Exploration of C–H Transformations of Aldehyde Hydrazones: Radical Strategies and Beyond

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CONSPECTUS: The chemistry of hydrazones has gained great momentum due to their involvement throughout the evolution of organic synthesis. Herein, we discuss the tremendous developments in both the methodology and application of hydrazones. Hydrazones can be recognized not only as synthetic equivalents to aldehydes and ketones but also as versatile synthetic building blocks. Consequently, they can participate in a range of practical synthetic transformations. Furthermore, hydrazone derivatives display a broad array of biological activities and have been widely applied as pharmaceuticals. Owing to the weak directing group effect of simple aldehydes and ketones in C–H bond functionalizations, the C–H bond functionalizations of hydrazones that have been developed in the past five years represent a significant step forward. These novel transformations open a new door to a broader library of functionalized and complex small molecules. Moreover, a wide range of biologically important N-heterocycles (dihydropyrazoles, pyrazoles, indazoles, cinnolines, etc.) can be efficiently synthesized in an atom- and step-economical manner through single, double, or triple C–H bond functionalizations of hydrazones. Both radical C–H functionalizations and transition-metal-catalyzed directing-group strategies have enhanced the synthetic utility of hydrazones in the chemical community because these strategies solve the long-standing challenge of C–H functionalizations adjacent to aldehydes and ketones.

We began this study based on our ongoing interest in visible-light photoredox catalysis. Visible-light photoredox catalysis has become a powerful tool in contemporary synthetic chemistry due to its remarkable advantages in sustainability and use of radical chemistry. By exploiting a photoredox-catalyzed aminyl radical polar crossover (ARPC) strategy, we successfully achieved visible-light-induced C(sp2)−H difluorooalkylation, trifluorometylation, and perfluoroalkylation of aldehyde-derived hydrazones. This intriguing result was later applied in the C(spin)−H amination of hydrazones and a cascade cyclization reaction for the synthesis of polycyclic compounds. Encouraged by this redox-neutral C–H functionalization of aldehyde hydrazones, we extended the oxidative C–H/P−H cross-coupling method, which represents a novel and efficient method for the synthesis of α-aminophosphine oxides. Furthermore, an elegant [3 + 2] cycloaddition of azides and aldehyde hydrazones for the synthesis of functionalized tetrazoles was advantageously developed during our investigation of the oxidative C(spin)−H azidation of aldehyde hydrazones with TMSN3. The sequential C(spin)−H/C(spin)−H bond functionalization of aldehyde-derived hydrazones with simple 2,2-dibromo-1,3-dicarbonyls was achieved by employing relay photoredox catalysis, and it provides a novel method of accessing bioactive fused dihydroxyazepine derivatives. The notable feature of this approach was further reflected in the formal [4 + 1] annulation of aldehyde-derived N-tetrahydroisoquinoline hydrazones with 2-bromo-1,3-dicarbonyls. To complement these radical C–H functionalization strategies, we recently applied a directing-group strategy in the Rh-catalyzed C(aldehyde)−H functionalization of aldehyde-derived hydrazones for the synthesis of distinctive and bioactive 1H-indazole scaffolds.

In summary, this Account presents recent contributions to the exploration, development, mechanistic insights, and synthetic applications of C–H bond functionalizations of aldehyde hydrazones.

1. INTRODUCTION

Hydrazones are valuable and versatile building blocks in synthetic chemistry. Owing to their similarities to carbonyl compounds, hydrazones can participate in a wide range of typical synthetic transformations such as free radical reactions, cycloaddition reactions, and transition-metal-catalyzed reactions (Scheme 1). They are often used as precursors for the synthesis of hydrazines and diazo compounds. For example, chiral N-acylhydrazones have been widely used as versatile imino acceptors in enantioselective amine syntheses. In addition, hydrazone derivatives display a broad array of biological activities and pharmacological properties such as antiprotozoal and antitrypanosomal activities. Additionally,
hydrazone units are attracting increasing attention in supramolecular chemistry,\textsuperscript{3a} dynamic combinatorial chemistry (DCC),\textsuperscript{3b} and hole-transporting optoelectronic devices.\textsuperscript{3c}

Organic transformations that directly convert C–H bonds into C–C and C–heteroatom bonds can potentially simplify and shorten synthetic routes, which makes such techniques particularly attractive to organic chemists.\textsuperscript{4} In this area, the introduction of a coordinating directing-group (DG) is a robust strategy for achieving site-selective C–H bond functionalization. In 2001, the Mino group proved hydrazone moieties are particularly attractive to organic chemists.\textsuperscript{4} In this area, the introduction of a coordinating directing-group (DG) is a robust strategy for achieving site-selective C–H bond functionalization. In 2001, the Mino group proved hydrazone moieties are particularly attractive to organic chemists.\textsuperscript{4} However, C–H bond functionalizations using hydrazone units as DGs did not receive substantial attention until 2007 when Inamoto and Hiroya developed an efficient protocol for the synthesis of indazole via the Pd-catalyzed intramolecular aromatic C(sp\textsuperscript{2})–H amination of hydrazones.\textsuperscript{6}

Compared with directing group-enabled C–H functionalizations, radical C–H functionalizations of hydrazones progressed rapidly along with the renaissance of radical chemistry. Intramolecular dehydrogenative cyclizations,\textsuperscript{8} hydrazonyl amino radical 1,5-H atom transfer (HAT)-enabled C(sp\textsuperscript{3})–H functionalizations,\textsuperscript{9} and hydrazone C(alddehyde)–H functionalizations have been developed (Scheme 1). These strategic and novel C–H transformations of hydrazones provide efficient pathways for the synthesis of a great number of functionalized nitrogen-containing molecules. Consequently, structurally diverse N-heterocycles (dihydropyrazoles, pyrazoles, indazoles, cinolines, etc.) have been concisely constructed through single or multiple C–H bond functionalizations. Both radical and DG strategies have been applied, which has undoubtedly accelerated the utility of hydrazones in contemporary synthetic chemistry.

Our group has been actively involved in the development and application of the C–H functionalizations of aldehyde-derived hydrazones. This is the right time to highlight this topic as a powerful platform that will benefit organic synthesis. The purpose of this Account is to give an overview of the C–H bond transformations of aldehyde-derived hydrazones in synthesis with an emphasis on our recent work.

### 2. REDOX-NEUTRAL C–H FUNCTIONALIZATIONS OF ALDEHYDE-DERIVED HYDRAZONES

One of the most important features of aldehyde-derived N,N-dialklyhydrazones is their ability to act as nucleophilic azenameine equivalents.\textsuperscript{10} This impressive umpolung of the imine reactivity is derived from the conjugation between the carbon–nitrogen π bond and the lone electron pair on the terminal nitrogen atom. Consequently, aldehyde-derived N,N-dialklyhydrazones can react with reactive electrophiles such as acyl chlorides,\textsuperscript{11} N-bromosuccinimide,\textsuperscript{12} and Vilsmeier-type reagents\textsuperscript{13} at the azomethine carbon to provide C(sp\textsuperscript{3})–H functionalization products (Scheme 2).

**Scheme 2. Electrophilic C(sp\textsuperscript{3})–H Functionalization of Aldehyde-Derived N,N-Dialklyhydrazones**

In 2013, Bouyssi and Baudoin reported a mild and practical copper-catalyzed C(sp\textsuperscript{3})–H trifluoromethylation of benzaldehyde-derived N,N-dialklyhydrazones I with electrophilic Togni reagent (Scheme 3).\textsuperscript{14} The radical-trapping experiment with TEMPO suggested a free CF\textsubscript{3} radical might be operating, which was in sharp contrast with previous electrophilic C(sp\textsuperscript{3})–H substitution processes. Later, they further realized the copper-catalyzed trifluoromethylation of conjugated hydrazones and aliphatic N-arylhydrazones.\textsuperscript{14c} Despite its numerous applications, hydrazone is rarely explored in photoredox catalysis.\textsuperscript{15} We began our study in this field based on our ongoing interests in visible-light-induced difluoroalkylations.\textsuperscript{16} The CF\textsubscript{2} group is a valuable motif because it can serve as a lipophilic hydrogen-bond donor and act as a bioisostere for an oxygen atom or a carbonyl group. Many contributions toward direct difluoroalkylations of carbon–carbon double bonds have been made,\textsuperscript{17} but few studies on the difluoroalkylation of aromatic carbon–nitrogen π bonds have been reported. We initially tested various aldehyde-derived imine-type substrates including hydrazones, oximes, and imines (Scheme 4).\textsuperscript{18} Only N,N-dialklyhydrazones and N-alkyl-N-aryl-hydrazones reacted well with BrCF\textsubscript{2}CO\textsubscript{2}Et under visible-light photoredox conditions, and they exclusively generated C–H difluoroalkylation products 3.

This photoredox-based protocol illustrates the breadth of the substrate scope; both aromatic and aliphatic aldehyde-derived hydrazones could successfully be applied to deliver the corresponding difluoroalkylated hydrazones 3 (Scheme 5).
The salient features of this reaction including facile follow-up transformations and that it is a one-pot, three-component coupling reaction, making this protocol highly attractive. First, the single electron reduction of Br\(\text{CF}_2\text{CO}_2\text{Et}\) by photoexcited \(\text{Ir}^{\text{ppy}}\) generates the difluoroalkyl radical. Subsequent electrophilic radical addition to the C=\(\text{N}\) bond gives aminyl radical intermediate \(\text{A}\). In a traditional reaction manifold, this aminyl radical would readily undergo H-atom abstraction to form hydrazine as the product. Here, this regular pattern is interrupted by a visible-light-promoted aminyl radical-polar crossover (ARPC) process in which aminyl radical \(\text{A}\) undergoes a stepwise SET oxidation and subsequent deprotonation to afford \(\text{C}\)−\(\text{H}\) difluoroalkylated product 3 (Scheme 6).

With a bench-stable dimeric gold complex as the photocatalyst, a conceptually new C(sp\(^2\))−\(\text{H}\) difluoroalkylation and perfluoroalkylation of hydrazones with various R\(_2\)-Br reagents was developed by the Hashmi group (Scheme 7).\(^{19}\) The coupling partner can be extended to Br\(\text{CF}_2\text{PO(OEt)}_2\), Br\(\text{CF}_2\text{SO}_2\text{Ph}\), Br\(\text{CF}_2\text{COPh}\), and perfluoroalkyl bromides using a dimeric gold complex as the catalyst. Interestingly, under certain reaction conditions, the dimeric gold photocatalyst gave better stereoselectivity than \(\text{fac-Ir}(\text{ppy})_3\). This may be because of the \(\text{fac-Ir}(\text{ppy})_3\)-mediated photoisomerization of the E-configuration product to the less stable Z-configuration product. Importantly, the reaction shows high functional group tolerance, and its synthetic robustness was explored by the late-stage modification of the medically important helicelide and vitamin E derivatives. Furthermore, the mild reduction of the products could afford gem-difluoroalkylated \(\beta\)-amino acid and \(\beta\)-amino phosphonic acid derivatives.

As shown in Scheme 8, the difluoroalkyl radical intermediate was further characterized by an EPR spin trapping experiment, and the results strongly supported a gold-catalyzed radical pathway.

By switching from perfluoroalkyl bromides to perfluoroalkyl iodides, we demonstrated a catalyst-free, photoinduced C(sp\(^2\))-\(\text{H}\) fluoroalkylation of aldehyde-derived hydrazones.
According to the results of the mechanistic studies, both the photoexcitation of the hydrazones and an electron donor–acceptor model are likely to be initiated by the generation of a perfluoroalkyl radical. Almost simultaneously, Bouyssi and Monteiro realized a Pd-catalyzed C(sp\(^2\))−H difluoroalkylation of aldehyde-derived hydrazones with difluoroalkyl bromides (Scheme 10).\(^\text{21a}\)

Significantly, the substrate scope can be extended to hydrazones bearing strong electron-withdrawing functional groups or heteroaromatic rings. Their method complements the above photoredox protocols. In this case, a single electron transfer (SET) mechanism involving a difluoroalkyl radical was also proposed. As a follow-up to this work, they later disclosed a Cu-catalyzed version with 1,10-phenanthroline as the optimal ligand.\(^\text{21b}\)

Inspired by these seminal reports, several similar radical C(sp\(^2\))−H fluoroalkylation protocols were recently reported.\(^\text{22}\)

Nitrogen-centered radicals are a class of useful synthetic intermediates that have received increasing attention from the synthetic community. In recent years, visible-light photoredox catalysis has been developed as a green and powerful tool for various transformations involving N-radicals.\(^\text{23}\) For example, in 2013, the MacMillan group demonstrated that nitrogen-centered radicals can be generated from hydroxylamine derivatives via photocatalytic SET reduction processes.\(^\text{24}\)
Based on this activation mode, we further utilized the intrinsic reactivity revealed by ARPC in the C(sp³)−H amination of aldehyde hydrazones. With N-methyl-N′-(phenylsulfonyl)oxy)sulfonamide as the nitrogen-centered radical precursor, the first visible-light-induced C(sp³)−H amination of aldehyde hydrazones was achieved by Wang and co-workers. The amination using N-is observed, and the reaction proceeds smoothly with the alternative method for the preparation of benzohydrazonamides.25 With aldehyde hydrazones, we demonstrated a practical procedure for the synthesis of (E)-iminophosphine oxides (Scheme 16). Deprotonation of this species affords α-iminophosphine oxides 3a (Scheme 16).

The N-1-radical can be formed from azido-I(III) reagents generated in situ from TMSN₃ with PhI(OAc)₂. Based on the success of the ARPC strategy in the oxidative C−H phosphonation, we next explored the oxidative C−H azidation of aldehyde hydrazones. In our previous work, we proposed an ARPC mechanism involving an aminyl cation intermediate. In this case, the generated azide radical first attacks the C=N bond to give aminyl radical intermediate L. Since a catalytic amount of Cu(OAc)₂ obviously improves the yield, radical intermediate L likely undergoes a SET oxidation with a Cu²⁺ species to produce key aminyl cation M, which is

Scheme 11. Visible-Light-Induced C(sp³)−H Amination of Aldehyde Hydrazones

Scheme 12. Synthesis of Benzohydrazonamides from Aldehyde Hydrazones

3. OXIDATIVE C−H FUNCTIONALIZATIONS OF ALDEHYDE HYDRAZONE

Encouraged by the previous results on photoredox-neural C−H functionalizations of aldehyde-derived hydrazones, we aimed to explore oxidative cross-couplings based on ARPC strategy. Phosphorus-containing compounds are an important class of fine chemicals that are commonly found in synthetic, materials, and agricultural chemistry. A diverse range of heterocycles containing P−C−N units show excellent bioactivity. Along with a method for the C−H functionalization of aldehyde-derived hydrazones, we demonstrated a practical procedure for oxidative C−H phosphonation of aldehyde hydrazones with commercially available diphenylphosphine oxides (Scheme 15). This protocol provides a new and efficient method for the synthesis of (E)-α-iminophosphine oxides 13, which remain challenging to prepare by previous methods. The optimized reaction conditions are 2.0 equiv of K₂S₂O₈ and 0.2 equiv of Cu(OAc)₂ as an oxidant in CH₃CN at 60 °C. Control experiments suggested that K₂S₂O₈ served as the oxidant and radical initiator for the generation of the phosphine-centered radical.

As illustrated in Scheme 16, the addition of a reactive phosphine-centered radical to the C=N bond gives aminyl radical intermediate I, which is then oxidized by K₂S₂O₈ or copper(II) to generate aminyl cation K or its mesomeric species J. Deprotonation of this species affords α-iminophosphine oxides 3a (Scheme 16).

The N-1-radical can be formed from azido-I(III) reagents generated in situ from TMSN₃ with PhI(OAc)₂. Based on the success of the ARPC strategy in the oxidative C−H phosphonation, we next explored the oxidative C−H azidation of aldehyde hydrazones. Interestingly, in the presence of PhI(OAc)₂/TMSN₃ and a catalytic amount of Cu(OAc)₂, unexpected tetrazole 14 was generated instead of the C−H azidation product (Scheme 17). In our previous work, we proposed an ARPC mechanism involving an aminyl cation intermediate. In this case, the generated azide radical first attacks the C=N bond to give aminyl radical intermediate L. Since a catalytic amount of Cu(OAc)₂ obviously improves the yield, radical intermediate L likely undergoes a SET oxidation with a Cu²⁺ species to produce key aminyl cation M, which is

Scheme 13. Strategy for the Generation of aminyl C−H Radical

Scheme 14. Protonation of Aldehyde Hydrazones

Scheme 15. Synthesis of Phosphorus-Containing Compounds

Scheme 16. Generation of C−H Functionalized Aldehydes

Scheme 17. Generation of C−H Functionalized Aldehydes

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then captured by a “nucleophilic” N₃ group in a concerted deprotonation/cyclization process (Scheme 18). This novel [3 + 2] cycloaddition of azides with aldehyde-derived hydrazones represents a rare route for the synthesis of functionalized tetrazoles.

4. MULTIPLE C–H FUNCTIONALIZATIONS OF ALDEHYDE HYDRAZONE

Since early 2010, visible-light photoredox catalysis has become a powerful tool for the α-C(sp²)–H functionalization of tertiary amines.³¹ In our recent work, the N-alkyl substituent was found to be a key unit that enables the successful transformation of the C(sp²)–H bond in aldehyde-derived hydrazones. A close consideration of the formulas inspired us to explore the feasibility of the functionalization of both sp² and sp³ C–H bonds. With 2,2-dibromo-1,3-dicarbonyl 15 as a radical precursor, we recently achieved a visible-light photoredox-catalyzed cascade of the C(sp²)–H/C(sp³)–H bond functionalization of aldehyde hydrazones in one step (Scheme 19).³² This reaction provides a simple and efficient pathway for the synthesis of complex fused dihydropyrazoles 16, which are widely found in medicinal and biocidal compounds. Two major
events are involved in this transformation, namely, (1) a photoredox-catalyzed C(sp²)−H alkylation through an ARPC process and (2) a photoredox-catalyzed intramolecular α-C(sp³)−H alkylation adjacent to a nitrogen atom (Scheme 20). Two possible pathways were proposed for the second event. In path 1, radical precursor Q undergoes a SET reduction by *Ir(ppy)₃ to give radical intermediate S. Then, a 1,5-HAT process occurs to generate α-aminoalkyl radical intermediate T, which is further oxidized by Ir(IV). Ultimately, an intramolecular Mannich-type reaction gives dihydropyrazoles 16. In path 2, carbon radical S may be in resonance with aminyl radical R, which can undergo a second ARPC process, to generate diazenium species V. Then, intermediate W proceeds through a sequential deprotonation and 6π electrocyclic process to give final product 16.

Concurrently, the Bouyssi and Monteiro group disclosed a conceptually new copper-catalyzed double C−H alkylation of aldehyde N,N-dialkylhydrazones with polyhalomethane derivatives, thus providing a practical and flexible approach to the preparation of various 4-functionalized pyrazoles 18 (Scheme 21). More recently, they further applied their C−H functionalization strategy to a novel Ru-catalyzed synthesis of 4-fluoropyrazoles 19. Both reactions were proposed to
undergo a cascade radical C(sp²)−H haloalkylation/C(sp³)−H cyclization/aromatization sequence. Similarly, Nenajdenko and co-workers recently disclosed a Cu-catalyzed polyhalomethyl radical addition to aldehyde hydrazones for the synthesis of a wide range of useful halogenated azabutadiene building blocks. 34

Indeed, hydrazones have already been recognized as versatile precursors for the synthesis of a broad range of functionalized pyrazoles. Ge et al. made great advances in intramolecular dehydrogenative cyclization reactions of hydrazones. 8 For example, in 2013, they reported an elegant copper-catalyzed C(sp³)−H dehydrogenative cyclization of N,N-dialkylhydrazones with O₂ as the sole oxidant (Scheme 22). 8b This novel transformation constitutes a practical and environmentally friendly approach to the construction of pyrazole derivatives. Inspired by these seminal works, we recently developed a novel [4 + 1] annihilation of aldehyde-derived hydrazones with diethyl 2-bromomalonate by exploiting a relay photoredox catalysis strategy, thus offering a convenient method for accessing biologically important pyrazoloisoquinolines 20 (Scheme 23). 35

The cascade functionalization of multiple C−H bonds can be efficiently accomplished in a step-economic manner under mild reaction conditions. Based on control experiments and previous studies, we reasoned that the reaction involved three successive photoredox quenching cycles (Scheme 24). In the first quenching cycle, hydrazone AA is generated through a photoredox-catalyzed ARPC process. In the second quenching cycle, hydrazone AA undergoes a SET oxidation with photoexcited *IrIII and C−H atom abstraction, producing reactive iminium ion BB or equilibrium species CC. Aldehyde EE was isolated in mechanistic experiments, which further confirmed the existence of possible intermediate DD. The intramolecular Mannich reaction of BB delivers key dihydropyrazole FF. Notably, both hydrazone AA and dihydropyrazole FF can be detected by high-resolution mass spectrometry.
Dihydropyrazole FF then undergoes decarboxylation to give intermediate GG, which acts as the reductive quencher in the third quenching cycle. Dihydropyrazole GG undergoes a SET oxidation and sequential deprotonation/aromatization to form final product 20a. More than 2 equiv of the alkyl bromides were used as they serve not only as the alkylation reagents but also as the oxidant in this reaction.

On the other hand, with the N−N bond as a Lewis basic unit, hydrazones can be utilized as directing groups in transition-metal-catalyzed C−H activations. In this context, Inamoto and Hiroya developed an efficient protocol for the synthesis of indazoles via a Pd-catalyzed intramolecular aromatic C(sp2)−H amination of hydrazones.6 Rao and co-workers realized the synthesis of tri- and tetrasubstituted C−H/N−H couplings of conjugated hydrazones.36a Fernández and Lassaletta reported an elegant Ir-catalyzed aromatic C(sp3)−H diborylation of N,N-dimethylhydrazones.36b Hua developed a novel Rh-catalyzed C−H activation and alkyne annulation strategy for the synthesis of indoles in which the generated hydrazone serves not only as a directing group but also as an internal oxidant.36c Recently, Dong reported a hydrazone-based directing-group strategy for the β-C(sp3)−H oxidation of aliphatic amines.36d Guided by these works and to complement the radical-type strategies, we attempted to exploit the DG strategy for the C−H bond functionalization of aldehyde-derived hydrazones. With readily available aldehyde phenylhydrazones as substrates, we successfully developed a Rh-catalyzed cascade involving a double C−H activation and an oxidative C−C coupling (Scheme 25).37 A series of 1H-indazoles were efficiently synthesized by this protocol, which shows excellent functional-group tolerance (Scheme 26). Compared with previous methods for the synthesis of 1H-indazoles, which all focused on C−N bond construction,38 the Rh-catalyzed C−C bond forming has the advantage of allowing the rapid synthesis of certain distinctive and bioactive 1H-indazoles.
indazole scaffolds. For instance, product 21h shows 5-HT$_4$/5-HT$_3$ receptor antagonist activity.

The deuterium labeling experiment showed that the process involved an initial reversible C−H bond metalation (Scheme 27), which is consistent with the results of DFT calculations (endothermic by 5.4 kcal/mol). In addition, the C−H bond deuteration at the ortho-position of the C-aryl ring indicated there were two competing coordination sites during the initial step. Both coordination modes can be clearly illustrated by the reported examples. Two paths were proposed for the second C−H activation event (Scheme 28). Five-membered rhodacyclic complex II may undergo a C(aldehyde)−H bond insertion and sequential reductive elimination of JJ to furnish the desired 1H-indazole. Another pathway involves a nucleophilic addition of the C(aryl)−Rh bond to the C=N bond to form N−Rh species KK. This species undergoes β-H elimination to generate product 21a. However, the DFT calculations suggest that the sequential C−H insertions are more responsible for the Rh(III)-catalyzed dual C−H bond cross-coupling reaction.

This Account has summarized the recent achievements in the C−H transformations of aldehyde-derived hydrazones with an emphasis on our own contributions. Radical strategies, such as transition-metal catalysis (Cu, Pd, Ru, etc.) and photoredox catalysis, have emerged as a powerful tool for the C−H functionalization (trifluoromethylation, difluoroalkylation, amidation, and phosphorylation) of aldehyde-derived hydrazones as these methods allow efficient access to various functionalized hydrazones. These novel C−H transformations are highly compatible with both redox-neutral and oxidative reaction conditions. Importantly, a wide range of valuable N-heterocycles such as dihydropyrazoles and pyrazoles can be concisely synthesized from easily accessible hydrazones by multiple C−H functionalization protocols. In addition, the new mode of intrinsic reactivity was further extended to other types of reactions including cascade cyclization and cycloaddition reactions. Furthermore, a transition-metal-catalyzed directing-group strategy can be successfully applied in this field, which makes it complementary to the radical C−H functionalization strategies. We believe the C−H bond functionalization of hydrazones will attract considerable attention in the near future and stimulate the broad application of hydrazones in contemporary chemistry.

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