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Redox-Neutral Manganese(I)-Catalyzed C–H Activation: Traceless Directing Group Enabled Regioselective Annulation

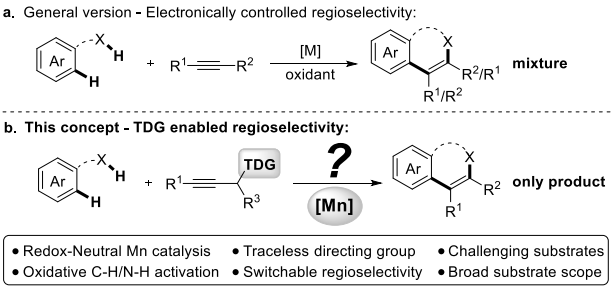
Qingquan Lu[+], Steffen Greßies[+], Sara Cembellín, Felix J. R. Klauck, Constantin G. Daniliuc and Frank Glorius*

Dedicated to Prof. Qi-Lin Zhou on the occasion of his 60th birthday

Abstract: An unprecedented strategy using traceless directing groups (TDG) to promote the redox-neutral Mn(I)-catalyzed regioselective synthesis of *N*-heterocycles is reported. Alkyne coupling partners bearing traceless directing group, which serve as both chelator and internal oxidant, were used to control the regioselectivity of the annulation reactions. This operationally simple approach is highly effective with previously challenging unsymmetrical alkyne systems, including unbiased dialkyl alkynes, featuring switchable regioselectivity, simple conditions, and gram-scale synthesis. The application of this strategy in the concise synthesis of bioactive compound PK11209 and pharmaceutical moxaverine is also described.

Over the past few decades, catalytic C–H activation has emerged as one of the most powerful and attractive methods for the construction of new carbon–carbon and carbon–heteroatom bonds using readily available hydrocarbon starting materials.[1] In particular, unsaturated hydrocarbons have seen extensive use as coupling partners in the synthesis of valuable cyclic compounds, which are frequently found in natural product, pharmaceutical and material frameworks.[2] Arguably, annulation reactions with alkynes are one of the most popular methods of this type, which have been extensively explored with Pd, Rh, Ir, Ru, Cu, Ni etc.[2,3] Despite great progress in this area, essentially almost all the methods reported to date suffer from uncontrolled regioselectivity, leading inevitably to mixtures of positional isomers, especially when unbiased unsymmetrical alkynes were utilized (Scheme 1a).[2,3] Furthermore, the application of unpolarized aliphatic alkynes in this field has become a significant challenge, possibly due to their weaker coordination and low boiling points. Considering these issues, the development of new surrogates for alkynes is of high interest.

In principle, the precoordination of a functional group with a metal can guide the site selectivity, which is the vital step in directed C–H activation.[4] However, the late stage removal of directing groups may lead to labor-intensive multistep operations and unexpected side products, which is a major drawback for any synthetic application. To address this issue, a directing group which can be removed directly *in situ* has been developed.[5] Although the installation of catalyst-directing groups to direct selective C–H activation has been widely applied, the use of a directing group in the coupling partner to control the regioselectivity has been seldom studied, especially with traceless directing groups.[6] In principle, the problem of the regioselectivity in oxidative annulations arises from the alkyne insertion step, which is controlled mainly by an orbital interaction of the occupied M−C σ bonding orbital with an unoccupied π* orbital of the alkyne.[7] Therefore, in almost all cases, the intermediate generated from the alkyne insertion cannot be exclusively obtained and the regioselectivity problem remains unsolved (Scheme 1a). Inspired by the well-developed methodologies for directed *ortho* metalation, we questioned whether a traceless directing group located in an alkyne can be used to control the regioselectivity of oxidative annulation (Scheme 1b), an approach which has not been realized to date. Theoretically, such a group would have to precoordinate to the metal catalyst and enable a regioselective alkyne insertion. Afterwards, the resulting transient intermediate would also have to selectively undergo β-TDG elimination rather than β-hydride elimination or reductive elimination, furnishing the active allene intermediate. Furthermore, a highly selective intramolecular cyclization has to be ensured to circumvent potential side reactions. On the basis of this hypothesis, control over the regioselectivity and ease of removal would be the important criteria for the efficiency of such a directing group.



Scheme 1. TDG enabled regioselective annulation.

To probe the feasibility of our assumption, we selected 1-phenylpentan-1-imine (**1a**) and tertiary propargylic carbonate (**2a**) as model substrates under manganese catalysis.[8,9] It is noteworthy that N-H imines are especially challenging substrates

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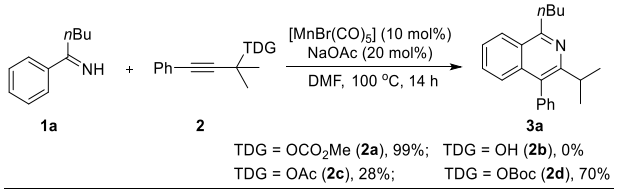
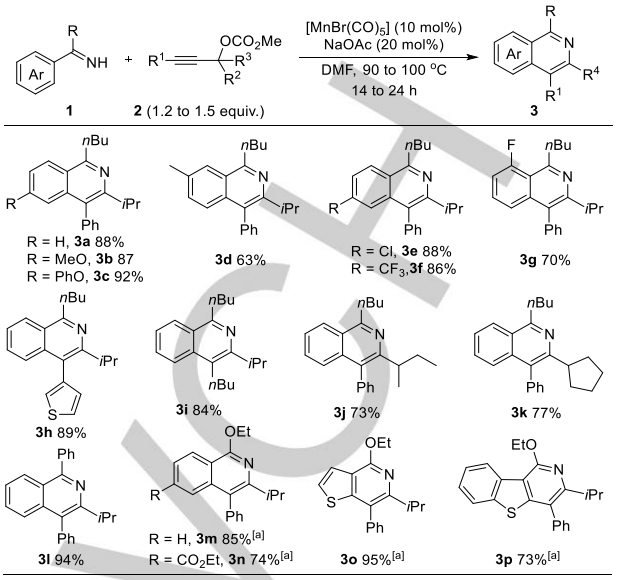
for C–H activation, since the possible enamine tautomerization, the nucleophilicity of the nitrogen and the facile hydrolysis to the ketone can lead to undesired side reactions.[10] Recently, the wang group has successfully utilized N–H imines to couple with alkynes, achieving an elegant dehydrogenative [4+2] annulation in the presence of manganese.[9f] Through an extensive screening (for details, see Table S1 in the Supporting Information (SI)), it was found that the solvent has a significant impact on promoting the reaction efficiency and the expected product **3a** can be isolated in 88% yield with exclusive selectivity when using $[MnBr(CO)_5]$ as a catalyst with 20 mol% NaOAc as a base and DMF as solvent at 100 °C. Further experiments showed that the traceless directing group also plays a crucial role in this transformation. Boc-protected propargylic alcohol **2d** displayed good reactivity while propargylic acetate **2c** and propargylic alcohol **2b** showed low or inert reactivity (Scheme 2).

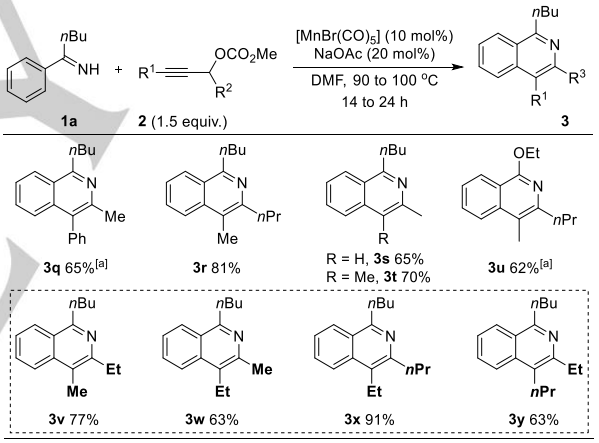


Scheme 2. All reactions were carried out using **1a** (0.10 mmol), **2** (0.15 mmol), $[MnBr(CO)_5]$ (10 mol%) and NaOAc (20 mol%) in DMF (0.25 mL) under argon for 14 h at 100 °C, GC-FID yields using mesitylene as internal standard.

With the optimized reaction conditions in hand, the scope of imines was first investigated. As shown in Scheme 3, a variety of alkyl aryl imines bearing either electron-donating groups (R = OMe, OPh, Me) or electron-withdrawing groups (R = F, Cl, CF_3) on the aryl ring, reacted smoothly with **2a**, affording the corresponding isoquinolines **3a**-**3g** in 63% to 92% yield. The less sterically congested C–H bond was preferably annulated in the *meta*-methyl imine, furnishing the desired product **3d** in 63% yield. When a sterically hindered *ortho*-fluoro substituted imine was employed, the corresponding product **3g** was obtained in 70% yield. Furthermore, the scope of the reaction with respect to propargylic carbonates was explored with **1a**. The R^1 group in the propargylic carbonates was tolerated with aryl, heteroaryl or alkyl groups (**3a**, **3h**, **3i**). The sterically hindered alkyl groups, such as ethyl and cyclopentyl, located on the tertiary carbon of the propargylic carbonate were found to marginally affect the efficiency of these reactions, providing the products **3j** and **3k** in 73% and 77% yields respectively. Furthermore, diaryl ketimine, as exemplified by diphenylmethanimine, could also serve as a suitable reaction partner and gave the desired product **3l** in 94% yield. Importantly, arylimidates were also effective, affording the corresponding desired products **3m**-**3p** in good to excellent yield. Notably, further extending this method to other heterocycles such as thiophene and benzothiophene was also successful, giving the expected products **3o** and **3p** in 95% and 73% yield respectively. The regioselectivity of this protocol was unequivocally confirmed by the X-ray crystallography of **3a** and **3m**.[11]



Scheme 3. Regioselective Synthesis of Isoquinolines. For details, see Supporting Information. [a] BPh_3 (10 mol%) and DME were employed.



Scheme 4. Regioselective switching synthesis of isoquinolines. For details, see Supporting Information. [a] BPh_3 (10 mol%) and DME were employed.

Encouraged by these promising results, we further attempted to apply our developed protocol to secondary propargylic carbonates. To our delight, a variety of secondary and even primary propargylic carbonates were applicable to this procedure, affording the desired products in good to excellent yields (Scheme 4). Intriguingly, complementary to the challenging use of aliphatic alkynes or terminal alkynes in C–H activation, dialkyl-substituted and monoalkyl-substituted propargyl carbonates were compatible as well and delivered the corresponding products **3r**-**3y** in 62% to 91% yield. It should be noted that a C3 building block, methyl prop-2-yn-1-yl carbonate, can also be applied to this annulation reaction and gave the expected product **3s** in 65% yield, while its C3 surrogate, propyne, is a gas and is therefore difficult to utilize. Spurred by these exciting results, we synthesized an array of isoquinolines (**3v**-**3y**) with switchable regioselectivity, which have

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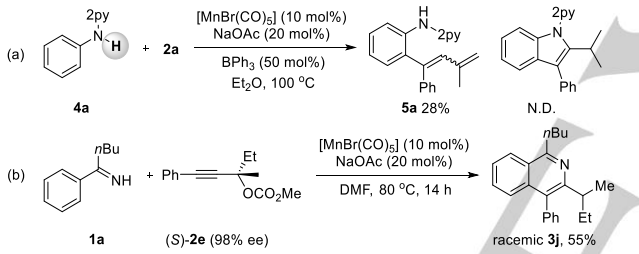
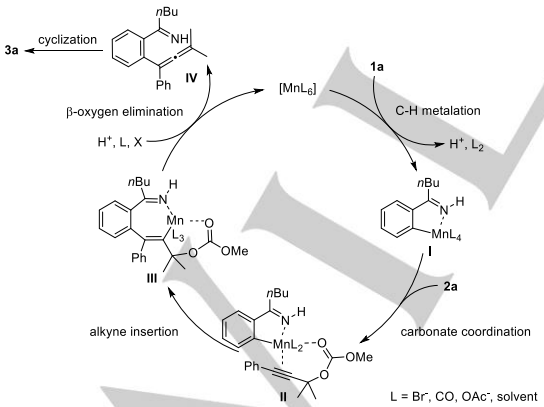
not been successfully prepared as single isomer using previously reported C–H activation methods, highlighting the unique practical application of this catalytic system. This protocol was also readily scaled up to gram quantities with high efficiency. For example, 1.11 g of **3a** was isolated with 73% yield (for details, see SI), further demonstrating the synthetic utility of this method.

To gain insight into the reaction mechanism, a series of experiments were conducted (Scheme 5). First, no oxidative annulation product was detected when *N*-phenyl-2-pyridinamine (**4a**) was employed, and the skipped diene **5a** was isolated instead in moderate yield [Eq. a], which might be formed from the isomerization of the corresponding allene generated *in situ*. This result revealed that an allene-species might be a key intermediate, and that the N-H imine directing group plays a crucial role for the selective intramolecular cyclization. Additionally, no chirality transfer was observed when chiral carbonate (S)-**2e** (98% ee) was applied, even when the reaction was conducted at a lower reaction temperature (80 °C) [Eq. b], implying the intramolecular cyclization might be a nucleophilic addition process.[8] Furthermore, a kinetic isotope effect (k_H/k_D = 1.62) was observed from two parallel reactions of **1a** or [D]-**1a** with **2a** (for details, see SI). Notably, a robustness screen was applied to demonstrate the good functional group and heterocycle tolerance of this protocol (for details, see SI).[12]



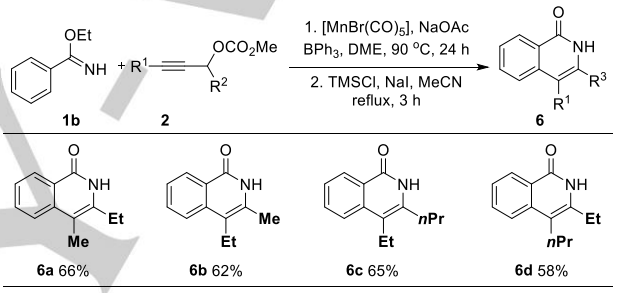
Scheme 5. Mechanistic studies.



Scheme 6. Proposed mechanism.

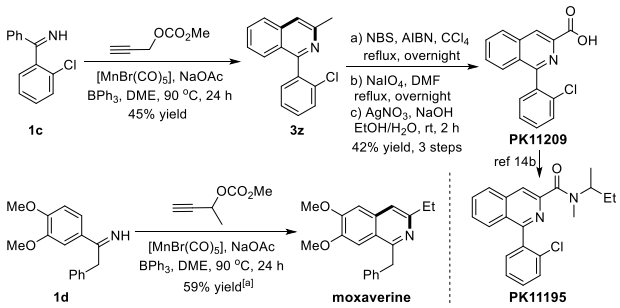
Based on the aforementioned results and previous reports,[8,9] a plausible mechanism was proposed in Scheme 6. The reaction commences with base-assisted cyclomanganation of imine **1a**, forming a five-membered manganacycle **I**. Afterwards, coordination of the carbonyl oxygen of the carbonate **2a** to **I** forms manganacycle **II**, which is followed by a regioselective alkyne insertion and subsequent selective β-oxygen elimination to deliver the active allene intermediate **IV** and regenerate the active Mn(I) complex. Finally, a highly selective intramolecular cyclization of **IV** would give the desired isoquinoline **3a**.[13]

Furthermore, the synthetic applications of our developed method were demonstrated. Isoquinolones are indispensable and ubiquitous structural motifs in bioactive compounds and natural products.[2d,3] Although great efforts have been devoted for their preparation, to date, the regioselective synthesis of isoquinolones is still a daunting challenge in C–H activation.[2d,3] Here, we synthesized a series of valuable isoquinolones with controlled regioselectivity in two steps without isolation of the isoquinoline intermediate, which cannot be achieved using the corresponding alkynes (Scheme 7). The identity of product **6c** was unequivocally established by its X-ray single-crystal structure.[11]



Scheme 7. Regioselective switching synthesis of isoquinolones. For details, see Supporting Information.

Additionally, isoquinoline and its derivatives are common motifs found in pharmaceuticals and natural products, such as antitumor compound PK11209, the peripheral benzodiazepine receptor ligand PK 11195, and the drug moxaverine, which was used to treat functional gastrointestinal disorders.[14] Pleasingly, these compounds were then concisely prepared using our protocol (Scheme 8). Again, the regioselectivity plays a crucial role in these processes.



Scheme 8. Application to the synthesis of bioactive compounds. For details, see Supporting Information.[a] Yield is based on the purity of **1d**.

In conclusion, we have developed a general and scalable strategy to regioselectively synthesize *N*-heterocycles by using alkyne coupling partners with traceless directing group and an earth abundant manganese-based catalyst. This protocol overcomes the previous limitations of C–H activation with unsymmetrical alkyne coupling partners and was also demonstrated to be effective with unpolarized aliphatic alkynes, affording the desired products with perfect regioselectivity. Various isoquinolines and isoquinolones were prepared with broaden scope and functional group tolerance. Related bioactive compound and pharmaceutical were also readily synthesized based on this methodology.

Keywords: C−H activation • regioselective annulation• manganese • unpolarized alkyne • heterocycle

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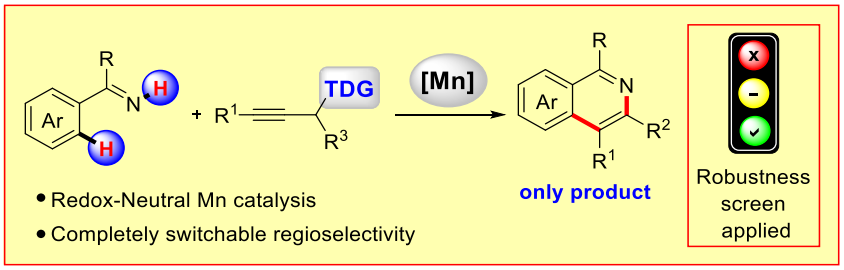

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Traceless Manganese Catalysis! An unprecedented strategy using traceless directing groups (TDG) to promote the redox-neutral Mn(I)-catalyzed regioselective synthesis of *N*-heterocycles is reported. This operationally simple approach is highly effective with previously challenging unsymmetrical alkyne systems, including unbiased dialkyl alkynes, featuring switchable regioselectivity, simple conditions, and gram-scale synthesis.