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Rh(III)-Catalyzed Olefination of *N*-Sulfonyl Imines: Synthesis of *Ortho*-Olefinated Benzaldehydes

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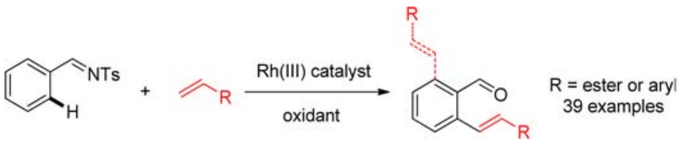
ABSTRACT



Rh(III)-catalyzed olefination of *N*-sulfonyl imines using acrylates and styrenes has been achieved for the synthesis of *ortho*-olefinated benaldehydes. This reaction proceeds via a chelation assisted C–H olefination/*in situ* hydrolysis process.

Direct functionalization of unreactive C–H bonds has been a dynamic research area in synthetic organic chemistry in the past decades.[1] This process takes advantage of the ubiquity of C–H bonds in organics and delivers products in a step- and atom-economic fashion. Ever since the seminal work by Fujiwara and Moritani on oxidative C–H olefination of arenes,[2] C–H olefination has been extensively explored using various transition metal catalysts such as Pd,[2,3] Ru,[1h,4] and Rh,[1c,j,m,f,g,5] among others. In most cases, a chelating group was preinstalled that facilitates the C–H activation and olefination. Despite the significant progress, the scope of the substrate still needs expansion.

Rh(III)-catalyzed C–H olefination has been achieved with the assistance of a variety of nitrogen[6] and oxygen

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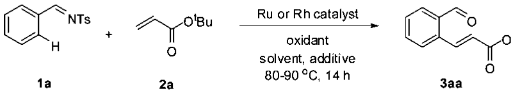
directing groups such as tertiary amide, ester, and ketones.[6,7] Thus aryl ketones have been well-studied in C−H olefination reactions. However, benzaldehydes are more challenging substrates,[8] and occasionally the aldehyde group can act as an efficient directing group for C−H olefination reactions[9] because of the low ligating ability of the aldehyde oxygen and related competitive side reactions. Furthermore, the oxidative conditions might not be compatible with the aldehyde group. It has been reported that aldimines offer stronger chelation assistance for C−H activation and act as a surrogate of aldehydes.[10] However, although imine-directed C−H olefination has been reported,[11] a challenge remains since the imine group is prone to hydrolysis prior to C−H activation. We now report usage of *N*-Ts imines as a removable directing group in Rh(III)-catalyzed olefination−*in situ* hydrolysis of *N*-Ts aldimines.

We recently reported metal-catalyzed C−H activation of *N*-Ts imines and subsequent redox-neutral functionalization with alkynes for the synthesis of indenamines, a process where the *N*-Ts group is retained.[12] We reasoned that under appropriate conditions, C−H olefination may also proceed. With this in mind, we initiated our studies by screening conditions for the coupling of *N*-Ts benzaldehyde imine with *tert*-butyl acrylate. We found that both the coupling efficiency and selectivity are low when [RuCl$_2$(*p*-cymene)]$_2$/AgSbF$_6$ (5 mol %/20 mol %) was used as a catalyst and AgOAc was used as an oxidant in the presence of acetic acid (85 °C, Table 1, entry 1).[4e−i] The coupled product was identified as an *ortho*-olefinated aldehyde (**3aa**) as a result of C−H olefination followed by *in situ* hydrolysis. Using anhydrous Cu(OAc)$_2$ as an oxidant slightly increased the yield (entry 2). In contrast, when the oxidant was changed to Cu(OAc)$_2$·H$_2$O, the coupling occurred with both good efficiency and high selectivity. Under these conditions the amount of AcOH only marginally affected the coupling efficiency. However, poor results were obtained when the solvent was switched to DCE, DCM, or THF (entries 6−8). To our delight, a slightly higher yield of the olefination product was isolated when the catalyst was simply switched to [RhCp*(MeCN)$_3$](SbF$_6$)$_2$ (5 mol %) at a slightly lower temperature, with the selectivity being retained (entry 11). Thus the following conditions were eventually chosen for subsequent mono-olefination studies: [RhCp*(MeCN)$_3$](SbF$_6$)$_2$ (5 mol %), Cu(OAc)$_2$·H$_2$O (2.0 equiv) acrylate (1.2 equiv), AcOH (2.0 equiv), 1,4-dioxane, and 80 °C. In contrast to the high efficiency of the *N*-Ts imine substrate, essentially no desired product was generated when simple benzaldehyde was applied as a more straightforward substrate, indicating that the imine is a more efficient directing group. Furthermore, no desired coupling occurred when the imine **1a** was switched to PhCH=N^{t}Bu,[13] where significant hydrolysis took place, highlighting the importance of the selection of a suitable imine.

Table 1. Optimization Studies on Mono-olefination[a,b]



entry	catalyst	oxidant	solvent	temp (°C)	yield[c] (%)
1	**A**	AgOAc	dioxane	85	47
2	**A**	Cu(OAc)$_2$	dioxane	85	51
3	**A**	Cu(OAc)$_2$·H$_2$O	dioxane	85	70
4	**A**	Cu(OAc)$_2$·H$_2$O	dioxane	90	66
5[d]	**A**	Cu(OAc)$_2$·H$_2$O	dioxane	85	65
6	**A**	Cu(OAc)$_2$·H$_2$O	DCE	85	trace
7	**A**	Cu(OAc)$_2$·H$_2$O	THF	85	27
8	**A**	Cu(OAc)$_2$·H$_2$O	DCM	85	trace
9	**A**	Cu(OAc)$_2$·H$_2$O	dioxane	85	71
10	**B**	Cu(OAc)$_2$·H$_2$O	dioxane	85	73
11	**B**	Cu(OAc)$_2$·H$_2$O	dioxane	80	75
12	**B**	Cu(OAc)$_2$	dioxane	80	68

[a] Reaction conditions: *N*-Ts imine (0.3 mmol), acrylate (0.36 mmol), catalyst, oxidant (0.6 mmol), HOAc (0.6 mmol), solvent (3 mL), 80−90 °C, 14 h, under argon. [b] **A** = [RuCl$_2$(*p*-cymene)]$_2$ (5 mol %)/AgSbF$_6$ (20 mol %), **B** = [Cp*Rh(MeCN)$_3$](SbF$_6$)$_2$ (5 mol %). [c] Isolated yield. [d] No HOAc was used.

With these optimal conditions in hand, we set out to explore the scope and limitations of this system. A series of acrylates underwent smooth coupling with **1a**, and the olefinated aldehydes were isolated in 71−79% yield. A broad scope of *N*-Ts imines has also been defined. Thus electron-donating, -withdrawing, and halogen groups at the different positions of the benzene ring are well tolerated, including a *para*-nitro substituent which is usually problematic in C−H activation reactions. Moderate to high yields of the coupled products were isolated although electron-poor imines tend to give lower yields. The good to

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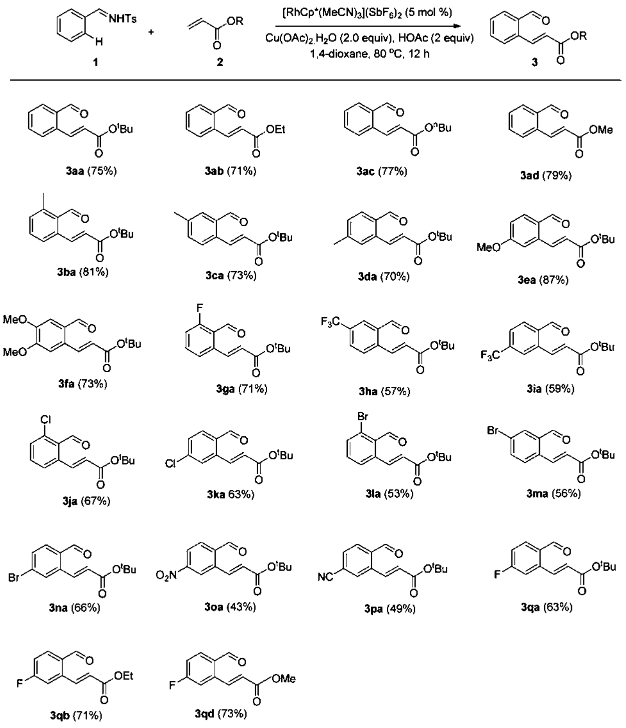
high yield synthesis of **3ba**, **3ja**, and **3la** (Scheme 1) indicates that steric hindrance of a relatively bulky aryl ring induced by *ortho* substitution can be tolerated. In the case of *meta*-substituted imines, the C−H activation occurred selectively and consistently at the less hindered site. These olefinated aldehydes are known as important precursors for the synthesis of a variety of complex structures.[14] The preinstalled halogen, nitro, and cyano groups in the coupled products are typically encountered in organic synthesis and should allow further chemical manipulation. In contrast to the efficient coupling of these imines of benzadehydes, subjection of the *N*-Ts imines of 2-furaldehyde and 2-picolinaldehyde to the standard conditions mostly returned the starting materials, with < 10% formation of the desired product.

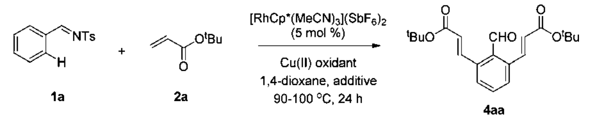
Scheme 1. Scope of Mono-Olefination with Acrylates[a,b]



[a] Reaction conditions: *N*-Ts imine (0.3 mmol), acrylate (0.36 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol %),$Cu(OAc)_2 \cdot H_2O$ (0.6 mmol), HOAc (0.6 mmol), 1,4-dioxane (3 mL), 80 °C, 12 h, under argon. [b] Isolated yield.

To achieve the complementary diolefination of these imines, the reaction conditions of the coupling of **1a** with *tert*-butyl acrylate were further optimized (Table 2). Using an excess of the acrylate (3 equiv) and anhydrous $Cu(OAc)_2$ (4 equiv) at 100 °C, we found that although the mono-olefination product was still generated, the diolefination product could be isolated in 78% yield with a ratio of 1:6 for the mono- to diolefination. HOAc has a miminal effect on the reaction selectivity and efficiency.

Table 2. Optimization Studies of Diolefination[a]

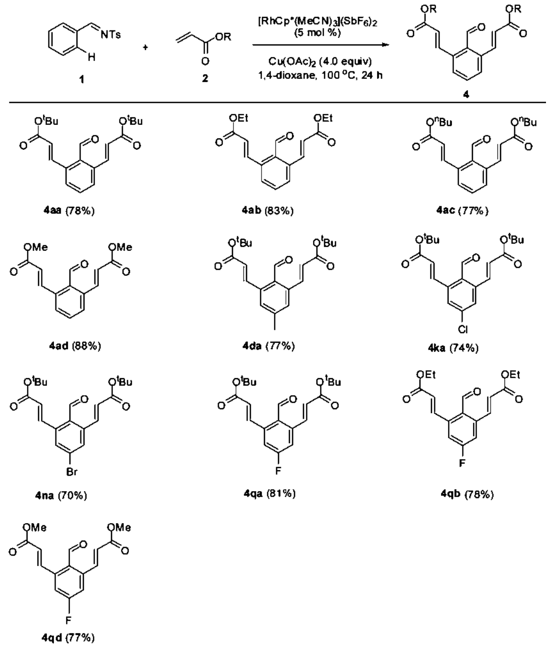


entry	oxidant	additive	temp (°C)	yield[b] (%)	mono/di
1	$Cu(OAc)_2 \cdot H_2O$	HOAc	90	70	1:3
2	$Cu(OAc)_2 \cdot H_2O$	HOAc	95	73	1:4
3	$Cu(OAc)_2 \cdot H_2O$	HOAc	100	76	1:5
4	$Cu(OAc)_2 \cdot H_2O$	HOAc	105	76	1:5
5	$Cu(OAc)_2$	HOAc	100	75	1:5
6	$Cu(OAc)_2$	none	100	78	1:6

[a] Reaction conditions: *N*-Ts imine (0.3 mmol), acrylate (0.9 mmol), $[RhCp^*(MeCN)_3](SbF_6)_2$ (5 mol %), copper salt (1.2 mmol), HOAc (0.6 mmol), 1,4-dioxane (3 mL), 100 °C, 24 h, under argon. [b] Isolated yield.

Under these diolefination conditions, the coupling partner to imine **1a** was extended to a series of acrylates to afford the diene product in high yields (Scheme 2). In addition, variation of the *para* substituent to methyl and halogens is well tolerated, and the coupled products were isolated in consistently high yields.

Scheme 2. Diolefination Using Acrylates[a,b]



[a] Reaction conditions: *N*-Ts imine (0.3 mmol), acrylate (0.9 mmol), $[RhCp^*(MeCN)_3](SbF_6)_2$ (5 mol %), $Cu(OAc)_2$ (1.2 mmol), 1,4-dioxane (3 mL), 100 °C, 24 h, under argon. [b] Isolated yield.

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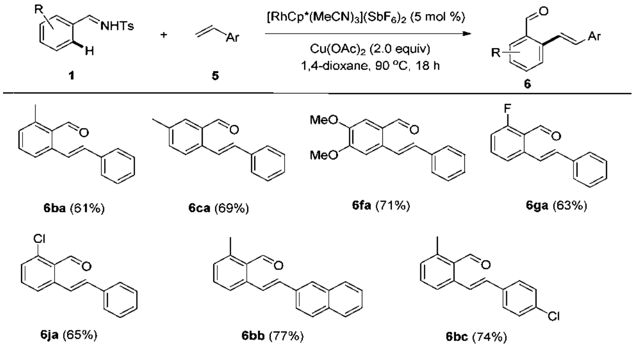
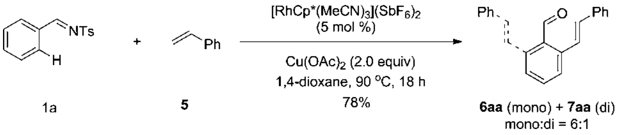
Scheme 3. Mono-olefination Using Styrenes[a,b]



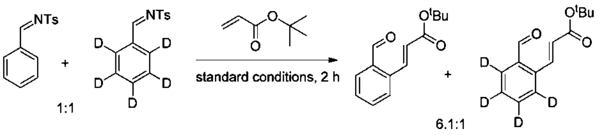
[a] Reaction conditions: *N*-Ts imine (0.3 mmol), styrene (0.36 mmol), [RhCp*(MeCN)$_3$](SbF$_6$)$_2$ (5 mol %), Cu(OAc)$_2$ (0.6 mmol), 1,4-dioxane (3 mL), 90 °C, 18 h, under argon. [b] Isolated yield.

Extension of the olefin substrate to styrenes met with failure when we directly applied the conditions of mono-olefination adopted for acrylates, but modified conditions for acrylates turned out to be applicable. Thus high efficiency was reached for the coupling of **1a** with simple styrene using anhydrous Cu(OAc)$_2$ as an oxidant (2.0 equiv) at 90 °C in the absence of AcOH. However, an inseparable mixture of the mono- and diolefination products was obtained in a 6:1 ratio and in 78% total yield (eq 1), even though an equimolar amount of styrene was provided. Further attempts to effectively improve the reaction selectivity met with failure. Hence a blocking group was introduced to the *ortho* and *meta* position of the benzene ring to ensure high regioselectivity. Indeed, good isolated yields were consistently achieved when methyl, halogen, and methoxy groups were introduced as blocking groups (Scheme 3). In addition to simple styrenes, 4-chloro- and naphthylstyrene also coupled efficiently.



(1)

Several experiments have been performed to obtain insight into the reaction mechanism. Subjection of the mono-olefinated benzaldehyde **3aa** to the reaction conditions for diolefination with *tert*-butyl acrylate only returned the starting material. This result suggests that the (di)olefination should occur prior to hydrolysis. To further probe this C−H activation process, the intermolecular KIE has been measured on the basis of the competitive coupling of *tert*-butyl acrylate with an equimolar mixture of **1a** and **1a**-d_5 (eq 2). ^{1}H NMR analysis revealed a rather large value of k_H/k_D = 6.1, and this large value indicates that the reaction proceeds via a C−H activation pathway. In addition, on the basis of ^{1}H NMR spectroscopy, no H/D exchange was detected at the *ortho* position of products **3aa** and **3aa**-d_4, suggesting that the C−H activation is irreversible under the catalytic conditions.



(2)

In summary, we have successfully applied *N*-Ts imine as a removable directing group for the olefination of imines, leading to an efficient synthesis of olefinated benzaldehydes. This coupling occurs via a C−H oxidative olefination/hydrolysis process, and it circumvents the poor directing effect of aldehydes. Under different conditions, both acrylates and styrenes are viable olefin substrates. In addition, efficient diolefination using acrylates was also achieved under control of the condition. These olefinated aldehydes are important building blocks in organic synthesis. This synthetic method demonstrated the removable directing effect of *N*-Ts imines and may find useful applications in the synthesis of related structures.

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Supporting Information Available. Standard experimental procedure, characterization data of the products, and copies of the NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.