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Ortho Alkylation of Aromatic Ketimine with Functionalized Alkene by Rh(I) Catalyst

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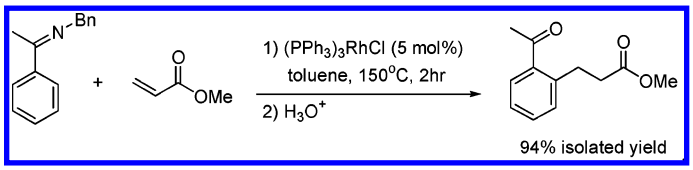
ABSTRACT



The reaction of the imine of aromatic ketones with functionalized alkenes was performed under a catalytic amount of $(PPh_3)_3RhCl$, and corresponding ortho-alkylated ketones were obtained after hydrolysis. A variety of functional groups in the alkene were tolerated in this ortho alkylation. This procedure expands the scope of ortho alkylation to the direct ortho functionalization of aromatic ketones.

The activation of unreactive bonds in organic molecules is one of the current interests in organometallic chemistry.[1] In particular, the catalytic C−H bond activation using transition metal complexes has been focused on by many synthetic organic chemists because it is one of the better ways of avoiding many environmental problems that can occur in industrial organic synthesis.[2] Since direct ortho alkylation of aromatic ketone compounds, known as Murai's reaction, was first devised using $RuH_2(CO)(PPh_3)_3$ in 1993,[3] tremendous developments have been achieved in this field.[4,5]

But one of the drawbacks has been a limited use of olefin substrates, because olefin-bearing functional groups could not be applied to this reaction. Recently, we have developed new procedures for ortho alkylation and ortho alkenylation using a ketimine of an aromatic ketone with various alkenes[6] and alkynes.[7] However, functionalized olefins have been rarely applied to this ortho alkylation.

During the course of our studies on ortho alkylation, we found that our strategy tolerated various functional groups in olefin substrates. In this communication, we report the ortho alkylation of aromatic ketimine with functionalized olefins.

Among many olefin substrates bearing functional groups, acrylate and acrylamide exhibited good reactivities for ortho alkylation.

For example, when the reaction of benzylimine **1a** and methyl acrylate (**2a**) was carried out in the presence of

(1) Kakiuchi, F.; Murai, S. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, German, 1999.

(2) For recent reviews, see: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (b) Ritleng, V.; Sirlins, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698.

(3) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

(4) For Murai's ortho alkylation, see: (a) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62. (b) Murai, S.; Chatani, N.; Kakiuchi, F. *Pure Appl. Chem.* **1997**, *69*, 589. (c) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117. (d) Sonoda, M.; Kakiuchi, F.; Kamatani, A.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, 109. (e) Kakiuchi, F.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, 111.

(5) For ortho alkylation, see: (a) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759. (b) McCallum, J. S.; Gasdaska, J. R.; Liebeskind, L. S. *Tetrahedron Lett.* **1989**, *30*, 4085. (c) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728. (d) Grigg, R.; Savic, V. *Tetrahedron Lett.* **1997**, *38*, 5737. (e) Busch, S.; Leitner, W. *Chem. Commun.* **1999**, 2305. (f) Lim, Y.-G.; Han, J.-S.; Yang, S.-S.; Chun, J. H. *Tetrahedron Lett.* **2001**, *42*, 4853. (g) Harris, P. W. R.; Woodgate, P. D. *J. Organomet. Chem.* **1997**, *530*, 211. (h) Guo, H.; Tapsak, M. A.; Weber, W. P. *Polym. Bull.* **1995**, *34*, 49. (i) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616. (j) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 9692. (k) Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *Ogr. Lett.* **2003**, *5*, 1301. (l) Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192.

(6) (a) Jun, C.-H.; Moon, C. W.; Hong, J.-B.; Lim, S.-G.; Chung, K.-Y.; Kim, Y.-H. *Chem. Eur. J.* **2002**, *8*, 485. (b) Jun, C.-H.; Hong, J.-B.; Kim, Y.-H.; Chung, K.-Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 3440.

(7) Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003**, *5*, 2759.

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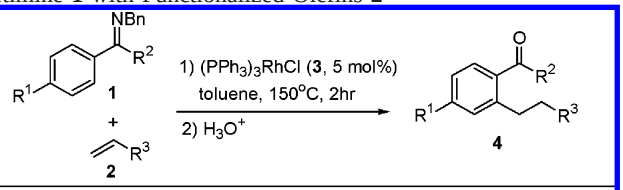
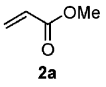
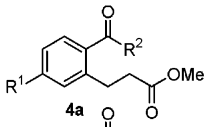
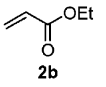
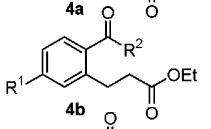
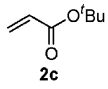
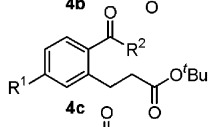
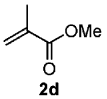
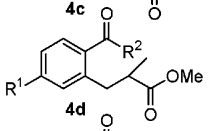
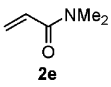
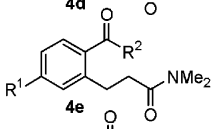
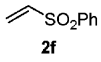
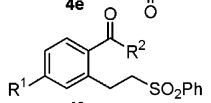
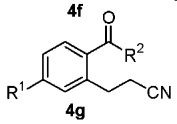
Table 1. Rh(I)-Catalyzed Ortho Alkylation of Aromatic Ketimine **1** with Functionalized Olefins **2**[a]



entry	**1** (R^1, R^2)	**2** (olefin)	**4** (product)	yield (%)[b]
1	**1a** (H, Me)	 **2a**	 **4a**	94 (100)
2	**1a**	 **2b**	 **4b**	93 (100)
3	**1a**	 **2c**	 **4c**	79 (100)
4[c]	**1a**	 **2d**	 **4d**	81 (100)
5	**1a**	 **2e**	 **4e**	75 (100)
6	**1a**	 **2f**	 **4f**	43 (46)
7	**1a**	 **2g**	 **4g**	32 (33)
8[d]	**1a**	**2a**	**4a**	44 (50)
9	**1b** (CF_3, Me)	**2a**	**4h**	95 (100)
10[d]		**2a**	**4h**	61 (63)
11	**1c** (OMe, Me)	**2a**	**4i**	90 (100)
12[d]		**2a**	**4i**	45 (50)
13	**1d** (H, Et)	**2a**	**4j**	65 (68)
14	**1e** (H, ^{n}Pent)	**2a**	**4k**	48 (51)

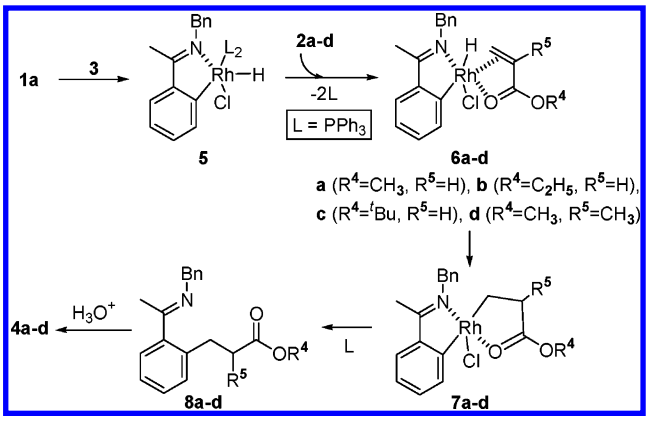
[a] Reagent and conditions: (1) **1** (1.0 equiv), **2** (1.2 equiv), **3** (5 mol %), toluene, 150 °C, 2 h. (2) 1 N HCl, room temperature, 12 h. [b] Isolated yield. GC yields are given in parentheses. [c] 2.0 Equiv of **2** and 10 mol % **3** were used. [d] Reaction was carried out at 100 °C for 30 min.

$(PPh_3)_3RhCl$ (**3**) in toluene at 150 °C for 2 h, ortho-alkylated acetophenone **4a** was isolated in a 94% yield after hydrolysis (Table 1. entry 1).[8] Other functionalized olefins were also applied in this reaction, and representative examples were tabulated in Table 1. The reaction of alkyl acrylate **2b**−**c** with **1a** led to the corresponding ortho-alkylated ketone in very high yields (entries 2 and 3).

The reaction mechanism is shown in Scheme 1. The Rh(I) complex **3** reacts with the *ortho*-C−H bond in the phenyl group to generate a five-membered ring metallacycle intermediate **5**. Subsequently, coordination of the functionalized olefin **2** to **5** and a hydride insertion in **6** affords **7**.[2] Reductive elimination of **7** leads to the ortho-alkylated ketimine **8**, which is hydrolyzed by acidic water to give **4**.

(8) For Rh(I)-catalyzed conjugate addition reactions of acrylates with arylsilanediols, see: Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

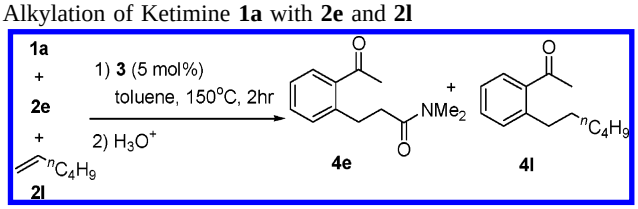
Scheme 1. Proposed Mechanism for Ortho Alkylation of Ketimine **1a** with **2**



Branched acrylate **2d**, involving a branched vinyl group, and *N*,*N*-dimethylacrylamide (**2e**) showed also good reactivity (entries 4 and 5), whereas phenyl vinyl sulfone (**2f**) and acrylonitrile (**2g**) appeared to give only moderate reactivities to produce ortho-alkylated aromatic ketone bearing γ-sulfonyl and γ-nitrile groups, respectively (entries 6 and 7). When the reactivities of the aromatic ketimines having different alkyl substituents (R^1) were compared, electron-withdrawing groups such as the *tri*-fluoromethyl group on the phenyl ring showed a better result than electron-donating groups such as the methoxy group under mild conditions (entries 10 and 12). In comparing the alkyl group (R^2) to the imine group by increasing the length of the alkyl chain as methyl, ethyl, and *n*-pentyl, the yield of the ortho-alkylated products decreases to 94, 65, and 48% (entries 1, 13, 14).

Regarding the reactivity of functionalized olefins in this reaction, functionalized olefins are much more reactive than nonfunctionalized olefins. A competitive reaction of *N*,*N*-dimethylacrylamide (**2e**) and 1-hexene (**2l**) with **1a** was

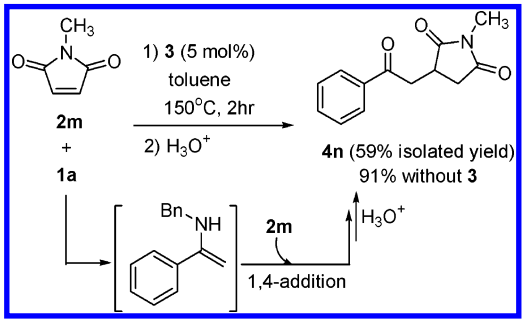
Table 2. Competitive Reaction of Rh(I)-Catalyzed Ortho Alkylation of Ketimine **1a** with **2e** and **2l**



entry	**1a** (equiv)	**2e** (equiv)	**2l** (equiv)	ratio of **4e**/**4l**	yield (%)[a]
1	1.0	1.2	1.2	90/10	73 (100)
2	1.0	1.2	3.0	72/28	67 (100)
3	1.0	1.2	5.0	62/38	69 (100)

[a] Isolated yield. GC yields are given in parentheses.

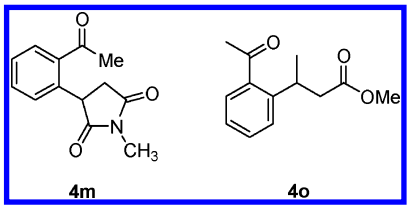
Scheme 2. 1,4-Addition of **1a** to **2m** with or without **3**



performed as shown in Table 2. With a 1/1 ratio of **2e**/**2l**, ortho-alkylated products, **4e** and **4l**, were obtained in a 90/10 ratio in 73% isolated yields (entry 1), informing us that the functionalized olefin **2e** had a much higher reactivity than nonfunctionalized olefin **2l**. Even with a large excess of **2l** compared to **2e** (1.2/5.0 of **2e**/**2l**), a 62/38 ratio of **4e**/**4l** was obtained in high yield (entry 3).

A dramatic driving force of ortho alkylation reaction with these functionalized olefins compared with the nonfunctionalized olefin might be a formation of the stable five-membered ring metallacyclic intermediate **7**. To confirm this hypothesis, *N*-methylmaleimide (**2m**), a functionalized olefin, which could not form the intermediate **7**, was applied in this reaction, as shown in Scheme 2.

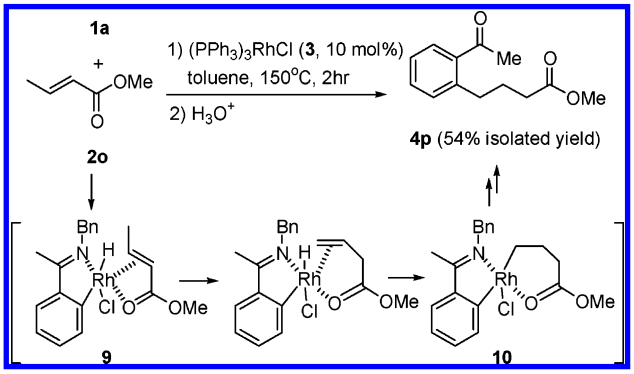
From the reaction of **2m** with **1a**, the expected ortho-alkylated product **4m** was not obtained. Instead, the 1,4-addition product **4n** was isolated in high yield with or without **3**. This is because intermediate **7** is important for driving the reaction of functionalized olefins.



The reaction of methyl crotonate (**2o**) with **1a** gave an unexpected ortho-linear alkylated product **4p**, not the ortho-branched alkylated **4o** (Scheme 3). The linear alkyl complex **10** is generated through the isomerization of methyl crotonate in **9** to methyl 3-butenoate. This type of isomerization can be seen in some organotransition metal catalytic reactions.[10] Reductive elimination and hydrolysis of the resulting ketimine affords **4p**.

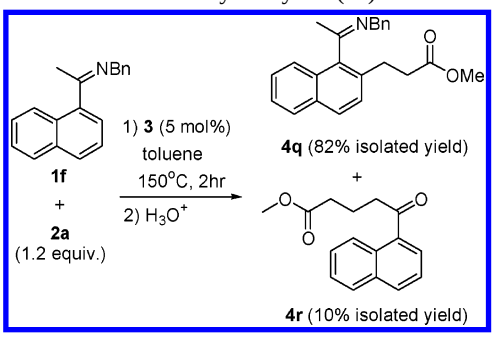
Benzylimine of 1-acetylnaphthalene, **1f**, is an interesting substrate since there are two active sites, 2- and 8-position of naphthalene, for ortho alkylation. When the reaction of

Scheme 3. Ortho Alkylation of **1a** with Methyl Crotonate (**2o**)

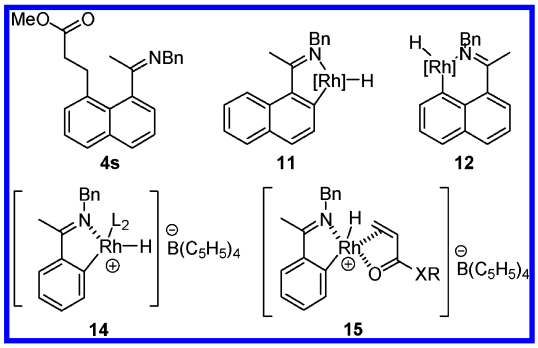


1f and **2a** was carried out under the previous reaction conditions, 2-alkylated 1-acetylnaphthalene **4q**[11] was isolated in 82% yield along with a 10% yield of a 1,4-addition product **4r**, as shown in Scheme 4. 8-Alkylated 1-acetyl-

Scheme 4. Rh(I)-Catalyzed Ortho Alkylation of Ketimine **1f** with Methyl Acrylate (**2a**)



naphthalene **4s** was not observed in product mixtures.[12] This is because the formation of the five-membered metallacyclic complex **11** is more favorable than that of the six-membered ring complex **12**.



Of the catalysts tested, Wilkinson's complex (**3**) showed that ortho alkylation with functionalized olefin produced the

(9) For homoenolate complexes of Rh(III) binding through the carbonyl oxygen, see: Hauptman, E.; Sabo-Etienne, S.; White, P. S.; Brookhart, M.; Garner, M. J.; Fagan, P. J.; Calabrese, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 8038.

(10) (a) Jun, C.-H.; Hwang, D.-C.; Na, S.-J. *Chem. Commun.* **1998**, 1405. (b) Reger, D. L.; Garza, D. G.; Baxter, J. C. *Organometallics* **1990**, *9*, 873.

(11) Ortho-alkylated ketimine **4q** was characterized by ^{1}H NMR and COSY spectroscopic analysis; see Supporting Information.

(12) Trace amount (less than 4%) of the unidentified compound was determined by GCD.

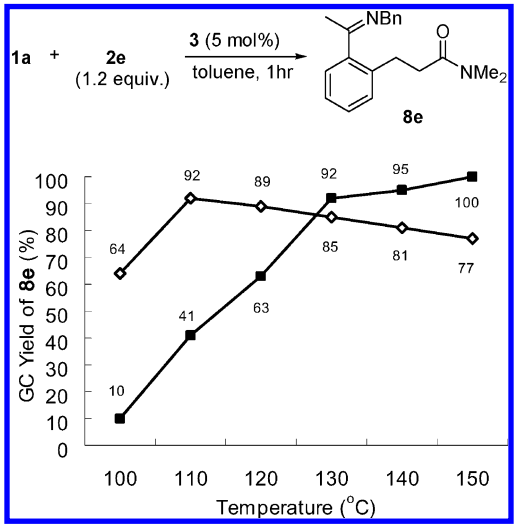


Figure 1. GC yield of **8e** by Rh(I)-catalyzed ortho alkylation of **1a** with **2e** without $(C_6H_5)_4BNa$ (**13**, ■) and with 5 mol % **13** (◊) under different temperatures.

best catalytic activity. As the reaction temperature increases, the reactivity of the catalyst **3** also increases as shown in Figure 1. The yield of the product **8e** dramatically increased from 100 °C up to 130 °C and increased moderately from 130 °C up to 150 °C. In contrast, when 5 mol % $(C_6H_5)_4BNa$ (**13**) was added to this reaction mixture, a much higher yield of **8e** was observed compared to the reaction without **13** at the lower temperature: with the addition of **13**, a 64% yield of **8e** was obtained at 100 °C, but without **13**, only a 10% yield of **8e** was observed. At 110 °C, the yield of **8e** was maximized and decreased gradually above that temperature. The reason for the high reactivity of the metal catalyst was likely the addition of **13**, which creates a vacant coordination site as in **14**. This allows a facile coordination of the functionalized olefins giving **15**. However, at high temperatures, the catalyst might well be decomposed.

In conclusion, ortho alkylation of aromatic benzylimine has been achieved with olefins bearing various functional groups. Some of these olefins are more reactive than those having no functional groups. Wilkinson's complex showed the best catalytic activity, and additional $(C_6H_5)_4BNa$ allowed the reaction to proceed smoothly under mild conditions. Further applications of these ortho alkylation reactions with functionalized olefins are under study.

Acknowledgment. This work was supported by the National Research Laboratory (NRL) (2000-N-NL-01-C-271) Program administered by the Ministry of Science and Technology and CBMH.

Supporting Information Available: Full experimental details and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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