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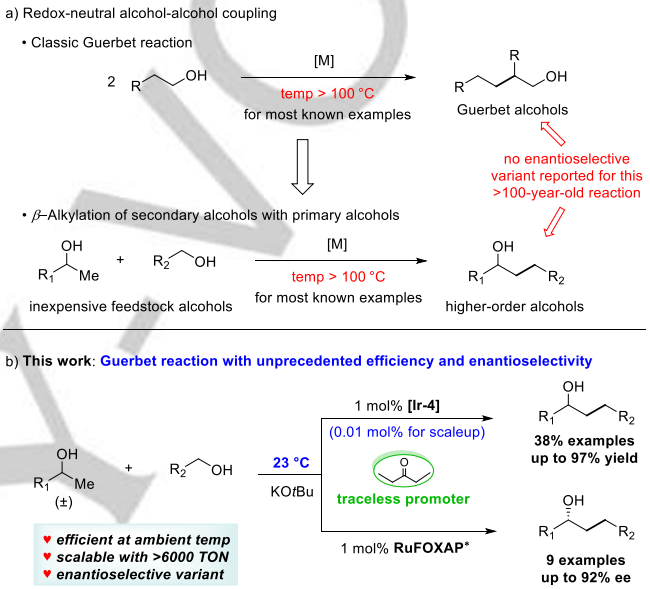
# Room-Temperature Guerbet Reaction with Unprecedented Catalytic Efficiency and Enantioselectivity

Teng Wei Ng,[a],+ Gang Liao,[a],+ Kai Kiat Lau,[a] Hui-Jie Pan,[a] and Yu Zhao*[a,b]

**Abstract:** We report herein an unprecedented highly efficient Guerbet-type reaction at room temperature (catalytic TON up to >6000). This *β*-alkylation of secondary methyl carbinols with primary alcohols has significant advantage of delivering higher-order secondary alcohols in an economical, redox-neutral fashion. In addition, the first enantioselective Guerbet reaction has also been achieved using a commercially available chiral ruthenium complex to deliver secondary alcohols with moderate yield and up to 92% ee. In both reactions, the use of a traceless ketone promoter proved to be beneficial for the catalytic efficiency.

Alcohols are one of the most fundamental functionalities in organic compounds. Given its importance as well as the current strong push for sustainable chemistry, the development of practical and economical synthesis of alcohols remains a focal point in synthetic chemistry. Although a plethora of methods have been developed to synthesize alcohols including enantioenriched chiral alcohols, most of them rely on the conversion of other functionalities and especially carbonyls.[1] In these processes, the necessity to use reactive reductants or organometallic reagents inevitably led to the generation of stoichiometric amount of salt-based waste. More economical and environmentally friendly syntheses of alcohols are still highly desired.

The strategy of borrowing hydrogen has gained much prominence for enabling redox-neutral synthesis of important building blocks with high atom-economy.[2] With this regard, simple feedstock alcohols can be converted to amines or higher-order alcohols through a one-pot dehydrogenation-condensation-hydrogenation procedure, with no use of external reagents nor generation of waste. Historically, the renowned Guerbet reaction that entails homo-coupling of primary alcohols to forge branched primary alcohols has found a wide spectra of applications in fine chemical and biofuel synthesis (Scheme 1a).[3] To extend the utility of such method, the hetero-coupling of two different alcohols, and especially *β*-alkylation of readily available secondary methyl carbinols with a primary alcohol has been extensively explored in recent years.[4] Despite the success with various transition-metal catalyzed systems, all the reported procedures required high temperature (mostly >100 ˚C) for high efficiency. Very often, the primary alcohol needs to be used in large excess to overcome the challenging chemoselectivity in cross aldol condensation. Addressing such issues is needed to realize the full potential of this transformation. More significantly, an enantioselective variant of this attractive higher-order alcohol synthesis remains elusive after decades of efforts.[5] Related to classic asymmetric transfer hydrogenation of ketones using isopropanol,[6] achieving kinetic enantioselectivity as well as minimizing product racemization in such a highly dynamic, reversible process presents a formidable challenge to overcome.




**Scheme 1.** Strategies for the synthesis of higher-order alcohols

In the past few years, our group has been devoted to enantioselective borrowing hydrogen method development, and reported the first examples of stereoconvergent amination of alcohols.[7-9] With an eye on the problem of higher-order alcohol synthesis, we sought to improve the practicality of the reaction with a focus on achieving high catalytic efficiency as well as enantioselectivity under mild reaction conditions. We present herein an efficient catalytic system that can achieve high catalytic turnover (TON up to >6000) for *β*-alkylation of methyl carbinols at room temperature (Scheme 1b). Efforts for the first enantioselective Guerbet-type reaction are also disclosed.

We started our investigation by attempting to couple 1-phenylethanol **1a** with benzyl alcohol **2a** in 1:1 ratio at ambient conditions (Table 1). Reactions were performed with 0.5 equiv. KO*t*Bu in a solution of *t*-amyl alcohol. Different catalysts that have been proven to be highly reactive in hydrogen transfer or borrowing hydrogen reactions were screened. Surprisingly, most of the catalysts tested failed to give the desired product with satisfactory results. Reactions catalyzed by ruthenium complexes were generally inefficient (entries 1–3). We then turned our attention to iridium catalysts (entries 4–7). To our delight, catalyst **[Ir]-4**[7d,10] showed a promising result with 15% yield (entry 7). Testing the loading of base disclosed that 1.0 equivalent of KO*t*Bu was optimal (entry 8 vs. entries 7 & 9). However, the yield remained moderate at this juncture, which left much room for improvement.

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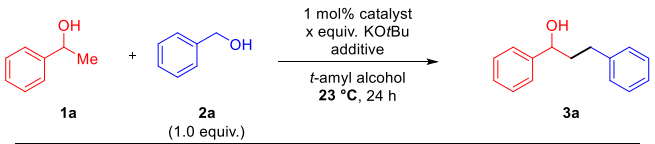
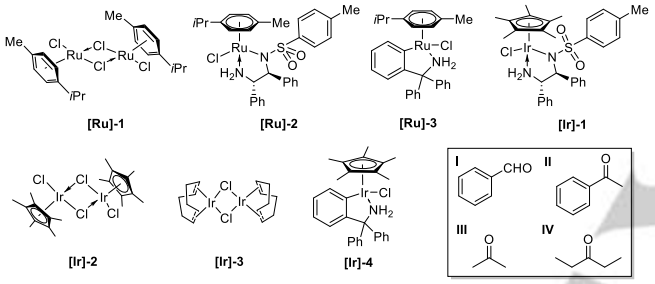
**Table 1.** Optimization of reaction conditions[a]




**1a** **2a** (1.0 equiv.) **3a**

| Entry | Catalyst | Additive | Base (equiv.) | Yield(%)[b] |
|---|---|---|---|---|
| 1 | **[Ru]-1** | -- | 0.5 | -- |
| 2 | **[Ru]-2** | -- | 0.5 | -- |
| 3 | **[Ru]-3** | -- | 0.5 | 8 |
| 4 | **[Ir]-1** | -- | 0.5 | 6 |
| 5 | **[Ir]-2** | -- | 0.5 | -- |
| 6 | **[Ir]-3** | -- | 0.5 | -- |
| 7 | **[Ir]-4** | -- | 0.5 | 15 |
| 8 | **[Ir]-4** | -- | 1.0 | 39 |
| 9 | **[Ir]-4** | -- | 2.0 | 18 |
| 10 | **[Ir]-4** | 5 mol% **I** | 1.0 | 95 |
| 11 | **[Ir]-4** | 5 mol% **I** | \ | <2 |
| 12 | **** | 5 mol% **I** | 1.0 | <2 |
| 13 | **[Ir]-4** | 5 mol% **II** | 1.0 | **95** |
| 14 | **[Ir]-4** | 5 mol% **III** | 1.0 | **85** |
| **15** | **[Ir]-4** | 5 mol% **IV** | **1.0** | **95** |




[a] Reaction conditions: **1a** (0.4 mmol), benzyl alcohol **2a** (0.4 mmol), catalyst (0.004 mmol), additive, KO*t*Bu (0.4 mmol) in *t*-amylol (0.2 mL) at 23 °C under $N_2$ for 24 h. [b] Isolated yield.

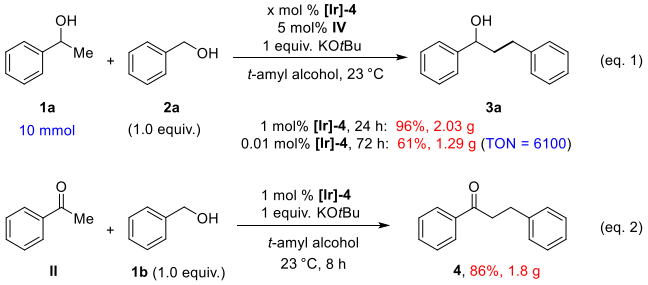
We sought to develop an alternative strategy to further improve the efficiency of the reaction. The use of either the ketone or aldehyde corresponding to the alcohol substrates as a catalytic promoter for alcohol coupling has been disclosed.[11] Inspired by this strategy, we examined the effect of carbonyl promotor by adding 5 mol% benzaldehyde **I** to the reaction (entry 10). Under this set of conditions, the starting materials **1a** and **2a** were fully converted to **3a** with a trace mount of the corresponding ketone as a byproduct. To rule out the possibility that our reaction is solely catalyzed by the carbonyl promoter, control reactions using **I** without either the base (entry 11) or **[Ir]-4** (entry 12) were performed. Neither of them gave any desired product, suggesting that aldehyde **I** could not catalyzed this reaction alone. Instead, it was likely promoting the initiation of this Ir-catalyzed process as the only hydrogen acceptor at the beginning. It is noteworthy that ketone **II** could also serve as the hydrogen shuttle to yield **3a** with a similarly high yield (entry 13).

Notably, the use of benzaldehyde or acetophenone will not be a general solution for a wide range of substrates as they lead to side product formation. A readily available and easily removable (traceless) promotor that does not interfere with the borrowing hydrogen reaction would be much more desirable. In this context, the use of **III** led to **3a** in slightly lower yield due to the generation of byproducts (entry 14). Considering that essentially all the reported *β*-alkylation of secondary alcohols only worked for methyl carbinols, we decided to examine the use of non-methyl ketones and in particular the smallest 3-pentanone **IV**. To our delight, in the presence of 5 mol% **IV**, **3a** was obtained in excellent yield without any undesired side reactions (entry 15). Importantly, **IV** could be easily removed together with the solvent. It thus represents an ideal, convenient choice of additive.

With the optimal conditions in hand, we moved on to explore the substrate scope of this catalytic reaction (Scheme 2). Various secondary alcohols were examined first. Aryl groups with electro-withdrawing and -donating substituents at the *para*-position were all well-tolerated to produce **3b**-**3j** with good to excellent yields. It is worthy mentioning that halogen and vinyl groups were all compatible with this reaction, which offered opportunities for downstream structural modification. *Meta*- and *ortho*-substituted aryl secondary alcohols also participated in the reaction under the standard conditions with the products obtained in moderate to high yields (**3k**-**3p**). Secondary alcohols bearing naphthyl substitutes smoothly reacted to yield products **3q**-**3r** in excellent yields. More significantly, different heteroaryl-containing secondary alcohols, such as those with pyridine, furan, benzofuran and benzthiophene were successfully converted to the corresponding products in good to excellent yields (**3s**-**3v**). As a significant extension of the scope, aliphatic secondary alcohols were also adapted to the catalytic system with a longer reaction time, affording the *β*-alkylated secondary alcohols with moderate to good yields (**3w**-**3z**).

Next, variations on the primary alcohol counterpart were examined. Substituted benzyl alcohols with either electro-donating or electro-withdrawing groups all gave excellent yields (**3aa-3ag**). Napthyl and furyl benzyl alcohols likewise were converted in high yields (**3ah**, **3ai**). Simple linear alcohols was also subjected to the standard reaction conditions and was found to give similarly high yields (**3aj**, **3ak**). Finally, a linear primary alcohol bearing a terminal alkene was also tolerated without observation of reduction of the alkene moiety (**3al**).

To further showcase the synthetic utility of this method, a range of gram-scale reactions were carried out. First, a 10 mmol scale reaction of **1a** with **1b** was performed, delivering the product **3a** in 96% yield (2.03 g, eq. 1). In addition, in an effort to reduce the catalyst loading, we were delighted to find that even at 0.01 mol% loading, **[Ir]-4** could promote the reaction with high efficiency (~6100 TON) in 72 h.




The mechanistically related but simpler alkylation of ketones using primary alcohol has also attracted much interest in recent years as an economical method for ketone functionalization.[12] Without the need for any optimization, our catalytic method could convert **II** and **1b** to the desired product **4** in high efficiency at mild conditions (1.8 g, eq. 2). The additive **IV** was not necessary in this case as ketone substrate was involved.

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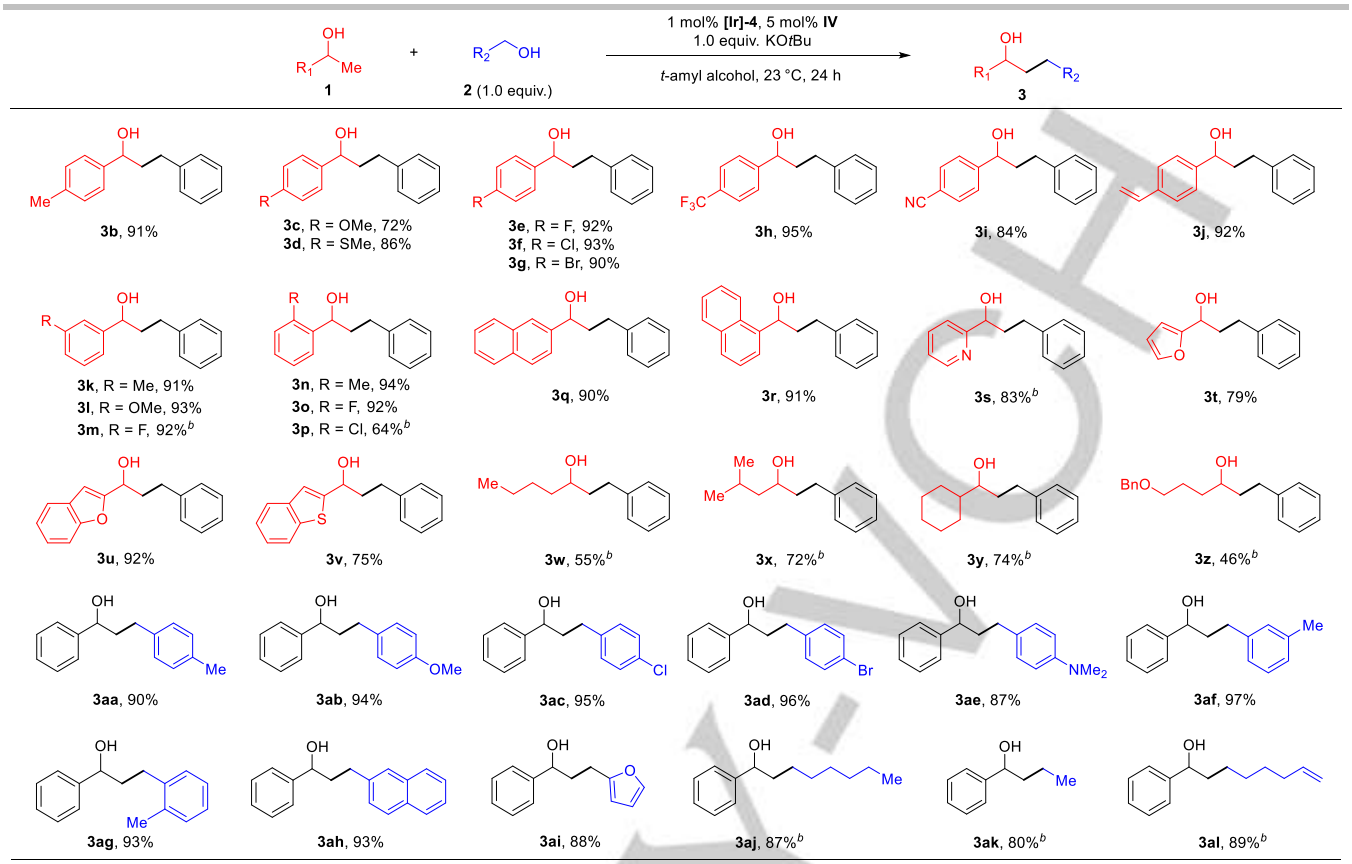
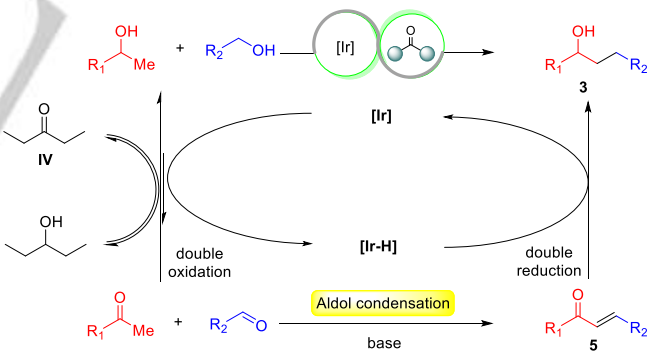



[a] Unless otherwise noted, the reactions were carried out with **1a** (1.0 mmol), benzyl alcohol **2a** (1.0 mmol), **[Ir]-4** (0.01 mmol), **IV** (0.05 mmol) and KO*t*Bu (1.0 mmol) in *t*-amyl alcohol (1.0 mL) at 23 °C under $N_2$ for 24 h. All are isolated yield. [b] 72 h reaction.

**Scheme 2.** Scope of β-alkylation of secondary alcohols with primary alcohols[a]

A plausible reaction pathway was proposed for this catalytic system. As depicted in Scheme 3, the active iridium-amide catalyst generated *in situ* by the base KO*t*Bu promotes dehydrogenation of two alcohol substrates to their respective carbonyl intermediates. We believe that ketone **IV** plays a significant role for the reaction initiation. As the only hydrogen acceptor at the beginning of the reaction with two alcohols **1** and **2** as well as a low concentration of the catalyst, the presence of **IV** allows an more efficient build-up of a reservoir of the aldehyde and ketone intermediates, which undergoes aldol condensation followed by reduction to deliver the desired product. Conveniently, **IV** does not involve in the aldol step so no side product is formed. In addition, the aldol condensation step likely involves the equilibrium of a complex mixture, while in the productive pathway enone **5** undergoes double hydrogenation by the **[Ir-H]** species to complete the redox cycle.

Despite the attractiveness of this redox-neutral synthesis of higher-order secondary alcohols from simple building blocks, it is extremely challenging to achieve an enantioselective variant of this transformation. The harsh conditions needed for the catalytic efficiency in previous studies presumably impeded the realization of high asymmetric induction during the enantio-determining ketone reduction step. In addition, product racemization would be a serious hurdle to overcome for such a complex reversible system. With the achievement of this reaction under mild conditions, we turned our attention to the identification of a suitable chiral catalytic system to achieve this long-sought-after goal.




**Scheme 3**. Proposed reaction pathway

As shown in Scheme 4a, the extensive screening of chiral Ir- and Ru-based chiral complexes met with limited success. The most promising commercially available **[Ru]-8** was chosen for further optimization. The increase in the loading of both ketone **IV** and primary alcohol turned out to be beneficial, which improved the formation of **3a** in 29% yield with 92% ee (entry 3 vs. entries 1 & 2). A control reaction without **IV** led to much lower efficiency and ee (entry 4). Finally, **3a** was obtained in 42% yield with 90% ee. Notably, the remaining **1a** was recovered with marginal ee (49%, 34% ee), suggesting a concomitant resolution of the secondary alcohol substrate. However, all further optimization failed at this point.

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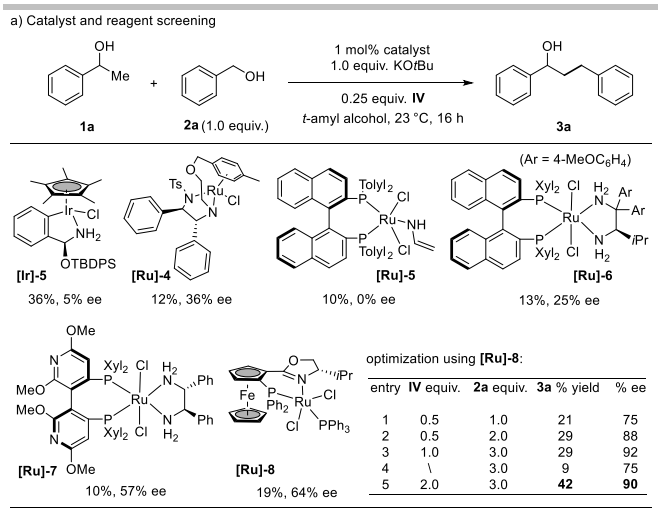
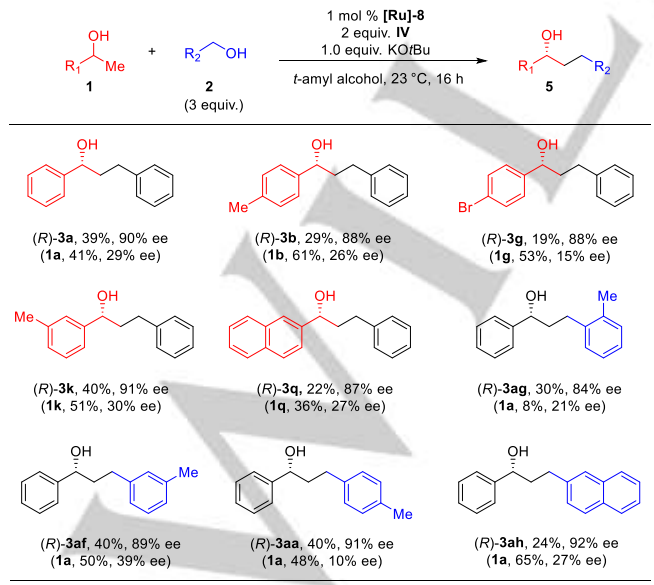



**Scheme 4**. Screening of reaction conditions for enantioselective variant

To better understand this catalytic system, the yield and ee of both **3a** and **1a** vs. time was followed (Scheme 4b). The conversion to **3a** gradually increased but stopped at ~40% yield, while a slow racemization of **3a** over time was also clearly observed (from >98% to 90% ee). For this dynamic reversible transformation, the catalyst is clearly doing redox chemistry on both the substrate and product, and the high kinetic selectivity slowly diminished when the conversion went on. While this does not provide a high-yield stereoconvergent synthesis of higher-order secondary alcohols, we decided to move on to probe the generality of this catalytic enantioselective Guerbet-type reaction nonetheless.




**Scheme 5**. Scope of enantioselective Guerbet-type reaction

As summarized in Scheme 5, variations on both the secondary alcohol and primary alcohols substrates were well-tolerated. The resulting alcohol products **3** were obtained in uniformly 84–92% ee, albeit with low to moderate isolate yield. The identification of a more reactive catalytic system to achieve high conversion and kinetic selectivity is under continuous investigation.

In conclusion, we have developed a highly efficient catalytic redox-neutral *β*-alkylation of secondary alcohols with primary alcohols at room temperature. A broad range of higher-order secondary alcohols are accessible with synthetic useful yields. Scaling up the reaction with low loading of the catalyst further highlighted the potential of this reaction for synthetic application. Importantly, an unprecedent enantioselective variant of this transformation has been achieved, where kinetic resolution of the starting secondary alcohol and enantioselective synthesis of the product alcohol proceed simultaneously.[13] The development of more efficient and selective catalytic system and extension to other related transformations are underway in our laboratory.

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**Keywords:** Guerbet reaction • borrowing hydrogen • higher-order alcohol • alkylation • enantioselectivity

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[13] During the review of our manuscript, we noticed a closely related, elegant report of enantioselective Guerbet reaction by the Wang group. Their Ru-catalyzed reactions at slightly higher temperature of 60 °C with an alternate 3:1 ratio of secondary alcohol to primary alcohol substrates led to a wide range of higher-order secondary alcohols in high efficiency. See: K. Wang, L. Zhang, W. Tang, H. Sun, D. Xue, M. Lei, J. Xiao, C. Wang. *Angew. Chem. Int. Ed.* **2020**, DOI: 10.1002/anie.202003104.

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## Entry for the Table of Contents

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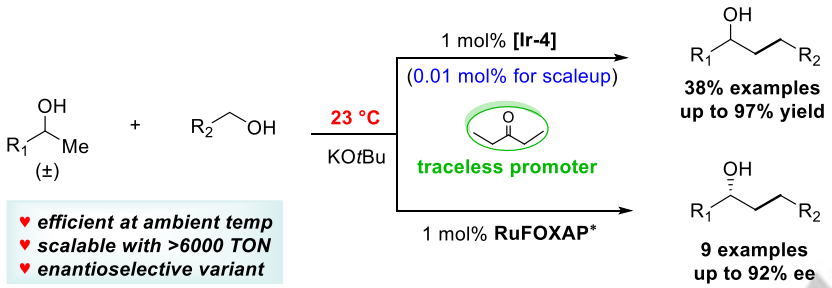


**redox-neutral Guerbet reaction with unprecedented efficiency and enantioselectivity**

We report herein an unprecedented highly efficient Guerbet-type reaction at room temperature (catalytic TON up to >6000). This *β*-alkylation of secondary methyl carbinols with primary alcohols has significant advantage of delivering higher-order secondary alcohols in an economical, redox-neutral fashion. In addition, the first enantioselective Guerbet reaction has also been achieved using a commercially available chiral ruthenium complex to deliver secondary alcohols with moderate yield and up to 92% ee.

*Teng Wei Ng, Gang Liao, Kai Kiat Lau, Hui-Jie Pan and Yu Zhao**

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**Room-Temperature Guerbet Reaction with Unprecedented Catalytic Efficiency and Enantioselectivity**