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Chelation-assisted β-alkylation of α,β-unsaturated ketone using Rh(I) catalyst and dialkyl amine

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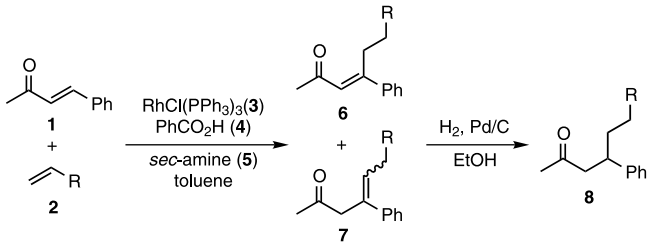
Abstract—A new Rh(I)-catalyzed β-alkylation of 4-phenyl-3-buten-2-one (**1**) was developed by utilizing diethylamine (**5a**) as a chelation-assistant tool. The key feature of this reaction is the vinyl C–H activation driven by amine-assisted cyclometalation to give the β,γ-unsaturated ketones **7** as a major product.

The activation of C–H bonds by transition-metal complexes is becoming more attractive in synthetic organic chemistry since it is not only atom economic but also highly chemoselective.[1,2] One of the most promising strategies for the C–H bond activation is to utilize the chelation-assisted cyclometalation.[3] By employing amines as a chelation-assistant tool, we have developed a series of Rh(I)-catalyzed hydroacylation of olefins via a C–H bond activation.[4] Recently, we also reported the Rh(I)-catalyzed *ortho*-alkylation of aromatic ketimines and ketones using the same strategy.[5] So far, only a few examples using Ru(0) catalysts for the β-alkylation of α,β-unsaturated ketones with specific alkenes were reported.[6] Herein, we wish to describe a new Rh(I)-catalyzed β-alkylation of α,β-unsaturated ketone for the preparation of highly functionalized ketones employing amines as a chelation auxiliary.[7]

Initially, we investigated the β-alkylation of α,β-enone using 4-phenyl-3-buten-2-one (**1**) as a model substrate. Thus, as shown in Scheme 1, the enone **1** was reacted with excess 1-hexene (**2a**, R = *n*-C_4H_9, 10.0 equiv.) in the presence of $RhCl(PPh_3)_3$ (**3**, 5.0 mol%), benzoic acid (**4**, 10.0 mol%), and diethylamine (**5a**, 50.0 mol%) at 130°C for 12 h. After the reaction, a mixture of β-alkylated products was obtained in 59% yield in a 34:66 ratio of **6a** and **7a** (entry 1 in Table 1). Increasing the reaction time showed a positive effect on the yield of the reaction but little effect on the ratio of **6a** and **7a**. Therefore, when the reaction was carried out for 24 h with fixing all other reaction conditions, the β-alkylated products were obtained in an excellent yield of 89% with an almost same ratio of **6a** and **7a** (entry 5).

Using optimized reaction conditions (5 mol% of **3**, 10 mol% of **4**, 50 mol% of **5a**, 130°C, and 24 h), various 1-alkenes were tested in the β-alkylation of **1** and the results are summarized in Table 1.[8] All reactions proceeded smoothly and good isolated yields were obtained still giving the β,γ-enone **7** with a ca. 2:1 ratio of *E*/*Z* isomer as a major product over the α,β-enone **6**. Especially, ethylene (**2b**) and trimethylvinylsilane (**2e**) were the most efficient and nearly quantitative isolated yields were obtained in both cases after simple column chromatography on silica gel (entries 8 and 11). For example, the reaction with trimethylvinylsilane (**2e**) gave the β,γ-unsaturated ketone **7e** predominantly in 99% isolated yield (entry 11).

To confirm the structure of the β-alkylated products, the mixture was hydrogenated over Pd/C to afford the saturated ketone **8** as a sole product (Scheme 1). It is noteworthy that the reaction catalyzed by



Scheme 1. Rh(I)-catalyzed β-alkylation of 4-phenyl-3-buten-2-one (**1**) with 1-alkene.

Keywords: C–H activation; alkylation; β,γ-unsaturated ketone; Wilkinson catalyst.

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Table 1. Rh(I)-catalyzed β-alkylation of 4-phenyl-3-buten-2-one (**1**) with various 1-alkenes in the presence of *sec*-amine[a]

Entry	R (**2**)	*sec*-Amine (**5**)	Time (h)	**6**/**7**[b]	*E*/*Z* ratio of **7**[b]	Yield[c] (%)
1	n-C_4H_9 (**2a**)	Et_2NH (**5a**)	12	34:66 (**6a**/**7a**)	67:33	59
2	n-C_4H_9 (**2a**)	Cy_2NH (**5b**)	12	32:68 (**6a**/**7a**)	68:32	6
3	n-C_4H_9 (**2a**)	i-Pr_2NH (**5c**)	12	–	–	0
5	n-C_4H_9 (**2a**)	Et_2NH (**5a**)	24	35:65 (**6a**/**7a**)	72:28	89 (71)
6	n-C_4H_9 (**2a**)	–[d]	24	–	–	0
7[e]	n-C_4H_9 (**2a**)	Et_2NH (**5a**)	24	–	–	0
8[f]	H (**2b**)	Et_2NH (**5a**)	24	24:76 (**6b**/**7ba**)	68:32	100 (99)
9	Cyclohexyl (**2c**)	Et_2NH (**5a**)	24	23:77 (**6c**/**7c**)	64:36	87 (77)
10	t-C_4H_9 (**2d**)	Et_2NH (**5a**)	24	15:85 (**6d**/**7d**)	68:32	73 (57)
11	$Si(CH_3)_3$ (**2e**)	Et_2NH (**5a**)	24	5:95 (**6e**/**7e**)	65:35	100 (99)

[a] All reactions were carried out at 130°C in dry toluene (**1**:**2**:**3**:**4**:**5**=1/10/0.05/0.1/0.5), unless otherwise stated.
[b] Determined by GC-analyses.
[c] Combined GC-yield of **6** and **7**. Isolated yield is given in a parenthesis.
[d] In the absence of Et_2NH.
[e] Carried out at 150°C using 5.0 mol% of $RuH_2(CO)(PPh_3)_3$.
[f] Carried out in dry benzene using a Parr reactor.

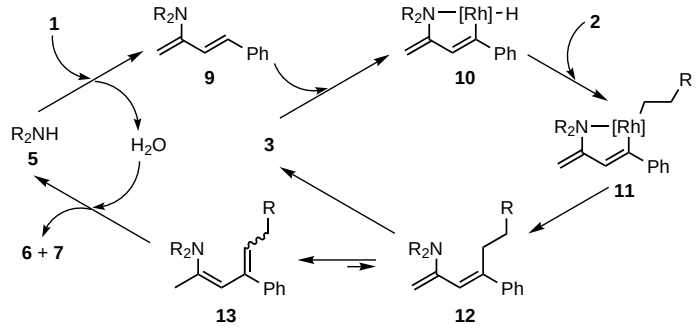
$RuH_2(CO)(PPh_3)_3$, which is known to be highly efficient in a similar β-alkylation process,[6a] did not proceed even when it was carried out at somewhat higher reaction temperature of 150°C (entry 7).

A plausible mechanism for this reaction is illustrated in Scheme 2. Precoordination of a rhodium species on the nitrogen functionality of the dienamide **9**, derived from the condensation of the enone **1** with **5**, can facilitate the cleavage of the vinylic C–H bond to generate the stable 5-membered metalacyclic rhodium hydride **10**. Coordination of an olefin **2** followed by the migratory insertion of the olefin **2** into the Rh–H bond gives the alkylrhodium species **11**. Reductive elimination in **10** furnishes the β-alkylated dienamine **12** that equilibrates with the regioisomer **13** and regenerates a rhodium catalyst to complete the catalytic cycle. Following acidic hydrolysis of both **12** and **13** leads to the β-alkylated products **6** and **7**.

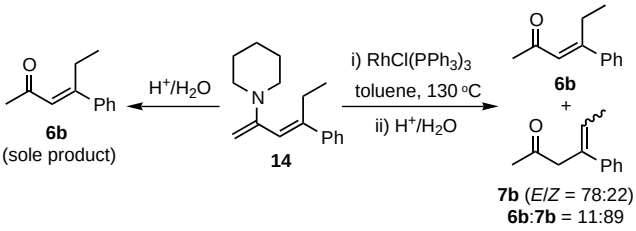
Some experimental results support the proposed mechanism: (1) β-Alkylation did not proceed at all and only the starting enone **1** was completely recovered in the absence of dialkylamine **5**, which implied that the dienamine **9** might be a key intermediate of the reaction. (2) Steric requirement of the diakylamines **5** also affects so strongly on the overall catalysis that no β-alkylated product is obtained when sterically more demanding diisopropylamine (**5c**) is used instead of **5a** (entry 3). This result shows that the facile chelation of a rhodium species to the nitrogen functionality of **9** is an important factor for the efficiency of the reaction.[9] (3) α,β-Unsaturated carbonyl compounds with no α-hydrogen (e.g. α,β-unsaturated phenyl ketones, α,β-unsaturated *t*-butyl ketones, α,β-unsaturated aldehydes, etc.) did not participate in this β-alkylation reaction, presumably due to the impossibility in generating the corresponding dienamines.

Although at this moment no clear explanation is available, it is quite interesting that the β,γ-enone **7**, which is generally not easy to be prepared, is a major component compared with the α,β-enone **6**. We hypothesize that the olefin isomerization from **6** to **7** takes place after the crucial C–C bond formation stage (Scheme 2).

As can be seen in Scheme 3, a couple of experiments were devised to support our hypothesis. Acidic hydrolysis of the dienamine **14**, which was prepared from (*E*)-4-phenyl-3-hexen-2-one[10] and piperidine using $TiCl_4$,[11] gave the α,β-unsaturated ketone **6b** as a sole product. It demonstrates that the isomerization does not take place during the hydrolysis. In contrast, the dienamine **14** was isomerized upon treatment with $RhCl(PPh_3)_3$ (**3**) to generate β,γ-unsaturated ketone **7b** after hydrolysis. Thereby, we believe that a rhodium complex probably plays a key role in causing deconjugation of the dienamine **14**.



Scheme 2. A plausible mechanism for the Rh(I)-catalyzed β-alkylation of **1** with 1-alkenes.



Scheme 3. Acidic hydrolysis and isomerization of **13**.

As described above, we developed a new Rh(I)-catalyzed β-alkylation of the α,β-unsaturated ketone **1** with various 1-alkenes employing diethylamine (**5a**) as a highly efficient chelation-assistant tool. By comparison with Ru-catalyzed β-alkylation of enones,[6] our Rh-catalyzed reaction exhibited higher efficiency and broad applicability to most 1-alkenes. The key feature of this reaction is the vinyl C–H bond activation driven by amine-assisted cyclometalation to give the β,γ-unsaturated ketones **7** as a major product. Extension of the scope of this reaction and mechanistic studies are currently under investigation.

Acknowledgements

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8. General procedure for the β-alkylation of **1** is exemplified by entry 5 in Table 1. A screw-capped pressure vial (1 mL) equipped with a magnetic stirring bar was charged with **1** (0.216 mmol), 1-hexene (**2a**, 2.16 mmol), $RhCl(PPh_3)_3$ (**3**, 11.0 μmol), benzoic acid (**4**, 22.0 μmol), diethylamine (**5a**, 108 μmol), and dry toluene (100 mg). The vial was closed and stirred at 130°C for 24 h. After cooling the vessel to room temperature, the reaction mixture was purified by column chromatography (*n*-hexane/EtOAc = 10:1) on silica gel to afford (*E*)-4-phenyl-3-decen-2-one (**6a**)[12] and (*E*/*Z*)-4-phenyl-4-decen-2-one (**7a**)[13] as a mixture. Isomeric ratio of the crude mixture was determined by a GC analysis. The mixture of **6a** and **7a** in EtOH was stirred under H_2 atmosphere (balloon) in the presence of 10% palladium on activated charcoal for 12 h. After the reaction, the reaction mixture was filtered on a small plug of silica gel, concentrated, and purified by column chromatography to afford 4-phenyl-2-dodecanone (**8a**) as a pale yellow oil. ^{1}H NMR data for **6** and **7** are as follows. (*E*)-4-Phenyl-3-decen-2-one (**6a**)[12] and (*E*/*Z*)-4-phenyl-4-decen-2-one:[13] ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.44–7.11 (m, 15H), 6.37 (s, 1H, **6a**), 5.97 (t, J = 7.2 Hz, 1H, (*E*)-**7a**), 5.58 (t, J = 7.3 Hz, 1H, (*Z*)-**7a**), 3.56 (s, 2H, (*E*)-**7a**), 3.40 (s, 2H, (*Z*)-**7a**), 3.04 (t, J = 7.4 Hz, 2H, **6a**), 2.23 (s, 3H, **6a**), 2.17 (q, J = 7.2 Hz, 2H, (*E*)-**7a**), 2.04 (s, 3H, (*E*)-**7a**), 2.02 (s, 3H, (*Z*)-**7a**), 2.02–1.96 (m, 2H, (*Z*)-**7a**), 1.50–1.21 (m, 18H), 0.93–0.82 (m, 9H); (*E*)-4-phenyl-3-hexen-2-one (**6b**)[14] and (*E*/*Z*)-4-phenyl-4-hexen-2-one (**7b**): ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.26–7.05 (m, 15H), 6.37 (s, 1H, **6b**), 6.06 (q, J = 6.9 Hz, 1H, (*E*)-**7b**), 5.68 (q, J = 6.9 Hz, 1H, (*Z*)-**7b**), 3.57 (s, 2H, (*E*)-**7b**), 3.40 (s, 2H, (*Z*)-**7b**), 3.04 (t, J = 7.5 Hz, 2H, **6b**), 2.24 (s, 3H, **6b**), 2.07 (s, 3H, (*E*)-**7b**), 2.02 (s, 3H, (*Z*)-**7b**), 1.79 (d, J = 7.0 Hz, 3H, (*E*)-**7b**), 1.65 (d, J = 6.5 Hz, 3H, (*Z*)-**7b**), 1.05 (t, J = 7.4 Hz, 3H, **6b**); (*E*)-6-cyclohexyl-4-phenyl-3-hexen-2-one (**6c**) and (*E*/*Z*)-6-cyclohexyl-4-phenyl-4-hexen-2-one (**7c**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45–7.15 (m, 15H), 6.39 (s, 1H, **6c**), 5.99 (t, J = 7.2 Hz, 1H, (*E*)-**7c**), 5.60 (t, J = 7.3 Hz, 1H, (*Z*)-**7c**), 3.59 (s, 2H, (*E*)-**7c**), 3.42 (s, 2H, (*Z*)-**7c**), 3.06–3.01 (m, 2H, **6c**), 2.27 (s, 3H, **6c**), 2.23–2.14 (m, 2H, (*E*)-**7c**), 2.08 (s, 3H, (*E*)-**7c**), 2.06 (s, 3H, (*Z*)-**7c**), 2.02–2.00 (m, 2H, (*Z*)-**7c**), 1.48–1.24 (m, 27H), 0.84–0.89 (s, 6H); (*E*)-7,7-dimethyl-4-phenyl-3-octen-2-one (**6d**) and (*E*/*Z*)-7,7-dimethyl-4-phenyl-4-octen-2-one (**7d**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.71–7.15 (m, 15H), 6.39 (s, 1H, **6d**), 6.05 (t, J = 7.6 Hz, 1H, **7d**), 5.68 (t, J = 7.5 Hz, 1H, (*Z*)-**7d**), 3.58 (s, 2H, (*E*)-**7d**), 3.42 (s, 2H, (*Z*)-**7d**), 3.06–2.99 (m, 2H, **6d**), 2.25 (s, 3H, **6d**), 2.09 (s, 3H, (*E*)-**7d**), 2.05 (s, 3H, (*Z*)-**7d**), 2.04 (d, J = 7.6 Hz, 2H, (*E*)-**7d**), 1.93 (d, J = 7.5 Hz, 2H, (*Z*)-**7d**), 1.33–1.26 (m, 2H, **6d**), 0.94 (s, 27H); (*E*)-4-phenyl-6-trimethylsilyl-3-hexen-2-one (**6e**) and (*E*/*Z*)-4-phenyl-6-trimethylsilyl-4-hexen-2-one (**7e**): ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.48–7.18 (m, 15H), 6.37 (s, 1H, **6e**), 6.08 (t, J = 8.8 Hz, 1H, (*E*)-**7e**), 5.67 (t, J = 8.6 Hz, 1H, (*Z*)-**7e**), 3.57 (s, 2H, (*E*)-**7e**), 3.43 (s, 2H, (*Z*)-**7e**), 3.09–2.97 (m, 2H, **6e**), 2.29 (s, 3H, **6e**), 2.09 (s, 3H, (*Z*)-**7e**), 2.08 (s, 3H, (*E*)-**7e**), 1.70 (d, J = 8.8 Hz, 2H, (*E*)-**7e**), 1.54 (d, J = 8.6 Hz, 2H, (*Z*)-**7e**), 0.10 (s, 9H, (*E*)-**7e**), 0.07 (s, 9H, **6e**), 0.00 (s, 9H, (*Z*)-**7e**).

9. When the reaction was carried out in the presence of a primary amine such as cyclohexylamine, the fragmentation of the enone **1** via a retro-Mannich type process was observed. For the use of primary amine in such a process, see: Jun, C.-H.; Lee, H.; Lim, S.-G. *J. Am. Chem. Soc.* **2001**, *123*, 751–752.
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