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Metal and Photocatalyst-Free Amide Synthesis via Decarbonylative Condensation of Alkynes and Photoexcited Nitroarenes

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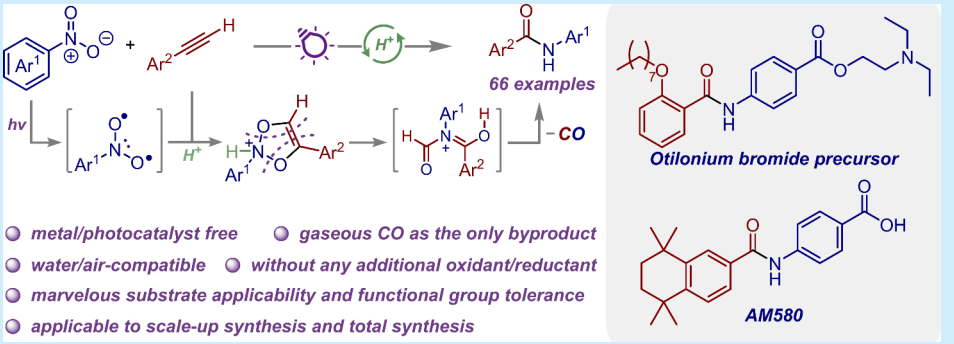

ABSTRACT: Depending on the intrinsic photoactivity of nitroarenes, we herein developed a practical Brønsted acid-catalyzed decarbonylative amide synthesis from alkynes and photoexcited nitroarenes without any metal or photocatalyst. This method exhibited compatibility with water and air, broad substrate applicability, marvelous functional group tolerance, and wide applications in scale-up synthesis, late-stage functionalization, and total synthesis. Mechanism studies and DFT calculations supported that a 1,3,2-dioxazole intermediate was involved, and gaseous carbon monoxide was the only byproduct during amide construction.

Amide is one of the most essential structural motifs in life science and also widely exists in natural products and pharmaceutical compounds as well as organic materials.[1] Traditionally, the synthesis of amides generally depends on active carboxylic acid derivatives such as acid chlorides and anhydrides or a combination of carboxylic acids and stoichiometric amounts of activating reagents that usually lead to toxic chemical waste byproducts.[2] Although millions of amides have been obtained successfully, these synthetic strategies still suffer from water- or air-sensitive conditions, tedious protection−deprotection processes, and unattainable reactivity with electron-deficient amines, especially arylamines with electron-withdrawing groups, as nucleophiles. Besides amines, nitroarenes have been treated as another potential aromatic nitrogen source with more accessibility and stability and lower cost.[3] Several years ago, the Hu group developed a series of impressive amidation reactions of esters,[4] amides,[5] and halides[6] with nitroarenes. Similar protocols were also reported by Zeng,[7] Li,[8] and other groups[9] (Scheme 1a). Nonetheless, transition metal catalysts, high temperatures, and excess metallic reductants (Zn/Mn/Mg) for nitro reduction were always indispensable in these systems.

During the last decades, photochemical synthesis has been developed as an environmentally friendly, sustainable, and unique process for the construction of C−N bonds with an open-shell pathway.[10] With this powerful tool, Xie and co-workers[3f] developed a triplet synergistic catalysis approach for umpolung amidations of carboxylic acids with nitroarenes. Recently, the Wu,[11] Zeng,[12] and Zhang[13] groups independently reported the photocatalytic synthesis of *N*-aryl amides from aldehydes, alcohols, and chlorohydrocarbons through photoinduced hydrogen atom transfer (HAT) pathways (Scheme 1b). Inside these impressive systems, excess reductants including silanes[3f,11] and alkanes,[12,13] and additional metallic photocatalysts were both essential elements for the cross-couplings. Interestingly, nitroarenes were found to be a compound class with photochemical activity almost 70 years ago.[14] Very recently, the Simonetti and Leonori group[15] and the Parasram group[16] pioneered the field of applying photoexcited nitroarenes as ozone-like oxidants for oxidation of alkenes (Scheme 1c). Further applications of the chemical reactivity of the nitroarene (n, π^*) excited state have been made in oxidative cleavage of C═N[17] and C(sp^3)−H[18] bonds and skeleton editing of aromatics.[19] Importantly, the chemo-

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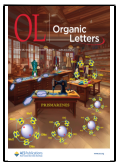

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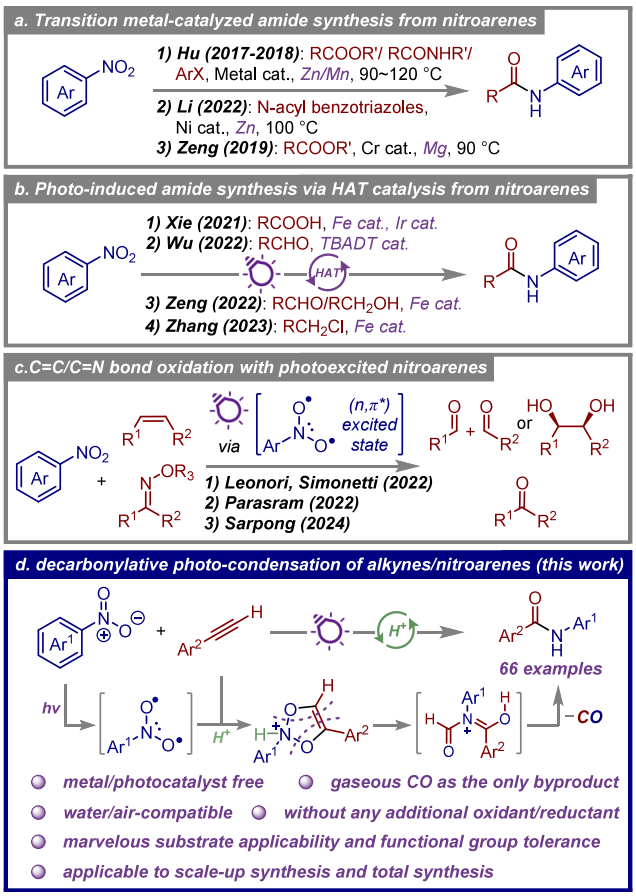
Scheme 1. Approaches for Amide Synthesis with Nitroarenes



selectivity between photoexcited nitroarenes and unsaturated bonds offers an opportunity for amide synthesis under mild and metal/photocatalyst-free conditions without complicated protection procedures of extra reactive functional groups such as −COOH and −CHO. Inspired by this thought and our previous experiences on photochemical synthesis,[20] we herein present a practical Brønsted acid-catalyzed decarbonylative condensation of alkynes and photoexcited nitroarenes without any metal or photocatalyst, releasing valuable amide products and gaseous CO as the only byproduct during amide construction (Scheme 1d). This method exhibited insensitivity toward water and air, broad substrate applicability, marvelous functional group tolerance, and wide applications in scale-up synthesis, late-stage functionalization, and total synthesis, paving a promising way for convenient amide synthesis and providing somewhat deep insights in catalyst-free photochemical processes.

Our experiments initiated with the model reaction between 3-nitroacetophenone (**19a**) and 1-(*tert*-butyl)-4-ethynylbenzene (**19b**) to optimize conditions (Table S1). After considerable efforts, we found that the reaction afforded the best result with L-proline (0.2 equiv) as catalyst and acetone as solvent under N_2 atmosphere and light irradiation at 5 °C (entry 1, more details see Tables S2−5). Variations on the acid type or removal of the acid catalyst resulted in an obvious drop in reaction efficiency (entries 2−6). Solvent scanning showed that only CH_3CN was a comparable choice to acetone among other organic solvents (entries 7−9). Remarkably, the amide synthesis reaction was able to take place in pure water (entry 10), and a yield of up to 88% was provided with a 10% acetone aqueous solution as the solvent (entry 11). Control experiments suggested light to be a requisite factor (entry 12), while air atmosphere or increased temperature just brought a slight decreases in yields (entries 13−14).

With the optimized conditions established, a variety of nitroarenes and aryl alkynes were selected as subjects to examine the generality of this method (Scheme 2). To our delight, various examples proceeded well with **19a**/**b** and afforded the corresponding amides in good to excellent yields (see **1c**−**52c**). Many functional groups, such as alkyl (**2c**−**6c**, **30c**−**32c**), ether (**7c**−**9c**, **27c**−**29c**, **39c**, **40c**), halogen (**10c**−**12c**, **34c**−**36c**), cyano (**14c**, **37c**), trifluoromethyl (**15c**, **38c**), ester (**17c**, **22c**−**25c**, **41c**), phenyl (**18c**, **33c**), and ketone groups (**19c**, **20c**), were introduced into substrates at different numbers and substituted positions, demonstrating the excellent functional group tolerance of this reaction. Among these examples, nitroarenes with electron-withdrawing groups displayed stronger reactivity than those with electron-donating groups, while the opposite characteristic was presented for aryl alkynes. Significantly, sensitive functional groups for traditional amide construction such as carboxyl and aldehyde groups were well tolerated in this system without protection (**13c**, **16c**, **21c**), affording a vital opportunity for simplification of multistep amide synthesis. Furthermore, aryl alkynes containing polycyclic and heterocyclic aromatics, including naphthalene (**42c**, **43c**), pyridine (**44c**−**46c**), thiophene (**47c**), furan (**48c**, **49c**), quinoxaline (**50c**), and quinoline (**51c**, **52c**), some of which were widely known as poisons to metal catalysts, were also examined and exhibited satisfying yields.

Significantly, expanding the applicable scope to late-stage modification of drugs and biorelevant compounds would greatly enhance the application value of our strategy (Scheme 2). For this purpose, a vast series of amide derivatives of bioactive molecules, including amide acids (**53c**, **61c**), amino alcohol (**54c**), terpenes (**55c**, **59c**), carbohydrates (**56c**, **57c**), and spice (**58c**) were synthesized in good yields. Moreover, alkynes prepared from commercial drugs including oxaprozin, gemfibrozil, ibuprofen, and naproxen were all compatible, delivering the corresponding amidation products with satisfying results (**60c**, **62c**−**64c**). Whether a synthetic reaction can be conveniently scaled up is a critical criterion to evaluate the synthetic practicability. For our amidation system, a gram-scale synthesis with **19a** (10 mmol) was carried out in batch reaction, obtaining 2.42 g of **19c** in 82.1% yield without obvious loss of efficiency (details see Figure S1). To further showcase the practicability of this method, we applied our strategy to the total synthesis of two amide-containing pharmaceuticals. As an antispasmodic and anticholinergic drug for all hyperkinesias of different causes and sites and spastic reactions due to pathological atrophy of smooth muscle fibers, otilonium bromide is traditionally synthesized with a multistep protection−deprotection protocol.[21] Impressively, these protecting steps could be directly omitted, with our strategy used as the pivotal amidation approach in synthesis, providing the desired otilonium bromide precursor in a gratifying total yield (**65**). Additionally, similar advantages on simplifying synthetic routes and promoting synthetic efficiency were also taken in the acquirement of a retinoic acid nuclear receptor (RAR) agonist AM580[22] (**66**) through straightforward condensation with *p*-nitrobenzoic acid (**16b**), further rendering a tremendous application potential in complicated amide access for our method.

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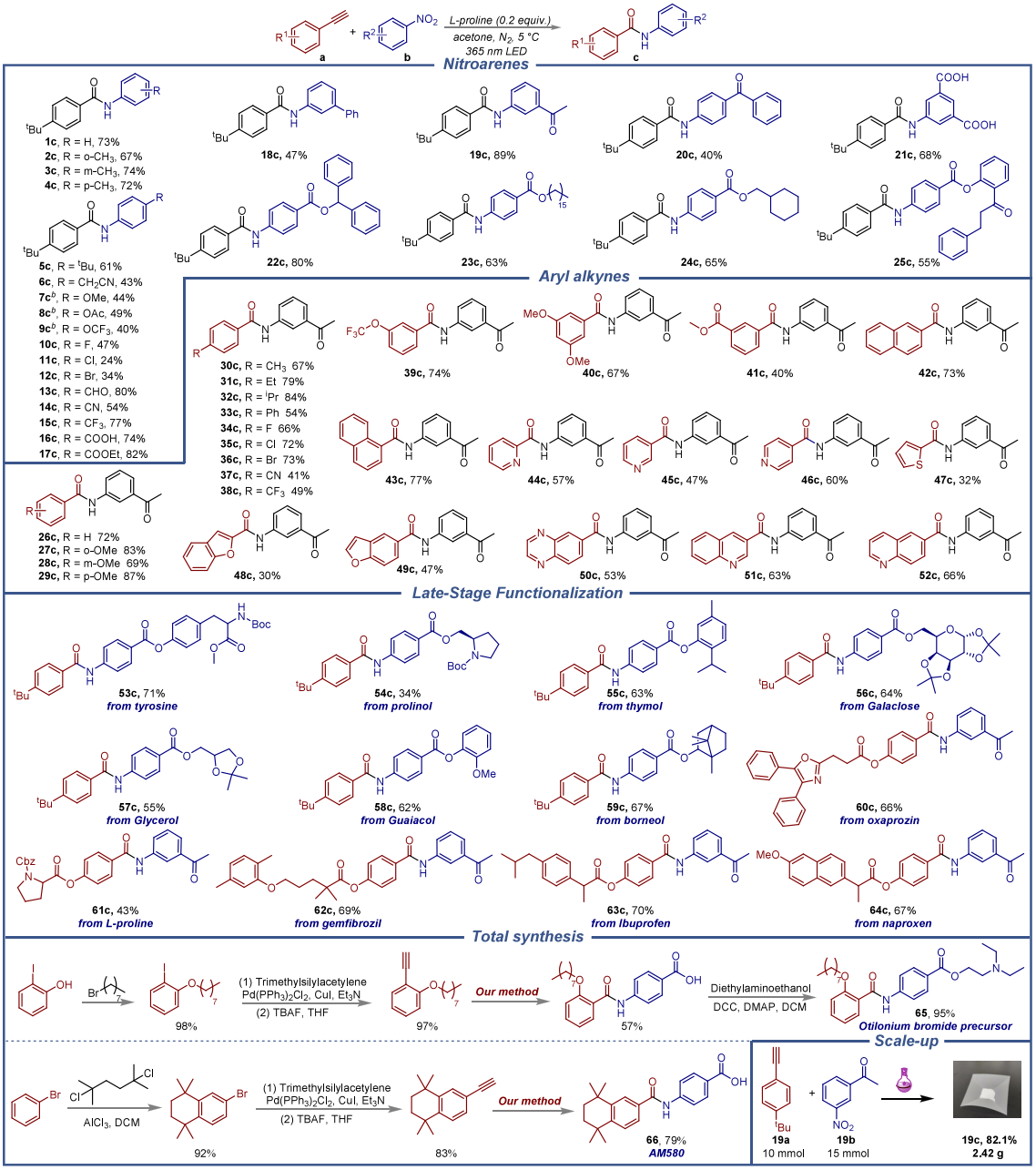
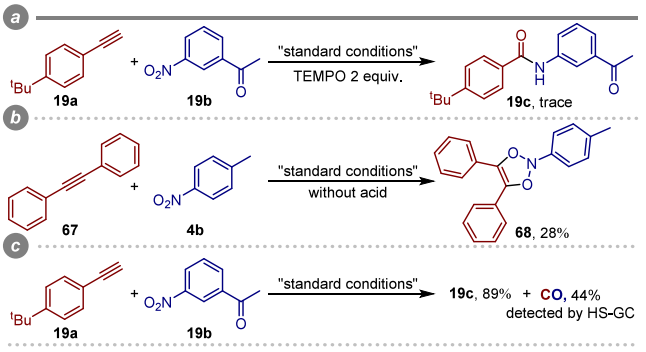
Scheme 2. Substrate Scope and Applications[a]



[a]Standard conditions: **a** (0.2 mmol, 1 equiv), **b** (0.3 mmol, 1.5 equiv), L-proline (0.04 mmol, 0.2 equiv), acetone (2 mL), N_2, 5 °C, 30 W 365 nm LED, 24 h. Isolated yield. [b]Two equiv of **b** was used.

As shown in Scheme 3, several control experiments were executed to explore the reaction mechanism. To attest to the existence of radical intermediates, a radical trapping experiment was performed by the addition of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) as a radical-trapping reagent (Scheme 3a). Only a trace amount of **19c** was detected, suggesting that this system underwent a radical pathway. A light on−off experiment was carried out next, revealing that continuous light irradiation was essential for this transformation and radical chain processes made little contribution (Figure S11). To further investigate the photoabsorption species and probe the possible formation of an electron donor−acceptor (EDA) complex in this system, UV−vis spectrum experiments were conducted with **19a**, **19b**, and L-proline in degassed acetone

Scheme 3. Mechanistic Study Experiments



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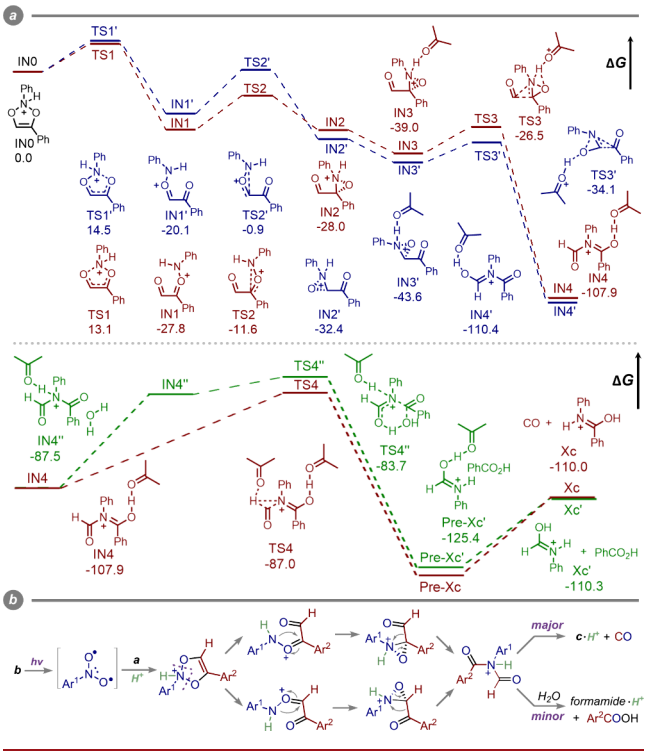
(Figures S2−8). According to these spectra, only nitroarene **19b** was found to possess an obvious absorption near 365 nm. Neither any pairwise combination nor a ternary mixture of the three stoichiometric components generated a bathochromic shift compared to the spectra of any individual reactants, therefore suggesting that an EDA complex is not formed in the ground state. Based on these results, the nitroarene is the only photoabsorbing species leading to an (n, π^*) long-lived excited state biradical.[15,16] In approaching the design of an alternative metal/photocatalyst-free method for amide synthesis from photoexcited nitroarenes, we were intrigued by the possibility of using 4-nitrotoluene **4b** as an ozone surrogate to access an intermediate 1,3,2-dioxazole through a radical cycloaddition event. However, our initial attempt between **4b** and a terminal alkyne **4a** failed to achieve the target five-membered ring maybe due to its unstable nature from powerful electronegativities of nitrogen, oxygen, and sp^2-carbon atoms.[15,16] Fortunately, we successfully isolated 1,3,2-dioxazole intermediate **68** from **4b** and internal alkyne **67** in a 28% yield to confirm our conjecture (Scheme 3b). Furthermore, a 44% yield of gaseous CO was quantitatively detected via headspace gas chromatography (HS-GC) (Scheme 3c, details see Figures S9−10), suggesting carbon monoxide to be a byproduct during the condensation reaction. Sequentially, some control experiments on possible intermediate compounds were managed (Section 4.5 in Supporting Information). When 1 equiv of benzaldehyde was added into the model reaction between **19a** and **19b**, a competitive amidation process occurred, giving the corresponding amide products **19c** and **26c** in respective yields of 36% and 34%. In contrast, a similar competitive phenomenon was not observed by the addition of one equivalent of *p*-toluidine instead. The reaction was almost inhibited with no **19c** and **4c** obtained. Reducing 1 equiv of *p*-toluidine would partly recover the reaction efficiency with **19c** gained solely. These outcomes revealed that an aldehyde group was involved in the amidation pathway, while an arylamine motif was not.

To acquire deep insights into the Brønsted acid-driven decarbonylative condensation procedures, density functional theory (DFT) calculations were executed on different ring-opening and bond-dissociation−recombination pathways. The geometry optimizations were performed in the gas phase at the M06-2X level with D3 corrections considered. All atoms were treated with a def2-tzvp basis set. As displayed in Scheme 4a, the calculated energy landscape of the reaction was initiated with the 1,3,2-dioxazole intermediate **IN0**. The N site from nitrobenzene was activated by the proton from proline, promoting the following fragmentation processes. The ring-opening processes at either of the two N−O bonds were both spontaneous, associated with modest energetic barriers (13.1 vs 14.5 kcal·mol^{-1}) and noteworthy energy releases (40.9 vs 34.6 kcal·mol^{-1}). Sequentially, an oxaziridinium intermediate was formed between the N center and the C═O bond of aldehyde (**IN2′**) or ketone (**IN2**), furnishing a reasonable explanation for the applicability of aldehydes in the reaction. The distinct Gibbs free energy gap ($\Delta\Delta G^{\ddagger}$ = 3.0 kcal mol^{-1}) between the activation energy of **IN1-TS2** (16.2 kcal·mol^{-1}) and **IN1′-TS2′** (19.2 kcal·mol^{-1}) may imply route 1 (**IN1-TS2**) to be the favorable one. Assisted with a molecular acetone to actuate proton migration, cascade bond-dissociation−recombination (**TS3** and **TS3′**) around the N-cation center including the key C−C bond cleavage occurred smoothly, generating a pair of resonance isomers (**IN4** and

Scheme 4. Computational Studies and Proposed Mechanism



IN4′′) and enormous energetic drops (over 70 kcal·mol^{-1}). The next decarbonylation courses were studied uniformly from **IN4**. To supply the final product **Xc**, a challenging H^+ migration with an energetic barrier of 20.9 kcal·mol^{-1} (**IN4-TS4**) was realized to liberate the CO with the aid of another acetone molecule. The corresponding decarbonylation on the other side was also examined. The calculated results demonstrated this pathway to be unfavorable due to a required preactivation process with water (**IN4″**) and an obvious free energy gap at transition state **TS4**/**TS4″** ($\Delta\Delta G^{\ddagger}$ = 3.3 kcal mol^{-1}). Based on the experimental and computational studies, a proposed mechanism for the acid-catalyzed decarbonylative condensation was concluded, as shown in Scheme 4b.

The results presented here exhibit a practical decarbonylative amide synthesis approach mediated by photoexcited nitroarenes with no need for additional metal/photocatalysts and oxidative/reductive reagents, compatibility with water and air, remarkable functional group tolerance and substrate suitability, and wide applications in scale-up synthesis, late-stage functionalization, and total synthesis. A detailed reaction mechanism involving a 1,3,2-dioxazole intermediate was adequately investigated in experimental and calculation studies. This novel method paves a viable avenue for simplified and sustainable amide synthesis and will provide rewarding inspiration for further developments in catalyst-free photochemical processes.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c02513.

Mechanism investigations, synthetic procedures, DFT calculations, characterization data and ^{1}H, ^{13}C NMR spectra of these synthesized compounds (PDF)

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‡R.C. and Q.L. contributed equally.

Notes

The authors declare no competing financial interest.

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