New Protocol for the Siteselective Alkylation and Vinylation of Aromatic Compounds. Catalyst-Specific Reactions

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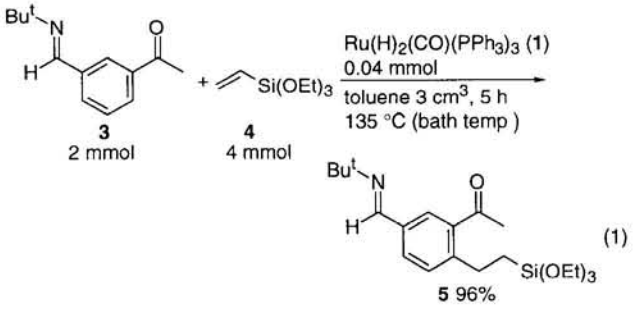
Catalyst-specific C-H/olefin as well as C-H/acetylene coupling has been accomplished for aromatics which contain both keto and imino substituents by simply changing the catalyst. By using $Ru(H)_2(CO)(PPh_3)_3$ as the catalyst, the C-H bond at the position *ortho* to the carbonyl group reacted to add across an olefin. When $Ru_3(CO)_{12}$ is used as the catalyst, the C-H bond at the position *ortho* to the imino group reacted with the olefin.

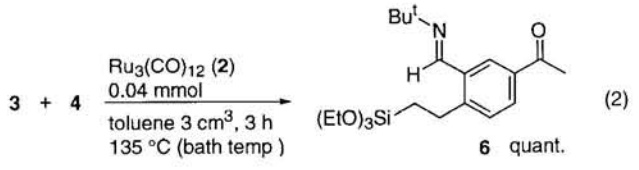
In the field of organic synthesis, selective bond formation represents all area of considerable interest.[1] To attain the desired reaction at one of two possible reaction sites in a molecule, modification of the molecule is often required, in order to activate one site.[1,2] A more efficient route would be to devise a siteselective or a chemoselective reagent, especially a catalyst.[3] During the course of our studies on the transition metal-catalyzed C-H/olefin and C-H/acetylene couplings,[4] we discovered that the combination of catalyst and substrate is highly important in accomplishing such catalytic coupling reactions. We report herein a new catalyst system which allows for the production of two different products, which are individually selective from the same combination of reactants by changing the catalyst. In this new C-H/olefin coupling reaction of aromatic compounds having both keto and imino substituents, the site of the C-H bond to be cleaved is catalyst-specific. The catalyst specific alkylation and vinylation of aromatic rings is described below.

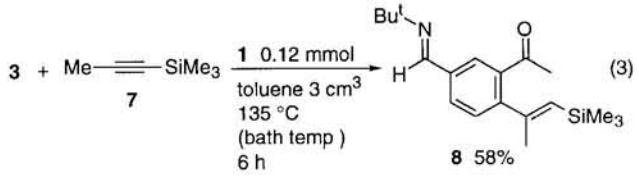
We previously reported that $Ru(H)_2(CO)(PPh_3)_3$ (**1**) showed the highest catalytic activity for the addition of C-H bonds in aromatic ketones and esters to olefins, and that $Ru_3(CO)_{12}$ (**2**) exhibited no catalytic activity.[4a,b] However, in the reaction of aromatic imines with olefins, **2** is highly effective as the catalyst, but **1** is only fairly effective.[4d] As a result, we concluded that these differencies in catalytic activity, with respect to substrates might well provide unique opportunities in exploiting intra- and intermolecular competitive reactions leading to useful synthetic methods.

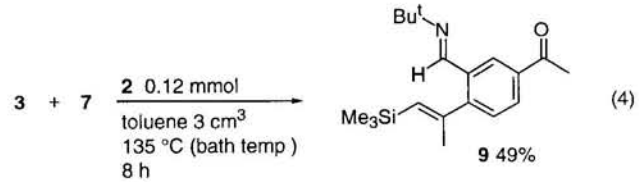
We initially examined the reaction of an aromatic compound which contains both an acetyl and an imino group on the aromatic ring (Eqs. 1 and 2).[5] As expected for the reaction using **1** as the catalyst, C-C bond formation took place only at the position *ortho* to the acetyl group (Eq. 1).[6] On the other hand, when **2** was used as the catalyst, the reaction occurred exclusively at the position *ortho* to the imino group (Eq. 2).[6] Note that the starting materials and reaction conditions for these two reactions are essentially identical. These results encouraged us to examine further examples with respect to catalyst-specific C-C bond formations.

This type of the C-C bond formation is also applicable to reactions involving internal acetylenes. When the reaction of **3** with 1-trimethylsilylpropyne (**7**), which showed complete regio- and stereoselectivities in a reaction with α-tetralone,[4c] was carried out in the presence of **1**, the expected coupling product was formed in 58% yield as the sole product. In this case, carbon-





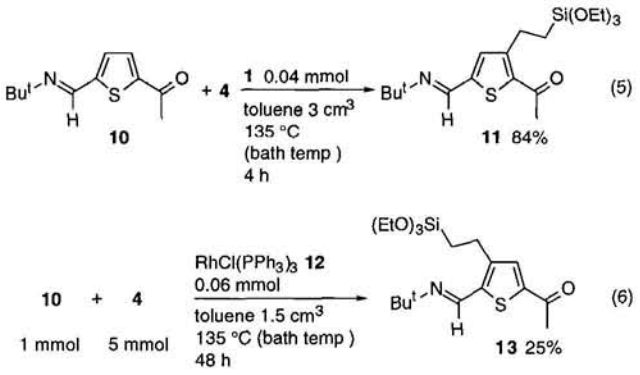




carbon bond formation took place exclusively at the position *ortho* to the acetyl group (Eq. 3). Changing the catalyst to **2** resulted in formation of coupling product **9** (Eq. 4). These results indicate that the present protocol can be used for C-H/acetylene coupling.

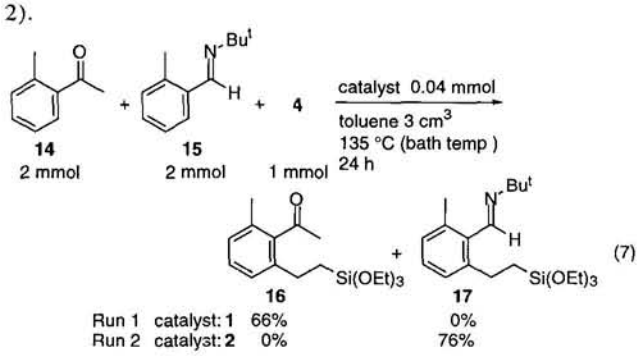
In the case of the reaction of 2-acctyl-5-iminothiophene **10** using **1** as the catalyst, the desired coupling occurred only at the acetyl group side (Eq. 5). Unfortunately, however, the use of complex **2** resulted in formation of a complicated mixture in low yields. After considerable effort, we discovered that $RhCl(PPh_3)_3$ (**12**) is capable of catalyzing the alkylation of **10** with the vinylsilane **4** at the imino group side, albeit in low yield (Eq. 6).

The origin of the observed catalyst-specificity is not clear. Generally, a nitrogen center is much stronger donor than an oxygen center. Thus, the nitrogen of the imine function binds preferentially to the ruthenium carbonyl **2** and, as a consequence, to Rh(I) complex **12**. However, ligation of the bulky *tert*-BuN moiety in the imines is unfavorable with respect to Ru(0) complex **1** which carries two or three bulky phosphine ligands in the intermediate metallacycle. Therefore, the Ru(0) complex binds to

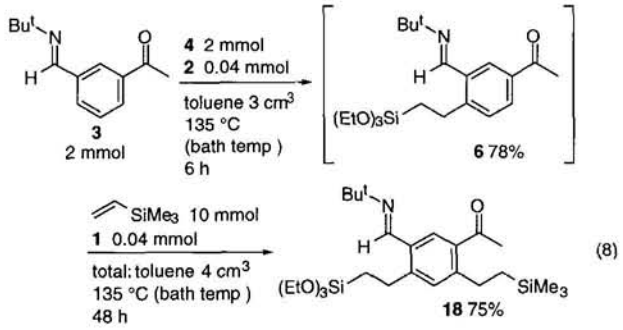


the oxygen center of the acetyl group. This explanation seems somewhat difficult when applied to the complex **12** which also has phosphine ligands. The ionic Rh(I) would be expected to bind more strongly and the intermediate having less than two phosphine ligands might be less crowded.[7]

This observed directing ability can be applied to the corresponding intermolecular version. When an intermolecular competitive reaction was run under the reaction conditions as shown in Eq. 7, complex **1** catalyzed the coupling of **14** with **4** to give only **16** in 66% yield (Eq. 7, Run 1). On the other hand, complex **2** catalyzed the addition of the C-H bond in **15** to **4** leading to **17** as the exclusive product in 76% yield (Eq. 7, Run 2).



Consequently, the introduction of different alkyl groups at the different *ortho* positions on the same aromatic ring can be accomplished by using the present technique. A typical example of the reaction is shown in Eq. 8. The first step of the reaction in Eq. 8 was carried out in the presence of the ruthenium carbonyl complex **2**, affording **6** in 78% GC yield. To the reaction mixture which had been cooled to near room temperature, was added a solution of trimethylvinylsilane in toluene (1 cm^3), along with the ruthenium phosphine complex **1**. Refluxing the resulting solution for 48 h gave the coupling product **18** in 75% yield based on **3**. A simple bulb-to-bulb distillation afforded an analytically pure material. Although the yield in the first step could be improved if the excess amount of olefin is used just as in Eq. 1, the unreacted olefin would also participate in the second step, which is not desirable. The amount of the second olefin in the second step can be sufficiently large to allow for the second coupling to be quantitative. Since the aldimine moiety can be easily converted to a formyl group, the result of Eq. 8 indicates that the introduction of different alkyl groups at positions *ortho* to



the acetyl and formyl groups can be carried out independently with perfect selectivity.

In summary, the catalyst-specific C-H/olefin and C-H/acetylene couplings is demonstrated herein. In all probability, such a catalyst specific reaction will be useful not only in conventional synthesis but also in combinatorial synthesis especially when the reactions proceed quantitatively as in Eqs. 1 and 2.

Supporting Information (4 pages) including spectral data of new compounds are available on request to the author by telefax (+81-6-879-7396).

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References and Notes

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3 For representative examples, see: regioselective cross-coupling, T. Hayashi, M. Konishi, K. Yokota, and M. Kumada, *J. Chem. Soc., Chem. Commun.*, **1981**, 313; regioselective hydroformylation, T. Fuchikami and I. Ojima, *J. Am. Chem. Soc.*, **104**, 3527 (1982); regiosclective alkylation of allylic compounds, J. Tsuji, I. Shimizu, I. Minami, and Y. Ohashi, *Tetrahedron Lett.*, **23**, 4809 (1982), B. M. Trost and M.-H. Hung, *J. Am. Chem. Soc.*, **106**, 6837 (1984); enantioselective hydrogenation, H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S.-I. Inoue, I. Kasahara, and R. Noyori, *J. Am. Chem. Soc.*, **109**, 1596 (1987); chemosclective hydrogenation of conjugated enones, J. M. Grosselin, C. Mercier, G. Allmang, and F. Grass, *Organometallics*, **10**, 2126 (1991).

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5 For the catalytic reactions, two equivalents of an olefin or an acetylene were used, unless otherwise noted.

6 The C-H bond at 2-position, i.e., position *ortho* to both of the acetyl and the imino groups, does not add to an olefin due to the steric congestion around this position.

7 For the $RhCl(PPh_3)_3$-catalyzed hydrogenation of olefins, rhodium intermediates having two phosphine ligands have been proposed, see: J. P. Collman, L. S. Hegedus, J. R. Norton, and R. G. Finke, "Principles and Applications of Organotransition Metal Chemistry," University Science Books, California (1987), pp 531-535; G. O. Spessard and G. L. Miessler, "Organometallic Chemistry," Prentice-Hall, New Jersey (1997), pp 277-281.