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Rh(III)-catalyzed aromatic C–H bond carbenoid functionalization of triazenes by α-diazomalonate

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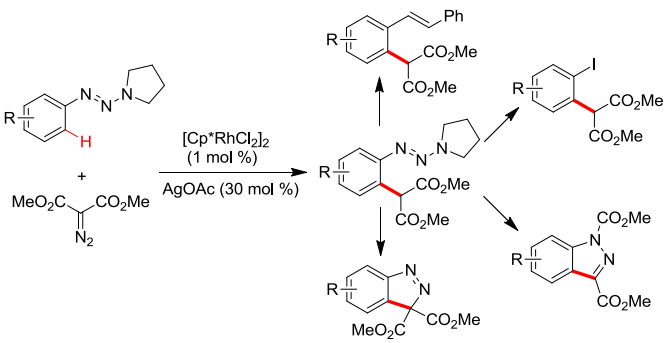
ABSTRACT

A Rh(III)-catalyzed aromatic C–H bond carbenoid functionalization of triazenes by α-diazomalonates has been developed, with features of mild reaction condition and high efficiency. Furthermore, the functionalized triazenes could be subject to divergent synthesis.

1. Introduction

Recently, Rh(III)-catalyzed functionalization of aryl C–H bond has enjoyed tremendous advance owing to their wide applications to the rapid assembly of various complex molecular structures, particular in the fields of medicinal chemistry.[1] The direct C–H functionalization has advantages over classical cross coupling reactions, avoiding the preactivation of coupling partners thus leads to a more atom-economical process.[2] In particular, diazo compounds have acted as alkylation precursors in Rh(III)-catalyzed C–H functionalization. For example, Yu reported a seminal work of Rh(III)-catalyzed carbenoid functionalization of oximes and *N*-Methylbenzylamines with diazomalonates.[3] Diazo compounds have also been investigated as coupling-cyclization components under Rh(III) catalysis.[4] Therefore, the development of Rh(III)-catalyzed C–H functionalization using diazo compounds as coupling partners remains interesting.

Triazenes are versatile building blocks in organic synthesis, which could be transformed to diverse compounds under acidic condition and transition-metal-catalysis.[5] Recently, Huang and coworkers explored the Rh(III)-catalyzed C–H activation of arenes using triazene as substrates,[6] which provides a versatile and removable directing group in C–H functionalization and useful synthetic utility. In continuation of our interest in Rh(III)-catalyzed C–H functionalization for biologically interesting small molecule synthesis,[7] herein we report a Rh(III)-catalyzed aromatic C–H bond carbenoid functionalization of triazenes by α-diazomalonate. Moreover, the functionalized triazenes could be subject to various transformations to access divergent compounds (Scheme 1).



Scheme 1. Rh(III)-catalyzed carbenoid functionalization of triazenes.

2. Results and discussions

We commenced our study by investigating the coupling of pyrrolidine-derived triazene **1a** and α-diazomalonate **2** using $[Cp^*RhCl_2]_2$ as catalyst. When the reaction was conducted in methanol at 70 °C without additives, the Rh(III) catalyzed C–H

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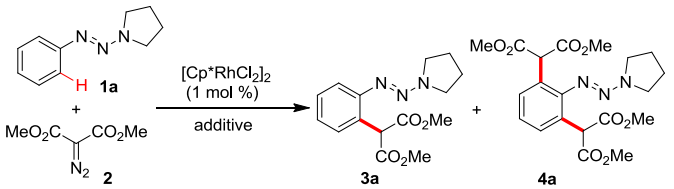
functionalized was completely shut down (Table 1, entry 1), gratifyingly, catalytic addition of CsOAc led to the formation of mono-alkylation triazene **3a** in 21% yield and di-alkylation triazene product **4a** in 10% yield (Table 1, entry 2). This encouraged us to screen other additives and found AgOAc was superior to afford **3a** in 48% yield and **4a** in 23% yield (Table 1, entries 3–4). The next survey of silver salts showed that Ag_2CO_3 and $AgSbF_6$ were inferior to afford trace products (Table 1, entries 5–6). Further screening of solvents were revealed that the use of EtOH would result in lower yield (Table 1, entry 7), while other solvents was inferior to generate trace products (Table 1, entries 8–11). Moreover, decreasing the temperature to 30 °C would result in trace product formation (Table 1, entry 12).

Table 1
Optimization of reaction conditions[a]



Entry	Additive	Solvent	T [°C]	Yield [%][b]	
				3a	4a
1	none	MeOH	70	0	0
2	CsOAc	MeOH	70	21	10
3	$Cu(OAc)_2$	MeOH	70	16	7
4	AgOAc	MeOH	70	48	23
5	Ag_2CO_3	MeOH	70	Trace	Trace
6	$AgSbF_6$	MeOH	70	Trace	Trace
7	AgOAc	EtOH	70	25	11
8	AgOAc	*t*-Amyl alcohol	70	Trace	Trace
9	AgOAc	CH_3CN	70	Trace	Trace
10	AgOAc	DCE	70	Trace	Trace
11	AgOAc	DMF	70	Trace	Trace
12	AgOAc	MeOH	30	Trace	Trace

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (1 mol %), additives (30 mol %), solvent (2 mL).
[b] Yields of isolated products.

With the optimized reaction condition in hand, we next the scope of this Rh(III)-catalyzed carbenoid functionalization using various triazenes. As depicted in Table 2, various *para*-substituted triazenes with valuable functional groups like methyl, chloro, acetyl, ethoxylcarbonyl, could react smoothly with **2** in this process to furnish the mono-alkylation products (**3b**–**3e**) and di-alkylation products (**4b**–**4e**) in moderate yields. The *ortho*-substituted triazenes were also applicable to exclusively furnish the mono-alkylation product in moderate to excellent yields (**3f**–**3i**), with functionalized group such as bromo, ethoxylcarbonyl, cyano, trifluoromethoxy, thus offering ample opportunity for further derivatization. Additionally, polysubstituted triazenes were also tolerated to afford the mono-alkylation products in moderate to excellent yields (**3j**–**3m**). Interestingly, when 3,5-dimethoxy substituted triazene **1n** was used, the reaction only delivered the mono-alkylation product **3n** in 53% yield, and the reaction of 2-naphthenyl substituted triazene exclusively generate the 3-alkylation product **3o** in 42% yield. Moreover, the structure of **3g** was unambibuously confirmed by X-ray analysis (Fig. 1).[8] As mentioned before, triazenes were versatile building block and could be subject to divergent transformations. The unique features were then studied using **3a** as modeling substrate. As shown in Scheme 2, when **3a** was treated with styrene in the presence of $Pd(OAc)_2$, the Heck reaction occurred to form *E*-stilbene derivative **5** in 73% yield, in which triazene served as leaving group. **3a** could also be transformed into an iodobenzene derivative **6** in the presence of NaI under acidic condition. Interestingly, **3a** would undergo divergent intramolecular cyclization to afford indazole compounds **7** and **8**.[9]

A proposed mechanism is depicted in Scheme 3. The initial rhodium diacetate was generated from $[Cp^*RhCl_2]_2$ and AgOAc, and a carboxylate-assisted C–H activation of triazenes occurred to form intermediate **A** with release of AcOH. Then **A** takes diazo insertion with α-diazomalonate **2** to generate **B**, which sequentially takes migratory insertion to provide **C**, with extrusion of N_2. The final protonation of **C** furnishes the carbenoid functionalized product **3**, with regeneration of Rh(III) catalysis. And another carbenoid functionalization of **3** would lead to dialkylation product **4**.

3. Conclusions

In conclusion, we have developed a Rh(III)-catalyzed aromatic C–H bond carbenoid functionalization of triazenes by α-diazomalonate under mild reaction condition. Furthermore, the functionalized triazenes could take divergent transformations to access a variety of small molecules.

4. Experimental section

4.1. General

All commercially available reagents were used without purification unless otherwise noted. Column chromatography was performed using silica gel (100–200 mesh). Visualization of the compounds was accomplished with UV light (254 nm) and iodine. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ operating at 400 MHz and 100 MHz, respectively. Proton chemical shifts are reported relative to the residual proton signals of the deuterated solvent $CDCl_3$ (7.26 ppm) or TMS. Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (77.16 ppm). Chemical shifts are reported in d (parts per million) values. Coupling constants *J* are reported in Hertz. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), and multiple (m). High-resolution mass spectra were recorded on Waters GCT Premier Time of Flight Mass Spectrometer (EI).

General procedure for the synthesis of compounds **3a**–**3o** and **4a**–**4e**. A mixture of Triazenes (0.2 mmol) and dimethyl diazomalonate (0.2 mmol) was dissolved in MeOH (2 mL), and $[Cp^*RhCl_2]_2$ (1.2 mg, 1 mol %) and AgOAc (10 mg, 30% mmol) was added. Then the reaction was proceeded in a sealed tube at a temperature of 70 °C for 10 h. The resulting reaction mixture was loaded on a silica gel column and flashed with 15–20 % ethyl acetate in petroleum ether to afford the desired products **3** and **4** as solid.

4.2. Compound (3a)

(*E*)-Dimethyl-2-(2-(pyrrolidin-1-yldiazenyl)phenyl)malonate **3a**. White solid (29.3 mg, 48%); Mp 87–93 °C; ^1H NMR ($CDCl_3$, 400 MHz), δ: 7.48 (dd, J_1=8.4 Hz, J_2=1.2 Hz, 1H), 7.32–7.30 (m, 1H), 7.29–7.25 (m, 1H), 7.15–7.11 (m, 1H), 5.55 (s, 1H), 3.92 (s, 2H), 3.74 (s, 6H), 3.59 (s, 2H), 2.01 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 169.6, 148.4, 129.0, 128.8, 127.5, 125.2, 116.2, 52.7, 52.6, 51.0, 46.7, 24.0, 23.7; IR (KBr) *v*: 2952, 2930, 2879, 1745, 1728, 1416, 1259, 1224, 1028, 768 cm^{-1}; HRMS (EI) (*m*/*z*): calcd for $C_{15}H_{19}N_3O_4$ (M^+): 305.1376; Found: 305.1377.

4.3. Compound (3b)

(*E*)-Dimethyl-(5-methyl-2-(pyrrolidin-1-yldiazenyl)phenyl) malonate **3b**. Pale yellow solid (21.7 mg, 34%); Mp 97–99 °C; ^1H NMR ($CDCl_3$, 400 MHz), δ: 7.39 (d, *J*=8.4 Hz, 1H), 7.11–7.07 (m, 2H),