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Variability of Rhodium(III)-Catalyzed Reactions of Aromatic Oximes with Alkenes

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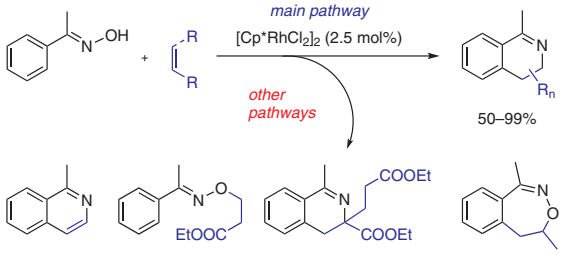
This work is dedicated to the memory of Prof. Keith Fagnou, who made a seminal contribution to rhodium(III)-catalyzed C–H functionalization reactions, and sadly passed away ten years ago at the age of 38.



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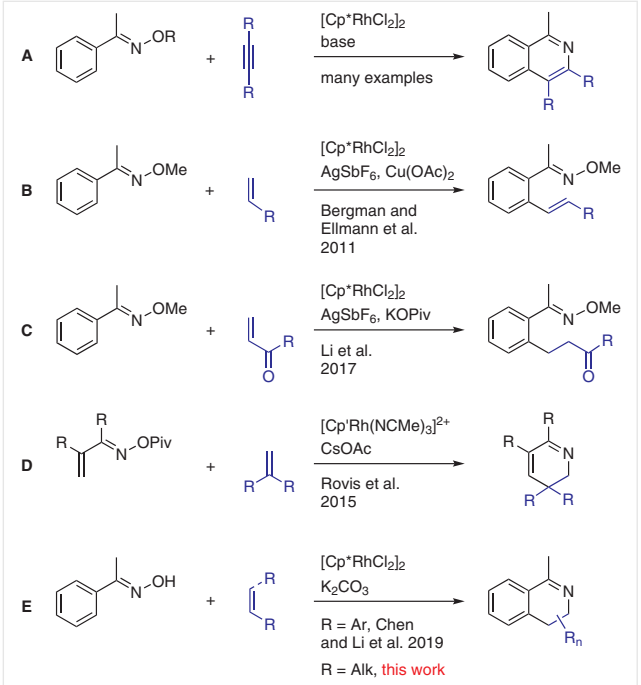
Abstract Acetophenone oxime reacts with various alkenes in the presence of the rhodium catalyst $[Cp^*RhCl_2]_2$ (2.5 mol%; Cp^* = pentamethylcyclopentadienyl) and 1,1,1,3,3,3-hexafluoropropan-2-ol as an important cosolvent. Styrene, aliphatic terminal alkenes, and strained cyclic alkenes gave the corresponding substituted dihydroisoquinolines in yields of 50–99%. On the other hand, alkenes containing functional groups close to the double bond gave a variety of different products. The reactions of acetophenone oxime with styrene or dec-1-ene in the presence of the chiral catalyst $[(C_5H_2{}^tBu_2CH_2{}^tBu)RhI_2]_2$ provided the corresponding dihydroisoquinolines with improved regioselectivity but a low enantiomeric ratio (61:39 in both cases).

Key words C–H activation, rhodium catalysis, oximes, alkenes, isoquinolines

Reliability is one of the most important characteristics of a synthetic method because it permits its use in preparations of previously unknown compounds. To establish the reliability of a method, organic chemists apply it to a variety of substrates. However, negative results that narrow the substrate scope are frequently not reported. Here, we would like to break away from this tendency and report not only the expected, but also the unexpected products of the Rh(III)-catalyzed reactions of aromatic oximes with alkenes.

In the last decade, C–H functionalization reactions catalyzed by the rhodium(III) complex $[Cp^*RhCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) have been widely used for the synthesis of various heterocycles.[1–3] In particular, rhodium-catalyzed reactions of aromatic oximes with alkynes to give isoquinolines (Scheme 1, equation A) have been studied in detail,[4–7] as have similar cobalt-catalyzed examples.[8–10] On the other hand, similar reactions of oximes with alkenes are still relatively underexplored, even though the expected products, namely partially hydrogenated isoquinolines, are common structural fragments of biologically active compounds.[11] Bergman, Ellman, and co-workers[12] and the Lee group[13] have reported that *O*-methyl oximes react with alkenes without ring closure to produce vinyl-substituted derivatives (Scheme 1, equations B and C). A related enantioselective reaction has been carried out by Wang and Cramer, with the help of binaphthyl-substituted Rh complexes.[14]



Scheme 1 Some typical rhodium-catalyzed reactions of oximes

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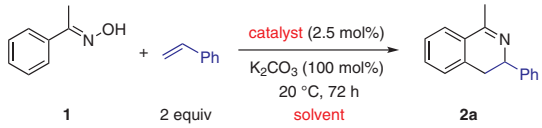
Several groups have shown that reactions of *O*-acetyl oximes with dienes,[15] vinyl acetates,[16,17] vinyl aldehydes,[18] or ketones,[18] are accompanied by aromatization and give isoquinolines. Similar reactions proceed without aromatization in the case of activated alkenes such as ketenes[19] or urea-derived bicycle olefins.[20] Rovis and co-workers found that acrylate oximes are apparently more active than aromatic ones, and their *O*-pivaloyl derivatives can react with various alkenes with or without aromatization (Scheme 1, equation D).[21–23] During the preparation of this manuscript, the group of Chen and Li reported the reaction of aromatic oximes with various styrenes to give dihydroisoquinoline heterocycles (Scheme 1, equation E).[24] However, similar reactions with aliphatic alkenes remained unexplored.

We started our investigation with the reaction of the most common substrates, namely that of acetophenone oxime (**1**) with styrene in the presence of the classical catalyst $[Cp^*RhCl_2]_2$ with K_2CO_3 as a base (Table 1). Optimization of the reaction conditions revealed an unexpected solvent dependence. In particular, the reaction proceeded only in MeCN (Table 1, entry 4); product **2a** was not detected in more polar solvents (MeOH, DMF) or less polar solvents (DCE, THF). Possibly, the coordinating ability of MeCN is responsible for this effect, although one would expect that its coordination with rhodium would inhibit the catalysis. We assumed that MeCN facilitates the dissociation of chloride ligands from $[Cp^*RhCl_2]_2$ to form $[Cp^*Rh(MeCN)_3]^{2+}$ or similar species, which can then coordinate with the oxime. However, the addition of Ag_2CO_3 or CsOAc had no positive effect on the reaction. On the other hand, the addition of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) markedly increased the reaction rate (entry 5). A similar positive effect of fluorinated alcohols has been observed previously.[22–23,25] Cobalt and iridium catalysts $[Cp^*MCl_2]_2$ (M = Co, Ir) (entries 6 and 7), as well as simple $RhCl_3{\cdot}4H_2O$ (entry 8), were found to be inactive in this reaction. The reaction also failed to proceed if the *O*-acetyl or *O*-pivaloyl oxime derivative was used instead of **1**. Possibly, the deprotonation of OH group of the oxime **1** is important because this improves its coordination with rhodium.[5] Overall, under the optimized conditions with $[Cp^*RhCl_2]_2$ catalyst (2.5 mol%) in a 10:1 MeCN–HFIP solvent mixture, the oxime **1** reacted with styrene to give the target product **2a** in 82% yield.[26] Notably, the 3-substituted regioisomer was formed exclusively.

Next, we investigated the reactions of **1** with aliphatic alkenes (Scheme 2). These were found to be less reactive than styrene and, consequently, two to five equivalents of the alkene and heating to 70 °C were required to achieve full conversion of the substrate **1** in a reasonable time (1–3 days). Under these conditions dec-1-ene, methyl undec-10-enoate, hexa-1,5-diene, and *i*-Pr_3Si-protected hex-5-en-1-ol gave the corresponding dihydroisoquinolines **2b–e** in yields of 53–75%. In contrast to styrene, the products were formed as mixtures of 3- and 4-substituted regioisomers in ratios of 2:1 to 4:1. These were separated by column chromatography. The 4-substituted isomers were formed predominantly; this can be explained by the need to avoid steric repulsion between the alkyl group of the alkene and the Cp* ligand during the alkene-insertion step of the catalytic cycle (see Supporting Information for a possible mechanism). A similar regioselectivity pattern has been observed previously in other Rh(III)-catalyzed C–H functionalization reactions.[5,27–29]

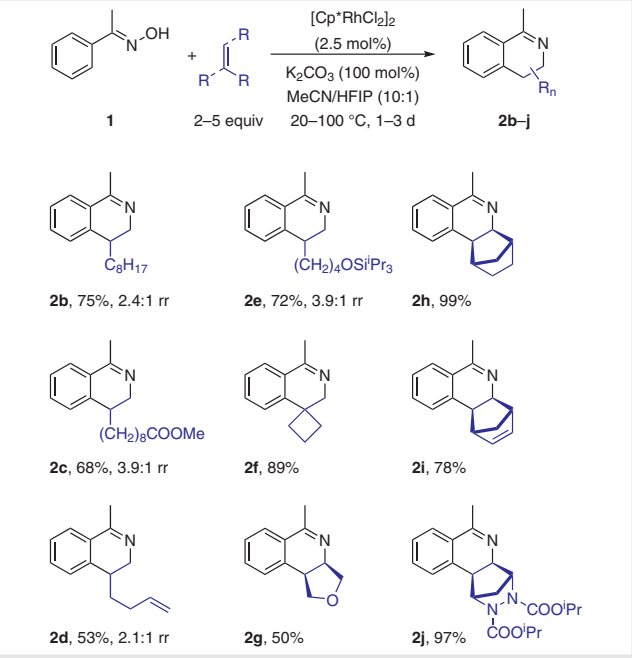
Table 1 Optimization of the Reaction Solvent and Catalyst



1 2 equiv 2a

Entry	Catalyst	Solvent	Yield[a] (%) of **2a**
1	$[Cp^*RhCl_2]_2$	MeOH	<2
2	$[Cp^*RhCl_2]_2$	THF	<2
3	$[Cp^*RhCl_2]_2$	DCE	<2
4	$[Cp^*RhCl_2]_2$	MeCN	25
5	$[Cp^*RhCl_2]_2$	MeCN + HFIP (10%)	82
6	$[Cp^*CoCl_2]_2$	MeCN + HFIP (10%)	<2
7	$[Cp^*IrCl_2]_2$	MeCN + HFIP (10%)	<2
8	$RhCl_3{\cdot}4H_2O$	MeCN + HFIP (10%)	<2

[a] NMR yields are given for all the entries except entry 5, for which the isolated yield is given.

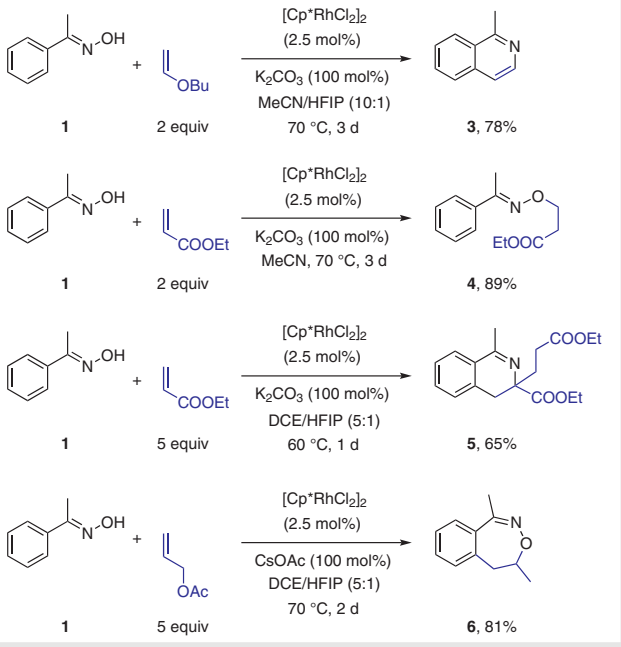


Scheme 2 The expected catalytic reactions of oxime **1** with alkenes; rr = ratio of 4- to 3-substituted regioisomers

Bulky terminal alkenes, such as 3,3-dimethylbut-1-ene and triethoxy(vinyl)silane, as well as disubstituted alkenes, such as cyclohexene and ethyl methacrylate, did not react with **1**, apparently as a result of steric hindrance. Strained cyclic alkenes such as methylenecyclobutane, 2,5-dihydrofuran, norbornene, norbornadiene, as well as the cyclopentadiene–DIAD adduct, were more active and gave the corresponding products **2f–j** in yields of 50–99%. Heating at 100 °C for 18 hours was required for full conversion of **1** in the reaction with methylenecyclobutane. On the other hand, all three norbornene-type alkenes reacted readily at room temperature. Interestingly, ring opening of the DIAD adduct[14,30,31] was not observed under these conditions.

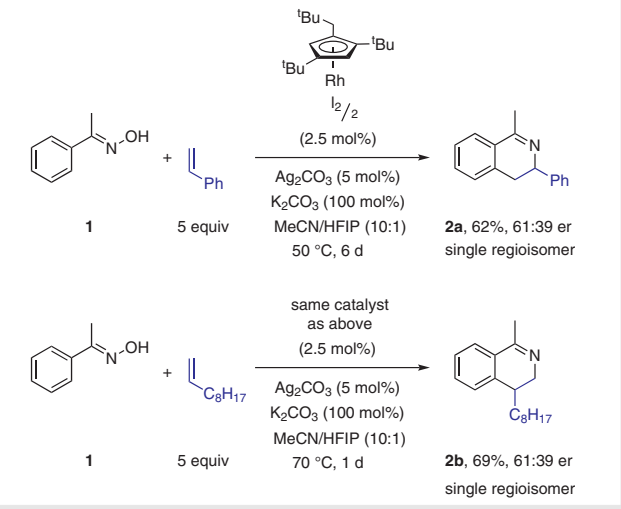
Despite these positive results, many common functionalized alkenes did not produce the expected dihydroisoquinolines **2** in good yields. In particular, allyl-substituted alkenes, such as allyl chloride, allyl bromide, allylic alcohol, N-tosylallylamine, or cyclohex-2-en-1-one, reacted sluggishly with **1**, eventually giving mixtures of several products. Even alkenes with more distant functional groups, such as homoallylic alcohol or pent-4-enoic acid, were problematic, possibly because intramolecular coordination of the double bond and hydroxy group to rhodium inhibited the catalyst. The reaction of **1** with butyl vinyl ether gave aromatic 1-methylisoquinoline (**3**) in 78% yield, apparently through elimination of BuOH from the expected butoxy-substituted dihydroisoquinoline (Scheme 3). A similar process has been observed previously for vinyl acetates.[16,17] The reaction of **1** with ethyl acrylate in MeCN resulted in Michael addition of the hydroxy group of the oxime to the activated double bond, giving product **4** in 89% yield. Interestingly, a similar reaction in DCE as solvent gave the disubstituted dihydroisoquinoline **5** in 65% yield (double substitution occurred even when only one equivalent of ethyl acrylate was used). Apparently, the initial reaction with the first alkene molecule gave the expected dihydroisoquinoline with a COOMe substituent, which then formed an enolate and underwent Michael addition to a second acrylate molecule. Similar processes have been reported for 3-COOR-substituted dihydroisoquinolines.[32,33] Most unexpectedly, the reaction of **1** with allyl acetate gave the benzoxazepine derivative **6** with a seven-membered ring. This compound was formed in both MeCN and DCE solvents, but the later provided a cleaner reaction and a higher yield of 81%. The mechanism for the formation of this product is unclear, although it may involve an initial *ortho*-allylation of the oxime **1**.[12,34–36]

We have recently synthesized the chiral rhodium catalyst $[(C_5H_2{}^tBu_2CH_2{}^tBu)RhI_2]_2$, in which the bulky cyclopentadienyl ligand is assembled from three 3,3-dimethylbut-1-yne molecules (Scheme 4).[37,38] Application of this catalyst in the reactions of **1** with styrene and dec-1-ene gave the expected products **2a** (62%) and **2b** (69%), respectively. As a result of steric hindrance, the reaction with styrene proceeded markedly more slowly than that in the presence of



Scheme 3 Unexpected catalytic reactions of the oxime **1** with alkenes

$[Cp^*RhCl_2]_2$ catalyst, and six days of heating at 50 °C were required for full conversion of **1**. The reaction with dec-1-ene proceeded faster and with markedly improved regioselectivity to give the 4-substituted dihydroisoquinoline **2b** exclusively. However, both **2a** and **2b** were formed as mixtures of enantiomers in an unsatisfactory ratio of 61:39 (coincidentally, the er values were almost identical). The low stereoselectivity of these reactions may be explained by insufficient steric crowding, in particular by the absence of a



Scheme 4 Reactions of **1** with alkenes in the presence of the chiral rhodium catalyst. Addition of Ag_2CO_3 was required for abstraction of iodide ligands from the rhodium atom.

substituent on the oxygen atom of the oxime **1**, which could deviate from the plane of the molecule.

To conclude, we have shown that aromatic oximes react with alkenes in the presence of $[Cp^*RhCl_2]_2$ catalyst to give substituted dihydroquinolines. At the same time, our results, as well as previous reports in the literature, indicate that the rhodium-catalyzed reactions of oximes with alkenes can give a variety of other products, depending on the structures of the substrates and the conditions. Notably, HFIP seems to be an important cosolvent that facilitates such reactions.

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Acknowledgment

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707961.

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(26) **1-Methyl-3-phenyl-3,4-dihydroisoquinoline (2a); Typical Procedure**
Acetophenone oxime (**1**; 27.0 mg, 0.20 mmol), $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol), K_2CO_3 (28 mg, 0.20 mmol), and styrene (0.092 ml, 0.8 mmol) were mixed in dry MeCN (0.5 mL). HFIP (0.05 mL) was added, and argon was bubbled through the solvent for 2 min. The vial was then sealed and the mixture was stirred for 3 d at 20 °C. The vial was then opened to air and the mixture was evaporated in vacuum. The residue was purified by column chromatography [silica gel; hexanes–EtOAc (10:1 to 1:1 gradient)] to give a colorless oil; yield: 36 mg (82%).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.4 Hz, 1 H, CH_{Ar}), 7.46 (d, *J* = 7.4 Hz, 2 H, CH_{Ar}), 7.40–7.35 (m, 4 H, CH_{Ar}), 7.29 (t, *J* = 7.2 Hz, 1 H, CH_{Ar}), 7.20 (d, *J* = 7.2 Hz, 1 H, CH_{Ar}), 4.60–4.50 (m, 1 H, CH), 2.96 (dd, *J* = 15.8, 5.5 Hz, 1 H, CH_2), 2.90–2.81 (m, 1 H, CH_2), 2.51 (d, *J* = 2.0 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.61, 144.50, 136.98, 130.95, 129.54, 128.58, 127.57, 127.26, 127.18, 127.00, 125.54, 61.01, 34.77, 23.47. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_{16}N$ = 222.1277; found: 222.1279.
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