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Rhodium(III)-Catalyzed Cyclization−Olefination of *N*-Acetoxyl Ketoimine-Alkynes

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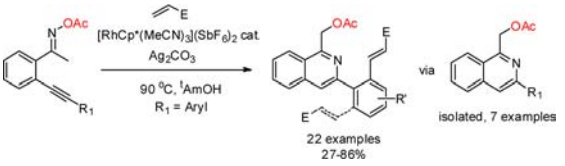
ABSTRACT



***N*-Acetoxyl ketoimine-alkynes undergo Rh(III)-catalyzed oxidative olefination to afford (2-acetoxymethyl)isoquinolines bearing an *ortho*-olefinated aryl group via a sequence that involves (1) Rh(III)-catalyzed alkyne cyclization with intramolecular 1,3-acetoxyl migration and (2) isoquinoline-directed *ortho* C−H olefination.**

Construction of C−C, C−N, and C−O bonds via metal-catalyzed C−H activation has attracted increasing attention for the past several decades owing to the ubiquity of C−H bonds.[1] By taking advantage of this strategy, a large number of synthetic methods have been developed and they have been effectively applied to the synthesis of complex structures.[2] Oxidative C−H olefination via a C−H activation pathway has been extensively studied since the 1980s,[3] and many systems have been developed using palladium[4] and ruthenium[5] catalysts. Recently Miura and Satoh,[6] Glorius,[7] Li,[8] and others[9] have reported that Rh(III) can catalyze the olefination of a number of arenes via cyclometalation with high efficiency, high selectivity, and high functional group tolerance.[1a,b] In addition, olefination reactions catalyzed by Rh(III) and Pd(II) can be complementary in selectivity since different reaction mechanisms may be followed.[9b] Despite the success, this strategy usually requires a preinstalled heteroatom directing group and has little to do with the

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construction of a new framework prior to olefination (Figure 1).[1a,b]

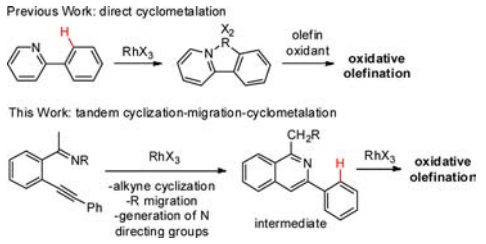


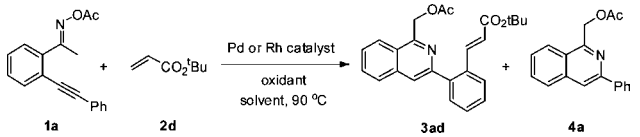
Figure 1. Different strategies in Rh(III)-catalyzed oxidative olefination.

As a continuation of our efforts in Rh(III)-catalyzed oxidative olefination of arenes,[8] we aim to deliver molecular complexity by executing a series of tandem reactions. Our objective is to construct a framework and generate a directing group for subsequent C−H olefination under the same conditions (Figure 1). This should broaden the scope and applications of Rh(III) catalysis in the construction of complex structures. We now report Rh(III)-catalyzed oxidative coupling between olefins and alkynes bearing an *N*-acetoxyl ketoimine functionality, leading to C−N and C−C bond formation.

We initiated our studies with the coupling between *N*-acetoxyl imine **1a** and *tert*-butyl acrylate (**2d**) (Table 1). Recent work indicated when catalyzed by Pd and Rh, the N−OR (R = H, OMe, Ac, and Piv) bond in imine and amide substrates can act as an internal oxidant in the external oxidant-free coupling with alkenes and alkynes.[10] Although the N−O bond in **1a** might serve this purpose, after extensive screenings of the external oxidant-free coupling with **2d** using palladium(II) and rhodium(III) catalysts, no desired olefinated isoquinoline could be detected. Interestingly, when $PdCl_2$ was applied as a catalyst (Table 1, entry 1), only a cyclization product (**4a**) was isolated (32% yield), which was generated as a result of a redox-neutral process that involves metal-catalyzed cyclization with a formal 1,3-acetoxyl migration. The observation of **4a** indicates that Rh-promoted cyclization did occur but the rhodium(III) aryl species was not functionalized by the olefin. Since the OAc group is retained in **4a**, we reasoned that a stoichiometric amount of oxidant is necessary for a subsequent olefination reaction. However, this was not achieved when various Cu(II) and Ag(I) oxidants were introduced under palladium catalysis. By switching to $[RhCp^*(MeCN)_3](SbF_6)_2$ (**A**) as a catalyst (5 mol %) using Ag(I) oxidants, the cyclization−olefination product (**3ad**) started to be obtained (entries 3−8). Further improvement of the efficiency of this coupling was achieved when Ag_2CO_3 was selected as an oxidant, and a maximum yield of **3ad** (68%) was obtained when this reaction was conducted in ^{t}AmOH (entry 9). Interestingly, reactions performed at a higher or lower temperature all resulted in a lower isolated yield of **3ad**. NMR analysis of product **3ad** showed that the olefination occurred at the *ortho* position of the phenyl group, instead of at the 4-position of the isoquinoline ring, which we would expect if the rhodium aryl intermediate generated is directly functionalized by an olefin. Here the rhodium aryl intermediate generated via a cyclization−acetoxyl shift process preferentially undergoes a relatively fast protonolysis to give isoquinoline **4a**, which constitutes an intermediate for further olefination via cyclometalation (vide infra).

With the optimized mono-olefination reaction in hand, we set out to explore the scope and limitations of this reaction (Scheme 1). Imine **1a** readily coupled with a series of acrylates in good yield (65−86%), together with the simple cyclization product **4a**. Styrenes are also viable coupling partners, and coupling with the simple and *para*-substituted styrenes afforded products **3ag**−**3al** in yields ranging from 57% to 68%. The coupling of **1a** is less efficient when acrylonitrile was used (27% yield), where **4a** is the major product. Different alkyne-imine substrates were explored in the coupling with *n*-butyl acrylate, and this coupling reaction proceeded well when *para*- and *ortho*-halogen, OMe, and Me groups were introduced into the phenyl ring of the imine substrate, and the desired products (**3bc**−**3fc**) were isolated in high yields. However, the olefination efficiency is decreased when a *para*-bromo group was introduced, and product **3gc** was isolated in 40% yield, although no Heck coupling product was detected. Under the same conditions, imine substrates bearing an alkyl alkyne unit only afforded the cyclization−acetoxyl migration product.

Table 1. Screening of the Reaction Conditions[a]



entry	cat.	oxidant	solvent	yield of **3ad** (%)	yield of **4a** (%)
1[b]	$PdCl_2$	–	dioxane	0	32
2[b]	$Pd(OAc)_2$	–	dioxane	trace	trace
3	**A**[c]	$Cu(OAc)_2$	dioxane	trace	18
4	**A**[c]	Ag_2CO_3	dioxane	35	28
5	**A**[c]	AgOAc	dioxane	30	21
6	**A**[c]	Ag_2O	dioxane	49	17
7	**A**[c]	Ag_2CO_3	THF	37	15
8	**A**[c]	Ag_2CO_3	PhCl	35	21
9	**A**[c]	Ag_2CO_3	^{t}AmOH	68	12

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.22 mmol), catalyst (5−10 mol %), oxidant (0.40 mmol for $Cu(OAc)_2$ or AgOAc and 0.30 mmol for Ag_2CO_3), solvent (2 mL), sealed tube under nitrogen, 90 °C, 12 h, isolated yield. [b] 10 mol % of the catalyst was used. [c] **A** = $[RhCp^*(MeCN)_3](SbF_6)_2$, 5 mol %.

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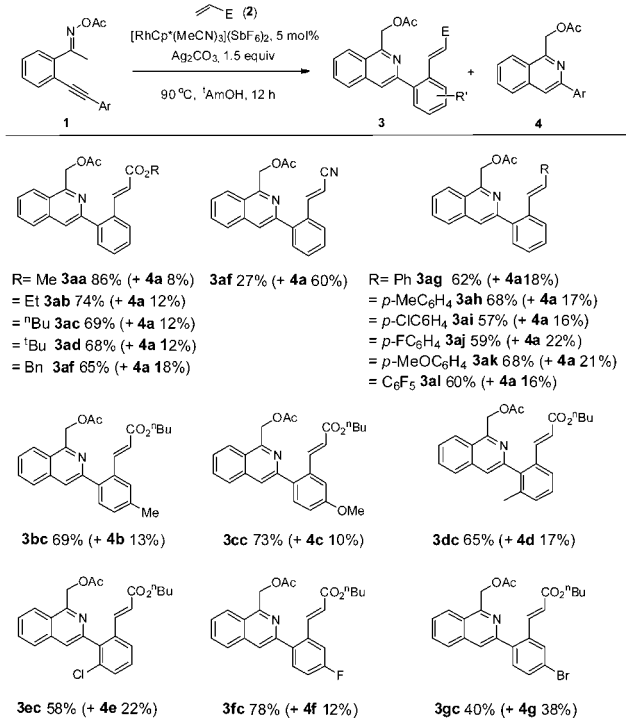
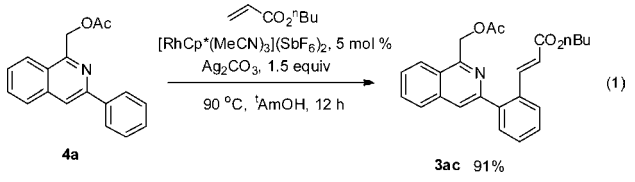
To establish the intermediacy of the cyclization product **4a** in the olefination of **1a**, an isolated sample of **4a** was allowed to react with **2c** under the standard conditions. The expected product **3ac** was isolated in 91% yield (eq 1). This result confirmed that **4a** is an intermediate that leads to olefination. A related Rh(III)-catalyzed olefination of 2-phenylpyridines has been reported by Miura and Satoh, where selective mono- and diolefination has been achieved by careful control of the stoichiometry of the olefin and of other reaction conditions.[11]

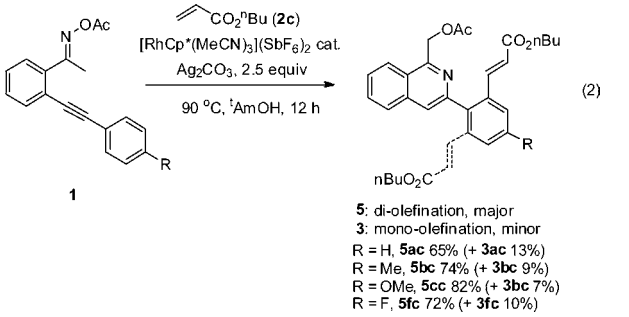
Scheme 1. Mono-olefination of Imine-Alkynes[a]



[a] Conditions: alkyne (0.2 mmol), olefin (1.05 equiv), Ag_2CO_3 (1.5 equiv), ^{t}AmOH (3 mL), 90 °C, 12 h, under Ar. [b] Isolated yield.

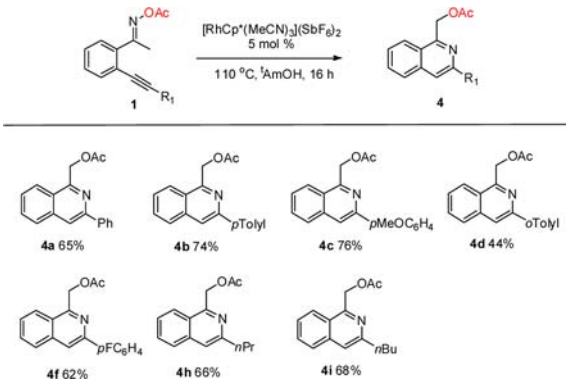


In addition to mono-olefination, selective diolefination can also be achieved when imine-alkyne substrates bearing a simple or a *para* substituted phenyl group were allowed to react with an excess of both *n*-butyl acrylate and Ag_2CO_3. Thus products **5ac**–**5fc** were isolated in good yields (eq 2). In addition to the diolefination product, the mono-olefination product was isolated as a side product, but no corresponding simple cyclization product was detected.



Formation of product **4a** suggests that [RhCp*-$(MeCN)_3$] $(SbF_6)_2$ (**A**) is intrinsically electrophilic and can activate the alkyne toward nucleophilic attack. Indeed, when no olefin or oxidant is present, the Rh(III)-catalyzed cyclization of **1a** afforded **4a** in 65% isolated yield (110 °C, ^{t}AmOH). Under these conditions various alkyne substrates are efficiently converted to the isoquinoline products in 44–76% yield (Scheme 2), and both alkyl and aryl alkyne units in the substrate can be tolerated. Zhang and co-workers have reported that silver-catalyzed cyclization of *N*-acetoxyl aldimine-alkyne afforded an isoquinolone.[12] While in their report acetoxyl shift is also involved, it is followed by elimination of an acetaldehyde to afford an NH isoquinolone product. In addition, the Au(I)-catalyzed cyclization of related alkyne-oximes afforded isoquinoline *N*-oxides without any cleavage of the N–O bond.[13]

Scheme 2. Cyclization of Imine-Alkyne[a,b]



[a] Conditions: alkyne (0.20 mmol), ^{t}AmOH (2 mL), [RhCp*$(MeCN)_3$]-$(SbF_6)_2$ (5 mol %), 110 °C, 16 h. [b] Isolated yield.

To probe the mechanism of the acetoxyl migration, crossover experiments were performed under the standard cyclization conditions for **1b** and **1k**. HPLC analysis of the reaction mixture reveals that only **4b** and **4k** were generated with no crossover (eq 3). These results confirmed that the formal 1,3-migration of the acetoxyl group is intramolecular. We noted that intramolecular migration of

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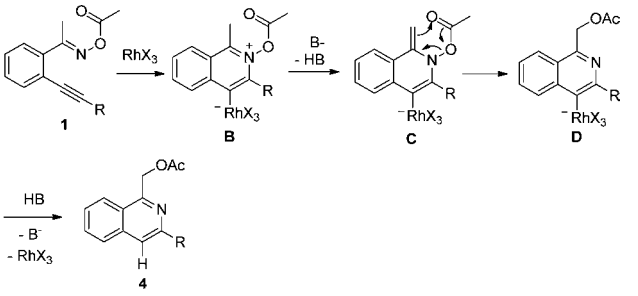
carboxyl and allyl groups has been reported in metal-catalyzed cyclization reactions.[14]

On the basis of these results, a plausible mechanism was proposed (Scheme 3). Activation of the alkyne by coordination to a Rh(III) species is followed by intramolecular imine attack to give a metal-stabilized Zwitterionic species (**B**). Being adjacent to the isoquinolinium nitrogen, the methyl group is somewhat acidic[15] and undergoes deprotonation by a catalytic amount of an adventitious base. The resulting active methyleneisoquinolinene intermediate (**C**) is proposed to undergo a 3,3-sigmatropic rearrangement, resulting in concomitant N−O cleavage and C−O formation. This Rh(III) aryl species (**D**) is protonolyzed to regenerate the Rh(III) catalyst while furnishing the isoquinoline product. Under rhodium-catalyzed oxidative olefination conditions, the failure to observe any olefination at the C(4) position in the isoquinoline ring suggests that protonolysis of the Rh−C bond generated from Rh-promoted cyclization is irreversible and faster than olefin insertion into the Rh−C bond.

In summary, we have achieved rhodium(III)-catalyzed oxidative coupling between olefins and aryl alkynes bearing an *N*-OAc imine functionality. This reaction produced isoquinolines bearing an *ortho*-olefinated 3-aryl group as a result of C−N and C−C coupling. An acetoxymethylisoquinoline has been established as an intermediate via a cyclization−1,3-acetoxyl migration process. This protocol allows the synthesis of functionalized isoquinolines under simple conditions and provides building blocks that may find applications in the synthesis of complex structures.

Scheme 3. Proposed Mechanism of the Cyclization of Imine-Alkynes



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Supporting Information Available. Detailed synthetic procedures and characterization data of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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