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Rhodium-Catalyzed Direct C–H Addition of 4,4-Dimethyl-2-oxazoline to Alkenes

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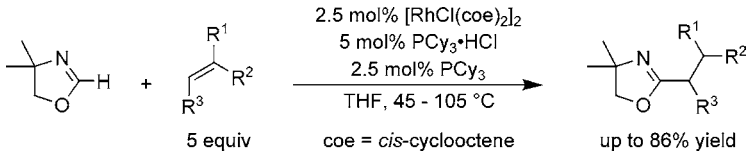
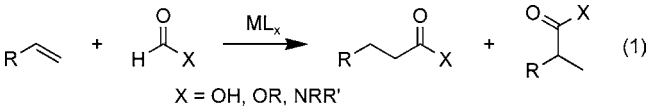
ABSTRACT



A new method for the preparation of 2-substituted oxazolines by rhodium-catalyzed coupling of alkenes with 4,4-dimethyl-2-oxazoline is reported. The oxazoline products are obtained in good yield with excellent selectivity for the linear product. A variety of alkene substitution patterns and functional groups are tolerated. This procedure represents an attractive alternative to hydroesterification because it does not involve the manipulation of CO gas.

New methods for the one-carbon elongation of alkenes employing a synthon other than toxic CO gas, would be broadly useful in synthetic chemistry.[1] Known examples make use of formic acid,[2,3] formates[4−7] and formamides[6,8] (eq 1). Early work was limited to ethylene[3,4] because of poor



(1)

reactivity or side reactions, but more recent methods have provided significant improvements in yield and selectivity.[2] However, most of these are limited to activated alkenes[5,6] or substrates bearing a pendant directing group.[7,8] A currently unexplored strategy for addressing this reaction manifold involves the use of a formate derivative with a C−N double bond. A C1 fragment without a C−O double bond cannot undergo decarbonylation, which is otherwise a significant pathway for reagent decomposition.[9] Oxazolines were chosen for this work because they are a well-studied class of heterocycles used as synthetic intermediates,[10] protecting groups,[11] and chiral ligands.[12] We now wish to report a general and efficient method for the functionalization of simple alkenes that operates by the metal-catalyzed C−H

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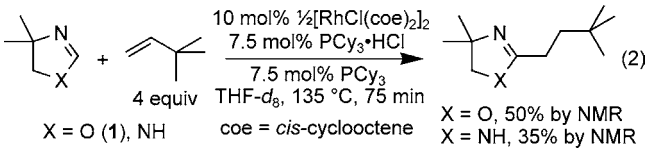
activation and addition of oxazolines across a carbon−carbon double bond.

Our interest in this area arose from research on the Rh(I)-catalyzed C−H functionalization of imidazole and related *N*-heterocycles.[13−16] Previous studies have shown that the C−H bond at the 2 position of such heterocycles can be efficiently added across alkene π-bonds both inter-[13] and intramolecularly.[14,15] Mechanistic data from the reaction of one benzimidazole derivative revealed the intermediacy of a Rh complex with substrate bound as a N-heterocyclic carbene (NHC).[16] Because some saturated N-heterocycles are known to be good NHC ligands,[17,18] we decided to attempt extension of the C−H activation reaction to azolines.[19] When 4,4-dimethyl-2-oxazoline (**1**) and 4,4-dimethyl-2-imidazoline were reacted with 10 mol % $^1/_2$[RhCl(coe)$_2$]$_2$, 7.5 mol % PCy$_3$·HCl, 7.5 mol % PCy$_3$, and 4 equiv of 3,3-dimethyl-butene in THF-d_8 at 135 °C (conditions found to be appropriate for azole activation),[14] the desired products were obtained in 50% and 35% yield, respectively, by NMR (eq 2).[20]



The reaction conditions for the coupling of **1** were quickly improved by dropping the reaction temperature to 45 °C and increasing the reaction time to 18 h. Prolonged heating of the reaction mixture did not result in increased yield.

To optimize the reaction conditions further, a number of phosphine hydrochloride salts were prepared and tested in the addition of **1** to 1-hexene to give 2-hexyl-4,4-dimethyl-2-oxazoline (**2**) (Table 1). Aryl phosphines (Table 1, entries 4 and 5), regardless of cone angle, were ineffective. The reaction requires a bulky, electron-rich phosphine. Despite efforts to obtain a trialkylphosphine with superior properties by varying the extent of α-branching (Table 1, entries 6−9), PCy$_3$·HCl continued to give the most effective catalysis. When PCy$_3$ was used instead of a phosphonium salt (Table 1, entry 1), no desired reactivity was observed. This result is consistent with the intermolecular alkene coupling of benzimidazole, for which an acid additive was also necessary.[13]

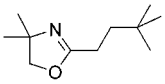
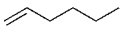
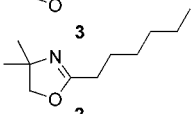
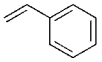
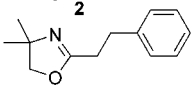
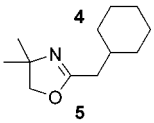
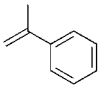
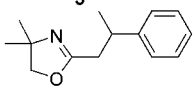
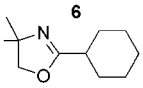
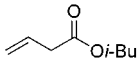
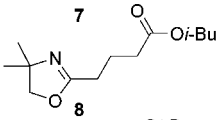
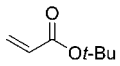
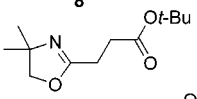
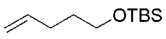
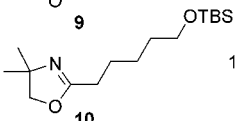
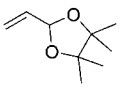
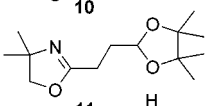
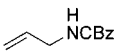
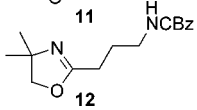
Following optimization efforts, standard conditions of 5 mol % $^1/_2$[RhCl(coe)$_2$]$_2$, 5 mol % PCy$_3$·HCl, 2.5 mol % PCy$_3$,

Table 1. Survey of Phosphine Effects on Coupling with **1**[a]

entry	phosphonium salt	1 (%)	2 (%)
1	none[b]	56	0
2	PCy$_3$·HCl	21	64
3	P(*i*-Pr)$_3$·HCl	29	49
4	PCy$_2$Ph·HCl	43	12
5	PCy$_2$(*o*-biPh)·HCl	50	4
6	PCy$_2$Et·HCl	37	31
7	P(*t*-Bu)$_2$Me·HCl	46	9
8	P(*t*-Bu)$_2$Et·HCl	34	32
9	P(*t*-Bu)$_3$·HCl	45	0

[a] Reactions run with 5 equiv of 1-hexene, 5 mol % $^1/_2$[RhCl(coe)$_2$]$_2$, and 7.5 mol % phosphonium salt in THF at 45 °C for 18 h; yields determined by GC analysis. [b] Reaction run with 7.5 mol % PCy$_3$.

Table 2. Alkene Generality[a]

Entry	Alkene	Product[b]	Temperature	Yield
1		 **3**	45 °C	86%
2		 **2**	45 °C	74% (46%)[c]
3		 **4**	45 °C	37%
4		 **5**	45 °C	79%
5		 **6**	45 °C	46%[d]
6		 **7**	45 °C	57%
7		 **8**	105 °C	71%
8		 **9**	105 °C	59%
9		 **10**	105 °C	58%
10		 **11**	105 °C	58%
11		 **12**	105 °C	48%

[a] Reactions run with 5 equiv of alkene, 5 mol % $^1/_2$[RhCl(coe)$_2$]$_2$, 5 mol % PCy$_3$·HCl, and 2.5 mol % PCy$_3$ in THF for 18 h. [b] Only the linear product was isolable in all cases. [c] Reaction run with 1 equiv of alkene. [d] Reaction run with 10 mol % $^1/_2$[RhCl(coe)$_2$]$_2$, 10 mol % PCy$_3$·HCl, and 5 mol % PCy$_3$.

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and 5 equiv of alkene in THF at 45 °C were adopted. This reaction temperature is significantly lower than that used in the coupling of aromatic azoles. The increased catalyst activity is consistent with trends observed for other transition-metal-catalyzed processes, which become more efficient when unsaturated NHC ligands are replaced by saturated analogues.[17] This trend is, however, difficult to rationalize because aromaticity in NHC ligands has been found to exert very little influence on basicity.[21] Attempts to isolate an NHC complex by stoichiometric reaction of **1** with the rhodium/phosphine catalyst mixture were unsuccessful, suggesting that such an intermediate may exist only transiently under the conditions investigated.

Using the standard reaction conditions, a study of alkene scope was undertaken. 1-Hexene proved to be a competent substrate (Table 2, entry 2), giving solely the linear product despite the ability of Rh(I) to isomerize olefinic double bonds. More highly substituted hydrocarbon substrates were also active. Cyclohexene underwent coupling with moderate yield (Table 2, entry 6) whereas the linear 1,2-disubstituted alkenes tested, *cis*- and *trans*-4-octene, gave only trace amounts of coupling product under the standard conditions. A 1,1-disubstituted alkene (Table 2, entry 4) demonstrated reactivity similar to that of terminal alkenes. In contrast, α-methylstyrene, which can form a new stereocenter upon coupling, exhibited severely attenuated activity (Table 2, entry 5). The low yields associated with aryl-substituted alkenes (Table 2, entries 3 and 5) are difficult to rationalize at present. Finally, a trisubstituted alkene, 1-methylcyclohexene, was evidently too highly substituted to couple effectively.

(19) Acyclic amidines and imidates were found to be unreactive toward alkene addition. Presumably this is because in the thermodynamically favored isomer the nitrogen lone pair and the C−H bond to which the metal must be directed are in a *trans* relationship to one another.

(20) This result complements previously published Rh-catalyzed arylation of **1** with iodobenzene, which also proceeds under the conditions effective for benzimidazole coupling. Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35−38.

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Another set of alkene substrates was tested in order to assay the functional group tolerance of the addition reaction (Table 2, entries 7−11). Alkenes with heteroatom substituents performed best at elevated temperatures. We demonstrated that protected aldehyde, acid, alcohol, and amine functionality can be incorporated into substituted oxazoline products.

In summary, we report a new method for the rhodium-catalyzed coupling of commercially available **1** with alkenes to give linear products with excellent selectivities and good yields. The products of this reaction are well suited to further elaboration or direct hydrolysis to esters or acids. A number of substitution patterns and functional groups are tolerated. The present method uses significantly milder reaction conditions than those reported for related hydroesterifications and does not require handling of CO or the use of high-pressure equipment, making this reaction an attractive tool for the synthetic chemist.

Efforts aimed at improving this reaction are underway. By varying the cyclic imidate component we hope to lower the alkene loading while maintaining reaction efficiency. In addition, chiral catalysts or chiral oxazolines derived from natural amino acids could permit selective formation of new stereocenters in reactions of unsymmetrical methylene compounds.

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Supporting Information Available: Experimental details, including analytical data for all compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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