



## Forum

Shining a light on  
Fe-catalyzed borrowing  
hydrogen alkylation

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**The borrowing hydrogen (BH) approach enables commodity alcohols to be employed as alkylating agents, generating water as the sole by-product. Recently, Fe-based catalysts have been utilized in combination with visible light irradiation to enable alkylation processes at near room temperature, which improves sustainability metrics while presenting opportunities for further reaction development.**

BH, sometimes referred to as hydrogen autotransfer, is a powerful synthetic strategy that combines transfer hydrogenation with a reaction on the *in situ*-generated intermediate [1]. A popular application of the BH approach is to utilize commodity alcohols as alkylating agents, which generate water as the sole by-product. This process provides a more sustainable alternative to traditional alkylation methods, which often employ hazardous reagents and produce significant quantities of waste. Considering the  $\alpha$ -C-alkylation of ketones as an illustrative example (Figure 1, left), the BH sequence begins with dehydrogenation of an alcohol by a metal catalyst [M] to form a reactive carbonyl intermediate. This unsaturated species undergoes an aldol condensation with an enolizable ketone to generate an enone. Subsequent hydrogenation by the [MH<sub>2</sub>] species generated in the initial dehydrogenation step forms the alkylated

ketone product and regenerates [M], completing the catalytic cycle.

Traditionally, homogeneous BH reactions have employed organometallic catalysts based on precious second and third row transition metals, such as Ru, Rh, and Ir, to promote hydrogen transfer. However, with the increasing global emphasis on the development of more sustainable synthetic methodologies, catalysts based on earth-abundant first row transition metals have also been employed for various C–C and C–N bond-forming BH alkylation processes [2]. Among these, (cyclopentadienone)iron carbonyl complexes have demonstrated notable effectiveness in the BH alkylation of different (pro)nucleophiles, including ketones, indoles, oxindoles, and amines [3]. Despite the diversity of catalysts available, BH alkylation processes are typically performed at high reaction temperatures (90–150°C), which requires significant energy input, limits substrate compatibility, and makes the development of enantioselective variants challenging. As such, the development of new strategies that allow BH alkylation processes to be performed at lower temperatures represents a primary goal in this field.

Pioneering studies by Knölker and co-workers demonstrated that photoirradiation using a 150 W medium-pressure mercury lamp can promote CO-ligand exchange

with acetonitrile within (cyclopentadienone)iron carbonyl complexes [4]. This observation encouraged further investigation into the use of photoirradiation in combination with (cyclopentadienone)iron carbonyl complexes for BH alkylation processes [5,6]. In 2022, the research groups led by Renaud and Sundararaju independently reported complementary protocols for the Fe-catalyzed  $\alpha$ -C-alkylation of ketones that proceed at near room temperatures using (cyclopentadienone)iron carbonyl complexes with visible light [7,8] (Figure 1, right). While Renaud, Poater, and coworkers employed blue light emitting diodes (LEDs) for alkylation with primary alcohols, the Sundararaju work focused on  $\alpha$ -methylation with methanol using white LEDs.

The protocol developed by Renaud, Poater, and coworkers employed the well-defined bench stable (cyclopentadienone)iron carbonyl complex **1** as a precatalyst (2.5 mol %) (Figure 2A), which contains a more electron-rich cyclopentadienone framework in comparison to precatalyst **2** (c.f. Figure 2B). The reactions were performed using NaOH (0.4–2 equiv.) as a base in *tert*-butanol as solvent under 450 nm blue light (40 W) for 16–72 h. This enabled the  $\alpha$ -C-alkylation of a diverse range of (aromatic/aliphatic) ketones using various primary (benzylic/aliphatic) alcohols, with the alkylated ketone products obtained

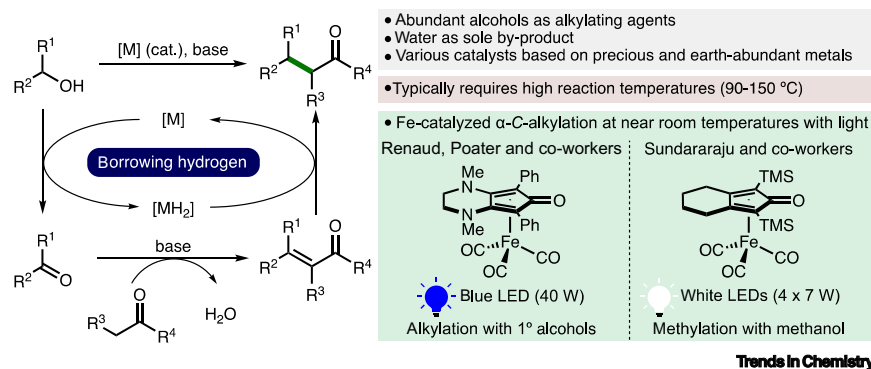
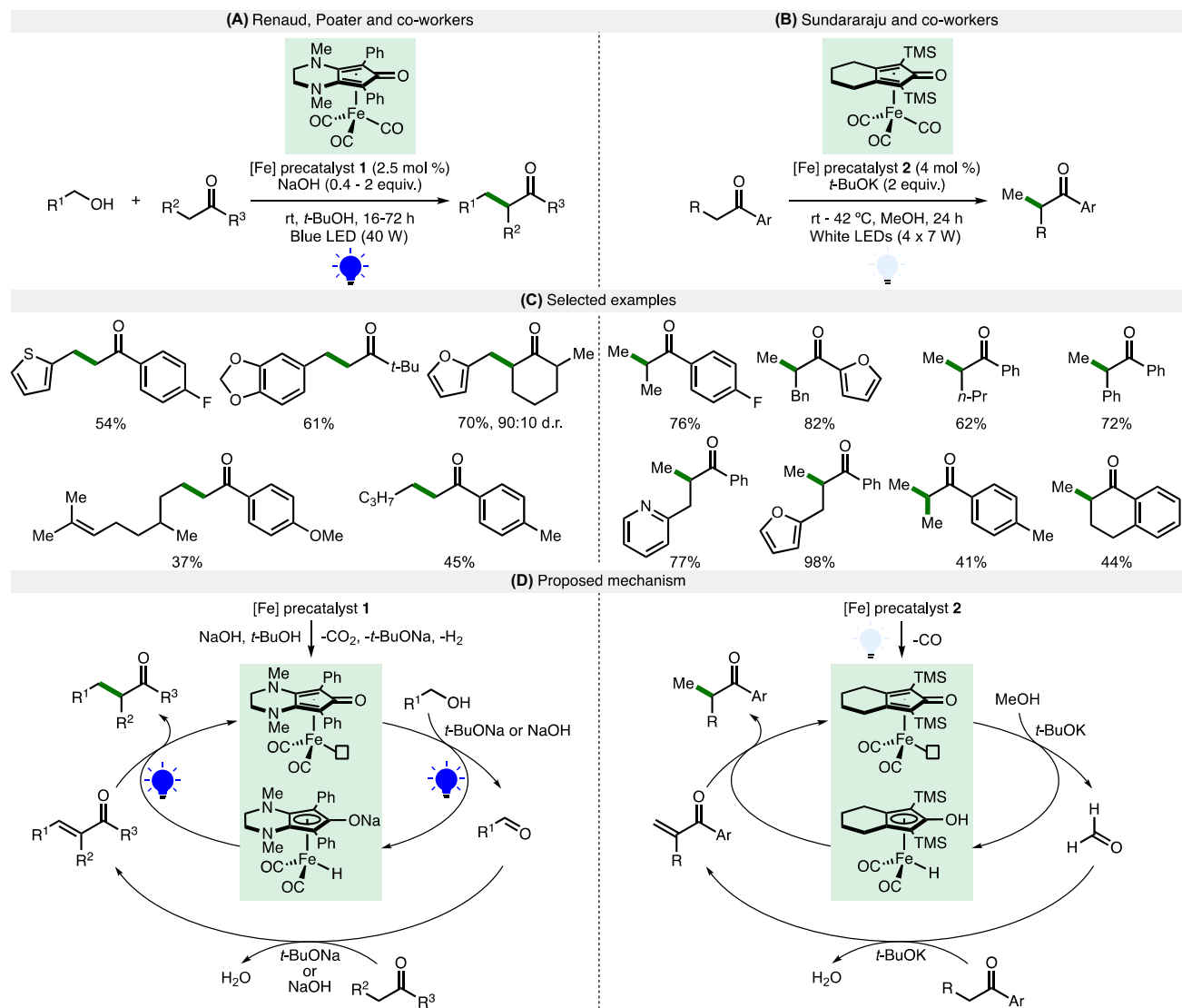


Figure 1. Overview of borrowing hydrogen C-alkylation of ketones. See [7,8]. Abbreviation: LED, light emitting diode.



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**Figure 2. Methods overview.** (A) The Renaud, Poater approach [7]. (B) The Sundararaju approach [8]. (C) Selected scope entries. (D) Simplified proposed reaction mechanisms. Abbreviations: LED, light emitting diode; rt, room temperature.

in moderate to high yields (Figure 2C). The reaction occurs at room temperature, which indicated that there is no observable increase in temperature due to heat generated by the blue LEDs employed. In the absence of 450 nm blue light photoirradiation, comparable reactions were previously reported to require heating at 90°C to achieve high product yields [6]. The Sundararaju procedure employed precatalyst **2** (4 mol %) and *t*-BuOK (2

equiv.) as base in MeOH under white LEDs (4 × 7 W) to efficiently promote α-C-methylation across a broad range of aromatic ketones in high yields (Figure 2B,C). The authors stated that the temperature increases to a maximum of 42°C due to heat generated by the white LEDs. The α-C-methylation of ketones using precatalyst **2** in the absence of photoirradiation was previously reported at temperatures of 60–80°C [9].

For both methods, various mechanistic experiments were performed to gain insight into the role of photoirradiation in facilitating the ketone α-C-alkylation processes. Renaud, Poater, and coworkers found that no light-induced ligand exchange of precatalyst **1** occurred in the absence of base, which suggested a Hieber-type activation of **1** in the presence of NaOH at room temperature (Figure 2D). Control experiments also revealed that blue light

photoirradiation was essential for the key hydrogenation and dehydrogenation steps of the BH cycle, with no conversion observed in the absence of light. As such, the authors proposed a light-mediated dehydrogenation of primary alcohols to form the corresponding aldehydes alongside an iron hydride species, followed by a base catalyzed aldol condensation and light-mediated hydrogenation of the resulting enone intermediate to generate the observed alkylated ketone products. Sundararaju and coworkers employed UV-Vis spectroscopy to determine that precatalyst **2** undergoes a red shift upon irradiation with white light, with an isosbestic point of 332 nm, which suggested that a carbon monoxide ligand can dissociate from **2** under these conditions. A control reaction using optimized reaction conditions except at 40°C without photoirradiation resulted in no product formation, while a separate experiment involving photoirradiation for 1 h followed by stirring in the dark for 23 h produced the methylated product in only 14% yield. These experiments confirmed that photoirradiation by white light is crucial for product formation and that it must be maintained throughout the course of the reaction to obtain high product yields.

These two independent studies highlighted how (cyclopentadienone)iron carbonyl complexes can harvest light to enable the BH  $\alpha$ -C-alkylation of ketones at near room temperatures. These advances have inspired related investigations that demonstrate the room temperature BH C-alkylation/allylation of indoles, arylacetonitriles, oxindoles, and ketones using visible light irradiation [10–13]. In a complementary study, Quintard, Kochem, and coworkers have developed novel isonitrile-substituted (cyclopentadienone)iron complexes, which exhibit a bathochromic shift in the light absorption spectra in comparison to precatalyst **2** [14]. These modified precatalysts can be photoactivated using 365 nm LEDs and used in combination with chiral enantiopure secondary amine

organocatalysts for the enantioselective  $\gamma$ -functionalization of allylic alcohols [15].

Looking forward, there are exciting opportunities for further development in this burgeoning area of sustainable synthesis. It has been clearly demonstrated that the integration of photoirradiation can enable important BH processes to occur under milder reaction conditions, further enhancing the sustainability metrics associated with this synthetic approach. It is anticipated that this strategy will be extended toward alternative bond-forming BH processes at room temperature, in addition to enabling novel transformations that do not occur under thermal conditions. Furthermore, the development of novel catalysts that are capable of efficiently harvesting light, particularly using lower energy visible light, may lead to the development of BH processes with broader substrate/product compatibility. Detailed studies into the mechanisms of these complex light-mediated catalytic processes will be important for further development in addition to careful design of reaction setups to unambiguously differentiate the impacts of photoirradiation and thermal energy (due to heat generation from light sources) upon reaction outcomes. While this forum article highlights recent advances using (cyclopentadienone)iron carbonyl complexes in the presence of light, the continued investigation into alternative catalyst systems that utilize other transition metals and ligand scaffolds will undoubtedly feature prominently in future developments within this domain.

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### Declaration of interests

The authors declare no competing interests.

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