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Manganese-Catalyzed *ortho*-C−H Alkenylation of Aromatic N−H Imidates with Alkynes: Versatile Access to *Mono*-Alkenylated Aromatic Nitriles

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Abstract: So far, the direct C−H alkenylation of aromatic nitriles with alkynes has not been achieved. Herein, we discribe the first manganese-catalyzed C−H alkenylation of aromatic N−H imidates to access *mono*-alkenylated aromatic nitriles. The reaction is accelerated by the presence of a catalytic amount of sodium pivalate. This protocol is also highlighted by the simple catalytic system, good compatibility of functional groups, and excellent mono-/dialkenylation selectivity as well as *E*/*Z* stereoselectivity.

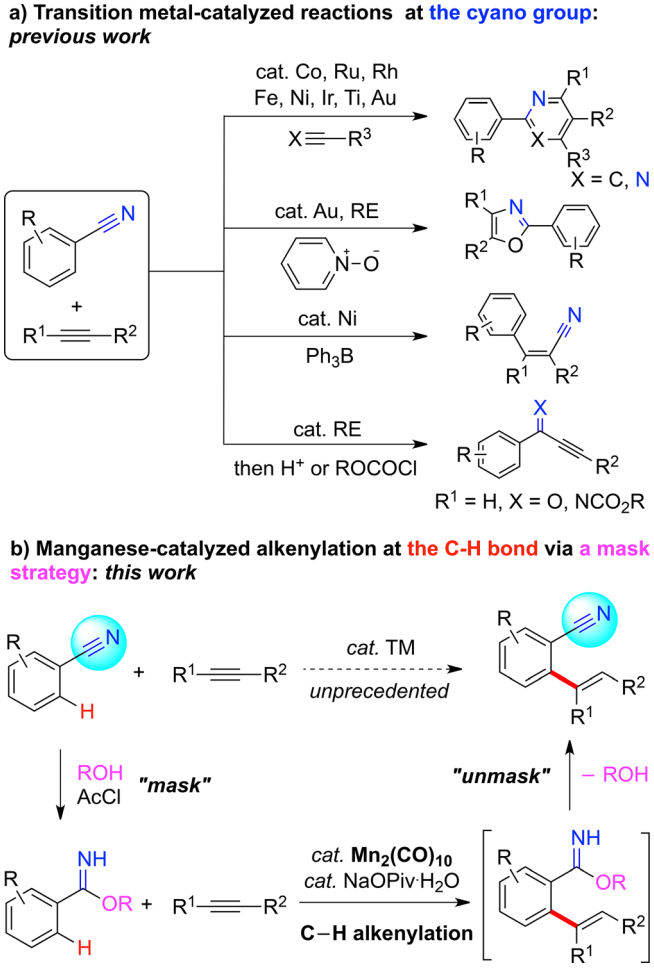
Keywords: alkynes; C−H activation; homogeneous catalysis; manganese; nitriles

Nitriles are provided with versatile utilities so that they are prevalent not only in organic synthesis but also in pharmacy and the chemical industry.[1] Specifically, nitriles play an important role in the traditional field of organic synthesis as precursors or intermediates of imines, ketones, amides, esters, and even alcohols or amines.[1a,b] Nowadays, nitriles also account for a significant proportion of clinical drugs, pesticides, and dyes because of the peculiar properties of the cyano group.[1c] The C≡N triple bond of nitriles possesses a linear configuration with a small size that only occupies one eighth of that of a methyl group so that the cyano group could penetrate into the target easily.[2]

Due to the diverse reactivity of the cyano group, reactions of aromatic nitriles mainly focused on the transformations of the cyano group. The reactions of benzonitrile derivatives with alkynes are illustrative examples. Generally, the nucleophilic reactivity of lone electron pairs on the N-atom, the π-coordination reactivity of the C≡N triple bond, and the electrophilic reactivity of the carbon center of the cyano group contribute to the varied transformations of benzonitriles with alkynes. For instance, transition metal (Co, Ru, Rh, Fe, Ni, Ir, Ti, and Au) catalyzed [2+2+2] cyclizations involving either two alkynes and one nitrile or two nitriles and one alkyne provide efficient approaches to the synthesis of multisubstituted pyridines and pyrimidines (Scheme 1a).[3a–o] Meanwhile, the [2+2+1] annulations of one nitrile, one alkyne, and the third external component give rise to oxazole and imidazole derivatives.[3p–r] In addition, the alkyne can also insert into the C−CN bond of benzonitriles *via* C−C bond activation.[3s] When terminal alkynes are used, the nucleophilic addition of alkynes to the C≡N triple bond of nitriles delivers ynimines or ynones after hydrolysis.[3t,u]

On the other hand, the recently emerging strategy of C−H bond activation provides an atom- and step-economical alternative to traditional synthetic methodologies which are mainly based on manipulations of preinstalled functional groups.[4] In contrast to the above reactions concerning the cyano group, transformations of aromatic nitriles at the *ortho*-C−H bond position have largely lagged behind due to the linear configuration of the cyano group. Only sporadic examples of *ortho*-C−H transformations of aromatic nitriles based on the cyano directing group were reported.[5] In 1999, Murai et al. demonstrated a Ru-catalyzed *ortho*-C−H alkylation of aromatic nitriles with vinylsilanes.[5a] Later, Sun and others discovered Pd-catalyzed *ortho*-C−H arylation, alkoxylation, and halogenation of benzonitriles.[5b–e] Very recently, Jeganmohan et al. reported a Ru-catalyzed oxidative Heck coupling of the *ortho*-C−H bond of aromatic nitriles with activated olefins.[5f] As far as we are aware, the direct C−H alkenylation of aromatic nitriles with alkynes remain elusive so far.

We proposed to meet the above challenge by using a mask strategy, namely, first masking the cyano



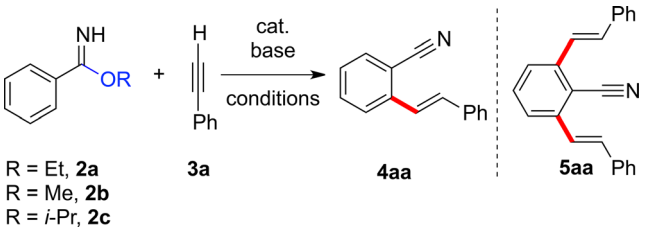
Scheme 1. Transition metal-catalyzed reactions of nitriles and alkynes.

group for the C–H bond activation and then unmasking back to the cyano group after the reaction with alkynes. Inspired by the elegant work from Glorius and Kuninobu on the Rh- and Re-catalyzed C–H transformations of aryl imidates, respectively,[6] we intended to mask the nitriles with alcohols to afford the imidates in order to circumvent the difficulty of the linear cyano functionality as an efficient directing group for C–H bond activation (Scheme 1b). Luckily, the interconversion of aromatic nitriles and imidates is easily accessible by simple tuning of the reaction conditions.[7] However, several challenges still remain: (i) transition metals in Scheme 1a which are capable of catalyzing the [2+2+2]/[2+2+1] cylizations, C–CN bond cleavage or nucleophilic addition of alkynes to nitriles should be avoided since the unmasking of imidates to nitriles is easy to occur in the reaction; (ii) the C–H bond activation of aryl imidates has only been known for rhodium[6a,b] and rhenium[6c] catalysis so far; (iii) the C–H alkenylation with alkynes must proceed faster than the dealcoholization of imidates; (iv) the selectivity of mono-/dialkenylation and *E*/*Z* stereoselectivity must be considered. With these aspects in mind and as part of our continuing interest on earth-abundant manganese catalysis,[8] herein we describe the first manganese-catalyzed *ortho*-C–H alkenylation of aromatic N–H imidates to access *mono*-alkenylated aromatic nitriles. (Scheme 1b). This protocol features manganese catalysis, a simple catalyst system, and excellent mono-/dialkenylation selectivity and *E*/*Z* stereoselectivity.

At the outset, benzonitrile **1a** was easily masked with various alcohols to afford benzimidates **2** in the presence of AcCl and alcohols at room temperature.[7c] Then, we selected ethyl benzimidate **2a** and phenylacetylene **3a** as model substrates to optimize the reaction conditions (Table 1).[9] There was no product detected when **2a** was simply treated with **3a** at 120 °C in DME without a catalyst (entry 1). While neither $Re_2(CO)_{10}$ nor Mn(II) could promote this reaction, delightedly, the expected C–H alkenylation product **4aa** was formed by using manganese carbonyls like $Mn(CO)_5Br$ and $Mn_2(CO)_{10}$ as catalysts (entries 2–6). The screening of solvents and ratios of substrates revealed DME and a **2a**/**3a** ratio of 2:1 as the optimal conditions (entries 7–10). Inspired by our previous work on amine-accelerated manganese-catalyzed C–H activation, the addition of various bases to the reaction was further tested.[9] It turned out that weak bases gave better performance than stronger ones presumably due to the instability of benzimidate **2a** under the reaction conditions, and the use of a catalytic amount of $NaOPiv·H_2O$ delivered the best yield of product **4aa** (entries 11–16). It is noteworthy that only traces of dialkenylation product **5aa** and no *Z*-isomer of **4aa** were detected under these conditions, which reflected the excellent mono-/dialkenylation selectivity and *E*/*Z* stereoselectivity of this reaction. In addition, methyl benzimidate **2b** and isopropyl benzimidate **2c** showed lower reactivity compared with **2a** (entries 18 and 19), probably because of the instability of **2b** and the steric hindrance of the isopropyl group in **2c**, respectively. It should be pointed out that alkenylation using benzonitrile as substrate in the presence of a catalytic or stoichiometric amount of ethanol did not give the desired product. When both AcCl and ethanol were added, there was still no reaction observed.

With the optimized conditions in hand, we first explored the substrate scope of alkynes (Scheme 2). Both electron-donating and electron-withdrawing groups were well tolerated on the benzene moiety of aromatic alkynes leading to the desired products smoothly (**4aa**–**ah**). Of note, the susceptible halogen functionalities like F, Cl, and Br remained intact after reaction, which provides handles for further synthetic elaborations (**4ad**–**af**). The presence of both *meta*- and *ortho*-substituents on the aromatic alkynes was amenable to the reaction (**4ai**, **4aj**). Other aromatic

Table 1. Optimization of the reaction conditions.[a]

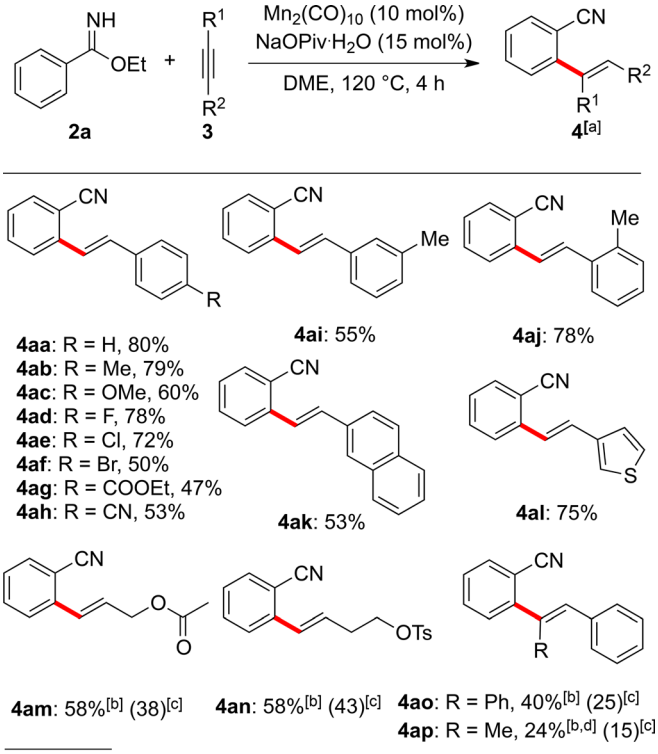


Entry	Catalyst	Base	**2a**:**3a**	Solvent	Yield [%][b]	**4aa**:**5aa**[c]
1	–	–	1:1	DME[d]	0	–
2	$Re_2(CO)_{10}$	–	1:1	DME	0	–
3	$Mn(OAc)_2$	–	1:1	DME	0	–
4	$Mn(CO)_5Br$[e]	–	1:1	DME	25	>99:1
5	$Mn_2(CO)_{10}$[e]	–	1:1	DME	30	98:2
6	$Mn_2(CO)_{10}$	–	1:1	DME	46	97:3
7	$Mn_2(CO)_{10}$	–	2:1[f]	DME	67	>99:1
8	$Mn_2(CO)_{10}$	–	2:1[f]	Et_2O	59	>99:1
9	$Mn_2(CO)_{10}$	–	2:1[f]	dioxane	44	>99:1
10	$Mn_2(CO)_{10}$	–	2:1[f]	THF	63	>99:1
11	$Mn_2(CO)_{10}$	CsOAc	2:1[f]	DME	0	97:3
12	$Mn_2(CO)_{10}$	Cy_2NH	2:1[f]	DME	66	97:3
13	$Mn_2(CO)_{10}$	NaOAc	2:1[f]	DME	70	98:2
14	$Mn_2(CO)_{10}$	NaOPiv·H_2O	2:1[f]	DME	76	97:3
15	$Mn_2(CO)_{10}$	NaOPiv·H_2O[g]	2:1[f]	DME	82	97:3
16	$Mn_2(CO)_{10}$	NaOPiv·H_2O[h]	2:1[f]	DME	86 (80)[i]	98:2
17	$Mn_2(CO)_{10}$	NaOPiv·H_2O[h]	1:2	DME	73	98:2
18[j]	$Mn_2(CO)_{10}$	NaOPiv·H_2O[h]	2:1[f]	DME	70	98:2
19[k]	$Mn_2(CO)_{10}$	NaOPiv·H_2O[h]	2:1[f]	DME	36	>99:1

[a] *Reaction conditions unless otherwise noted:* **2a** (0.2 mmol), catalyst (0.02 mmol), base (0.04 mmol), solvent (0.8 mL), 120 °C, 4 h, N_2 atmosphere.
[b] Detected by ^1H NMR analysis with mesitylene as an internal standard.
[c] Determined by GC-MS.
[d] DME = 1,2-dimethoxyethane.
[e] Catalyst (5 mol%).
[f] **3a** (0.2 mmol).
[g] NaOPiv·H_2O (10 mol%).
[h] NaOPiv·H_2O (15 mol%).
[i] Isolated yield on 0.5 mmol scale.
[j] **2b** (R = Me).
[k] **2c** (R = *i*-Pr).

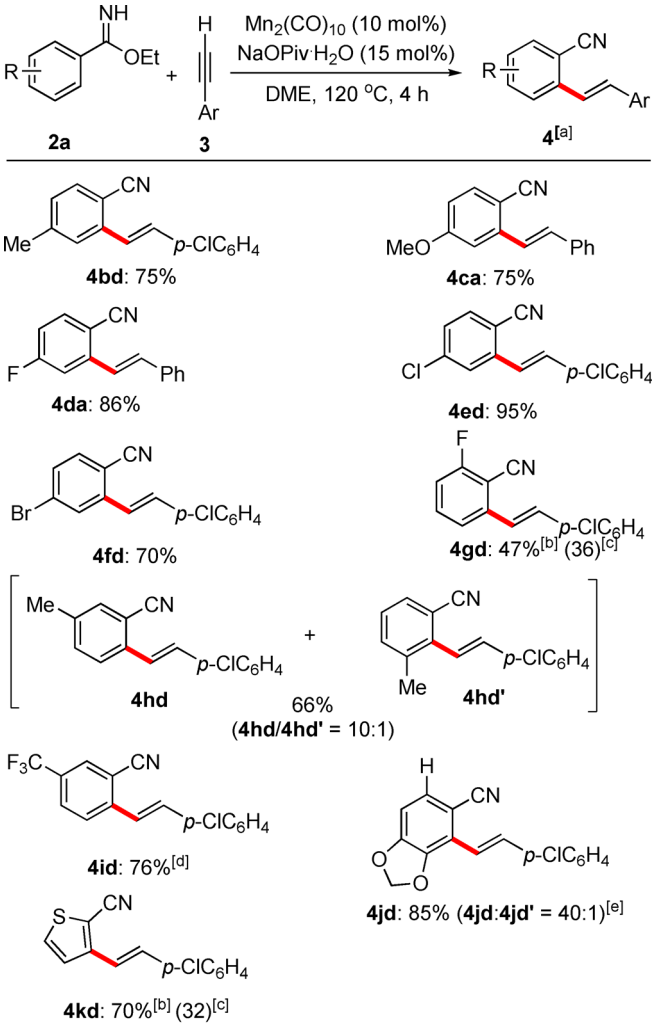
alkynes like 2-ethynylnaphthlene and 3-ethynylthiophene were also amenable to this reaction (**4ak**, **4al**). In addition, aliphatic alkynes with functional groups are compatible with the reaction conditions when additional $Mn(OAc)_2$ was used (**4am**, **4an**). An internal alkyne, diphenylacetylene, was also tolerated in this reaction affording the corresponding product in synthetically useful yield (**4ao**). The use of 1-phenyl-1-propyne only delivered the expected product in 24% isolated yield with sole regioselectivity (**4ap**).

Next, a variety of nitrile-derived imidates were further examined (Scheme 3). Again, a number of electronically varied functionalities were well tolerated on the skeleton of benzimidates affording the C–H monoalkenylation products in good to excellent yields (**4bd**–**fd**). However, the *ortho*-substitutent had an obvious influence on the reaction outcome (**4gd**), which provided a clue about the origin of the high mono-/di-alkenylation selectivity in the reaction. When *meta*-methyl benzimidate was used, the less sterically hindered C–H bond was preferably alkenylated in a good regioselectivity (**4hd**, **4hd′**). Interestingly, only one regioisomer was selectively obtained from the benzimidate bearing a *meta*-CF_3 group (**4id**). Besides, the derivative of piperonylonitrile was also a good substrate for the reaction, surprisingly giving the C–H alkenylation product at the more sterically hindered position (**4jd**). This result might arise from the second coordination of the adjacent oxygen atom to the manganese metal center in the C–H activation step. Final-



[a] Isolated yields of **4** are given.
[b] $Mn(OAc)_2$ (0.25 mmol) was added.
[c] Isolated yield of **4** without using $Mn(OAc)_2$.
[d] Single regioisomer was detected.

Scheme 2. Scope of alkynes. *Reaction conditions:* **2a** (1.0 mmol), **3** (0.5 mmol), $Mn_2(CO)_{10}$ (0.05 mmol), NaOPiv·H_2O (0.075 mmol), DME (2 mL), 120 °C, 4 h.



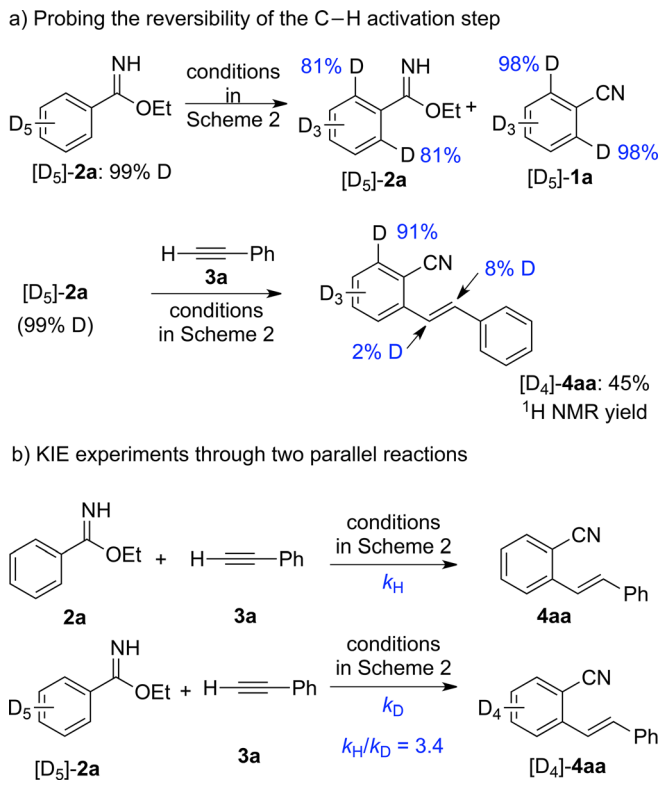
[a] Isolated yields of **4** are given.
[b] $Mn(OAc)_2$ (0.25 mmol) was added.
[c] Isolated yield of **4** without using $Mn(OAc)_2$.
[d] Single isomer was detected.
[e] Determined by GC-MS.

Scheme 3. Scope of imidates. *Reaction conditions:* **2** (1.0 mmol), **3** (0.5 mmol), $Mn_2(CO)_{10}$ (0.05 mmol), NaOPiv·H_2O (0.075 mmol), DME (2 mL), 120 °C, 4 h.

ly, the alkenylation reaction occurred smoothly at the 3-position of 2-cyanothiophene with the assistance of $Mn(OAc)_2$ (**4kd**).

In order to probe the reversibility of the C–H activation step, fully deuterated imidate [D_5]-**2a** was first synthesized and subjected solely to the reaction conditions (Scheme 4a). It turned out that the deuterium loss was observed at the *ortho* positions of remaining [D_5]-**2a** while almost no H/D scrambling was found in the unmasked deuterated benzonitrile [D_5]-**1a**, which implied that the C–H activation step was reversible and might occur through a cyclometallation–deprotonation (CMD) mechanism. This result was also in agreement with our previous work on amine-accelerated manganese-catalyzed C–H activation reactions.[8b,d] Moreover, it showed that the dealcoholization of [D_5]-**2a** was faster than the C–H activation step in the absence of alkynes, which resulted in the nearly no deuterium loss in [D_5]-**1a**. Then, the reaction of [D_5]-**2a** with alkyne **3a** was further examined under the reaction conditions. Only a small amount of deuterium incorporation was observed on the olefinic positions of product [D_4]-**4aa** and, interestingly, the amount of deuterium loss decreased at the remaining *ortho* position of the cyano group, which suggested that the C–H alkenylation step was competing with the dealcoholization.[10] To gain insights on the turnover-limiting step of the reaction, the kinetic isotope effect (KIE) experiments were carried out through two parallel reactions of **2a** and [D_5]-**2a** with alkyne **3a** respectively (Scheme 4b). As a result, the KIE value was determined to be 3.4, which illustrated that the C–H activation step might be the turnover-limiting step or the step before that in the reaction.[11]

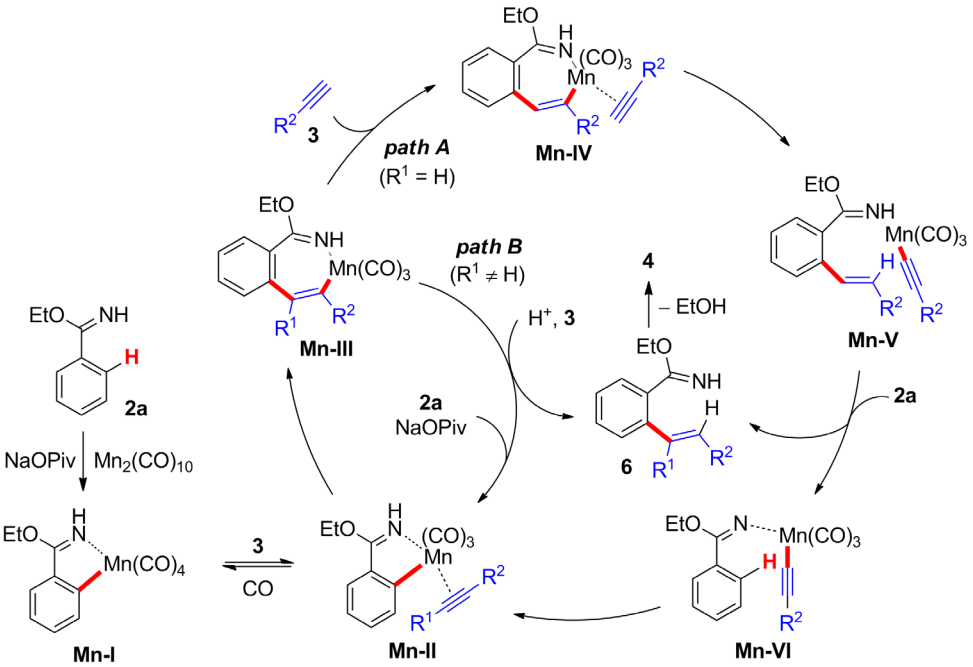
Based on the above experiments and our previous work,[8b,d] a plausible reaction mechanism is shown in Scheme 5. The reaction starts with the NaOPiv-assisted cyclomanganation of benzimidate **2a** giving five-



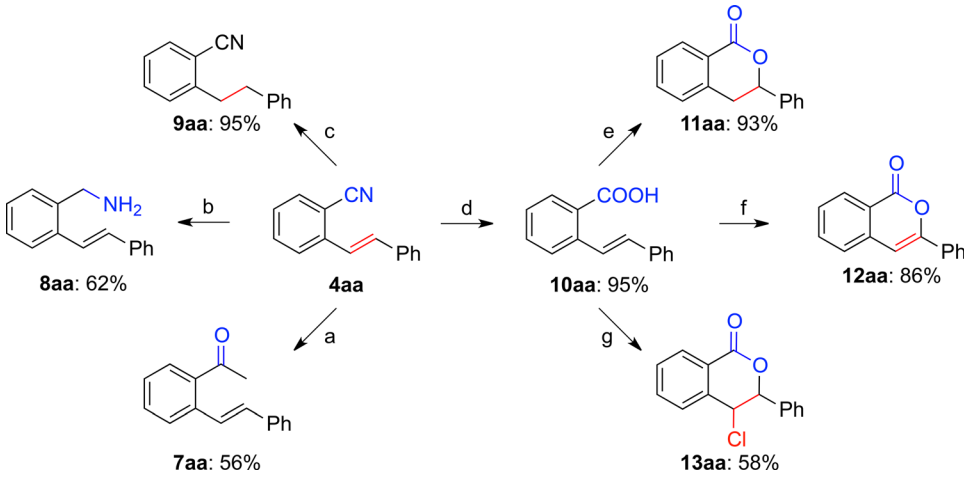
Scheme 4. Deuterium labelling experiments.

membered manganacycle **Mn-I**, which undergoes an alkyne-insertion of the Mn–C_{aryl} bond affording seven-membered manganacycle **Mn-III** *via* the alkyne-manganese complex **Mn-II**.[12] Two possible pathways may occur from species **Mn-III**. If the alkyne **3** is a terminal one (*path A*), the coordination of the second alkyne (**Mn-IV**) followed by an intramolecular H-shift lead to the formation of alkynyl manganese **Mn-V**.[8b,12d] The ligand exchange of **Mn-V** with substrate **2a** gives C–H alkenylated benzimidate **6** and alkynyl manganese species **Mn-VI**, which undergoes an alkynyl-assisted C–H activation regenerating intermediate **Mn-II**, thus closing the catalytic cycle. Alternatively, direct protonation of the Mn–$C_{alkenyl}$ bond of **Mn-III** could afford C–H alkenylated benzimidate **6** when the alkyne is an internal one (*path B*). The following complexation of substrates and C–H activation of **2a** in the presence of NaOPiv would regenerate mangancycle **Mn-II** as well.[13] Finally, the unmasking elimination of ethanol from **6** gives rise to the formation of the desired product **4** ultimately.

At last, the synthetic potentials of the *ortho*-C–H alkenylation products were demonstrated by the derivatization reactions of **4aa** (Scheme 6). Due to the coexistence of both the olefinic double bond and the cyano group, the transformations of **4aa** were rather diverse. Specifically, nucleophilic attack of the cyano group by the Grignard reagent delivered ketone **7aa** smoothly.[14] The C=C bond and the cyano group could be selectively reduced to form amine **8aa** and *ortho*-alkylated benzonitrile **9aa**, respectively.[15,16] Besides, simple hydrolysis of the cyano functionality of **4aa** gave styrylbenzoic acid **10aa** in high yield, which could be further elaborated for the synthesis of diverse products **11aa**–**13aa** through redox-neutral, oxidative, and olefin-oxychlorinated cylizations, respectively.[17–19]



Scheme 5. A proposed mechanism.



Scheme 6. Derivatizations of product **4aa**. *Reagents and conditions:* a) 3.0 M MeMgBr (in Et_2O, 1.2 equiv.), THF (0.1 M), reflux, 6 h; HCl (20 equiv., 4 M), reflux, 56%; b) $LiAlH_4$ (4 equiv.), Et_2O (0.2 M), 0 °C, 1 h; 4 M NaOH (aq., 10 equiv.), 62%; c) 10% Pd/C (10 mol%), H_2 (1 atm), EtOH (0.1 M), CH_2Cl_2 (0.2 M), reflux, 4 h, 95%; d) 1.5 M NaOH (aq., 30 equiv.), ethylene glycol (0.04 M), 130 °C, overnight; 2 M HCl (40 equiv.), 95%; e) conc. H_2SO_4 (ice-cooled, 50 equiv.), 93%; f) PhSeSePh (10 mol%), $PhI(OCOCF_3)_2$ (1.2 equiv.), CH_3CN (0.2 M), room temperature, 1 h, 86%; g) DABCO (0.2 equiv.), 1,3-dichloro-5,5-dimethylhydantoin (1.2 equiv.), room temperatrure, 5 h.

In summary, a manganese-catalyzed *ortho*-C–H alkenylation of aromatic N–H imidates with alkynes has been developed for the first time to access *mono*-alkenylated aromatic nitriles. A catalytic amount of sodium pivalate was found beneficial to the reaction. Also, this protocol is highlighted by a simple catalytic system, good compatibility of functional groups, and excellent mono-/dialkenylation selectivity as well as *E*/*Z* stereoselectivity. Mechanistic studies revealed a reversible deprotonative C–H activation step. Moreover, the diverse synthetic transformations of the *ortho*-C–H alkenylation products were showcased.

Experimental Section

General Procedure

In an oven-dried Schlenk tube, a mixture of the imidate (1 mmol), the alkyne (0.5 mmol), $NaOPiv·H_2O$ (0.075 mol, 15 mol%), $Mn_2(CO)_{10}$ (0.05 mol, 10 mol%) and 1,2-dimethoxyethane (DME, 2 mL) was stirred at 120 °C for 4 h under an N_2 atmosphere. After completion of the reaction, the mixture was cooled down to room temperature. The solvent was removed under reduced pressure and the product was isolated by column chromatography on silica gel with EtOAc/PE.

Acknowledgements

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[9] For more details, see the Supporting Information.

[10] For the reason why the *ortho*-H-incorporation in the second equation was lower than that in the first one, see the Supporting Information.

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