Letter

Ruthenium-NHC Catalyzed #-Alkylation of Methylene Ketones Provides Branched Products through Borrowing Hydrogen Strategy

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Ruthenium-NHC Catalyzed α-Alkylation of Methylene Ketones Provides Branched Products through Borrowing Hydrogen Strategy

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KEYWORDS borrowing hydrogen, ruthenium, N-heterocyclic carbenes, homogenous catalysis, alkylation

ABSTRACT: The α-alkylation of a broad range of methylene ketones was achieved using a ruthenium(II)-NHC catalyst under borrowing hydrogen conditions. Primary alcohols served as alkylating agents and could be used in a one-to-one stoichiometry with respect to the ketone. The selectivity of the process for methyl over branched ketones enabled a one-pot double alkylation protocol utilizing two different alcohols with a single catalyst. Moreover, this methodology could directly be applied in the one-step synthesis of donepezil, the best-selling drug for the treatment of Alzheimer's disease.

The use of the borrowing hydrogen (BH) strategy for the alkylation of ketone enolates has emerged as a powerful and green alternative for the construction of C-C bonds.[1] The main advantage is the use of readily available and easy to handle alcohols as alkylating agents. Furthermore, salt waste is reduced as water is formed as the sole by-product. A typical BH process involves the transfer of hydrogen from the alcohol to a suitable transition metal catalyst to form the corresponding aldehyde *in situ*, which then forms a C-C bond with a nucleophilic enolate. Finally, addition of the 'borrowed' hydrogen to the olefin intermediate delivers the product.

The monoalkylation of methyl-ketones is well-established,[2] however, the use of α-substituted ketones to form α-branched alkylation products is less developed and almost exclusively relies on the use of methanol as the alkylating agent (Scheme 1, Eq. 1),[3,4] presumably due to steric reasons as well as to the high reactivity of *in situ* generated formaldehyde.

Donohoe and co-workers advanced this field of chemistry by employing an iridium catalyst with a bulky monodentate phosphine ligand, which interrupts the catalytic BH cycle before hydrogenation of the enone. Subsequent addition of a pronucleophile allowed for conjugate addition to the enone to occur and thus gave rise to various branched products (Eq. 2).[3c] Very recently, they also reported an Ir-catalyzed α-alkylation of hindered *ortho*-substituted phenyl and cyclopropyl ketones. However, a large excess of alcohol (5–10 equivalents) was required (Eq. 3).[5] Similarly, the Zhang group showed that a catalytic ruthenium-bisphosphine system could achieve the α-alkylation of methylene ketones when pyridyl methanols were employed as alkylating agents (Eq. 4).[6]

Scheme 1. Strategies for the formation of α-branched products with primary alcohols via borrowing hydrogen (BH) methodology

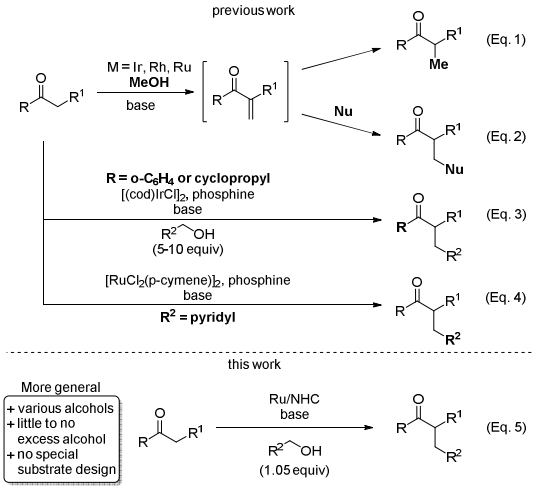
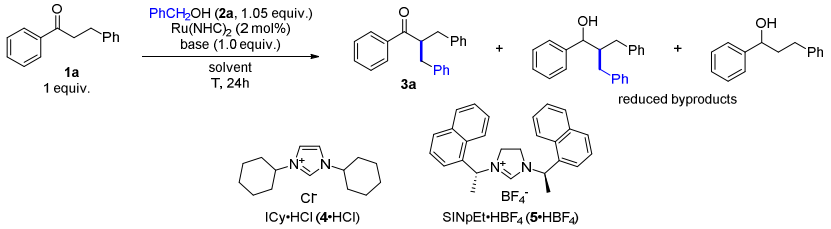


Table 1. Optimization of the reaction conditions.[a]



No.	NHC	Temperature	Base	Solvent	Ratio[b] of starting material (**1a**) : product (**3a**) : reduced byproducts
1	**4**	80 °C	LDA	THF/*n*-hexane	57:10:33
2	**5**	80 °C	LDA	THF/*n*-hexane	0:41:59
3	**5**	100 °C	LDA	THF/*n*-hexane	0:47:53
4[c]	**5**	100 °C	LDA	THF/*n*-hexane	27:35:38
5	**5**	100 °C	LDA	*t*-AmylOH/*n*-hexane	33:60:7
6	**5**	100 °C	LiO*t*-Bu	*t*-AmylOH/*n*-hexane	33:61:6
7	**5**	100 °C	LiOH	*t*-AmylOH/*n*-hexane	100:0:0
8	**5**	100 °C	KO*t*-Bu	*t*-AmylOH/*n*-hexane	78:5:17
9	**5**	100 °C	Cs_2CO_3	*t*-AmylOH/*n*-hexane	93:7:0
10[d]	**5**	**100 °C**	**LiO*t*-Bu**	***t*-AmylOH/*n*-hexane**	**2:96:2 (91%)**[e]
11[d],[f]	**5**	100 °C	LiO*t*-Bu	*t*-AmylOH/*n*-hexane	24:71:5
12[d],[g]	-	100 °C	LiO*t*-Bu	*t*-AmylOH/*n*-hexane	22:10:68
13	**5**	100 °C	-	*t*-AmylOH/n-hexane	100:0:0

[a] General reaction conditions: [Ru(cod)(2-methylallyl)$_2$] (4 μmol), KO*t*-Bu (8.4 μmol) and NHC·HX (8 μmol) were stirred at 70 °C in *n*-hexane (0.4 mL) for 16 h, after which the mixture was added to a solution of **1a** (0.2 mmol) and base (0.2 mmol) in *t*-AmylOH (0.5 mL). To this reaction mixture was then added BnOH (**2a**, 0.2 mmol) and the reaction was heated to the indicated temperature for 24 h. [b] Determined by GC-MS analysis of the crude reaction mixture. [c] 2.0 equivalents of benzyl alcohol were used. [d] 2.0 equivalents of base were used. [e] Isolated yield in parentheses. [f] The ruthenium complex was not pre-stirred prior to the reaction. [g] Neither ruthenium source nor NHC precursor were added.

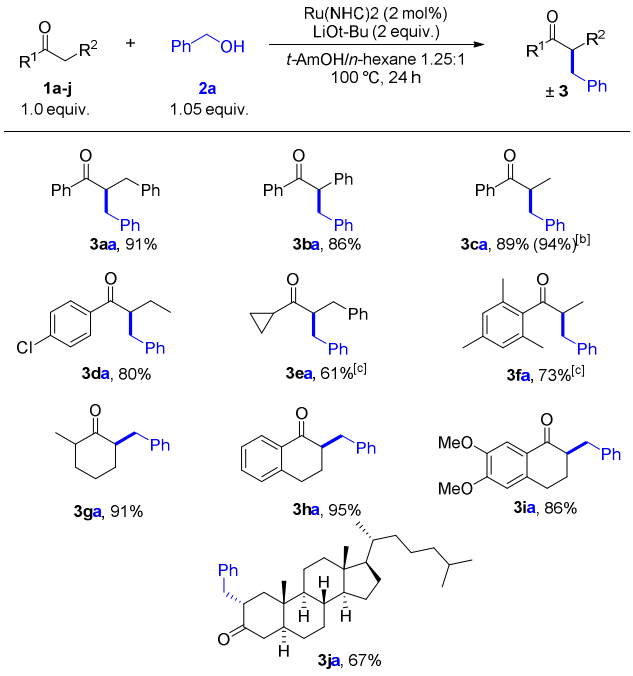
We previously reported a ruthenium(II)-N-heterocyclic carbene (NHC) catalyst system which proved to be highly reactive in the dehydrogenative activation of methanol to achieve *N*-formylation of amines[7] as well as in arene hydrogenations.[8] We envisioned that this reactive catalyst system could also promote the α-alkylation of enolates via a BH mechanism. Herein, we report on the Ru(NHC)$_2$ catalyzed α-alkylations of diversely functionalized methylene ketones with a variety of primary alcohols as alkylating agents. Notably, the alkylating agent could be used in a one-to-one stoichiometry with respect to the ketone. To showcase the synthetic potential of this method, donepezil, the best-selling drug for the treatment of Alzheimer's disease, was synthesized in one step.

As an initial test reaction, the coupling of dihydrochalcone **1a** with benzyl alcohol (**2a**, 1.05 equiv.) was conducted using 2 mol% of Ru-catalyst and one equivalent of lithium diisopropylamide (LDA) at 80 °C (Table 1). In a mixture of THF/*n*-hexane, using Ru/ICy as catalyst, only trace amounts of the desired product **3a** could be observed. However, presumably due to the high potency of the Ru/ICy catalyst in transfer hydrogenation, a number of reduced byproducts were observed, and >50% of unreacted starting material **1a** remained (Entry 1). During our studies in the field of arene hydrogenation, the SINpEt NHC precursor (**5**•HBF4) showed unique reactivity when combined with a ruthenium(II) precursor.[8] Indeed, employing this catalytic system[9] enhanced our transformation and provided a promising product distribution. Ketone **1a** was completely consumed and a significant amount of the desired product **3a** could be observed along with the reduced byproducts (Entry 2). Increasing the temperature to 100 °C caused a slight increase in the selectivity for **3a** (Entry 3), while increasing the amount of alcohol to two equivalents proved detrimental for the reaction (Entry 4). Changing the solvent system to *t*-AmOH/*n*-hexane led to a slight decrease in reactivity, but enhanced the selectivity for the formation of **3a** (Entry 5). Among other bases, LiO*t*-Bu gave slightly better results, whereas LiOH, KO*t*-Bu and Cs_2CO_3 are inefficient (Entry 6-9). Finally, increasing the amount of base to two equivalents resulted in the selective formation of **3a** and the desired product could be isolated in 91% yield (Entry 10). The product could also be detected when the ruthenium catalyst was not pre-

formed prior to the reaction, but the ruthenium and NHC precursors were used directly (Entry 11). A control experiment without any ruthenium catalyst revealed that **3a** could only be formed in trace amounts (Entry 12), similar to the observations made by the group of Xu and co-workers.[2j] Without any base no reaction could be observed at all (Entry 13).

We then set out to investigate the reaction scope. A range of α-substituted ketones were benzylated under these conditions in good to excellent yields (Scheme 2). Neither the ketone substituent nor the α-substituent affected the outcome of the reaction. Abundant and readily available unsubstituted phenyl ketones were smoothly converted to the corresponding branched products bearing either small groups such as methyl (**3ca**) or more sterically demanding benzyl (**3aa**) or phenyl (**3ba**) groups. When propiophenone (**1c**) was reacted with benzyl alcohol on gram-scale, the corresponding product was isolated in 94% yield, highlighting the practicability of this protocol. Notably, despite the use of a lithium base, the chloro substituent in **1d** was tolerated in the reaction, giving the α-branched product **3da** in 80% yield. A cyclopropyl ketone **1e** was converted to the corresponding branched product **3ea** in 61% yield with increased reaction time of 36 h. Cyclohexyl (**1g**) or tetralone substrates (**1h-i**) bearing a cyclic carbon skeleton were successfully benzylated in excellent yields. Interestingly, when cholestanone **1j** was subjected to the reaction conditions, 67% of one single regio- and stereoisomeric product was isolated which was assigned to be **3ja** by 2D NMR studies. Only a trace amount of another product could be detected (see the supporting information for details). We attribute the observed regioselectivity to steric reasons.

Scheme 2. α-Alkylation of various methylene ketones 1 with benzyl alcohol 2a[a]

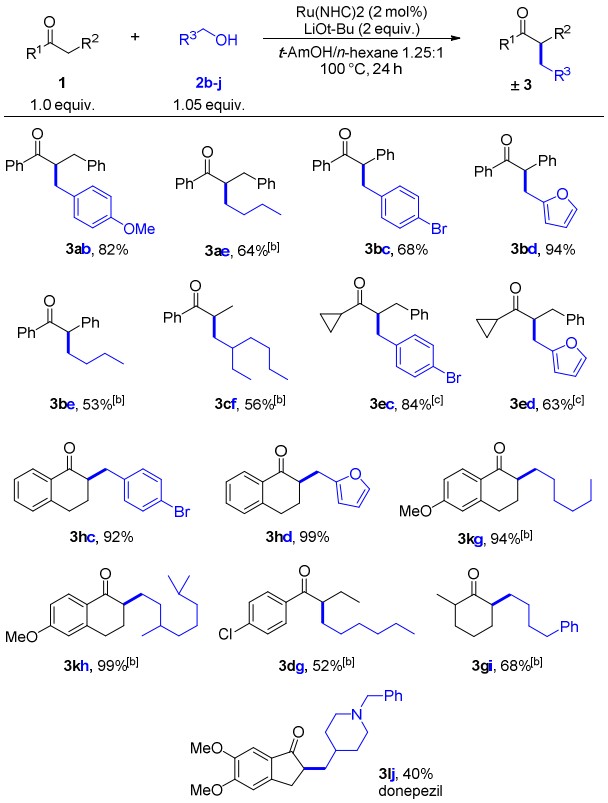


[a] General reaction conditions: See Table 1, Entry 7. Yields of the isolated products are given. [b] 1.00 g (7.45 mmol) of **1c** was used. [c] Reaction run for 36 h.

Next, we further explored the scope of the primary alcohol (Scheme 3). In general, a wide variety of primary alcohols **2a-j** with different electronic and steric properties could be employed under the reaction conditions to deliver the α-branched products in good to excellent yields with a minimal excess of substrate. The bromo substituent on 4-bromo benzyl alcohol **1c** was well tolerated in the reaction providing **3bc**, **3ec**, and **3hc** in good to excellent yields. The cyclopropyl ketone **1e** required a prolonged reaction time (48 h) to achieve good conversions with either **1c** or furfuryl alcohol **1d** giving the corresponding products **3ec** and **3ed**. When aliphatic alcohols **2e-j** were employed, the use of 3 equivalents of base was needed to increase the conversion, presumably in order to sustain high enolate concentrations throughout the reaction. Nonetheless, after treatment with purely aliphatic long chain alcohols *n*-hexanol (**2g**) and tetrahydrogeraniol (**2h**), the tetralone derivative **1k** could be converted into the corresponding branched products **3kg** and **3kh** in excellent yields (94% and 99% yield respectively). Similarly the α-branched product **3gi** was obtained in 68% yield from 2-methyl cyclohexanone (**1g**). We also applied this process to the direct synthesis of donepezil (**3ij**), which is currently the best-selling drug for treatment of Alzheimer's disease.[10] Although donepezil was isolated in a moderate 40% yield, this represents the shortest synthetic route to this important molecule, requiring only one step from commercially available starting materials.[11]

To further investigate the functional group tolerance of this reaction, we conducted a robustness screen as previously reported by the Glorius group (see the supporting information).[12] We found that aryl halides (chlorides, bromides, iodides), cyanides and heterocycles (imidazole, pyridine, pyrrole, benzofuran, thiophene) are tolerated. However, reducible functional groups such as nitro, esters, amides and alkynes deteriorate the reaction outcome.

Scheme 3. α-Alkylation of various ketones 1 with primary alcohols 2b-j[a]

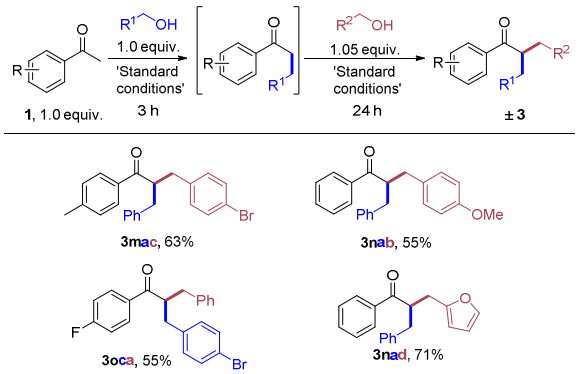


[a] General reaction conditions: See Table 1, Entry 7. Yields of isolated products are given. [b] 3 equivalents of LiO*t*-Bu were used. [c] Reaction run for 48 h.

To exploit the potential of this method to deliver branched products, we conducted a one-pot double alkylation process. This protocol could allow for rapid access to highly branched carbon skeletons from very simple and readily available starting materials (α-methyl ketones and primary alcohols) with a single catalyst. Acetophenones were chosen as ketone substrates that were alkylated by different primary alcohols in a successive manner (Scheme 4).

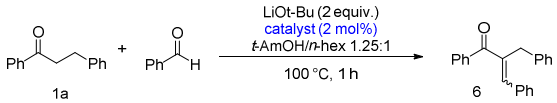
Crucial to the success of this transformation is the selective monoalkylation in the first step. After subjecting **1m** to the standard reaction conditions with exactly one equivalent of benzyl alcohol, we were pleased to detect only the mono-benzylated product **3ma** by means of GC-MS analysis after three hours. Although a second alkylation with the same alcohol is, in principle, possible with this catalytic system, the higher reactivity of the α-unsubstituted enolate of **1m** compared to the substituted enolate of **3ma** is presumably the reason for the observed product selectivity. A second addition of catalyst and base, together with the alcohol **2c**, led to the formation of hetero- bis-alkylated compound **3mac** which could be isolated in 63% yield, proving the concept of one-pot double alkylation with a single catalyst. Several other ketones and alcohols could be coupled *via* this method, although we found that aliphatic alcohols work less efficient in this process.[13]

Scheme 4. One-pot double alkylation of acetophenone derivatives by sequential addition of primary alcohols



To probe the unusually high reactivity of this ruthenium(II)-NHC system in alkylating various methylene ketones under borrowing hydrogen conditions, the key aldol condensation reaction between dihydrochalcone **1a** and benzaldehyde was carried out under transition metal free conditions, our Ru-NHC catalyzed conditions as well as conditions based on established Fe[2g] (Knölker's complex), Ir[3c] and Rh[3a] catalysts in BH reactions (Scheme 5).

Scheme 5. Control experiments



	no catalyst	$Ru(NHC)_2$	Knölker's complex	$[Ir(cod)Cl]2 + PPh_3$	$[\{Cp^*RhCl_2\}_2]$
1a:**6**[a]	1:1.9	1:11.5	1:1.7	1:1.7	1:1.3

[a] Determined by GC-MS analysis of the crude reaction mixture.

The catalyst-free reaction shows a ratio of 1:1.9 between **1a** and **6** after one hour with **6** as the sole product. While Ir, Rh and Fe-based catalysts gave similar results compared to the uncatalyzed reaction, the Ru-NHC catalyst significantly improved the conversion, giving a ratio of 1:11.5 between **1a** and **6**. This result indicates that the ruthenium-complex is not only catalyzing the borrowing hydrogen steps (dehydrogenation of the primary alcohol and hydrogenation of the aldol condensation product), but is also involved in the crucial C–C bond forming condensation reaction.

In summary, we have developed a ruthenium(II)-NHC catalyzed practical and scalable α-alkylation of methylene ketones with primary alcohols under borrowing hydrogen conditions to give rise to a variety of branched ketones. In general, good to excellent yields of the α-branched products were obtained either without or with only a minimal excess of the alcohol substrate. This protocol significantly broadens the scope of borrowing hydrogen catalysis in alkylation reactions, enabling the access to the blockbuster drug donepezil in a single synthetic step. Furthermore, we were able to exploit the inherent

reactivity of methyl *vs.* methylene ketones to accomplish the double alkylation of methyl ketones in a one-pot procedure with a single catalyst.

ASSOCIATED CONTENT

Supporting Information.
Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra.
This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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α-Branched ketones are accessible under borrowing hydrogen conditions by using a ruthenium(II)-NHC catalyst. Primary alcohols serve as alkylating agents and can be used in a one-to-one ratio. A one-pot double alkylation with a single catalyst but two different alcohols is also possible under these conditions, as is the one-step synthesis donepezil, the best-selling Alzheimer's disease drug.