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Recent Progress in the Development of Multitasking Directing Groups for Carbon–Hydrogen Activation Reactions

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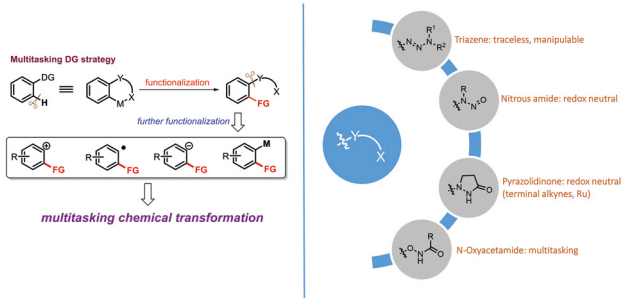

Novel, removable and multitasking directing groups for the synthesis of heterocycles

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Abstract Selective carbon–hydrogen activation reactions can be accomplished in a predictive manner using directing auxiliaries. However, the majority of directing groups discovered to date are difficult to remove or to transform into a desirable functionality. Recently, removable, cleavable, and redox-neutral directing groups have been developed that significantly broaden both the substrate scope and synthetic diversity of carbon–hydrogen functionalization reactions. In this short account, we summarize recent progress we have made in the development of multitasking (removable, cleavable, redox-neutral, manipulable) directing groups for carbon–hydrogen activation reactions.

Key words carbon–hydrogen activation, directing groups, multitasking functional groups, transition metals, substituted heterocycles

1 Introduction

Over the past decades, the development of new carbon–hydrogen activation strategies has re-emerged as a goal for next-generation synthetic organic chemists.[1] The ability to carry out direct functionalization reactions of 'inert (non-activated)' carbon–hydrogen bonds is one of the most straightforward approaches to increasing molecular complexity in organic molecules. The field of carbon–hydrogen activation has enjoyed tremendous advances, thanks in part to the design of various directing groups (DGs) that enable selective carbon–hydrogen bond cleavage and functionalization.[2] A DG generally contains an electron lone pair that coordinates to a transition metal in a catalyst in order to orient it properly for insertion into a neighboring carbon–hydrogen bond (Scheme 1). This property enables the DG to govern the site selectivity of carbon–hydrogen functionalization reactions.

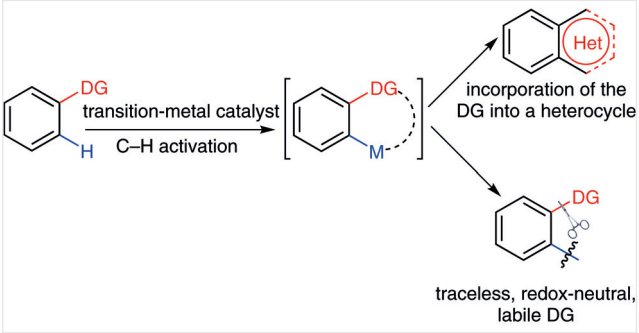
Many DGs, ranging from strongly chelating to weakly binding, have been developed for a wide range of carbon–hydrogen coupling and annulation reactions.[3] However, it must be pointed out that this approach is a double-edged sword because although it provides precise site selectivity, it suffers from the fact that the DG remains as a functional entity in the product of the reaction. For example, DGs for sp^2-carbon–hydrogen functionalization reactions are typically linked to aromatic substrates via stable carbon–carbon, carbon–oxygen, or carbon–nitrogen bonds, which are difficult to cleave.

Consequently, strategies have been devised to address this problem, including incorporation of the DG into a heterocyclic ring[4] and use of a traceless DG that can be removed or is capable of a wide range of desirable ensuing chemical manipulations (Scheme 1).[5] Recently, a number of traceless, cleavable, and redox-neutral DGs have been developed that significantly broaden the applications of carbon–hydrogen activation reactions and the resulting products.

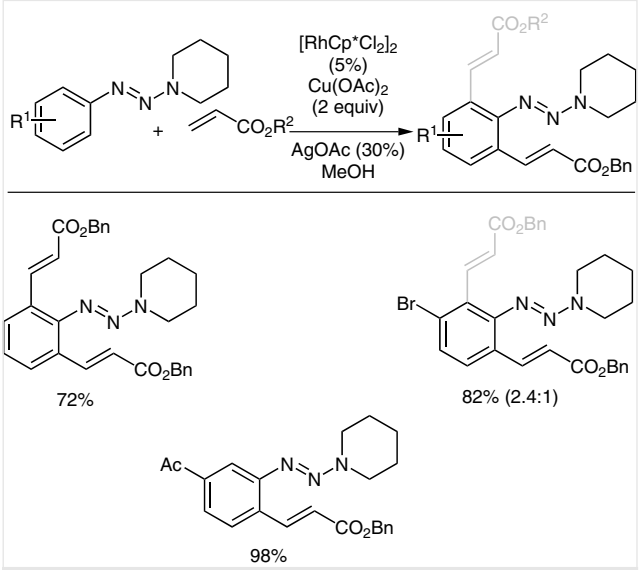
In this account, we summarize the results of recent investigations we have carried out aimed at uncovering new multitasking DGs for carbon–hydrogen functionalization reactions.

2 Triazene

In 2012, we reported that the triazene moiety serves as a new traceless DG for rhodium(III)-catalyzed carbon–hydrogen functionalization reactions.[6] In the study, we found that the central nitrogen atom of the triazene group



Scheme 1 Strategies for transformations of directing groups



Scheme 2 Rhodium(III)-catalyzed carbon–hydrogen olefination reactions using triazene as a new directing group

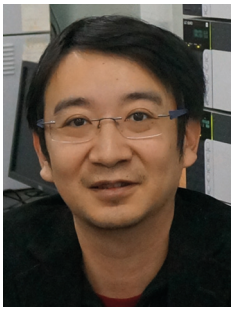
coordinates with rhodium(III) and guides its insertion into *ortho*-aryl–hydrogen bonds to form five-membered metallacycles. Subsequent insertion of an electron-deficient olefin into the labile rhodium–carbon bond leads to regioselective carbon–hydrogen olefination (oxidative Heck reaction) (Scheme 2). The catalytic cycle in this process is closed using stoichiometric copper(II) acetate [$Cu(OAc)_2$] to regenerate the rhodium(III) catalyst.

Similarly, a dialkyltriazene group was shown by the Bräse group to direct *ortho*-selective, silver(I)-promoted arene trifluoromethylation reactions (Scheme 3).[7] It should be noted that excellent *ortho*-selectivity attends these processes even though, as the authors suggested, a radical mechanism might be operating.

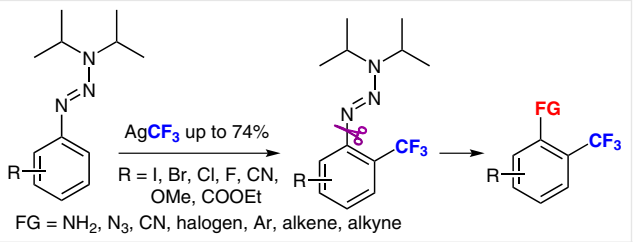
The triazene-directed carbon–hydrogen olefination reactions were observed to display a broad substrate scope. Electron-rich arenes undergo functionalization at room temperature, while reactions of electron-deficient substrates require gentle heating. Notably, although substances containing the strong electron-withdrawing nitro group are often poor substrates for the carbon–hydrogen activation reactions, they are well tolerated under the conditions employed in the triazene-guided process. When a 2-bromo-

Biographical Sketches

Huan Sun, originally from Anyang, Henan Province, P. R. of China, received her B.S. degree in chemistry from Zhengzhou University in 2011. She is now a Ph.D. candidate in the research group of Professor Yong Huang at Peking University, Shenzhen Graduate School. Her research interests are focused on novel transition-metal-catalyzed processes.



Yong Huang received his B.S. degree in chemistry from Peking University in 1997. He received his M.S. and Ph.D. degrees from the University of Chicago in 1998 and 2001, respectively. He worked as a postdoctoral fellow at Caltech (the California Institute of Technology) from 2002 to 2004. He subsequently worked as a senior medicinal chemist at Merck Research Laboratories in Rahway, NJ, until 2009. In 2009, he started his independent academic career as a professor at Peking University, Shenzhen Graduate School. He is the receipt of the 2014 *Organic Letters* Outstanding Author of the Year Award, the Bayer Investigator Award, the Roche Chinese Young Investigator Award, and the Asian Core Program Lectureship Award (2013 and 2014).



Scheme 3 Triazene-directed trifluoromethylation reactions

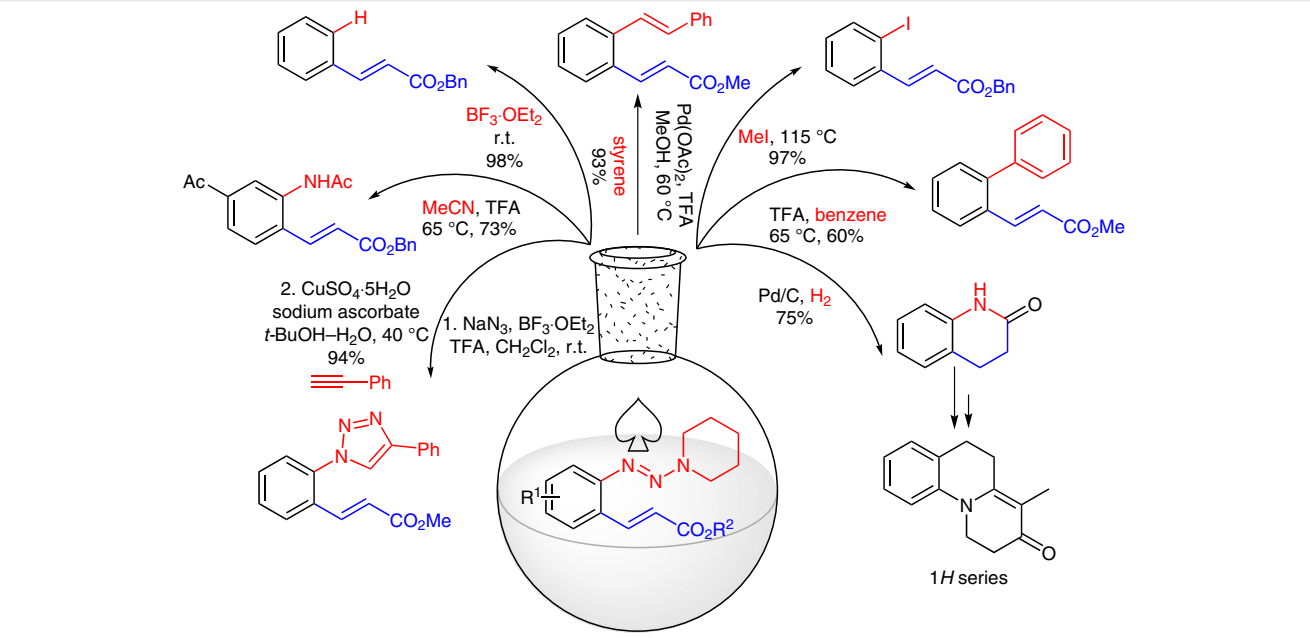
substituted substrate is used, double olefination occurs, suggesting that the triazene moiety also directs carbon–bromine bond insertion. In contrast, the carbon–bromine bond in a 3-bromo-substituted arene is not activated for olefination in this system. Interestingly, the triazene moiety is stronger than other DGs in directing carbon–hydrogen insertion.

The use of the triazene moiety as a DG for carbon–hydrogen activation reactions is highly advantageous because it can undergo a wide variety of reactions following the carbon–hydrogen functionalization step. For example, compared with common DGs, the aryl–nitrogen bond of aryltriazenes is polarized and significantly weak owing to the electron negativity of the two other nitrogens. In fact, aryltriazenes are documented to undergo a number of reactions that mimic aryl cation, radical, and organometallic processes.[8]

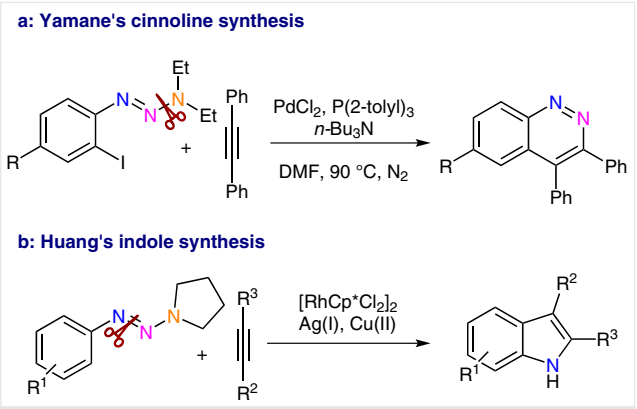
We and Bräse both described the chemical versatility of triazene products generated by carbon–hydrogen functionalization reactions (Schemes 3 and 4). We found that the DG can be removed using boron trifluoride–diethyl ether complex under ambient conditions to yield the corresponding arene–hydrogen product in near quantitative yield (Scheme 4). Upon treatment with methyl iodide, the triazene group is replaced by an iodine, which is capable of participating in a large number of cross-coupling reactions. In the presence of an acid, the aryltriazene can be converted into an aryl cation or radical, which reacts with nucleophiles or 'SOMOphiles' (SOMO = singly occupied molecular orbital), respectively. In addition, transition metals readily insert into the aryltriazene carbon–nitrogen bond as part of direct cross-coupling reactions. Because of its chemical flexibility toward structure diversification, the triazene moiety is unique among DGs.

Like other DGs, triazenes can be converted into *N*-heterocycles. In 2011, Zhu and Yamane described a method for the synthesis of cinnolines through reactions between 2-iodo-1-triazenylarenes and internal alkynes (Scheme 5, part a).[9] In our attempt to carry out a carbon–hydrogen version of the Yamane cinnoline synthesis, we were surprised to find that the triazine was converted instead into an NH indole via an unprecedented nitrogen–nitrogen double bond cleavage process (Scheme 5, part b).[10]

Although carbon–hydrogen activation/annulation strategies for indole synthesis using rhodium(III) have been explored previously, the formation of unprotected NH indoles in reactions of acetylenes with triazenes has unique advantages.[11,12] To demonstrate this feature, we applied this methodology to the preparation of a number of drug scaffolds and substances that play a role in organic light-emitting diode devices (Scheme 6).

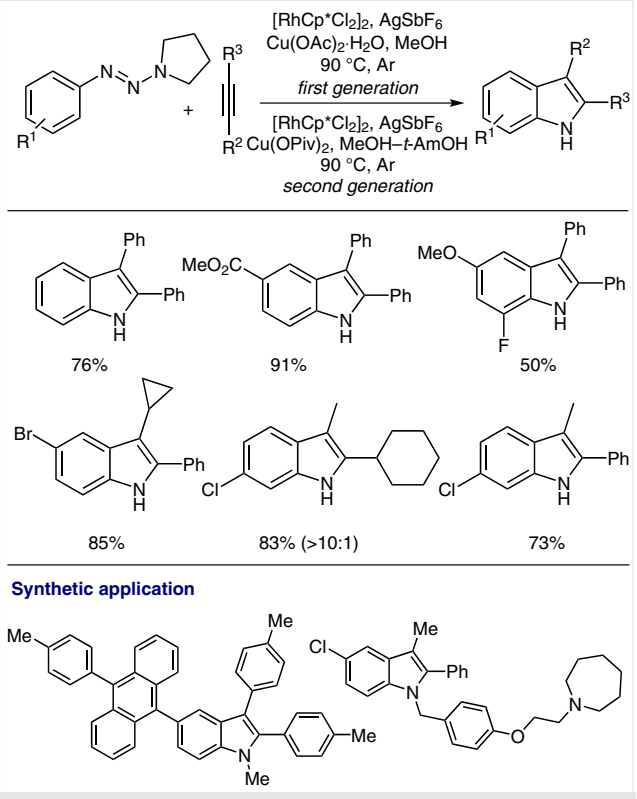


Scheme 4 Transformations of the triazene directing group



Scheme 5 *N*-Heterocycle synthesis through in-situ condensation

The initial conditions for alkyne annulation using [RhCp*Cl$_2$]$_2$, Cu(OAc)$_2$, and methanol were only applicable to electronically neutral substrates. Arenes bearing either electron-rich or -poor substituents reacted in very low yields. Subsequently, we found that the combination of copper(II) pivalate and a solvent mixture (MeOH–*t*-AmOH, 1:1) led to significantly higher conversions for these substrates (Scheme 6).[13] Also, aryl,aryl-, aryl,alkyl-, and alkyl,alkyl-disubstituted acetylenes were all well tolerated. It is noteworthy that alkynes bearing two different alkyl groups react with impressive levels of regioselectivity (Scheme 6). In comparison, reactions using other directing groups, such as NHAc, yield mixtures of regioisomers.[12a,b]



Scheme 6 Triazene-directed NH indole synthesis

The mechanism of the indole-forming, nitrogen–nitrogen double bond cleavage reaction has been studied. The results of collision-induced diossociation–high-resolution mass spectrometry (CID–HRMS) experiments suggest that 1,2-rhodium and 1,2-alkyl migrations might be major steps taking place in the pathway which lead to loss of nitrogen as part of the highly exergonic formation of tetrahydropyridazine,[13] a byproduct observed using HRMS. The observation of a primary kinetic isotope effect (KIE, k_H/k_D = 2.7) associated with deuterium replacement of the *ortho*-hydrogens showed that carbon–hydrogen activation is the rate-determining step of the reaction.

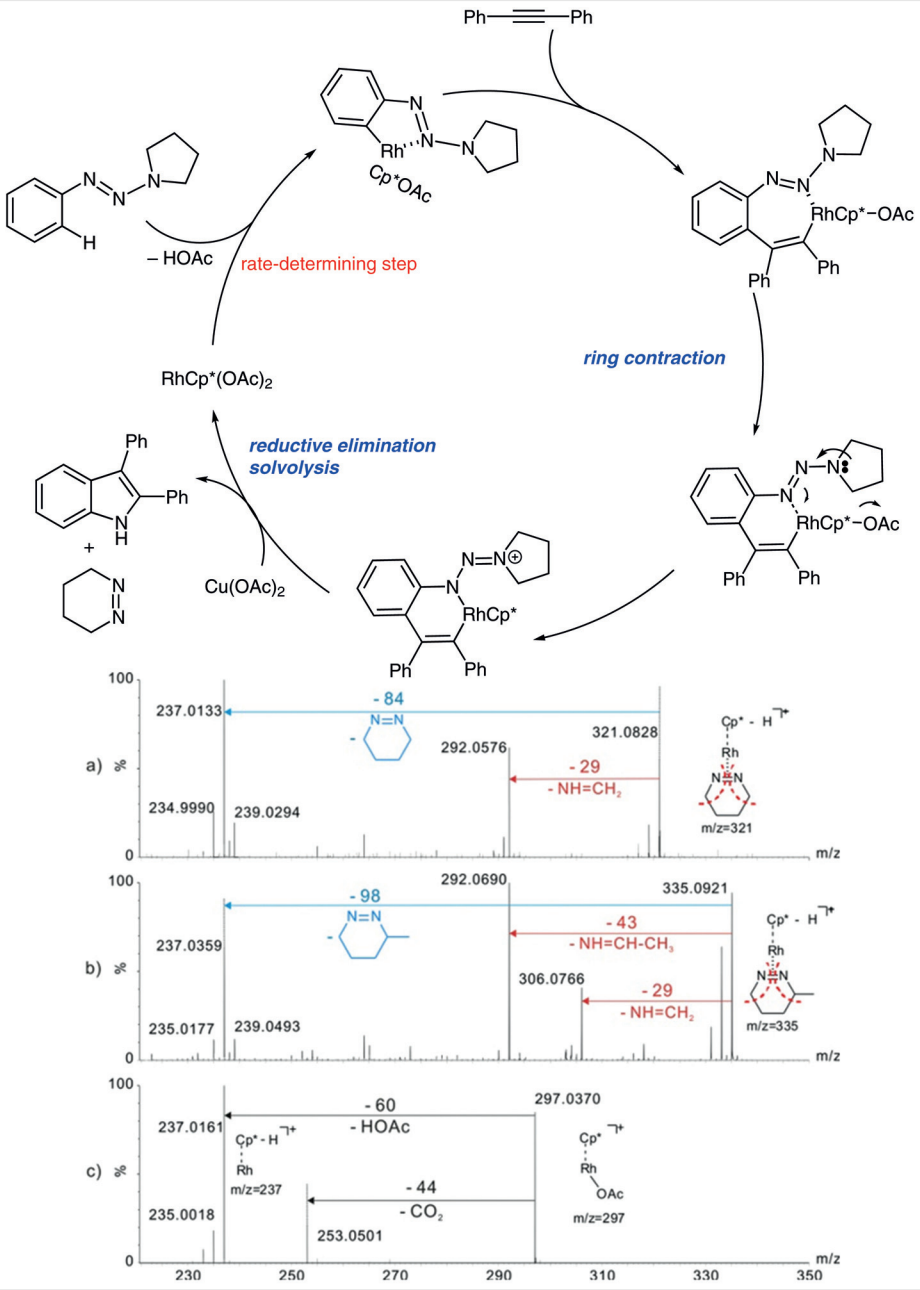
Based on these data, we proposed that the seven-membered rhodacycle formed by the addition of the acetylene to the initially generated five-membered rhodacycle undergoes rapid ring contraction by migration of rhodium to produce a six-membered intermediate. Subsequent 1,2-alkyl migration and reductive elimination then lead to the formation of the indole and tetrahydropyridazine products (Scheme 7).

To gain an understanding of the scope of reactions between triazenes and alkynes, substrates in which the reacting moieties are intramolecularly disposed were treated with different metal ions. We found that the reaction of (2-alkynylaryl)triazenes follows two distinct cyclization pathways depending upon whether it is promoted by copper(II) or silver(I). Specifically, substrates of this type produce 2*H*-indazoles through oxidative cyclization when treated with copper(II) salts. In contrast, 2-substituted indoles are generated via a nitrogen–nitrogen bond cleavage pathway when silver(I) is used as the metal cation (Scheme 8).[14]

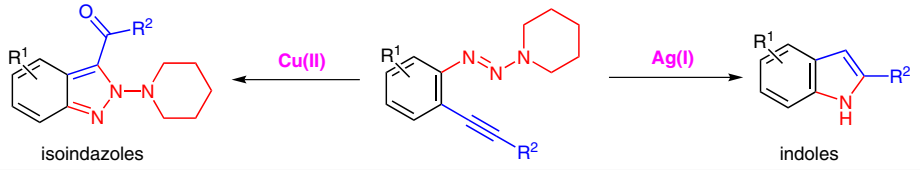
The results of computational studies of these processes suggest that the reaction promoted by copper(II) involves Lewis acid catalysis and that silver(I) in the indole-forming reaction serves as a π-acid catalyst.

The observation that unprotected NH indoles are produced in reactions using triazene as the DG inspired us to design a novel cascade carbon–hydrogen activation/annulation sequence. We envisaged that in the reaction of the triazene with an excess of the alkyne, the initial NH indole product would undergo a second carbon–hydrogen activation using the indole NH as the DG. In this event, the process would generate an indolo[2,1-*a*]isoquinoline in one pot.[13]

While intriguing, this seemingly straightforward cascade reaction turned out to be nontrivial. We found that the two carbon–hydrogen activation steps in the cascade require different sets of conditions (Scheme 9) because those that lead to a high yield for the first step normally cause the second step to be inefficient. Eventually, two solvent sys-



Scheme 7 Mechanism for the indole-forming reaction

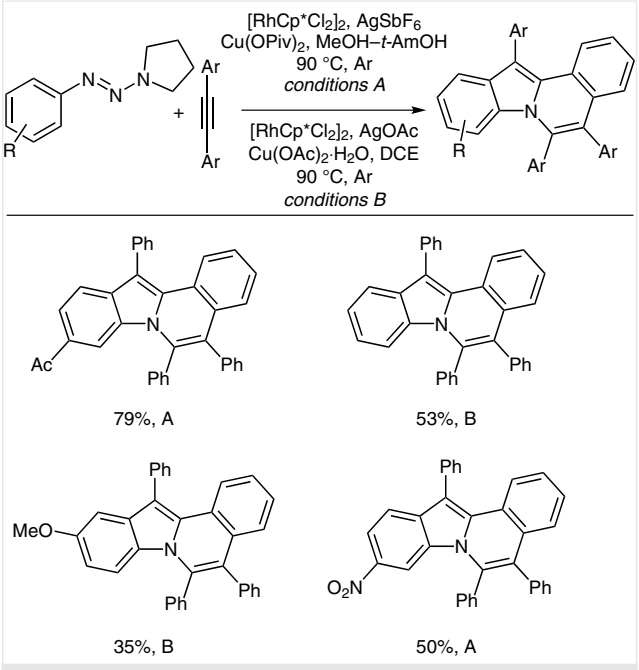


Scheme 8 Selective intramolecular triazene–alkyne cyclization using different metal ions

tems were identified as being applicable for carrying out reactions of two, electronically different families of substrates.

For electron-poor triazenylbenzenes, use of a methanol–*tert*-amyl alcohol solvent mixture (1:1) was required to bring about efficient formation of the corresponding indolo[2,1-*a*]isoquinolines, while reactions of electron-neutral or -rich arenes required the use of 1,2-dichloroethane. Furthermore, we observed that diarylacetylenes containing various substituents were viable substrates for this process when carried out under the optimized conditions.

To gain insight into this double carbon–hydrogen activation reaction, density functional theory calculations were performed on the second catalytic cycle. Owing to the congested environment in the rhodacycle intermediate formed in the second cycle, the barrier for alkyne insertion is energetically the highest. Moreover, analysis of the calculated potential energy surface showed that the carbon–hydrogen activation step is reversible, which is consistent with the observation of a small deuterium KIE (1.1).



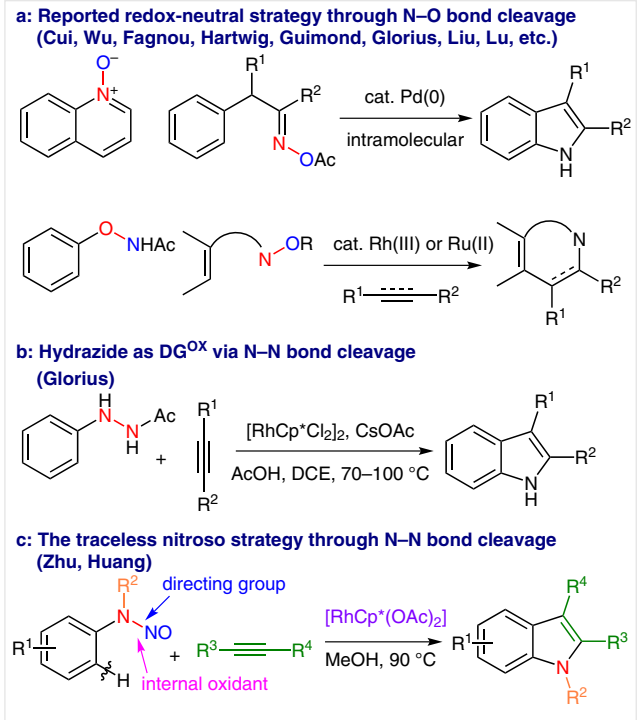
Scheme 9 Synthesis of indolo[2,1-*a*]isoquinolines via cascade carbon–hydrogen activation/annulation reactions

3 Nitrous Amide

Generally, carbon–hydrogen functionalization is oxidative in nature and, as a result, stoichiometric amounts of an oxidant are required to regenerate the precious metal catalyst produced in the final reductive elimination step. Copper and silver salts most often serve as efficient oxidants for this purpose. However, the required use of more than two equivalents of the metal oxidant is highly impractical and not suitable for redox-labile substrates. Recently, a strategy involving redox-neutral carbon–hydrogen activation has guided a large effort aimed at the development of self-oxidative DGs.[15] In this approach, a nitrogen–oxygen or nitrogen–nitrogen bond serves as both the DG and an internal oxidant. Groups of this type, referred to as DG^{ox}s, have been particularly effective for promoting regioselective carbon–hydrogen activation/annulation reactions.

The nitrogen–oxygen bond was first identified as a highly efficient internal oxidant to turn over rhodium, palladium, ruthenium, and other transition-metal catalysts. In particular, *N*-oxides, *O*-ethers of oximes, and *N*-hydroxyamides were successfully used in reactions carried out in the absence of an external oxidant (Scheme 10, part a).[16] In contrast, the use of a nitrogen–nitrogen bond as the DG^{ox} was not investigated until a recent study by Glorius and coworkers which showed that a hydrazide acts as an internal oxidant via nitrogen–nitrogen bond cleavage (Scheme 10, part b).[4f]

Although the triazene moiety also contains potentially oxidatively active nitrogen–nitrogen single and double bonds, it is not able to oxidize rhodium(I) to form rhodium(III). We envisioned that replacement of the terminal nitrogen in triazenes with more-electronegative oxygen might yield a nitrogen–nitrogen moiety that could be used as a DG^{ox} in indole-forming reactions (Scheme 10, part c).[17] Indeed, the results of studies showed that the nitrous am-



Scheme 10 Carbon–hydrogen activation/annulation reactions using nitrogen–oxygen and nitrogen–nitrogen DG^{ox}s

ide (NR–NO) moiety serves as an excellent DG^{ox} in reactions that were demonstrated to have a very broad substrate scope.

Thus, a straightforward redox-neutral protocol for the carbon–hydrogen activation/annulation governed synthesis of *N*-alkylindoles, using the acetate salt of the rhodium catalyst ([RhCp*(OAc)$_2$]) and nitrous amide DG^{ox}s, was devised. Reactions promoted in this manner take place efficiently and they are not sensitive to air and moisture.

In addition, many substrates found to be unreactive under previously developed conditions are well tolerated using the new DG^{ox}-based protocol (Figure 1). Specifically, indoles bearing multiple electron-donating substituents, commonly found motifs in natural products, can be prepared in high yields employing this technique. Moreover, when nitrous amide is tethered to the arene, fused [5,6,n]-tricyclic scaffolds are formed. Also, reactions with various diaryl, aryl,alkyl-, and alkyl,alkyl-disubstituted alkynes occur smoothly, and those of unsymmetrically disubstituted acetylenes take place with regioselectivities that match those of processes directed by the triazene DG.

Mechanistic experiments suggested that the nitrous amide directed carbon–hydrogen insertion process is asynchronous, with the arene/rhodium interaction contributing more to the carbon–hydrogen insertion step than the acidity of the *ortho*-carbon–hydrogen bond. The KIE, determined using a deuterium-labeled substrate, indicated that carbon–hydrogen activation is the rate-determining step of the process and, as a result, that the oxidation step takes place rapidly.

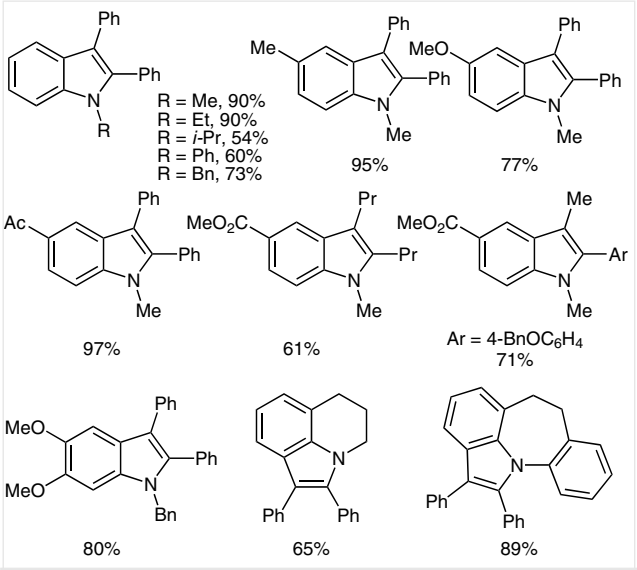


Figure 1 Substrate scope for *N*-alkylindole synthesis via *N*-nitroso-directed carbon–hydrogen activation/annulation

At nearly the same time, Zhu and co-workers reported a very similar strategy using a nitrous amide as the DG^{ox}.[12f] Subsequently, the groups of Hua, Cheng and Matsuda independently described the use of a hydrazone moiety as the combined DG and internal oxidant for rhodium(III)-catalyzed indole-forming reactions (Scheme 11).[18] Owing to the fact that the directing hydrazone group is formed in situ, the process developed by these researchers corresponds to a one-pot synthesis of indoles using arylhydrazines.

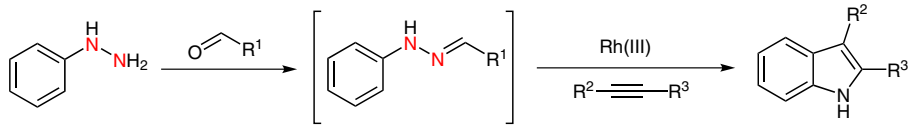
4 Pyrazolidinone

Interestingly, a large majority of carbon–hydrogen activation reactions explored to date have focused on nonterminal alkynes. Generally, both rhodium and palladium form inactive metal acetylides with terminal alkynes, and homocoupling of these alkynes is a serious and often unavoidable side reaction.[16d,o] Considering the prevalence of the 2-substituted indole moiety in the structures of natural products, the development of carbon–hydrogen activation/annulation reactions that utilize terminal alkynes as substrates is a highly desirable goal.

To address these issues, our attention turned to the use of ruthenium-based catalysts. Although ruthenium has been employed extensively in carbon–hydrogen activation reactions[19] and it is significantly cheaper than both rhodium and palladium, processes promoted by ruthenium catalysts are not fully compatible with triazene, nitrous amide, and simple hydrazide based DG^{ox}s without an external oxidant. The reason for this lies in the inability of these functionalities to oxidatively regenerate the ruthenium catalyst in situ because of their relatively low oxidation potentials.

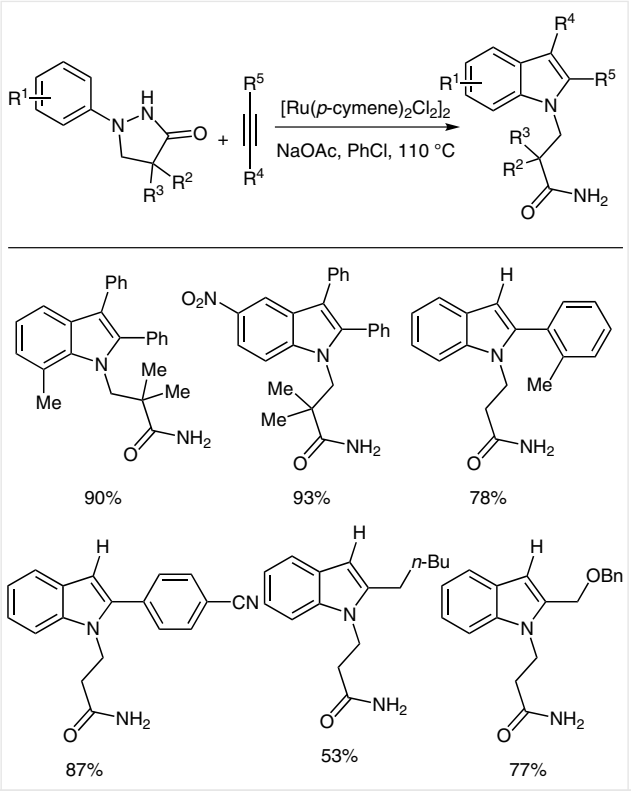
We proposed that a cyclic hydrazide would have a weaker nitrogen–nitrogen bond because of ring strain and, as a result, might have a relatively higher oxidation potential than acyclic hydrazides. This type of potential DG^{ox} is exemplified by a pyrazolidin-3-one moiety (Scheme 12), which has a slightly longer/weaker nitrogen–nitrogen bond than its acyclic counterpart.[20]

The results of studies exploring this proposal demonstrated that the pyrazolidin-3-one moiety is an excellent DG^{ox} for ruthenium-catalyzed carbon–hydrogen activa-



Scheme 11 Redox-neutral carbon–hydrogen activation/annulation via hydrazone as a nitrogen–nitrogen DG^{ox}

tion/annulation reactions of arenes and alkynes (Scheme 12). The process is applicable to a very broad range of substrates, including *ortho*-, *meta*-, and *para*-substituted arenes regardless of their electronic nature. It is noteworthy that a substrate bearing the strongly electron-withdrawing nitro group reacted smoothly to form the desired 5-nitro-substituted indole in 93% yield. Furthermore, excellent levels of regioselectivity were observed for reactions involving unsymmetrically substituted internal alkynes. Most significantly, terminal alkynes serve as reactants for highly efficient and regioselective 2-substituted indole forming reactions. In addition to terminal arylacetylenes, their alkyl-substituted analogues participate in this process. The products of these reactions contain a three-carbon moiety on the indole nitrogen which is a privileged pattern for many drug pharmacophores.



Scheme 12 Ruthenium(II)-catalyzed redox-neutral carbon–hydrogen activation/annulation of 1-arylpyrazolidinones and alkynes

Unlike reactions using rhodium(III), the ruthenium(II)-catalyzed process has a unique feature: the ruthenium species with a higher oxidation state is likely involved in the pathway. Based on only limited mechanistic information, we proposed that a ruthenium(II)–ruthenium(IV)–ruthenium(II) catalytic cycle is likely involved and that, following alkyne insertion, ruthenium(II) is internally oxidized before the reductive elimination step.

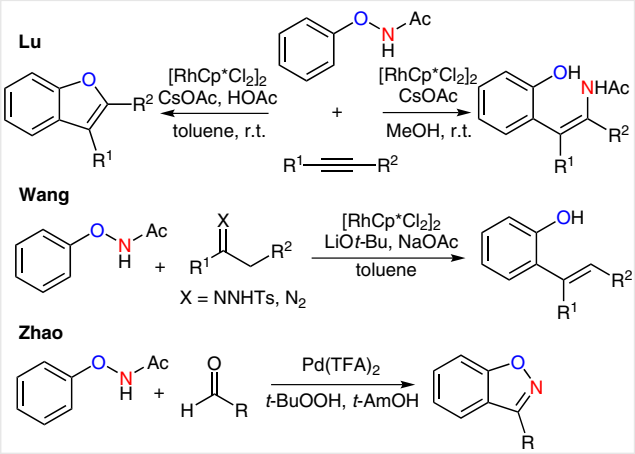
5 *N*-Oxyacetamide

In the studies described above, we and others have shown that the DGs can play many roles in carbon–hydrogen activation/annulation reactions. As a result, they are not innocent auxiliaries whose sole purpose is directing carbon–hydrogen activation. In fact, the DGs also serve as central building blocks to increase molecular complexity. However, the structural diversity of the DGs probed to date remains low and, as a result, challenges remain in the design of new, cascade carbon–hydrogen activation/annulation reactions that can be utilized to install structural complexity. Complex, multiply substituted heterocyclic scaffolds, which can be generated in a direct, one-pot manner from simple starting materials, would be ideally suited for this purpose.

To address this challenge, we proposed the concept of 'multitasking functional groups' (MFGs). We envisaged that an MFG would play multiple roles in a cascade carbon–hydrogen activation/annulation reaction. Firstly, it would serve as a DG to activate and govern the selectivity of carbon–hydrogen insertion. Secondly, it would be an internal oxidant to both turn over the transition-metal catalyst and initiate redox processes that form new structural motifs. Thirdly, the reactivity of the MFG would be used to trigger versatile rearrangement, cyclization, and other bond reassembly processes. Finally, the function of the MFG should be controllable using either an orthogonal catalyst or by variation of common condition parameters.

The results of recent investigations focusing on this issue demonstrate that the *N*-oxyamide moiety can function as a desirable MFG.[21] The redox properties of the nitrogen–oxygen bond and amide functionality in these substances are particularly attractive for designing multitasking cascades. During the course of our investigation, Lu and co-workers reported that the *N*-oxyacetamide group acts as a DG^{ox} in redox-neutral carbon–hydrogen olefination reactions of internal alkynes.[4c,d] Subsequently, Wang and co-workers described other redox-neutral carbon–hydrogen olefination reactions with hydrazones or diazo substrates which are guided by the same DG^{ox}.[22] Zhao and co-workers later disclosed the discovery of a method for palladium-catalyzed benzisoxazole synthesis using an *N*-oxyacetamide as a DG (Scheme 13).[4e] It is noteworthy that in the reactions studied by Lu's group, either *ortho*-olefinic phenols or benzofurans could be generated by controlling the reaction conditions.

These initial observations highlighting the multitasking ability of *N*-oxyacetamides encouraged us to carry out a more-detailed study focusing on the preparation of more-complex targets. During our efforts, we found that olefination products generated in the reactions Lu studied undergo an intriguing oxidative double ring-closure reaction to produce dihydrobenzofuro[2,3-*d*]oxazoles containing two contiguous stereogenic centers (Scheme 14).



Scheme 13 Redox-neutral carbon–hydrogen activation/annulation reactions using an *N*-oxyacetamide

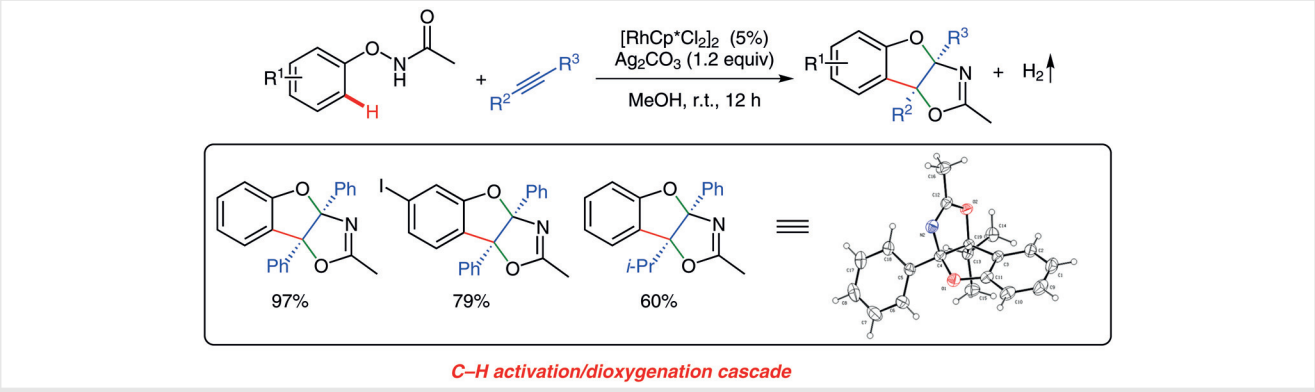
This process occurs smoothly at room temperature using 1.2 equivalents of silver(I) carbonate (Ag_2CO_3). Interestingly, hydrogen is released in this transformation. Thus, by simply adding Ag_2CO_3 to the product mixture generated using Lu's conditions, a double cascade reaction between the *N*-oxyacetamide and alkyne functionalities takes place to form a dihydrobenzofuro[2,3-*d*]oxazole directly.

The 5,5-fused heterocyclic ring system in dihydrobenzofuro[2,3-*d*]oxazoles contains a chemically labile hemiaminal group, which has the potential of being used to trigger interesting rearrangement/oxidation pathways that lead to the generation of substituted polycondensed heterocycles. Therefore, *N*-oxyacetamides, serving as MFGs, might enable rapid structural diversification following carbon–hydrogen activation/annulation through multistep cascade processes.

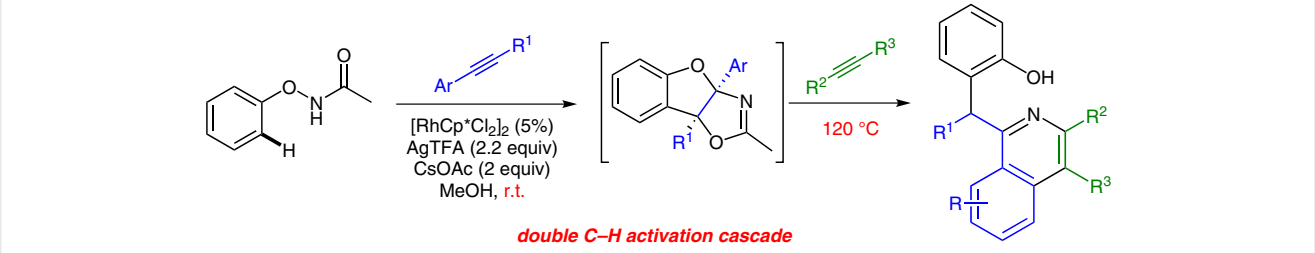
To explore this proposal, the dihydrobenzofuro[2,3-*d*]oxazole formed by the reaction of an *N*-(aryloxy)acetamide and an alkyne was treated with another alkyne under the carbon–hydrogen activation/annulation conditions. The ensuing reaction produced a polysubstituted isoquinoline product (Scheme 15).

Observations made in mechanistic studies revealed that dihydrobenzofuro[2,3-*d*]oxazole undergoes reversion to the initial olefination product, which then participates in an enamine-directed alkyne annulation reaction to yield the new heterocyclic ring system. In a subsequent effort, we demonstrated that it is possible to utilize two different alkynes in a one-pot reaction. The chemoselectivity in each step of this cascade, which forms an isoquinoline derivative, was achieved by controlling the reaction temperature. Specifically, the second alkyne insertion occurs after the first alkyne reaction is completed when the temperature is raised to 120 °C.

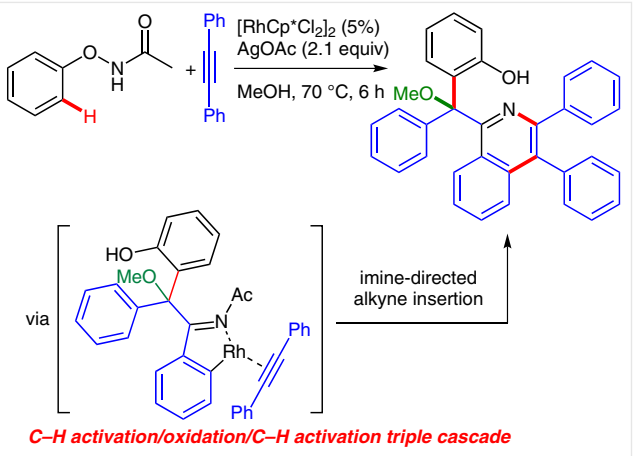
Treatment of *N*-phenoxyacetamide with excess diphenylacetylene, $[RhCp^*Cl_2]_2$, and silver(I) acetate (AgOAc, 2.1 equiv) in methanol leads to the formation of an isoquinoline, a higher oxidation state product, via a three-step carbon–hydrogen vinylation, oxidation, and carbon–hydrogen activation/annulation cascade reaction (Scheme 16). Interestingly, this product is not produced upon subjecting the



Scheme 14 Double cascade reaction for dihydrobenzofuro[2,3-*d*]oxazole formation using an *N*-oxyacetamide as a multitasking functional group



Scheme 15 Double cascade reaction for isoquinoline formation using an *N*-oxyacetamide as a multitasking functional group



Scheme 16 Triple cascade reaction to form an isoquinoline using an *N*-oxyacetamide as a multitasking functional group

corresponding double cascade product to benzylic oxidation conditions. We propose that in this process, an enamine oxidation reaction, taking place prior to isoquinoline formation, generates an imine intermediate that directs the second carbon–hydrogen activation/annulation reaction.

Finally, we observed that by increasing the amount of oxidant to 6 equivalents, this reaction leads to the formation of a rearranged isoquinoline product in 80% yield via a quadruple cascade route (Scheme 17). Treatment of the triple cascade product with methanol-d_4 (CD_3OD) and excess AgOAc (5 equiv) was observed to produce the hexadeuterated product. We proposed that the mechanism for this process involves silver-mediated single-electron transfer (SET). Upon dearomatization by phenolate addition, the resulting dihydropyridine intermediate is readily oxidized by silver to generate a conjugated radical cation. The radical cation then undergoes β-fragmentation to yield a more-stable α-methoxy diarylmethyl radical. Further oxidation of this radical, followed by CD_3OD addition to the resulting cation then forms the observed product.

6 Conclusion

In summary, great progress has been made over the past several years in the development of traceless, cleavable, redox-neutral, and multitasking DGs for carbon–hydrogen activation/annulation reactions. The advances have significantly extended the synthetic utility of the carbon–hydrogen functionalization strategy so that it is now applicable to practical and straightforward methods to prepare polysubstituted heterocycles. The examples discussed in this account capture some of the most recent developments made in the design of new DGs. We expect that the new concept of MFGs will stimulate further innovative studies leading to the discovery of novel strategies for heterocycle synthesis.

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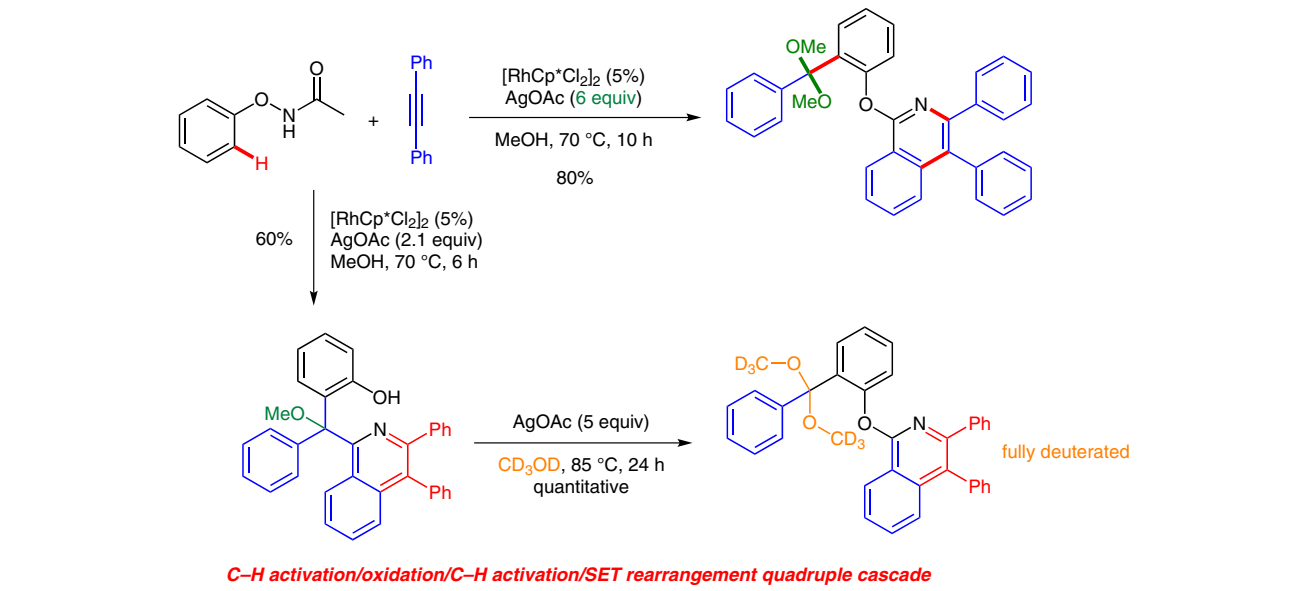

Scheme 17 Quadruple cascade reaction using an *N*-oxyacetamide as a multitasking functional group

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