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Late-stage *ortho*-C–H alkenylation of 2-arylindazoles in aqueous medium by Manganese(I)-catalysis†

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Earth-abundant and water-tolerant manganese(I) catalyzed alkenylation of 2-arylindazole with alkyl and aryl alkynes through C–H bond activation is described with a unique level of *E*-selectivity. The reaction proceeds through the control of C3 nucleophilicity of 2-aryl indazoles. This method is applied to the late-stage functionalization of complex molecules including ethinylestradiol, norethisterone, and N-protected amino acid derivatives. The kinetic isotope studies suggest that the C–H bond activation step may not be the rate-determining step.

Introduction

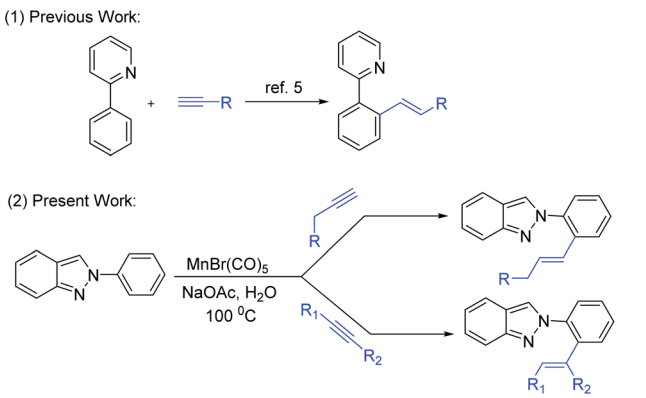
Direct functionalization of inert C–H bonds is still one of the most attractive strategies due to the formation of the versatile fundamental linkage in organic compounds.[1] In this context, noble metals such as iridium,[2a,b] ruthenium,[2c–e] rhodium,[2f,g] and palladium[2h–k] have been extensively employed for C–C and C–hetero atom bond formation reactions in the past two decades because of their high catalytic performance. However, these noble metal catalysts usually suffer from toxicity, low natural abundance, and high cost. In recent years, remarkable progress in 3d-transition metals such as Mn,[3a] Fe,[3b,c] Co,[3d,e] Ni,[3f] and Cu[3g] based C–H activations have been observed due to the metals' low price, high earth abundance, low toxicity, and potential to develop unique reactivity. In this topic, Mn-complexes typically exhibit low toxicity, thus the utilization in C–H functionalization is highly desirable.[4] The Wang group first reported the alkenyation of hetero-arene with alkynes *via* C–H bond activation using $Mn(CO)_5Br$ as a catalyst.[5] Afterward, various research groups such as Ackermann,[6a] Glorius,[6b] Kuninobu[6c] and others[6d–j] independently developed Mn-catalyzed C–H functionalization. Even though C–H bond activation in an aqueous medium is sought after, only a few examples of such reactions are known that occur in water.[7]

Indazole, a nitrogen-containing heterocycle is widely used in pharmaceutical and material science. In particular, antitumor, antiplatelet, anticancer, anti-inflammatory, HIV-protease inhibition, *etc.*, are shown by indazole.[8] Various marketed drugs contain indazole moiety, such as pazopanib, gamendazole, anticancer agent (MK-4827), bendazac (tyrosine kinase inhibitor, votrient), *etc.*[9] Therefore, various methodologies have been developed for the synthesis and functionalization of indazoles because of their extensive biological applications.[10]

Recently few methodologies of *ortho* C–H activation in 2-arylindazole moiety have been developed.[11] However, C–H activation of 2-aryl indazoles using water-tolerant metal-catalyst has not been explored yet. We concentrated our focus on Mn-catalyzed selective *ortho*-C–H functionalization of 2-aryl indazoles through the control of C3 nucleophilicity.[12] Herein, we have described manganese-catalyzed *ortho*-C–H alkenylation of 2-arylindazole with alkyl and aryl alkynes in water (Scheme 1).

Results and discussion

The study was initiated by investigating the reaction of 2-phenyl-2*H*-indazole (**1a**) and prop-2-yn-1-yl 4-methylbenzoate (**2a**) in the presence of Mn-catalyst. The reaction was performed using 10 mol% $MnBr(CO)_5$ as a catalyst and 20 mol% NaOAc as an additive in 1,4-dioxane at 100 °C under N_2 atmosphere.



Scheme 1 Indazole-Directed C–H Alkenylation.

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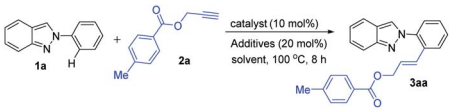
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst (10 mol%)	Additives (20 mol%)	Solvent (2.0 mL)	Yield (%)
1	$MnBr(CO)_5$	NaOAc	1,4-Dioxane	85
2	$Mn_2(CO)_{10}$	NaOAc	1,4-Dioxane	65
3	$MnCl_2$	NaOAc	1,4-Dioxane	nr
4	$Mn(OAc)_2$	NaOAc	1,4-Dioxane	nr
5	$MnBr(CO)_5$	NaOAc	1,2-DCE	61
6	$MnBr(CO)_5$	NaOAc	THF	46
7	$MnBr(CO)_5$	NaOAc	Toluene	52
8	$MnBr(CO)_5$	NaOAc	DMF	21
9	$MnBr(CO)_5$	NaOAc	CH_3CN	10
10	**$MnBr(CO)_5$**	**NaOAc**	**H_2O**	**91**
11	$MnBr(CO)_5$	KOAc	H_2O	78
12	$MnBr(CO)_5$	K_2CO_3	H_2O	62
13	$MnBr(CO)_5$	K_3PO_4	H_2O	57
14	$MnBr(CO)_5$	Et_3N	H_2O	45
15	—	NaOAc	H_2O	nr
16	$MnBr(CO)_5$	—	H_2O	36
17	$MnBr(CO)_5$	NaOAc	H_2O	67[b], 62[c]
18	$MnBr(CO)_5$	NaOAc	H_2O	69[d], 72[e]

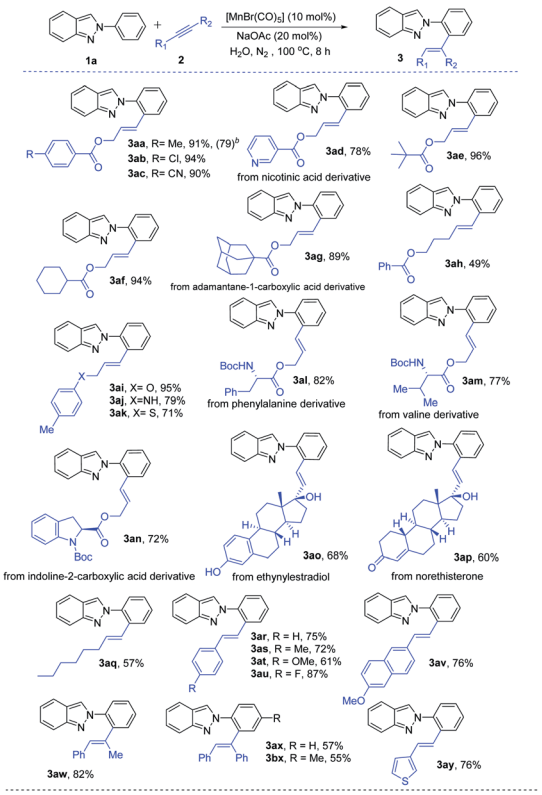
[a] Reaction conditions: All reactions were carried out with 0.25 mmol of **1a**, 0.3 mmol of **2a**, 10 mol% of $MnBr(CO)_5$, 20 mol% NaOAc in 2.0 mL solvent for 8 h at 100 °C under N_2. [b] Stirred at 120 °C. [c] Stirred at 80 °C. [d] Under air. [e] 2.0 equiv. of **2a** was used. nr = no reaction.

Gratifyingly, the coupling product (*E*)-3-(2-(2*H*-indazol-2-yl) phenyl)allyl 4-methylbenzoate (**3aa**) was obtained in 85% yield after 8 h (Table 1, entry 1). Next, we screened the effect of various Mn-catalyst like $Mn_2(CO)_{10}$, $MnCl_2$, and $Mn(OAc)_2$. But in all the cases, unsatisfactory results were observed (Table 1, entries 2–4). Further optimization was carried out using various solvents such as 1,2-DCE, THF, Toluene, DMF, CH_3CN, and H_2O (Table 1, entries 5–10). It was found that polar protic solvent H_2O afforded the desired product in 91% yield (Table 1, entry 10). No significant improvement of the yield was observed on further screening of additives like KOAc, K_2CO_3, K_3PO_4, and Et_3N (Table 1, entries 11–14). However, no product was formed in the absence of catalyst (Table 1, entry 15). Next, we checked the reaction without additives (Table 1, entry 16). In addition, varying the reaction temperature did not improve the yield of the product (Table 1, entry 17). The reaction yield did not enhance under air atmosphere, and no difunctionalized product was obtained in the presence of 2.0 equiv. of **2a** (Table 1, entry 18). From these results, the optimum reaction conditions was determined to be those in entry 10.

After getting the optimized reaction conditions for the manganese-catalyzed C–H alkenylation in hand, we next investigated its versatility (Table 2). The electron-donating (–Me), halogen (–Cl), and electron-withdrawing (–CN) substituted benzoic acid derived alkynes smoothly underwent with indazole (**1a**) through C–H activation, effectively providing the expected products (**3aa–3ac**) with excellent yields even on a gram scale of **3aa**. Nicotinic acid derived alkyne was examined, furnishing the corresponding alkenylated product **3ad** in 78% yield. It is noteworthy that aliphatic acids like pivalic acid, cyclohexanecarboxylic acid, and adamantane-1-carboxylic acid derived alkynes were successfully employed, leading to the desired products **3ae–3ag** in good to excellent yields of 89–96%. Pent-4-yn-1-yl benzoate (**2h**) was treated with 2-phenyl-2*H*-indazole (**1a**), and the expected alkenylation reaction occurred with moderate yield. Remarkably, phenol, aniline, and thiophenol derivatives alkynes were efficiently converted to the desired products **3ai–3ak** with complete *E*-selectivity. Specifically, N-Boc-protected amino acid derivatives **2l** and **2m** were well tolerated, which will be precious for further post-synthetic application. Furthermore, N-Boc-protected indoline-2-carboxylic acid derived alkyne (**2n**) was converted to the desired product in 72% yield. Inspired by the incredible versatility of Mn(I)-catalyzed alkenyation, we became interested in performing this alkenylation reaction with more challenging steroid structures. In this regard, ethinylestradiol and norethisterone took part effectively in the reaction to deliver **3ao** and **3ap** in 68% and 60% yields, respectively. Again, 1-octyne was smoothly reacted, giving the desired product **3aq** in 57% yield with excellent *E*-selectivity. Moreover, 3-hexyne was reacted with 2-phenyl-2*H*-indazole (**1a**) under the standard reaction conditions, but unfortunately obtained an inseparable mixture.

A number of electron-neutral and -donating (–Me, –OMe) and electron-deficient (–F) phenylacetylenes (**2**) were taken part in the reaction with 2-arylindazole (**1a**) to afford the desired products (**3ar–3au**) up to 87% yields. 2-Ethynyl-6-methoxynaphthalene (**2v**) was also amenable to this method. Moreover, internal alkyne (**2w** and **2x**) also provided *ortho*-

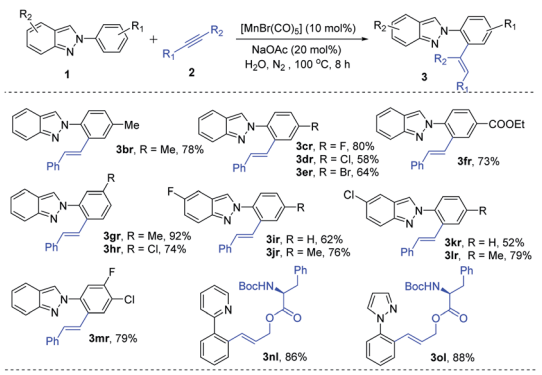
Table 2 Substrate Scope of Alkynes[a]



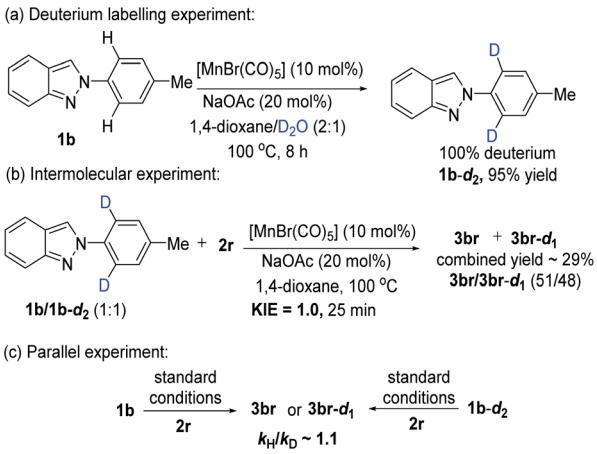
[a] Reaction conditions: 0.25 mmol of **1**, 0.3 mmol of **2** in presence of 10 mol% of $MnBr(CO)_5$, 20 mol% NaOAc in 2.0 mL of H_2O at 100 °C for 8 h under N_2. [b] 5 mmol scale.

alkenyated product **3aw–3bx** in moderated yields (55–82%). Interestingly, heteroaryl substituted alkyne such as 3-ethynyl thiophene (**2y**) was successfully converted into the corresponding alkenylated product **3ay** in decent yields. The regioselectivity of unsymmetrical alkynes (direction of alkynes) have been determined from the ^{1}H-NMR data and coupling constant (*J*) values.

Table 3 Substrate Scope of Hetrocycles[a]

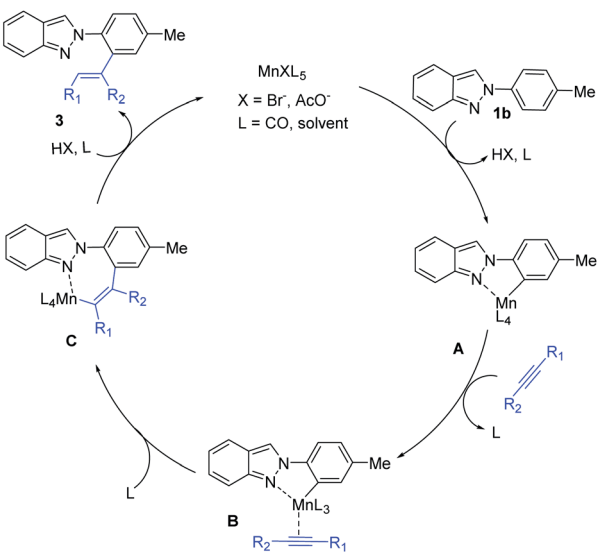


[a] Reaction conditions: 0.25 mmol of **1**, 0.3 mmol of **2** in presence of 10 mol% of $MnBr(CO)_5$, 20 mol% NaOAc in 2.0 mL of H_2O at 100 °C for 8 h under N_2.



Scheme 2 Control experiments.

Motivated by the versatility of the Mn(I)-catalysis, a variety of indazoles were examined. Electron-donating group (–Me) at the phenyl ring of 2-arylindazole gave the corresponding alkenylated product **3br** in excellent yields. Halogen (–F, –Cl, and –Br) containing substrates produced the desired products (**3cr–3er**) in moderate to good yields. An electron-withdrawing (–COOEt) group containing 2*H*-indazole was well tolerated in this method and gave the expected products in moderate yields (**3fr**). *meta*-Substituted 2-arylindazoles (**1g** and **1h**) were also reacted under the optimal reaction conditions (**3gr** and **3hr**) with good yields. 2*H*-indazoles, bearing halogens (–F and –Cl) on the C-5 position of arene, successfully reacted to produce the desired products (**3ir** and **3kr**). Furthermore, disubstituted indazoles (**1j**, **1l**, and **1m**) were explored and gave the corresponding products without any difficulties (**3jr**, **3lr**, and **3mr**). On the other side, due to the difficulty in the formation of a five-membered mangancyclic intermediate, indazole substituted at the *ortho*-position did not produce the desired product. Interestingly, similar N-containing heterocycles such as 2-phenylpyridine (**1n**)



Scheme 3 Plausible mechanistic pathway.

and 1-phenyl-1*H*-pyrazole (**1o**) also reacted with N-Boc-protected amino acid derivative alkyne (**2l**) and provided their corresponding products **3nl** and **3ol** in 86% and 88% yields, respectively (Table 3).

The deuterium labeling experiment, kinetic isotope effect (KIE), and parallel experiments were performed to realize the mechanistic pathway of this reaction (Scheme 2). Initially, a H/D exchange experiment was executed under the optimized reaction conditions using D_2O as a co-solvent which led to the incorporation of deuterium at *ortho*-position of the phenyl ring (Scheme 2a). This result indicated that the reversible cleavage of C–H bonds might be involved in the reaction. In addition, the intermolecular competition reaction (Scheme 2b) and parallel reaction (Scheme 2c) gave low KIE values of 1.0 and 1.1, respectively. This data suggested that the C–H bond cleavage step was unlikely to be the rate-determining step.

Based on the above results and previous reports,[4,5] a plausible reaction mechanism is shown in Scheme 3. At first, NaOAc-assisted cyclomanganation of 2*H*-indazole (**1b**) forms a five-membered manganacycle **A**. Coordination of alkyne (**2**) with **A** gives intermediate **B**. Subsequently, migratory insertion of alkyne generates intermediate C. Finally, protonation of **C** furnishes the desired product, and regenerate the active Mn(I) complex to complete the catalytic cycle.

Conclusions

In summary, we have successfully developed a highly stereo- and regioselective Mn(I)-catalyzed *ortho*-alkenylation of indazole with various alkynes. The salient features of this methodology includes (1) robust C–H activation in H_2O, (2) Mn(I)-catalyzed C–H functionalization, (3) broad substrate scope and good to excellent yields, (4) excellent *E*-stereoselectivity, (5) the late-stage functionalization of complex molecules, (6) scalable. We believe this method will gain much attraction in organic synthesis, pharmaceutical chemistry, and as well as in material sciences.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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