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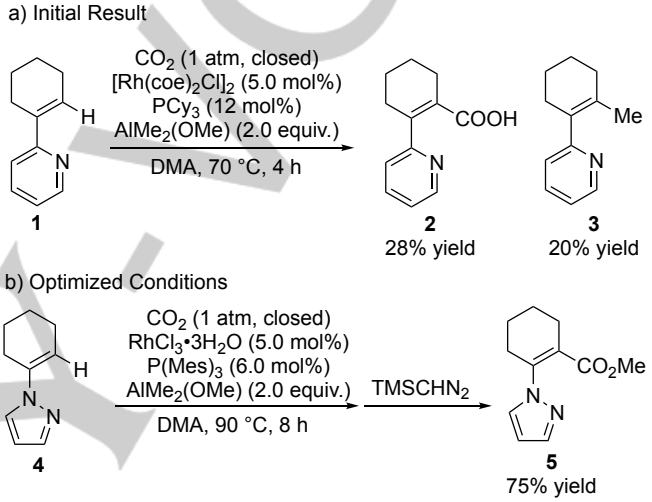
Rh-Catalyzed Direct Carboxylation of Alkenyl C–H Bonds of Alkenylpyrazoles

Takanobu Saitou, Yushu Jin, Kotaro Isobe, Takuya Suga, Jun Takaya, Nobuharu Iwasawa*

Abstract: The Rh-catalyzed direct carboxylation of alkenyl C–H bonds was achieved by using pyrazole as a removable directing group. In the presence of 5 mol% $RhCl_3•3H_2O$, 6 mol% $P(Mes)_3$, and 2 equiv. of $AlMe_2(OMe)$, the alkenyl C-H bond of various alkenylpyrazoles was directly carboxylated in good yields under CO_2 atmosphere. Furthermore, several useful transformations of the pyrazole moiety of the product were achieved to afford synthetically useful carboxylic acid derivatives in good yields.

Transition metal-catalyzed direct C–H carboxylation reactions have been attracting much attention as a useful method for the utilization of carbon dioxide as a one-carbon source,[1,2] and several approaches have recently been reported for the direct carboxylation of aryl C–H bonds. For examples, Nolan's group along with Hou's group reported gold(I) hydroxide or copper(I) alkoxide-catalyzed direct carboxylation of aromatic compounds having rather acidic hydrogens (pKa <30).[3,4] We also reported rhodium(I)-catalyzed direct carboxylation of phenylpyridines and phenylpyrazoles utilizing the oxidative addition of aryl C–H bonds by using a methylaluminum reagent as a stoichiometric reductant,[5a] and the reaction was further extended to the direct carboxylation of simple aromatic compounds.[5b,c] In contrast to the direct carboxylation of aryl C–H bonds, the transition metal-catalyzed direct carboxylation of alkenyl C–H bonds based on C–H bond activation has rarely been achieved partly because of the increased difficulty due to possible side reactions such as further conjugate addition to the produced α,β-unsaturated carboxylic acid derivatives under the reaction conditions. Actually, only one example has been reported for the transition metal-catalyzed alkenyl C-H carboxylation reaction, that is, palladium(II)-catalyzed direct carboxylation of *o*-hydroxystyrenes to give coumarins.[6] However, this reaction was limited to *o*-hydroxystyrene derivatives, and it is desirable to develop a new method which is potentially applicable to alkenes in general.[7-10] In this regard, the Rh(I)-catalyzed direct carboxylation of aryl C–H bonds developed in our group is attractive because it would be applicable to the reaction of alkenes. In this paper, we report a rhodium-catalyzed direct carboxylation of alkenyl C–H bonds utilizing oxidative addition of the sp^2 C-H bond of alkenylpyrazole derivatives along with further transformation of the product utilizing pyrazole as a removable directing group.

Initially, the reaction of cyclohexenylpyridine **1** was examined under the best reaction conditions developed for the reaction of phenylpyridine derivatives.[5a] When a mixture of cyclohexenylpyridine **1**, 5 mol% $[Rh(coe)_2Cl]_2$ (10 mol% Rh metal), 12 mol% tricyclohexylphosphine, and 2 molar amounts of $AlMe_2(OMe)$ was heated in DMA at 70 °C for 4 hours under 1 atm of CO_2, the desired carboxylated product **2** was obtained in 28% yield, along with the direct methylated compound **3** in 20% yield (Scheme 1a).



Scheme 1. Optimization of reaction conditions.

To suppress the formation of the direct methylation product, various directing groups were investigated. After examination of representative directing groups and several other reaction conditions,[11] it was found that when installing a pyrazole moiety as the directing group, carboxylation of cyclohexenylpyrazole **4** proceeded smoothly in high yield without detection of methylation product.[12] In addition, use of $RhCl_3•3H_2O$ as a rhodium precursor improved the yield to some extent. The olefinic ligand derived from the Rh catalyst was thought to compete with the substrate to coordinate to the rhodium metal resulting in decrease of the yield. No carboxylation product was detected when the reaction was conducted without the rhodium catalyst. Finally, the best result was obtained by heating a mixture of cyclohexenylpyrazole **4**, 5 mol% $RhCl_3•3H_2O$, 6 mol% trimesitylphosphine, and 2 molar amounts of $AlMe_2(OMe)$ at 90 °C for 8 hours. The desired C–H carboxylation product **5** was isolated in 75% yield after methyl esterification with trimethylsilyldiazomethane. No undesired methylation product was obtained under these conditions. (Scheme 1b). It should be noted that despite the potential reactivity of α,β-unsaturated carboxylic acid derivatives to alkenylrhodium nucleophiles, the product remained intact under the reaction conditions and decomposition or further reaction of the product was not observed.

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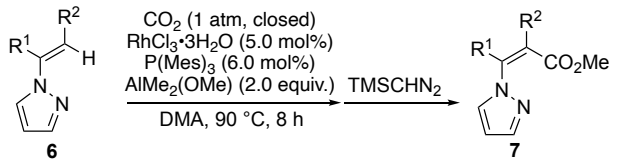
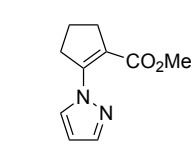
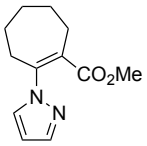
Under the best reaction conditions, the generality of the reaction was examined (Table 1). Cycloalkenylpyrazoles such as cyclopentenyl (**6a**) and cycloheptenylpyrazoles (**6b**) gave the corresponding products in good yield.

Table 1. Generality of the reaction.[a]

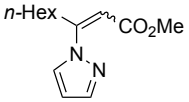




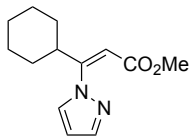
7a 69%[b]



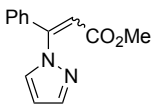
7b 78%



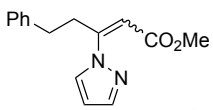
7c 64%
(*E* : *Z* = 4 : 96)



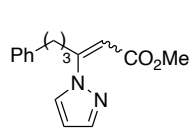
7d 69%
(*E* : *Z* = <5 : >95)



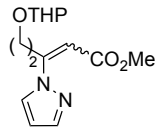
7e 53%[c]
(*E* : *Z* = 8 : 92)



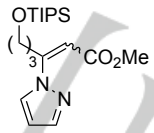
7f 64%
(*E* : *Z* = 3 : 97)



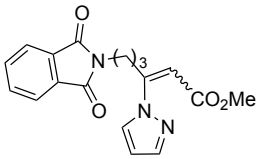
7g 48%
(*E* : *Z* = 3 : 97)



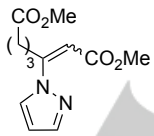
7h 51%
(*E* : *Z* = 11 : 89)



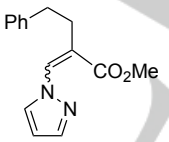
7i 62%[b]
(*E* : *Z* = 4 : 96)



7j 60%
(*E* : *Z* = 6 : 94)



7k 69%[bd]
(*E* : *Z* = 5 : 95)



(*Z*)-**7l** 45%
(*E*)-**7l** 7%
(*E* : *Z* = 13 : 87)[de]

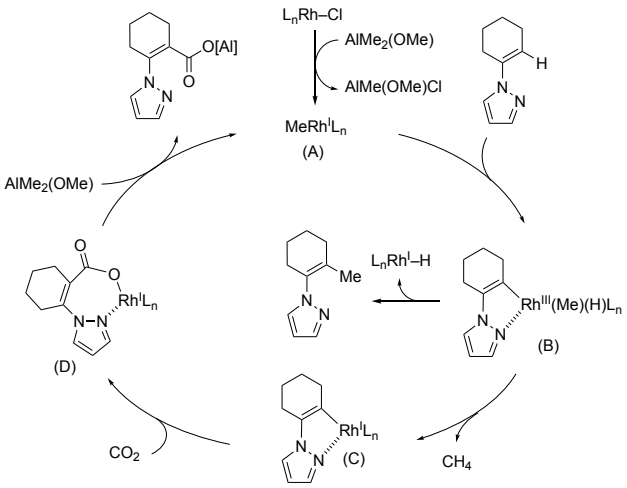
[a]All reactions were conducted on a 0.3 mmol scale in DMA (3.0 mL) at 90 ˚C for 8 hours unless otherwise noted. The yields shown are isolated yields of major isomers. The *E*/*Z* ratio in parentheses were determined according to the crude products. [b]4 h. [c]80 ˚C, 12 h. [d]110 ˚C. [e]10 mol% $RhCl_3•3H_2O$,12 mol% $P(Mes)_3$, the *E*/*Z* ratio was calculated by isolated yield.

Furthermore, acyclic 1,1-disubstituted alkenylpyrazoles such as 1-octen-2-ylpyrazole (**6c**), 1-cyclohexylethen-1-ylpyrazole (**6d**), 4-phenylbutene-2-ylpyrazole (**6f**) gave the corresponding direct C−H carboxylation products **7c**, **7d**, **7f** in good yields. Functional groups such as OTHP (**6h**), silyl ether (**6i**), imide (**6j**), and ester (**6k**) were tolerated under the reaction conditions and the corresponding products **7h~k** were obtained in synthetically useful yields. In the reactions of these 1,1-disubstituted alkenylpyrazoles, small amounts of (*E*)-alkenoates were also obtained due to the partial isomerization of initially produced (*Z*)-isomers under the reaction conditions in most cases. Finally, the carboxylation of 1,2-disubstituted alkenylpyrazole (**6l**) also proceeded selectively at the β-position by carrying out the reaction at an elevated temperature (110 ˚C) to give (*Z*)-**7l** as the major product, although the yield was moderate. It should be noted that the alkene substrates were mostly consumed in these reactions and several unidentified products were detected, especially with acyclic substrates.

To exhibit the usefulness of this transformation, a gram scale carboxylation of **6a** was conducted (Scheme 2). To our delight, the reaction proceeded smoothly even with a decreased catalyst loading (1.0 mol%) at lower temperature (70˚C). After methyl esterification, **7a** was isolated in 70% yield, showing the strong power of our Rh(I)-catalyst in this carboxylation (TON = 70).

Scheme 2. Gram scale carboxylation of **6a** using CO_2.

Currently, the reaction is thought to proceed in a similar manner to the reaction of phenylpyridines as shown in Scheme 3.[5a,c] Initially, MeRh(I) species (A) is generated by the reaction of $RhCl_3$ with $AlMe_2(OMe)$. Then, the pyrazole-directed oxidative addition of the alkenyl C-H bond occurs to give MeH(alkenyl)Rh(III) (B), which undergoes reductive elimination of methane to give (alkenyl)Rh(I) species (C). Carboxylation occurs at this stage to give Rh(I) carboxylate (D). Finally, transmetallation with $AlMe_2(OMe)$ regenerates MeRh(I) species (A) along with liberation of the aluminum carboxylate product.



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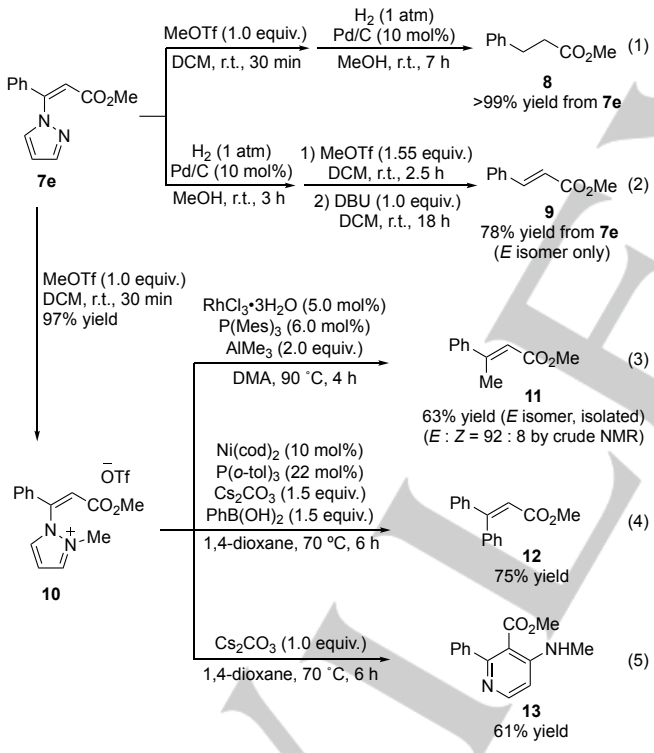
Scheme 3. Proposed mechanism.

Finally, replacement of the pyrazole moiety of the carboxylated product **7e** was examined to prepare synthetically useful carboxylic acid derivatives. As summarized in Scheme 4, methylation of the pyrazole moiety was found to be very important for the transformations. Thus, methylation of the product followed by hydrogenation gave saturated carboxylic ester **8** in quantitative yield, while hydrogenation followed by methylation and base treatment gave unsaturated carboxylic ester **9** in good yield (Scheme 4, [Eq. (1) and (2)]). Replacement of the methylated pyrazolium moiety of **10** with methyl or phenyl group was successfully achieved by Rh(I)-catalyzed 1,4-addition reaction of trimethylaluminum followed by elimination of *N*-methylpyrazole or Ni-catalyzed coupling reaction with phenylboronic acid (Scheme 4, [Eq. (3) and (4)]).[13] Furthermore, pyridinecarboxylic acid derivative **13** was obtained in reasonable yield on treatment of **10** with cesium carbonate (Scheme 4, [Eq. (5)]).[14] These results clearly show the superiority of pyrazole as a removable directing group for the C–H functionalization reactions.



Scheme 4. Transformation of the product.

In conclusion, we have realized an efficient direct carboxylation of the alkenyl C-H bonds of alkenylpyrazole derivatives. The reaction is applicable to various cyclic and acyclic alkenylpyrazoles containing functional groups to give the products in good yield. Further transformations of the pyrazole moiety of the product were achieved to afford synthetically useful carboxylic acid derivatives in good yields. Application of this reaction to simple alkenes is now in progress in our group.

Experimental Section

A DMA suspension (3.0 mL) of $RhCl_3•3H_2O$ (4.0 mg, 0.015 mmol, 5.0 mol%), $P(Mes)_3$ (7.0 mg, 0.018 mmol, 6.0 mol%) and 1-(cyclohex-1-en-1-yl)-1*H*-pyrazole **4** (44.8 mg, 0.3 mmol) was stirred in a glass tube (ϕ = 1.7 cm, 18 cm) under an atmospheric pressure of CO_2. $AlMe_2(OMe)$ (0.3 ml, 0.60 mmol, ca. 2.0 M in toluene) was added to the mixture at room temperature and then the system was closed. The mixture was heated at 90 °C for 8 h. After the mixture was cooled to room temperature, 1N HCl aq. (3.0 ml) was slowly added to the reaction mixture, which was stirred until an evolution of gas ceased. Chloroform was added to the mixture to induce separation of two layers. The mixture was kept stirring vigorously for a certain period until both the organic and aqueous phase became homogeneous. Adding more chloroform and/or 1N HCl aq. was allowed when a small amount of precipitate remains undissolved after a long period. The mixture was then extracted with chloroform five times. The combined organic layer was added a small portion of $NaHCO_3$ powder to neutralize HCl and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was treated with $TMSCHN_2$ (2.0 M sol. in Et_2O, 0.3 mL, 0.6 mmol) in Et_2O/MeOH (3 : 1, 4.0 mL) at 0 °C in a 50 mL round bottom flask under N_2. After 1 h, all volatiles were removed under reduced pressure and the residue was purified by preparative TLC plate to give methyl 2-(1*H*-pyrazol-1-yl)cyclohex-1-ene-1-carboxylate **5** (46.5 mg, 0.23 mmol, 75%).

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Keywords: carboxylation• alkenyl C–H activation • pyrazole • Rh(I) catalyst

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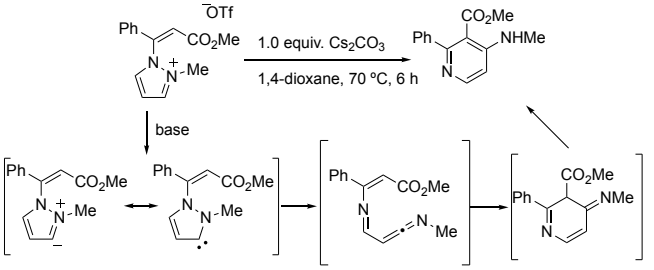

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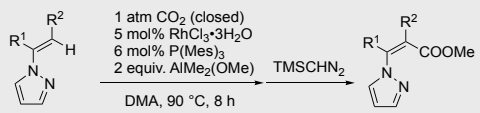

Direct carboxylation of alkenyl C-H bonds was achieved.

The Rh-catalyzed direct carboxylation of alkenyl C–H bonds was achieved by using pyrazole as a removable directing group. Furthermore, several useful transformations of the product were achieved to replace the pyrazole moiety to afford synthetically useful carboxylic acid derivatives in good yields.

*Takanobu Saitou, Yushu Jin, Kotaro Isobe, Takuya Suga, Jun Takaya, Nobuharu Iwasawa**

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