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Direct synthesis of dialkyl ketones from deoxygenative cross-coupling of carboxylic acids and alcohols†

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Carboxylic acids and alcohols are widely commercially available, structurally diverse, benchtop stable, and ubiquitous in both natural products and pharmaceutical agents, making them ideal coupling partners for organic synthesis. Though various transformations have been developed by enabling the activation and subsequent cross-coupling of carboxylic acids and alcohols in separate contexts, the direct coupling of these two structural motifs to build value-added molecules is rare. Herein, we developed a direct deoxygenative cross-coupling between carboxylic acids and alcohols for dialkyl ketone synthesis *via* photoredox/nickel dual catalysis. This protocol provides a powerful platform to construct a wide range of structurally diverse ketone scaffolds with broad substrate scope, good functional group tolerance, step-economy and mild reaction conditions, using simple and readily available substrates. Moreover, the large-scale synthesis and late-stage functionalization of biological molecules also demonstrate the potential practicality.

Due to the prevalence of ketones in natural products and bioactive drugs[1] and their central role as versatile reactants in synthetic chemistry,[2] the development of powerful methods for ketone synthesis is highly desirable. In this context, a vast number of methods have been developed to construct ketones. Typically, ketone synthesis most often relies upon the addition of an organometallic reagent to an aldehyde followed by oxidation[3] or more recently, the use of carboxylic acid derivatives to couple with various nucleophiles (Fig. 1a).[4] While significant contributions have been made to this field, these methods typically necessitate a prefunctionalization step and often require nonabundant starting materials, such as air- and moisture-sensitive alkyl organometallics,[4e,k–l] and organoboron and organosilicon reagents,[4c–e] which are not step-economical and might lead to issues with functional group tolerance and waste generation, thereby limiting the reaction scope and practicality. To address this problem, we sought to develop a robust platform to deliver ketones utilizing easily accessible and commercially available starting materials under mild conditions.

Carboxylic acids and alcohols are widely commercially available, structurally diverse, benchtop stable, relatively

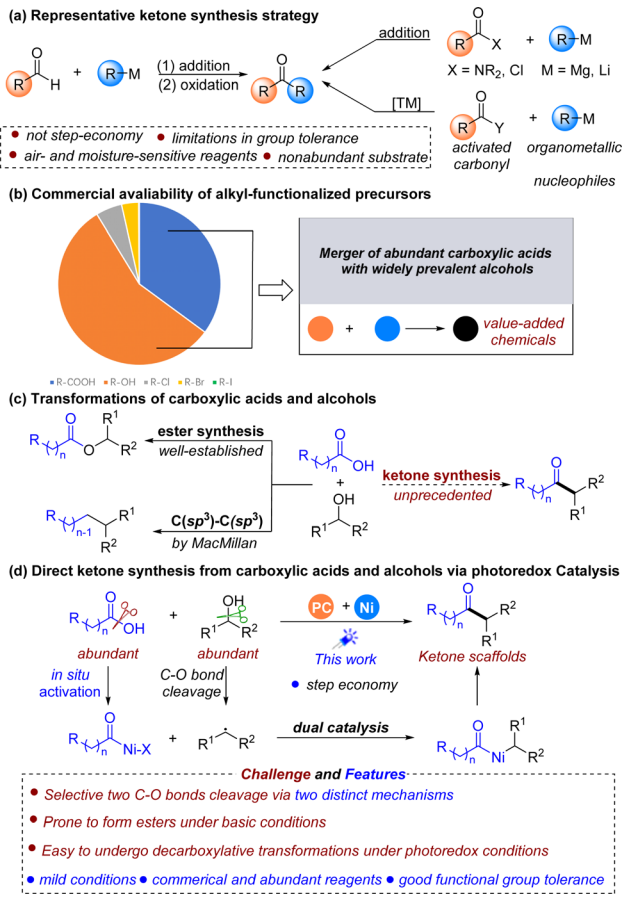

Fig. 1 Background of ketone synthesis and cross-coupling of carboxylic acids and alcohols.

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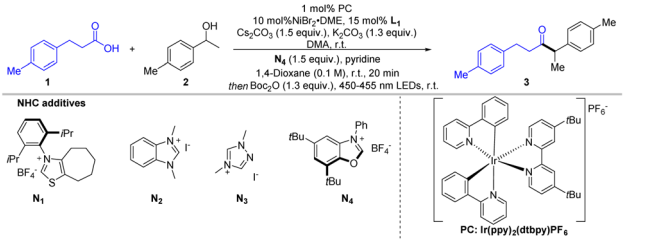
nontoxic, and ubiquitous in both natural products and pharmaceutical agents,[5] making them ideal coupling partners for organic synthesis (Fig. 1b). In recent years, a variety of transformations have been developed by enabling the activation and subsequent cross-coupling of carboxylic acids and alcohols *via* metallaphotoredox catalysis in separate contexts.[6] The direct coupling of these two prevalent structural motifs to build value-added molecules is significantly rare but highly of interest. Conventionally, alcohols and carboxylic acids are most commonly coupled to form esters,[7] and fragment cross-coupling of these two structural motifs has been explored to a lesser extent. Recently, the efficient direct coupling of carboxylic acids and alcohols to forge new C(sp^3)–C(sp^3) bonds has been developed *via* an N-heterocyclic carbene (NHC)-promoted deoxygenation process by the MacMillan group (Fig. 1c, left).[8] Despite this great achievement, developing new types of cross-coupling reactions between these two molecules has remained an appealing yet elusive goal. Considering the importance of ketone scaffolds, we wondered if diverse ketones could be accessed from the direct coupling of abundant carboxylic acids and alcohols, where acids serve as acyl electrophiles, and alcohols serve as nucleophiles (Fig. 1c, right). On this subject, Hong developed a photoinduced method for synthesizing ketones from alcohols and carboxylic acid derivatives through NHC catalysis under mild reaction conditions.[6g] This approach worked well for benzoic acid, but was not effective for the alkanoic acid substrates. As a consequence, developing an efficient and new catalytic methodology to convert carboxylic acids and alcohols into dialkyl ketone scaffolds is still highly of interest and would complement Hong's strategy.

However, direct coupling of these two structural motifs forming ketones in a desired manner is not as easy as might be expected due to the potential competing cleavage of two C–O bonds in these two molecules. The main challenge for realizing this transformation was how to selectively achieve C–O bond cleavage in both alcohols and carboxylic acids *via* two distinct mechanisms. In recent years, the combination of photoredox and nickel catalysis has emerged as a powerful tool in chemical bond construction,[9] which might provide an alternative protocol for the ketone preparations from alcohols[10,11] and acids. In such a reaction, a transition-metal catalytic unit could engage sequentially with the acyl electrophiles formed *in situ* from carboxylic acids[12] and radicals generated from alcohols through oxidative addition[13] and radical capture.[12a,14] Then the resulting diorganonickel adduct undergoes reductive elimination to afford the desired ketone scaffolds (Fig. 1d). Nevertheless, to achieve this goal, other potential competing reactions, such as the esterification reaction[6l] and decarboxylative transformation,[15,6e,h,i] which are commonly encountered under basic and photoredox conditions, are also a big problem and need to be avoided.

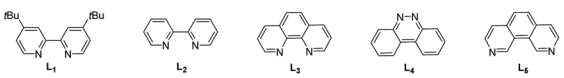
In this work, we developed a photoredox-catalyzed synthetic protocol for diverse dialkyl ketone synthesis from naturally abundant carboxylic acids and alcohols under mild conditions with good functional group compatibility, and broad substrate scope. This protocol features no protection and deprotection steps. Given the structural diversity of carboxylic acids and alcohols, the success of this protocol could potentially enhance the synthesis of complex ketones. More significantly, ketones can be directly constructed from two abundant starting materials, thus expanding the existing ketone synthetic routes.

To start our investigation, the synthetic method for ketones was explored with the commercially available carboxylic acid **1** and alcohol **2** as the model substrate (Table 1). Based on previously reported elegant carboxylic acid activations in ketone synthesis,[6h,j,12a,14] Boc_2O was chosen as the activating reagent to generate mixed anhydride *in situ* from carboxylic acids. After extensive reaction condition screening (see the ESI† for details), we were pleased to find that the corresponding ketone **3** was obtained in 73% isolated yield using **N4** as the alcohol-activating agent and Cs_2CO_3/K_2CO_3 and pyridine as bases in the presence of a catalytic amount of $NiBr_2$·DME and **L1** under visible light irradiation in DMA/1,4-dioxane using $Ir(ppy)_2$(dtbbpy)PF_6 as the photocatalyst (entry 1). The thiazole-based NHC reagent **N1** and other simple triazole-based NHC molecules **N2** and **N3** are ineffective in this transformation (entry 2). These initial optimization studies revealed the importance of NHC types for the reaction efficiency. A slightly lower yield was obtained when *t*BuOMe was used instead of 1,4-dioxane (entry 3). Other solvents, such as benzotrifluoride, tetrahydrofuran and acetonitrile were also tested and the results indicated that

Table 1 Optimization of reaction conditions[a]



Entry	Variation from optimized conditions	Yield[b] (%)
1	None	75 (73)
2	$\mathbf{N_1}$, $\mathbf{N_2}$, and $\mathbf{N_3}$ instead of $\mathbf{N_4}$	0, trace, 0
3	BuOMe instead of 1,4-dioxane	60
4	PhCF, THF, and MeCN instead of 1,4-dioxane	54, 13, <10
5	$\mathbf{L_2}$, $\mathbf{L_3}$, $\mathbf{L_4}$, and $\mathbf{L_5}$ instead of $\mathbf{L_1}$	37, 32, 30, trace
6	5 mol% $NiBr_2$·DME, 7.5 mol% **L1**	78 (75)
7	No light irradiation	0
8	No NHC	0
9	No PC	0



[a] Reaction conditions: **1** (0.3 mmol), **2** (0.42 mmol), 1 mol% $Ir(ppy)_2$(dtbbpy)PF_6, 10 mol% $NiBr_2$·DME, 15 mol% $\mathbf{L_1}$, Cs_2CO_3 (0.45 mmol), K_2CO_3 (1.3 equiv.), DMA (3 mL), **N4** (1.5 mmol), pyridine (1.4 equiv.), 1,4-dioxane (3 mL), Boc_2O (1.3 equiv.), 450–455 nm LEDs. [b] Yields of **3** were determined by ^{1}H NMR spectroscopy with mesitylene as an internal standard and the isolated yield is shown in parentheses. r.t., room temperature; NHC, N-heterocyclic carbene; DME, 1,2-dimethoxyethane; DMA, *N*,*N*-dimethylacetamide.

1,4-dioxane was more suitable for this transformation (entry 4). Screening of a range of ligands revealed that acylation product **3** could also be generated, albeit in diminished yields (entry 5). A slight increase in the yield was observed on reducing the amount of $NiBr_2 \cdot DME$ and **L1** (entry 6). Light irradiation was essential for this transformation as it did not progress under dark conditions (entry 7). Further control experiments showed that NHC and the photocatalyst were indispensable in this transformation (entries 8–9). It was worth noting that the side products due to decarboxylation and esterification could be detected.

With the optimized reaction conditions in hand, we then investigated the scope of carboxylic acids and alcohols (Fig. 2). We first probed the ability of various aliphatic acids for cross-coupling in our system (**3–22**). Substituted phenyl propionic acid and butyric acid derivatives yielded desired products in moderate to good yields (**3–10**). A range of aliphatic acids, including linear and cyclic acids, were amenable substrates, providing the cross-coupling products in good to excellent yields (**11–18**). Notably, carboxylic acids with additional functionalities were also compatible with this protocol. For example, various functional groups, such as alkyl chloride, ester, protected amine and ketone remain intact to furnish the corresponding cross-coupling products, potentially allowing for the subsequent orthogonal functionalization (**15–19**). In particular, carboxylic acids with synthetic handles, such as halide (**10** and **15**), were readily incorporated into the accessible ketone scaffolds, which highlights the potential applications for the incorporation of these scaffolds into more complex targets. Products derived from alkenyl acids were also tolerated, as demonstrated by β,β-dimethylacrylic acid (**20**) and lineoic acid (**21**). These results show the great potential for structural modification and resource utilization of naturally existing carboxylic acids. Heterocycle-containing carboxylic acid reacted smoothly in this system, affording the deoxygenated cross-coupling product in moderate yield (**22**). Of particular note is that substituted phenyl acetic acid and hindered carboxylic acids (**23**), such as N-Boc proline (**24**) and 2-phenyl propionic acid (**25**) were not suitable for this transformation, yielding no product. Additionally, experiments with various benzoic acid derivatives were also performed under the standard conditions. Unfortunately, these substrates were not compatible with our system (**26–27**). This phenomenon could be attributed to the diminished reactivity in carboxylic acid activation.

Having established that this transformation tolerates various carboxylic acids, we turned our attention towards evaluating the scope of alcohol components. Consistent with our expectation, we were pleased to find that a wide variety of primary alcohols were successfully applied in this protocol, furnishing the desired ketones in moderate yields (**28–32**). The instability of the corresponding alkyl radicals originating from alcohols could be responsible for the relatively lower yield (**29–32**). Of particular note is that the developed protocol was also tolerant of the alcohol containing protected amine, as demonstrated by **31**, which was isolated in 40% yield. Notably, the alkene-retained product (**32**) was obtained in 39% yield, while intramolecular radical cyclization was not observed. This result suggests the faster capture of the alkyl radical than 5-*endo*-trig cyclizations under the specific reaction conditions. Secondary alcohols, especially cyclic alcohols, ranging from four- to seven-membered rings, were found to be viable coupling partners, successfully delivering the corresponding products in 40–61% yields (**33–38**). It is noteworthy that sterically encumbered polycyclic alcohols, such as 2-adamantanol, were employed without an appreciable decrease in the reaction efficiency (**37**). A relatively increased yield was obtained when benzyl alcohols were used, which is in line with the stability of the corresponding radical intermediates from alcohols (**38–41**). With these positive results in hand, we finally tested the feasibility of tertiary alcohols, such as 1-methylcyclohexanol and *tert*-butanol, and the experimental results indicated that no corresponding cross-coupling product could be observed (**42–43**).

Given the exceptionally mild and simple conditions, we sought to demonstrate the utility of this operationally convenient method in the late-stage functionalization of complex molecules. As shown in Fig. 3, the oxaprozin analogue **44** could be generated efficiently with our strategy in 55% yield. Lithocholic acid analogues could also underwent smoothly, providing the deoxygenative ketone in 60% and 62% yield, respectively (**45** and **46**). With stearic acid as an acyl donor, the

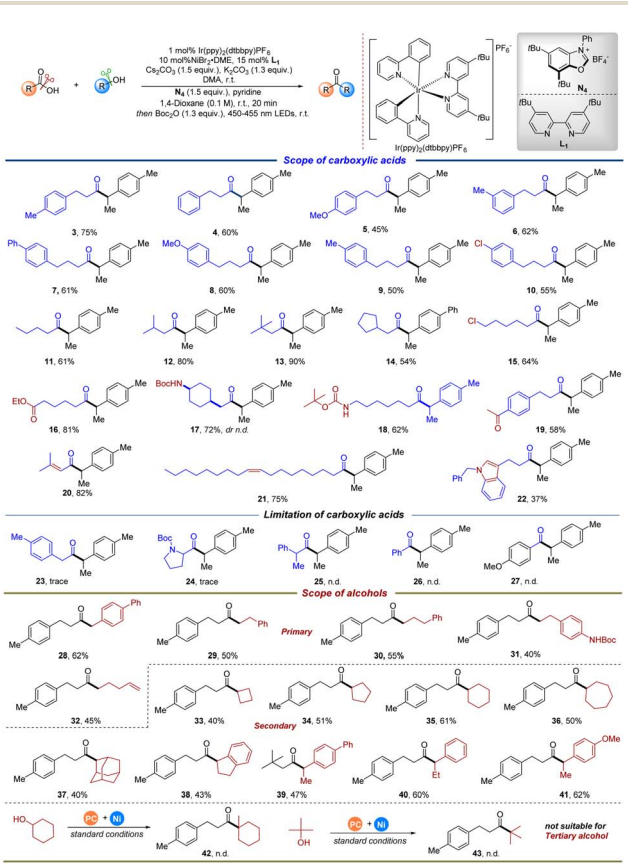


Fig. 2 Substrate scope for ketone synthesis. Standard conditions: carboxylic acid (0.3 mmol), alcohol (0.42 mmol), 1 mol% $Ir(ppy)_2(dtbbpy)PF_6$, 10 mol% $NiBr_2 \cdot DME$, 15 mol% **L1**, Cs_2CO_3 (0.45 mmol), K_2CO_3 (1.3 equiv.), DMA (3 mL), **N4** (1.5 mmol), pyridine (1.4 equiv.), 1,4-dioxane (3 mL), Boc_2O (1.3 equiv.), 450–455 nm LEDs. Isolated yield.

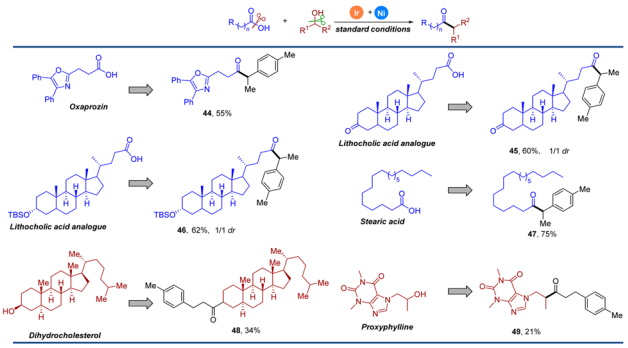


Fig. 3 Late-stage functionalization. Standard conditions: carboxylic acid (0.3 mmol), alcohol (0.42 mmol), 1 mol% $Ir(ppy)_2(dtbbpy)PF_6$, 10 mol% $NiBr_2 \cdot DME$, 15 mol% L_1, Cs_2CO_3 (0.45 mmol), K_2CO_3 (1.3 equiv.), DMA (3 mL), **N4** (1.5 mmol), pyridine (1.4 equiv.), 1,4-dioxane (3 mL), Boc_2O (1.3 equiv.), 450–455 nm LEDs. Isolated yield.

transformation proceeded efficiently, yielding **47** in 75% yield. A naturally occurring steroid was also successfully employed and afforded the corresponding product **48** in moderate yield. Bronchodilator proxyphylline showed good reactivity to deliver the product **49** in 21% yield. These results show great potential for the structural modification of an array of complex biological molecules, especially in medicinal chemistry.

To further showcase the synthetic utility of this developed strategy, a large-scale experiment was conducted, providing the desired ketone **3** in 71% yield (Fig. 4). There was almost no change in the chemical yield, suggesting that large-scale chemical production might be possible.

To gain further insight into the reaction mechanism, a series of mechanistic studies were performed (Fig. 5). In the presence of radical trap TEMPO, the reaction was completely shut down (Fig. 5a), indicating that a radical intermediate might be involved in this transformation. More importantly, a benzyl-trapped product, 2,2,6,6-tetramethylpiperidin-1-yl benzoate **50** was observed *via* high resolution mass spectrometry, further supporting that the reaction proceeds through a radical deoxygenative pathway and the intermediacy of a benzylic radical. Furthermore, the generation of a benzylic radical from **2** in the reaction also could be demonstrated by the observation of **51** when phenyl vinyl sulfone was added to the system. Additionally, to further elucidate the possible reaction pathway, a radical clock experiment was performed with cyclopropanemethanol **52** and the observation of ring-opening product **53** suggested the involvement of a radical intermediate (Fig. 5b). In our hypothesis, carboxylic acid is activated by Boc_2O, leading to the corresponding acyl-Ni oxidative insertion complex. The control experiments are consistent with this hypothesis. First, when

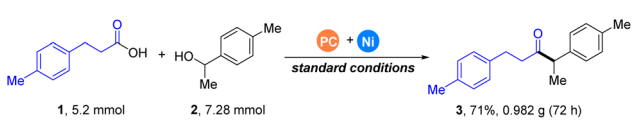


Fig. 4 Large-scale synthesis.

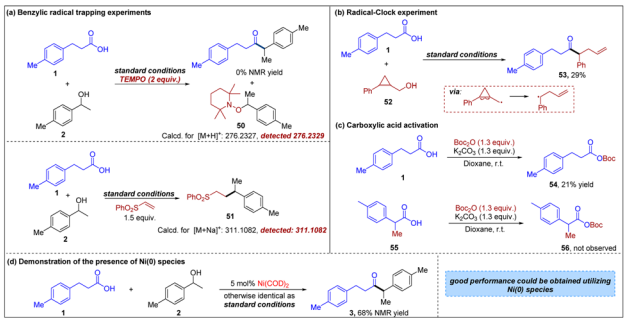


Fig. 5 Mechanistic studies.

primary carboxylic acid **1** is treated with Boc_2O and K_2CO_3, moderate conversion to the expected mixed anhydride is observed within 3 h (Fig. 5c). In the parallel experiment using secondary carboxylic acid **55**, there is no observable formation of the mixed anhydride **56** at the same time point, resulting in the formation of the acyl–Ni complex being difficult. These results are in line with the limitations of carboxylic acids shown in Fig. 2. It is noteworthy that the desired ketone **3** could be detected in 68% NMR yield when $Ni(COD)_2$ was used in place of $NiBr_2 \cdot DME$ (Fig. 5d), indicating the presence of Ni(0) species.

Based on the previously reported literature[6d,f,16] and the aforementioned mechanistic studies, a plausible mechanism for this transformation is proposed in Fig. 6. The proposed mechanism starts with the condensation of alcohol and NHC ($\mathbf{N_4}$), providing activated alcohol **57**. Upon irradiation with visible light, the photocatalyst $Ir(ppy)_2(dtbbpy)PF_6$ **I** is known to access the highly oxidizing excited state species **II** ($^*Ir^{III}$) ($E_{1/2}^{red}$ $^*Ir^{III}/Ir^{II}$ = + 0.66 V *vs.* SCE),[17] which could be reductively quenched by the activated alcohol **57**, affording aminium radical cation **58**. Then a deprotonation process occurred at the α-position of **58**, yielding radical intermediate **59**. Subsequent β-scission occurred, thus generating the key alkyl intermediate **60**. The nickel catalytic cycle is initiated by the oxidative addition of the Ni(0) catalyst **62** to an *in situ*-activated carboxylic acid **61** formed by Boc_2O under basic conditions, to afford Ni(II) species **64**. Subsequently, efficient trapping of the alkyl radical

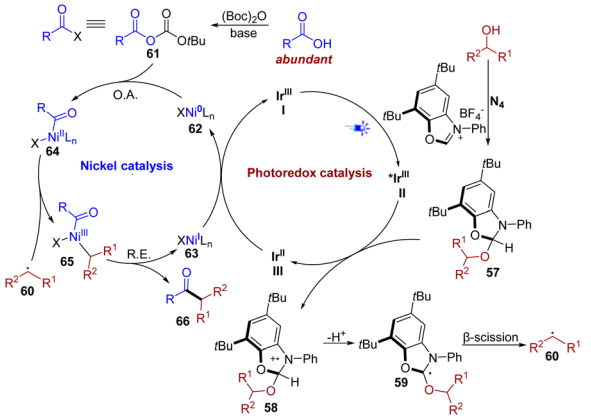


Fig. 6 A plausible mechanism.

60 provides Ni(III) complex **65**, which undergoes reductive elimination to yield the desired ketone **66** and Ni(I) complex **63**. Finally, the single electron transfer between Ni(I) species **63** and reduced photocatalyst **III** (Ir^{II}) regenerates the ground-state photocatalyst **I** (Ir^{III}) and the Ni(0) catalyst, completing both catalytic cycles.

Conclusions

In summary, we have developed a direct deoxygenative cross-coupling between carboxylic acids and alcohols for ketone synthesis *via* photoredox/nickel dual catalysis under mild conditions. This protocol provides a powerful platform to construct a wide range of structurally diverse ketone scaffolds with broad substrate scope, good functional group tolerance, step-economy and mild reaction conditions, using simple and readily available carboxylic acids and widely abundant alcohols as starting materials. Given the structural diversity of carboxylic acids and alcohols, the success of this metallaphotoredox-catalyzed deoxygenative cross-coupling protocol could potentially enhance the synthesis of complex ketones. In addition, this developed method will promote the resource utilization of naturally abundant acids and alcohols and enhance the preparation of ketone scaffolds. The exact roles of carboxylic acids and alcohols were demonstrated by mechanistic studies, as we hypothesized, that the carboxylic acids provide the acyl group and the alcohols afford the alkyl group. Asymmetric transformations of carboxylic acids and alcohols into ketones are underway in our laboratory and will be reported in due course.

Data availability

The ESI† is available and includes experimental procedures for all reactions and characterization data for all products, including ^{1}H and ^{13}C spectra and HRMS data.

Author contributions

Conceptualization and funding acquisition were done or provided by B. Y.; resources and supervision were done by B. Y.; project administration, data curation, investigation and formal analysis were done by B. Y. and R.-Y. T.; writing was done by B. Y. and revised by B. Y. and R.-Y. T.

Conflicts of interest

There are no conflicts to declare.

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