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Nickel-Catalyzed Three-Component Reductive Alkylacylation of Electron-Deficient Activated Alkenes

Lin Wang and Chuan Wang*

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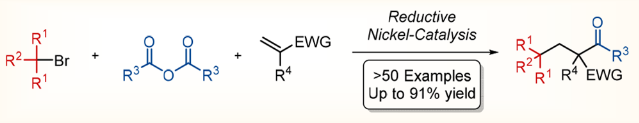
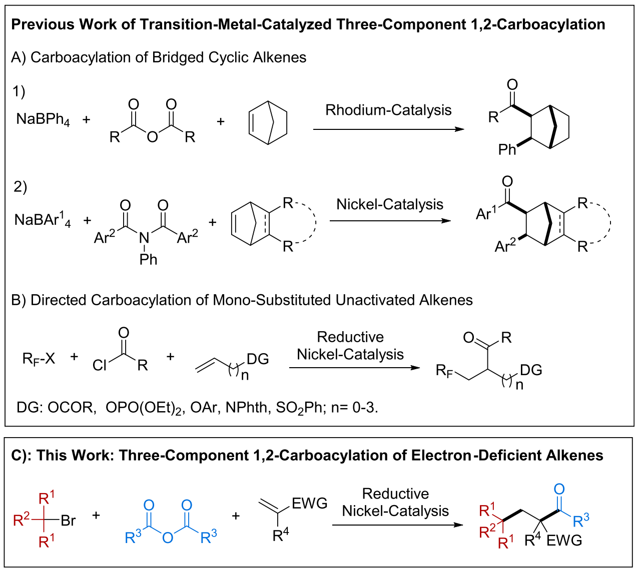
ABSTRACT: Herein, we present a nickel-catalyzed three-component reductive alkylacylation of electron-deficient activated alkenes with tertiary alkyl bromides and acid anhydrides. This method enables the efficient preparation of a variety of ketones with broad substrate scope and high functionality tolerance starting from simple precursors. On the basis of the preliminary mechanistic investigations, a catalytic cycle involving the synergistic interaction of nickel, zinc, and $MgCl_2$ is proposed as the major reaction pathway.



Transition-metal-catalyzed 1,2-dicarbofunctionalization of alkenes represents a powerful method for rapid increasing of molecular complexity via concomitant formation of two C−C bonds across an olefinic unit in one step and thus has experienced a surge of developments in recent years.[1−3] Among various dicarbofunctionalizations, carboacylation[4−8] of alkenes is an important subset, providing a novel approach to prepare ketones, which are not only a ubiquitous moiety in natural products, pharmaceuticals, and agrochemicals but also versatile building blocks in organic synthesis. Fully intermolecular three-component carboacylation allows for preparation of structurally complex products starting from simple precursors and thus is highly desirable. However, major advances in carboacylation are constrained to an intramolecular one-component version[4] and a few two-component variants.[5] In most of these cases, the substrates tether a pendant alkene moiety. To date, successful examples of transition-metal-catalyzed three-component carboacylation are rare. In 2002, Miura et al. reported a rhodium-catalyzed phenylacylation of norbornene with sodium tetraphenylborate and acid anhydrides (Scheme 1A, eq 1).[6] Very recently, Stanley et al. successfully applied imides as an acyl source in the nickel-catalyzed arylacylation of bridged cyclic alkenes (Scheme 1A, eq 2).[7] Since the pioneering work of Nevado,[2w] rapid progress has been achieved in nickel-catalyzed reductive three-component difunctionalization of alkenes using alkyl and aryl (pseudo)-halides.[2x−ad,8,9] According to this strategy, Chu and co-workers developed a perfluoroalkyl acylation of monosubstituted alkenes bearing a chelation functionality as a directing group under reductive nickel catalysis (Scheme 1B).[10] The key step of this reaction lies in the addition of electron-deficient perfluoroalkyl radicals to electron-rich alkyl-substituted unactivated alkenes followed by trapping with an acyl Ni(II) complex. Therefore, expansion of the scope of transition-metal-catalyzed three-component carboacylation regarding the alkene precursors is still needed. Herein, we report a nickel-catalyzed reductive alkylacylation of electron-deficient activated alkenes with tertiary alkyl bromides and acid anhydrides, which is complementary to the aforementioned methods (Scheme 1C).[11]

Scheme 1. Transition-Metal-Catalyzed Three-Component 1,2-Carboacylation of Various Types of Alkenes



For optimization of the reaction conditions, *tert*-butyl bromide (**1a**), benzoic anhydride (**2a**), and *tert*-butyl acrylate (**3a**) were utilized as the benchmark substrates. Systematic

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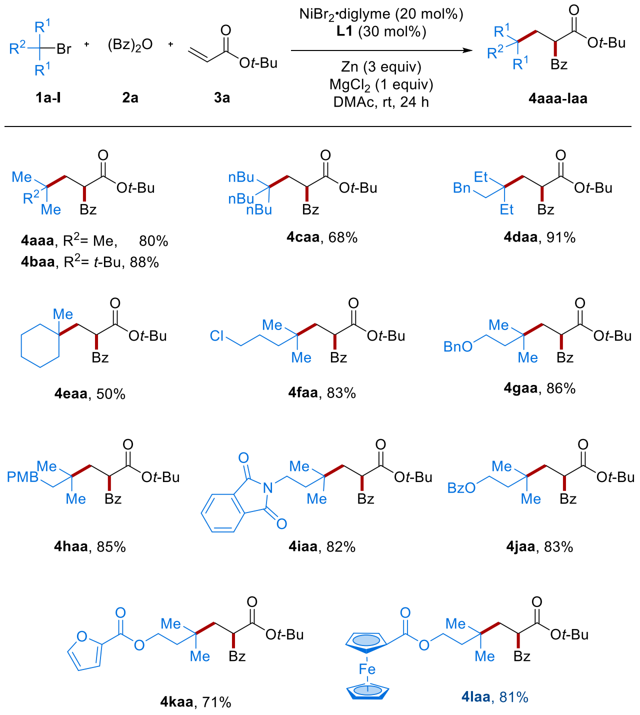
screening of various parameters allowed us to define the optimal conditions as follows: $NiBr_2$·diglyme (20 mol %) as a precatalyst, bis(pyridine) **L1** (30 mol %) as a ligand, Zn as a reductant (3 equiv), and $MgCl_2$ (1 equiv) as an additive in DMAc at room teperature for 24 h.[12] Under this condition, the alkylacylation product **4aaa** was obtained in 80% yield. After establishing the optimal reaction conditions, we started to evaluate the substrate scope of this Ni-catalyzed three-component 1,2-alkylacylation reaction. First, a series of tertiary alkyl bromides **1a−l** were reacted with benzoic anhydride (**2a**) and *tert*-butyl acrylate (**3a**), and the results are summarized in Scheme 2. To our delight, all of these reactions proceeded smoothly under the standard conditions, furnishing the corresponding products **4aaa−laa** in good to high yields. Unfortunately, primary and secondary alkyl bromides and iodides turned out to be unsuitable precursors for our reaction due to a high tendency to undergo a direct cross-coupling reaction with benzoic acid anhydride.[13,14] Moreover, the use of tertiary alkyl chlorides as substrates was also unsuccessful because the relatively inert carbon−chlorine bond could not be cleaved efficiently under this catalytic system.

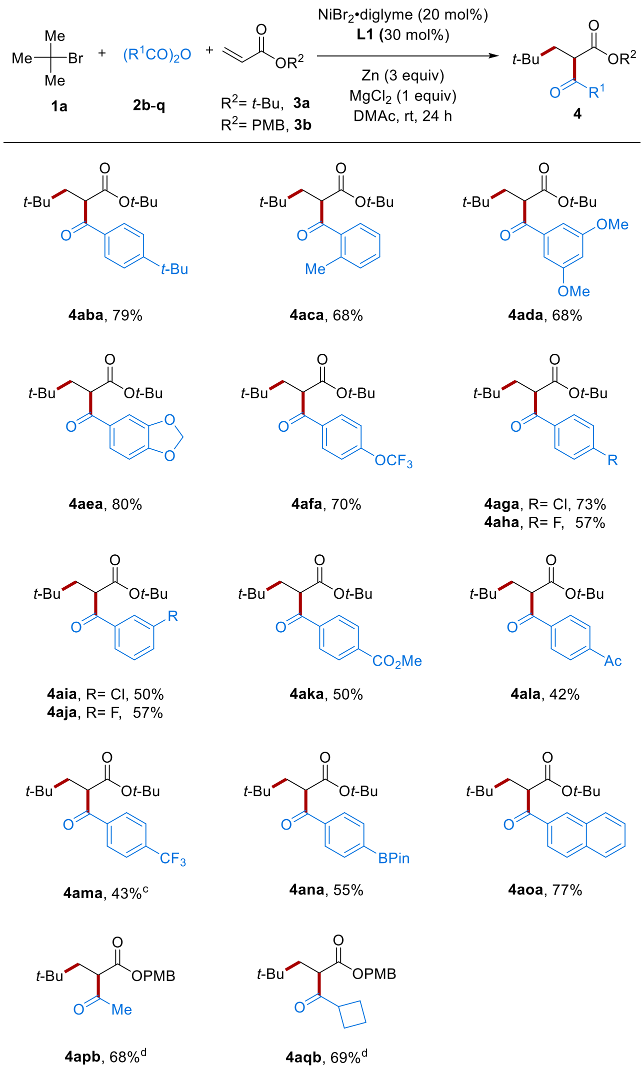
Scheme 2. Evaluation of the Substrate Scope by Variation of *tert*-Alkyl Bromides[a,b]



[a]Reactions were performed on a 0.2 mmol scale of *tert*-butyl acrylate (**3a**) using 1.5 equiv of the tertiary bromides **1a−l**, 1.5 equiv of benzoic anhydride (**2a**), 20 mol % $NiBr_2$·diglyme, 30 mol % of ligand **L1**, 3 equiv of Zn, and 1 equiv of $MgCl_2$ in 0.5 mL of DMAc at room temperature for 24 h. [b]Yields of the isolated products after column chromatography.

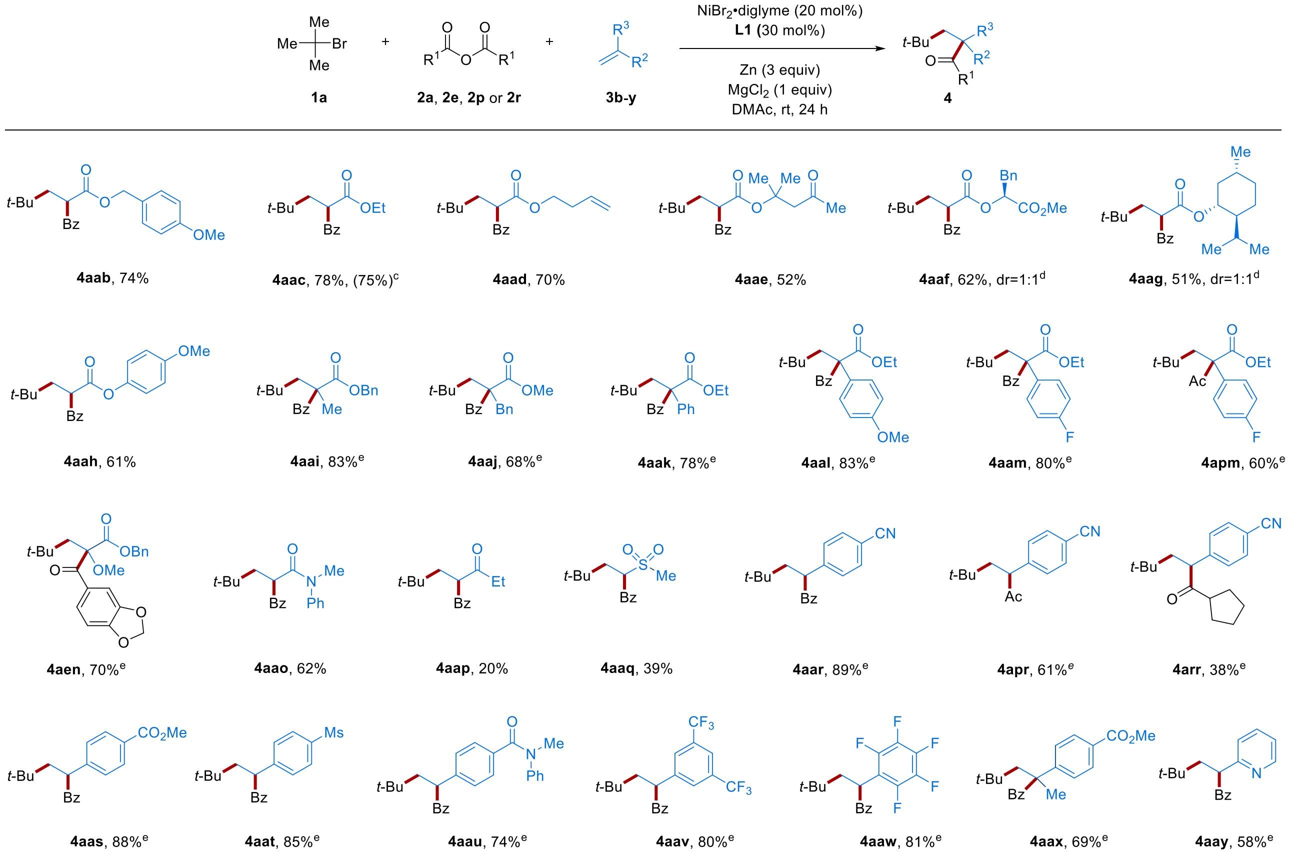
Next, we continued to investigate the substrate spectrum of this Ni-catalyzed reaction by varying the structure of the acid anhydrides (Scheme 3). Both electron-donating and electron-withdrawing groups on different positions of the phenyl ring of benzoic anhydrides were tested. Gratifyingly, these reactions afforded the desired coupling products **4aba−aoa** in moderate to good efficiency. In general, higher yields were achieved in the case of electron-donating substituents. Under modified reaction conditions, aliphatic anhydrides posed no problem, and the corresponding products **4apb** and **4aqb** were obtained in good yields. No desired product was formed in the case of cinnamic acid anhydride as a precursor.[13]

Scheme 3. Evaluation of the Substrate Scope by Variation of Acids Anhydrides[a,b]



[a]Reactions were performed on a 0.2 mmol scale of *tert*-butyl acrylate (**3a**) or *p*-methoxybenzyl acrylate (**3b**) using 1.5 equiv of *tert*-butyl bromide (**1a**), 1.5 equiv of the acid anhydrides **2b−o**, 20 mol % of $NiBr_2$·diglyme, 30 mol % of ligand **L1**, 3 equiv of Zn, and 1 equiv of $MgCl_2$ in 0.5 mL of DMAc at room temperature for 24 h. [b]Yields of the isolated products after column chromatography. [c]Reaction was performed at 15 °C. [d]Reactions were performed with 2 equiv of **2p** or **2q**, 4 equiv of Zn, 2 equiv of $MgCl_2$, and 4 Å molecular sieves.

Subsequently, we explored the generality of our method with respect to the alkene component (Scheme 4). First, various nonsubstituted alkyl, benzyl, and phenyl acrylates **3b−h** turned out to be pertinent substrates, providing products **4aab−aah** in moderate to good yields. Notably, the homoallyl acrylate **3d** selectively underwent the alkylacylation on the electron-deficient C−C double bond. However, in the case of β-substituted acrylates, no carboacylation reaction occurred.[13] Under the amended reaction conditions (4 equiv of Zn, 2 equiv of $MgCl_2$, and 4 Å molecular sieves), α-substituted acrylates **3i−n** could be successfully employed as the starting materials, Scheme 4. Evaluation of the Substrate Scope by Variation of Activated Alkenes[a,b]



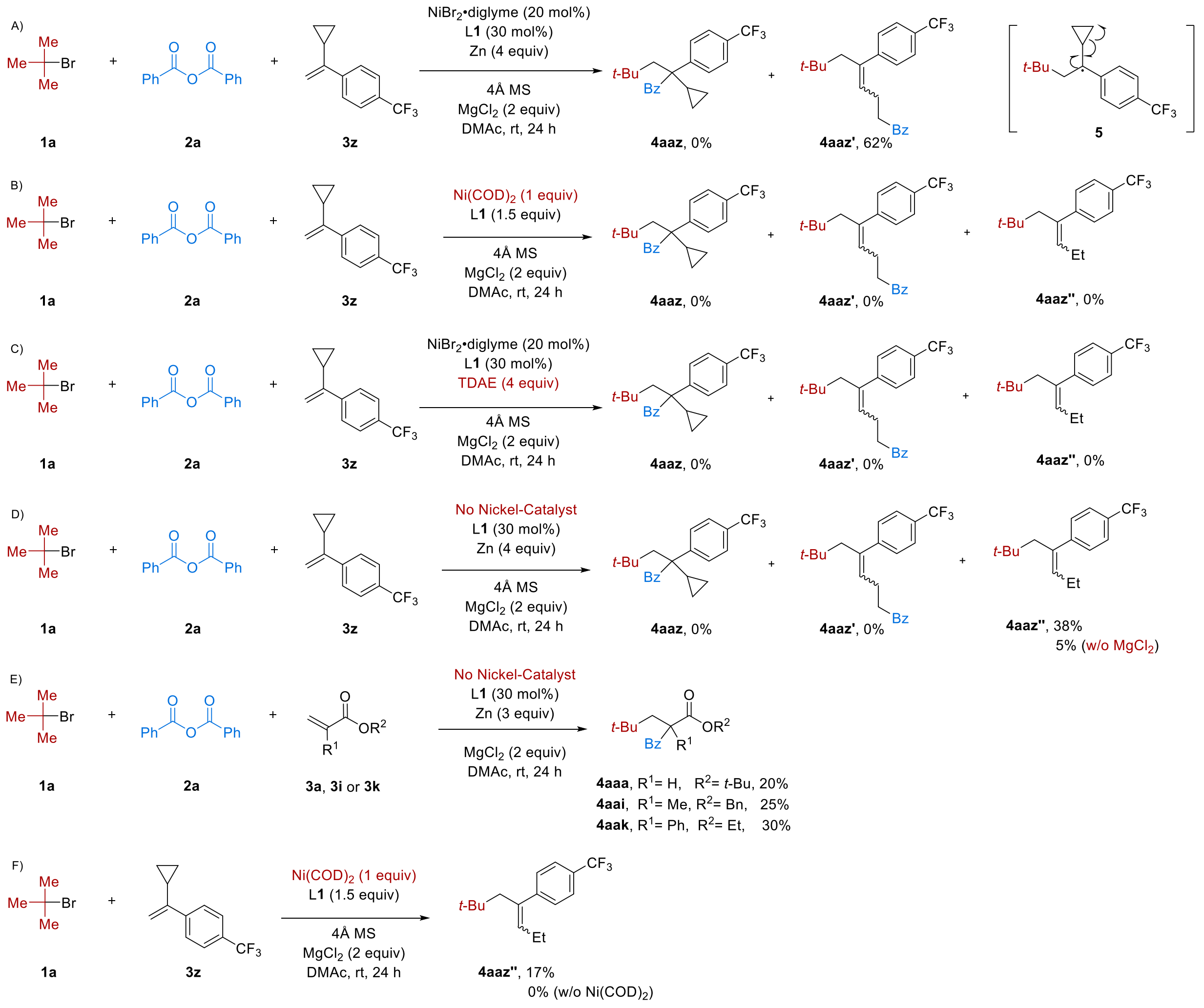
[a]Unless otherwise specified, reactions were performed on a 0.2 mmol scale of alkenes **3b−y** using 1.5 equiv of *tert*-butyl bromide (**1a**), 1.5 equiv of the anhydride **2a**, 20 mol % of NiBr$_2$·diglyme, 30 mol % of ligand **L1**, 3 equiv of Zn, and 1 equiv of MgCl$_2$ in 0.5 mL of DMAc at room temperature for 24 h. [b]Yields of the isolated products after column chromatography. [c]Reaction was performed on a 6 mmol scale. [d]Determined by ^{1}H NMR spectroscopy. [e]Reactions were performed with 2 equiv of **2a**, **2e**, **2p**, or **2r**, 4 equiv of Zn, 2 equiv of MgCl$_2$, and 4 Å molecular sieves.

delivering the coupling products **4aai−aam**, **4apm**, and **4aen** bearing a quaternary center in moderate to good yields. This method was also applicable to the α,β-unsaturated amide, ketone, and sulfone (**4aao−aaq**). Moreover, styrenes **3r−x** with electron-withdrawing substitution proved to be competent precursors in this Ni-catalyzed reaction, furnishing the corresponding products **4aar**, **4apr**, **4arr**, and **4aas−aax** in moderate to high yields. Additionally, the reaction employing 2-vinylpyridine (**3y**) also formed the alkylacylation product **4aay** in a moderate yield. Notably, this reaction could be simply scaled up to 6 mmol, giving compound **4aac** in 75% yield.

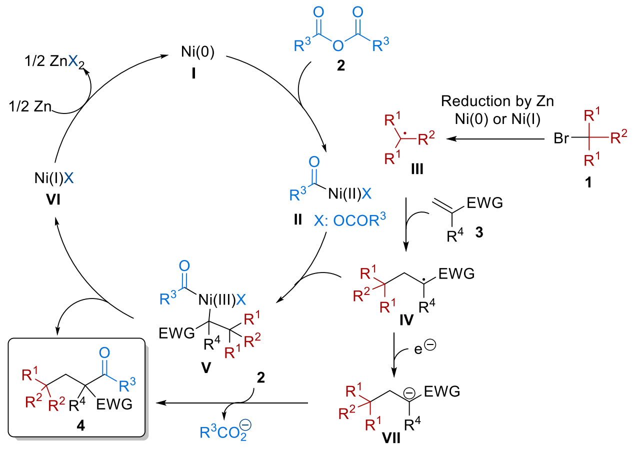
We conducted a set of control experiments to shed light on the mechanism of this Ni-catalyzed reaction (Scheme 5). First, a radical clock reaction using the α-cyclopropyl styrene **3z** as a precursor was carried out. In this case, the ring opening product **4aaz′** was afforded in 62% yield, whereas the formation of the direct coupling product **4aaz** was not observed (Scheme 5A). This result indicates an addition of *tert*-butyl radical to the olefinic unit, leading to the generation of a benzyl radical **5**, which could induce the cyclopropane ring opening. Next, we performed a stoichiometric reaction using Ni(COD)$_2$, which delivered none of compounds **4aaz**, **4aaz′**, or hydroalkylation product **4aaz″** (Scheme 5B). However, we noticed that benzoic anhydride was completely consumed, suggesting that Ni(0) favors an irreversible oxidative addition with benzoic anhydride over *tert*-butyl bromide, and the reaction ceases at this stage. This observation is consistent with Gong's report.[14a] Subsequently, Zn was replaced by tetrakis(dimethylamino)ethylene (TDAE), and no reaction occurred in this case (Scheme 5C). To study the effect of Zn in this reaction, we conducted the reaction in the absence of Ni. Although the carboacylation product was not formed, it turned out that Zn was capable of promoting the hydroalkylation reaction, producing compound **4aaz″** in 38% yield. In the absence of MgCl$_2$, the yield of **4aaz″** decreased to 5%, revealing that MgCl$_2$ could assist the Zn-mediated hydroalkylation (Scheme 5D). When the acrylates (**3a**, **3i**, or **3k**) were used as the precursors instead of the styrene derivative **3z**, the reactions without nickel could still deliver the alkylacylation products **4aaa**, **4aai**, and **4aak** in low yields (Scheme 5E). These results suggest that Zn is able to mediate the addition of alkyl bromides to the alkenes in a radical pathway, whereas nickel plays a crucial role in the step for installation of an acyl moiety. Furthermore, Ni(0) proved to be able to mediate the hydroalkylation process, as well, albeit in an efficiency lower than that with Zn (Scheme 5F). In addition, no hydroalkylation reaction occurred in the absence of Ni(COD)$_2$.

On the basis of the preliminary results of the mechanistic investigations, we proposed a plausible catalytic cycle for the major reaction pathway in Scheme 6. Initially, a Ni(0) species **I** was formed under the reductive conditions, which undergoes subsequent oxidative addition with the anhydrides **2** to afford a Ni(II) intermediate **II**. Meanwhile, the alkyl bromides **1** are reduced by Zn or a low-valent Ni species,[15] and the resultant alkyl radical **III** performs a Giese addition[16] to the electron-

Scheme 5. Control Experiments for Mechanistic Studies



Scheme 6. Proposed Reaction Mechanism



deficient alkenes **3**. Next, the generated carbon-centered radical **IV** oxidizes the Ni(II) complex **II** to provide a Ni(III) species **V**. The facile reductive elimination from **V** furnishes the alkylacylation product **4** and a Ni(I) species **VI**. The latter is reduced by Zn in the final step to regenerate the Ni(0) **I** for the next catalytic cycle. In the minor noncatalytic reaction pathway, the carbon-centered radical **IV** is reduced to a carbanion **VII** via single electron transfer from Zn, which attacks the anhydride **2** as a nucleophile to yield the coupling product **4**.

In summary, we have developed a new approach for expanding the scope of transition-metal-catalyzed three-component 1,2-carboacylation of alkenes. Under the reductive nickel catalysis, an array of electron-deficient alkenes including *α*,*β*-unsaturated carbonyl compounds and styrenes with electron-withdrawing substitution are successfully reacted with various tertiary alkyl bromides and acid anhydrides to pave a new path to synthesize a variety of ketones with high functionality tolerance. According to the preliminary mechanistic studies, the synergistic interaction of Zn and MgCl$_2$ enables the efficient C−Br bond cleavage to generate carbon-centered radicals for the following Giese addition, whereas the nickel catalyst mediates the elementary step for installation of the acyl moiety as the framework of the coupling product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03210.

> Representative experimental procedures and necessary characterization data for all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

Chuan Wang − *Hefei National Laboratory for Physical Science at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, P.R. China; Center for Excellence in Molecular Synthesis of CAS, Hefei, Anhui 230026, P.R. China;* orcid.org/0000-0002-9219-1785; Email: chuanw@ustc.edu.cn

Author

Lin Wang − *Hefei National Laboratory for Physical Science at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, P.R. China*

Complete contact information is available at:
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Notes

The authors declare no competing financial interest.

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