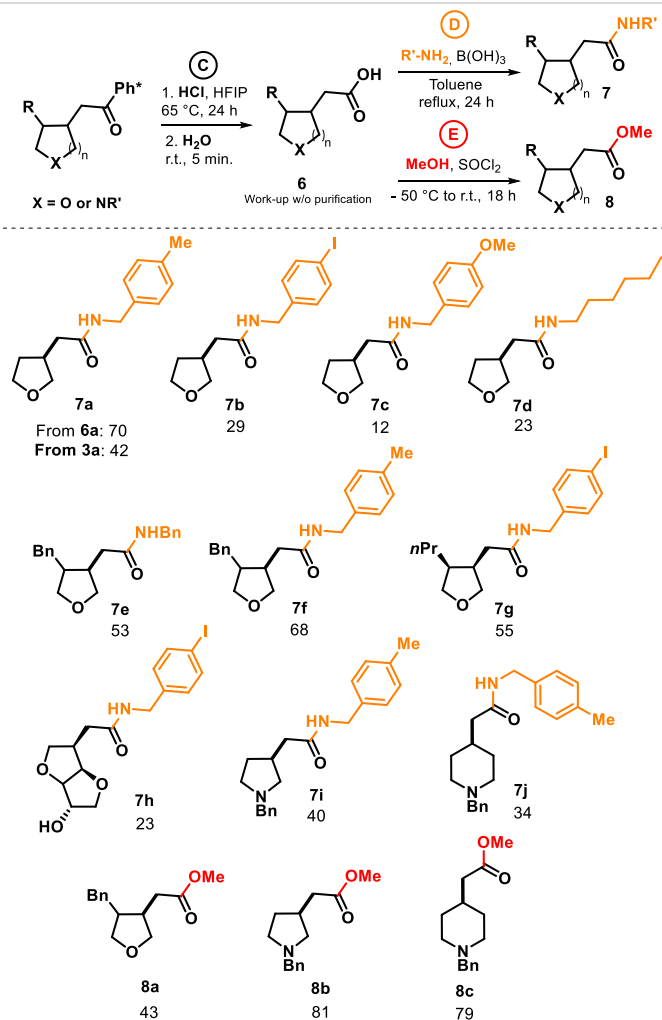


#### Scheme 4. Sequential C-N / C-C transformations

Reaction conditions: (A) triol (1.2 eq.), R-NH<sub>2</sub> (1.0 eq.), KO<sup>t</sup>Bu (2 mol%), Ir-2 (2 mol%) in *t*-amyl alcohol [1M] at 100 °C for 7 h. (B) Ph\* ketone **1** (1.1 eq.), KO<sup>t</sup>Bu (2.0 eq.), Ir-2 (2 mol%) in *t*-amyl alcohol [1M] at 120 °C for 24 h. NMR yields (%) of **5** are given over two-step using 1,3,5-trimethoxybenzene as internal standard and isolated yields (%) are given under brackets.

As mentioned above, in addition to the effectiveness of this hindered ketone in BH *C*-alkylation with alcohols, the Ph\* group can then be converted to other functional groups, considerably extending its

versatility.<sup>31,32</sup> Donohoe reported the Br<sub>2</sub>- and acid-mediated release of Ph\* *via* a *retro*-Friedel-Crafts acylation followed by in situ reaction with a nucleophile (alcohol, amine, etc.).<sup>16</sup> However, the THF scaffold appeared to be more sensitive and the use of Br<sub>2</sub> at -17 °C in CH<sub>2</sub>Cl<sub>2</sub> led to degradation of the starting material. Ph\* cleavage of **3a** was thus envisioned using smoother conditions. Pleasingly, the use of HCl in highly polar HFIP (hexafluoroisopropanol) led to the formation of acid **6a** with 69% isolated yield.<sup>33</sup>



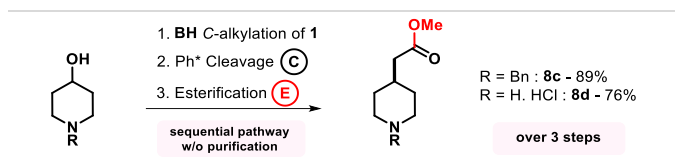
#### Scheme 5. Ph\* cleavage and further functionalization

Reaction conditions: (C) **3** (1.0 eq.), 1.5M HCl in HFIP [0.1M], 65 °C, 24 h then H<sub>2</sub>O, r.t., 5 min. (D) R-NH<sub>2</sub> (1.0 eq.), B(OH)<sub>3</sub> (30 mol%), toluene [0.1M], reflux in Dean-Stark, 24 h. (E) SOCl<sub>2</sub> (1.1 eq.), MeOH [0.5M], -50 °C to r.t., 18 h. Isolated yields (%) over two steps.

The conversion of **6a** into esters or amides was then investigated for more chemical diversity (**Scheme 5, D and E**). Based on our expertise, amidation reaction was first envisioned using boric acid as catalyst.<sup>34</sup> The acid **6a** reacted with 4-methylbenzylamine in the presence of 30 mol% of B(OH)<sub>3</sub> in refluxing toluene and led to the formation of **7a** within 70% yield. But due to purification and reproducibility issues encountered for the Ph\* release (**Scheme 5, C**), we decided to use directly the crude acid for the amidation and **7a** could be obtained in 42% yield over two steps. In that way, 4-iodobenzylamine, 4-methoxybenzylamine and hexylamine gave respectively **7b**, **7c** and **7d** within 29, 12 and 23% yield after isolation. We assumed that low yields were due to the degradation of the THF scaffold and attempts with more stabilized 4-benzyltetrahydrofuran ketone **3i** were

initiated. Pleasingly, **7e** and **7f** were obtained within 53% and 68% yield respectively. The mono-protected (*tert*-butyl ether) isosorbide C-C elongated **3p** was also subjected to post-functionalization affording the isosorbide amide **7h** within 23% yield.

Noticeably, ether deprotection also occurred under those reaction conditions. The methodology was finally applied to *N*-heterocycles **5b** and **5j** (5- and 6-membered ring) yielding to **7i** and **7j** in 40 and 34% yield respectively over two steps. Conversion into ester was thus envisioned: after Ph\* release of **3i** using HCl in HFIP, the crude acid was treated with SOCl<sub>2</sub> in MeOH affording the corresponding ester **8a** within 43%. Using the same procedure, pyrrolidine **8b** and piperidine **8c** were obtained in 81 and 79% yield respectively. With confidence in the sequential pathway, the reaction proceeded directly from piperidinol derivatives without intermediate purification. Compound **8c** could thus be isolated in 89% within 3 steps from 1-benzylpiperidin-4-ol (vs 50% with intermediate purification of **5h**). Very pleasingly, free piperidin-4-ol also led to **8d** in 76% overall yield, still leaving further possibilities for functionalizing the free amine (**Scheme 6**). Those experiments showed that this sequential BH C-alkylation / post-functionalization could be an interesting method in terms of solvent economy and efficiency for more complex molecules.



#### Scheme 6. Rapid synthesis of 4-alkylated piperidines

Reaction conditions: 1. (BH) piperidinol (1.0 eq.), Ph\* ketone **1** (1.1 eq.), NaO<sup>t</sup>Bu (2.0 eq.), Ir-**1** (5 mol%) in toluene [1M] at 120 °C for 24 h; 2. (C) 1.5M HCl in HFIP [0.1M], 65 °C, 24 h then H<sub>2</sub>O, r.t., 5 min; 3. (E) SOCl<sub>2</sub> (1.1 eq.), MeOH [0.5M], 50 °C to r.t., 18 h. Isolated yields

## Conclusions:

The development of metal-catalyzed C-alkylation reactions using a hindered ketone (Ph\* ketone **1**) and secondary saturated heterocyclic alcohols under basic conditions represents a significant advancement in synthetic chemistry. Herein, we have reported the challenging C-C elongation of *O*- and *N*-heterocycles with yields ranging from 21 to 79%. This study emphasized the pivotal role of the catalytic system in influencing both reactivity and diastereoselectivity. Furthermore, we have extended this methodology to the synthesis of substituted pyrrolidines and piperidines directly from a triol precursor, demonstrating its broad applicability. In addition, our achievement in post-functionalizing the BH products by introducing functionalities such as amide and ester groups further expands their potential applications. In conclusion, by addressing the under-explored nature of secondary saturated heterocycles, this methodology could unlock new opportunities in innovation and discovery. It could pave the way for the development of sustainable and highly efficient synthetic routes for synthesizing bioactive heterocyclic compounds.

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## Table of Content:

Access to functionalized saturated *N*- and *O*- Heterocycles *via* the metal catalyzed Borrowing Hydrogen methodology.

