Rhodium(III)-Catalyzed C–H Activation of Arenes Using a Versatile and Removable Triazene Directing Group**

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In the past decade, transition-metal-catalyzed arene C-H bond functionalization reactions have enjoyed tremendous advances owing to their widespread applications to the rapid assembly of diversified complex molecular structures, particularly in the fields of medicinal chemistry and material sciences.^[1] Direct C-H activation and functionalization has advantages over classical cross coupling reactions based on aryl halides.^[1b,j,2] The direct method bypasses the need for preactivated reaction partners (such as halides), and leads to a more atom-economical process. In these reactions, a directing group combined with a proper transition metal and a terminal oxidant is often required to achieve C-H chemoselectivity and catalytic turnover.^[1i,3] The directing groups, possessing functional groups containing a metal-binding heteroatom, can either undergo further cyclizations to form heterocycles or remain part of the products (Scheme 1). Such



Scheme 1. Transtion-metal-catalyzed C-H functionalization. DG = directing group, M = metal, TM = transition metal.

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groups can rarely be conveniently removed under ambient conditions^[4,7c,i] or undergo versatile cross-coupling reactions. This restriction has greatly limited the structural diversity of the products and subsequent application to complex molecule synthesis, as the directing group will become part of the product. Therefore, the need for new directing groups that can address this drawback remains urgent. Herein, we report the first triazene-directed, Rh^{III}-catalyzed oxidative olefination reactions under mild conditions.^[3] The directing triazene group can either be removed at room temperature in quantitative yield, or participate in various transformations, such as cross coupling reactions to generate bis(aryl) olefin products.

The Heck-type arene olefination is arguably one of the most important reactions in this field, owing to its excellent compatibility with the conditions for transition-metal-catalyzed C–H activation.^[5,6] The introduction of a chemically versatile, α , β -unsaturated carbonyl moiety greatly increased the synthetic applications of the Heck products. The oxidative Heck reaction, has recently emerged as an attractive method for olefin-arene coupling reactions, because it eliminates the arene activation step required by classic aryl-halide-based Heck reactions. A number of directing groups (Scheme 2) for this particular reaction, including amides, amines, alcohols, oximes, carboxylic acids, esters, ketones, and aldehdyes, have been developed quite recently.^[1i,5b,7]



Scheme 2. Various directing groups developed for arene olefination through C–H activation. DG = directing group, M = metal, TM = transition metal.

In most cases, the directing groups are attached to the arenes by a rather stable C-C or C-N bond, which makes it difficult to remove those groups after C-H activation/functionalization. Furthermore, the complete replacement of those directing groups by C-C or C-N bond cleavage chemistry, such as cross coupling reactions or functional



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group transformations, is highly restricted. We speculated that a loosely connected directing group would overcome these limitations and substantially enrich the synthetic utility of the directing group after C–H functionalization. Herein, we introduce triazenes as an effective directing group for C–H activation. Because of the electron-withdrawing effects of the two appending nitrogens, the C–N bond attached to the arenes is significantly weakened, allowing for gentle removal and subsequent modification.^[8,9] To the best of our knowledge, triazenes have never been utilized as directing groups in such transformations.^[10]

We began by attempting to couple a substrate containing a piperidine-derived triazene^[8] with benzyl acrylate by C–H activation. Among the metals screened, only [{Cp*RhCl₂}₂] (Cp*=pentamethylcyclopentadienyl) promoted C–H activation in any appreciable conversion (Table 1). The reactions

CO₂Bn

 Table 1: Reaction conditions screening.

CI	N N N 1 equiv	+ CO ₂ Bn -	5% cat. 2 equiv oxidant 90 °C, Ar	
Entry	Solvent	Catalyst	Oxidant	Yield (m/d) [%] ^[a]
1 2 ^(b) 3 ^(c) 4 5 ^[d] 6 7 8	toluene MeOH dioxane MeOH MeOH EtOH DCE	PdCl ₂ [{Cp*RhCl ₂ } ₂] [{Cp*RhCl ₂ } ₂] Pd(OAc) ₂ [{Cp*RhCl ₂ } ₂] [{Cp*RhCl₂}₂] [{Cp*RhCl ₂ } ₂] [{Cp*RhCl ₂ } ₂]	$\begin{array}{l} Ag_{2}CO_{3} \\ K_{2}CO_{3} \\ Cu(OAc)_{2}\cdot H_{2}O \\ Cu(OAc)_{2}\cdot H_{2}O \\ Cu(OAc)_{2}\cdot H_{2}O \\ \textbf{Cu}(OAc)_{2}\cdot H_{2}O \\ \textbf{Cu}(OAc)_{2}\cdot H_{2}O \\ Cu(OAc)_{2}\cdot H_{2}O \\ Cu(OAc)_{2}\cdot H_{2}O \end{array}$	- <5 43:27 - 44:10 63:31 35:11 19:5
9	DMF	$[{Cp*RhCl_2}_2]$	$Cu(OAc)_2 \cdot H_2O$	45:20

[a] Yield of isolated product; m/d = mono-/di-olefinated products; for entries 4–8, 30% AgOAc was added. [b] 60°C. [c] 80°C. [d] Under O₂, with 0.1 equiv of oxidant. Cp*=pentamethylcyclopentadienyl, DCE=1,2-dichloroethane, DMF=dimethylformamide, OAc=acetate.

did not occur in the absence of an oxidant. It was found that acetate (^{-}OAc) was crucial for efficient catalyst turnover, possibly by facilitating cyclometalation^[7j,1,11] and regeneration of the Rh catalyst. Other counterions led to significantly lowered conversions. Methanol appeared to be the best solvent for this reaction. The optimized conditions were eventually identified as: 5 mol % of [{Cp*RhCl₂}₂], 30 mol % AgOAc and 2 equiv Cu(OAc)₂·H₂O in methanol under argon at 90 °C (for details on reaction condition screening, see the Supporting Information).

This method was applied to various triazene-substituted arenes and acrylates. Triazenes derived from both cyclic and acyclic amines were effective directing groups for the oxidative Heck reaction (Table 2, entries 18 and 19). Electron-rich arenes were the most reactive, as has previously been observed.^[7j] The reactions occurred readily at room temperature for those substrates. Nevertheless, electron-deficient arenes smoothly underwent olefination at elevated temperatures in high yields. In particular, strong electron-withdrawing groups, such as NO₂, are rarely compatible with directed C–H functionalizations. We were pleased to find that

Table 2: Rh^{III}-catalyzed olefination by triazene-directed C-H activation.



[a] Combined yield of isolated mono- and di-olefinated products. [b] Reactions carried out at room temperature. [c] 80 °C. Ac = acetyl, Bn = benzyl.

both 2-NO₂ and 4-NO₂ triazenes led to the desired products with reasonable yields (Table 2, entries 3 and 9). Interestingly, the 2-Br-substituted substrate led to a C–H activation olefination–Heck cascade to render a double olefinated product (Table 2, entry 20). Various acrylates were equally effective. Acrylonitrile also participated in this reaction with moderate conversion, despite its high tendency to polymerize. More electron-rich olefins gave much lower yields due to the competing Heck coupling.

Surprisingly, even when a second directing group was present, the C-H activation reaction occurred on the less hindered *ortho* position of the triazene, not the doubly

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directed site (Table 2, entries 4 and 7; Figure 1). When substrates substituted with $3\text{-CO}_2\text{Me}$ or 3-Ac (Ac = acetyl) were examined, the olefination still occurred at the position *ortho* to the triazene with almost complete chemoselectivity, even though esters and acetyl groups have also been demonstrated to be good directing groups for this reaction.^[7],q] It is likely that the doubly directed position (Figure 1, red arrow) is either less accessible upon chelation to Rh, or the corresponding aryl Rh is less reactive compared with its counterpart (Figure 1, blue arrow).

The unique features of the triazene directing group were studied and the results summarized in Scheme 3. The triazene group can be subsequently used in cross-coupling reac-



Scheme 3. Transformation of the triazene directing group. Ac = acetyl, Bn = benzyl, OAc = acetate, TFA = trifluoroacetic acid.



Figure 1. Selectivity in the presence of a second directing group.

tions by first converting it into the corresponding iodide with a yield of 97% by treatment with MeI.^[12] Selective hydrogenation can be achieved by switching catalysts. When Pd(OH)₂ was used, the triazene could be reduced to a simple aniline moiety, while 3,4-dihydroquinolin-2(1*H*)one (**6**) was produced directly with palladium on charcoal in methanol. Following a literature method, **6** can be converted into 4-methyl-benzo[c]quinolizin-3-one (**7**), which belongs to a novel class of potent and selective 5α -reductase type I inhibitors used for the treatment of androgen-dependent skin disorders.^[13]

The triazene moiety can be quantitatively removed using $BF_3 \cdot Et_2O$ in DME at room temperature. This method is particularly attractive, as none of the previously developed directing groups can be removed in such a straightforward manner. Triazenyl arenes can also undergo direct arylation with various benzene derivatives and heterocycles in the presence of trifluoroacetic acid.^[14] This reaction is believed to proceed by a radical mechanism through a diazonium intermediate. The triazene product could also undergo transition-metal-catalyzed cross-coupling reactions.^[8c] When treated with styrene in the presence of Pd(OAc)₂, the Heck reaction occurred, in which the triazene served as a leaving group.

In summary, we have developed the first triazene-directed aromatic C–H activation and oxidative coupling to synthesize olefinated arenes. This versatile directing group was shown to participate in various transformations: convenient removal, reduction to amino acids, halogen exchange, and direct C–H cross-coupling. This strategy also provides an efficient synthesis of 3,4-dihydroquinolin-2(1H)-ones from simple anilines. Further exploration of the synthetic utility of this chemistry is currently in progress in our lab and will be reported in due course.

Experimental Section

[{Cp*RhCl₂}₂] (0.0015 mmol, 9.3 mg, 5 mol%), triazene **1** (0.3 mmol, 1.0 equiv), Cu(OAc)₂·H₂O (0.6 mmol, 120 mg, 2.0 equiv) and AgOAc (0.090 mmol, 15 mg, 0.3 equiv) were weighed into an oven-dried Schlenk tube. The reaction vessel was capped and subjected to three vacuum-purge/argon-flush cycles. A solution of acrylate (0.75 mmol, 2.5 equiv) in methanol (2.0 mL) was then added through the side-arm by syringe. The reaction was stirred under argon at 90°C and the progress of the olefination was monitored by TLC. Upon complete consumption of **1**, the reaction was cooled to room temperature. Solvent and volatile reagents were removed by rotary evaporation and the residue was purified by silica gel flash chromatography using petroleum ether/EtOAc (50:1–10:1) to afford product **3**.

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Communications



Functionalizable Directing Groups

C. Wang, H. Chen, Z. Wang, J. Chen, Y. Huang* _____

Rhodium(III)-Catalyzed C-H Activation of Arenes Using a Versatile and Removable Triazene Directing Group



Diverse opportunities: A Rhodium(III)catalyzed *ortho*-selective olefination of arenes using a novel triazene as a directing group is reported. This method exhibits substantial post-functionalization synthetic versatility, overcoming a vital limitation in sp² C–H activation/ functionalization products: restricted structural diversity.