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Rhodium-Catalyzed Acyl-Transfer Reaction between Benzyl Ketones and Thioesters: Synthesis of Unsymmetric Ketones by Ketone CO–C Bond Cleavage and Intermolecular Rearrangement

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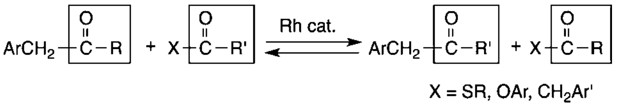
ABSTRACT

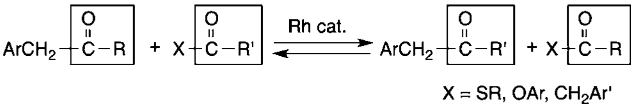


In the presence of catalytic amounts of RhH(CO)(PPh_3)$_3$ and 1,2-bis(diphenylphosphino)benzene (dppBz), acyl groups were transferred between benzyl ketones and thioesters/aryl esters. The rhodium complex catalyzed the cleavage of ketone CO–C bonds and intermolecular rearrangement giving unsymmetric ketones. The acyl-transfer reaction also occurred with 1-(*p*-chlorophenyl)-3-(*p*-cyanophenyl)propane-2-one giving unsymmetric ketones.

Unsymmetric ketones are important intermediates in organic synthesis, and their synthesis using acylation reactions with concomitant CO–C bond formation is well developed. In general, the reactions employ activated acid derivatives with electron-rich nucleophiles[1] or organometallic reagents,[2] which inevitably form inorganic waste materials. Acyl-transfer reactions between ketones and acylating reagents can be an attractive novel method, providing unsymmetric ketones by the exchange of acyl groups between organic molecules in an intermolecular manner without forming inorganic waste materials.

Described in this study is the rhodium-catalyzed acyl-transfer reaction between benzyl ketones and thioesters/aryl esters: acyl groups were exchanged at the benzyl position (Scheme 1). Transition-metal-catalyzed CO–C bond cleavage was reported for 1,3-diketones[3] and strained cyclic ketones.[4] The reactions of unactivated ketones have not been reported, with the exception of the chelation assisted method.[5] The method described here involves the CO–C bond cleavage of unstrained acyclic ketones without chelate assistance.

Scheme 1



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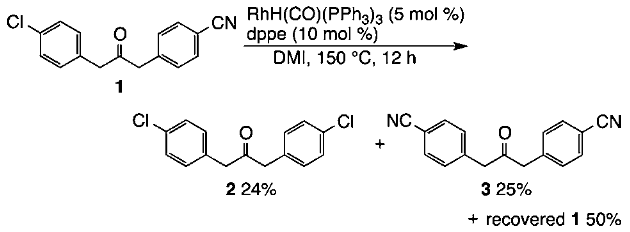
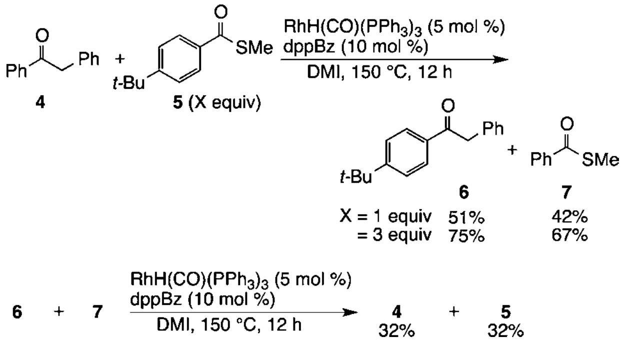
The study was initiated based on the finding that a rhodium complex catalyzes the acyl-transfer reaction of a symmetric dibenzyl ketone. When 1-(*p*-chlorophenyl)-3-(*p*-cyanophenyl)propane-2-one **1** was reacted in *N*,*N*′-dimethylimidazolidinone (DMI) at 150 °C for 12 h in the presence of RhH(CO)(PPh$_3$)$_3$ (5 mol %) and 1,2-bis(diphenylphosphino)ethane (10 mol %), 1,3-bis(*p*-chlorophenyl)propane-2-one **2** (24%) and 1,3-bis(*p*-cyanophenyl)propane-2-one **3** (25%) were obtained with the recovery of **1** (50%) (Scheme 2). No reaction occurred in the absence of the rhodium complex. The rhodium complex cleaved the CO−C bond of one molecule of **1** and transferred the (*p*-chlorophenyl)acetyl group to another molecule of **1** in an intermolecular manner, likely via acylrhodium and/or benzylrhodium intermediates.

Scheme 2



We then considered that the CO−C bond of benzyl ketones and the C−S bond of organosulfur compounds could be cleaved and exchanged.[6] It was expected that such rhodium-catalyzed reactions could be used to form new CO−C bonds in unsymmetric ketones without using stoichiometric amounts of acid, base, or organometallic reagent. When 1,2-diphenyl-1-ethanone **4** (1 equiv) was reacted with *S*-methyl 4-(*tert*-butyl)benzothioate **5** (1 equiv) in the presence of RhH(CO)(PPh$_3$)$_3$ (5 mol %) and 1,2-bis(diphenylphosphino)benzene (dppBz, 10 mol %) in DMI at 150 °C for 12 h, 1-[4-(1,1-dimethylethyl)phenyl]-2-phenylethanone **6** (51%) and *S*-methyl benzothioate **7** (42%) were obtained (Scheme 3). No reaction occurred in the absence of the rhodium complex or dppBz. Other metal complexes exhibiting activity in the presence of dppBz were RhH(PPh$_3$)$_4$ (49%), Rh(acac)(CO)$_2$ (43%), and Rh(acac)(CH$_2$=CH$_2$) (20%). The bidentate ligands with phosphino groups separated by two carbon atoms were also essential. When the molar ratio of **5** to **4** was changed from 1 to 3, the yields of **6** and **7** increased to 75 and 67%, respectively.[7] These results suggested the equilibrium nature of the reaction, because the statistical yields were calculated as 50% for a 1:1 ratio of substrates and 75% for a 3:1 ratio. Accordingly, the reverse reaction of **6** (1 equiv) and **7** (1 equiv) with the same catalyst in DMI at 150 °C for 12 h gave **4** and **5** in 32 and 32% yields, respectively.

Scheme 3



2-Aryl-1-phenyl-1-ethanones reacted with various *S*-methyl thioesters (3 equiv) giving acyl-transferred ketones and **7** in about 75% yields (Table 1). Aroyl groups were effectively transferred from aromatic thioesters to the benzyl carbon of 2-aryl-1-phenyl-1-ethanones, which possessed either *p*-electron-donating groups or *p*-electron-withdrawing groups on the aryl moiety (Table 1, entries 1, 4−7). In the reaction of aliphatic thioesters, alkanoyl groups were transferred in higher yields to the substrates possessing *p*-cyano-, *p*-(ethoxycarbonyl)-, and *p*-chlorophenyl groups (entries 13−15), and the yield decreased for a substrate with a phenyl group (entry 16). The reaction could be applied to a thioester having the *S*-(*p*-tolyl) group (entry 3). Chlorobenzene could be used as solvent in place of DMI (entry 2). These reactions replaced the benzoyl group of 1-aryl-2-phenyl-2-ethanones with various acyl groups.

The alkanoyl group of 1-aryl-2-decanones could be replaced with acyl groups as well as with the benzoyl group in the above reactions (Table 2). The reaction of 1-(*p*-cyanophenyl)-2-decanone and *S*-methyl *p*-(*tert*-butyl)benzothioate (3 equiv) in the presence of RhH(CO)(PPh$_3$)$_3$ (8 mol %) and dppBz (16 mol %) in DMI at 150 °C for 12 h gave 4-[2-[*p*-(1,1-dimethylethyl)phenyl]-2-oxoethyl]benzonitrile (80%) and *S*-methyl nonanethioate **8** (72%) (entry 1). The reaction of 1-aryl-2-decanones showed a similar tendency to 1-aryl-2-phenyl-1-ethanones in regard to the substituent effect on the aryl group (entries 1−11). Even the reaction of 1-aryl-2-decanones and aliphatic thioesters proceeded, which is an exchange reaction of alkanoyl groups (entries 12−15). This method has the advantage that benzyl ketones having functional groups can be synthesized from other benzyl ketones and thioesters.

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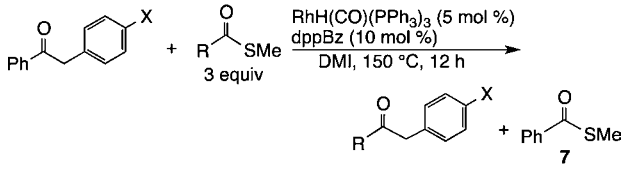
(7) Typical Experimental Procedures. In a two-necked flask were placed 1,2-diphenyl-1-ethanone **4** (0.25 mmol, 49.1 mg), *S*-methyl 4-(1,1-dimethylethyl)benzothioate **5** (0.75 mmol, 152.2 mg), RhH(CO)(PPh$_3$)$_3$ (5 mol %, 11.5 mg), and dppBz (10 mol %, 11.2 mg) in DMI (0.25 mL) under an argon atmosphere, and the solution was stirred at 150 °C for 12 h. The mixture was purified by flash column chromatography on silica gel, giving 1-[4-(1,1-dimethylethyl)phenyl]-2-phenylethanone **6** (47.5 mg, 75%) and *S*-methyl benzothioate **7** (25.5 mg, 67%).

Table 1. Rh-Catalyzed Reaction of 2-Aryl-1-phenyl-1-ethanones and Thioesters

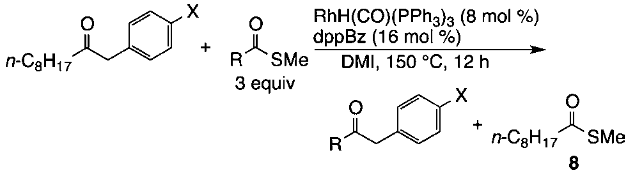


entry	X	R	yield (%) of benzyl ketone	7
1	CN	p-(t-Bu)C_6H_4	70	60
2[a]	CN	p-(t-Bu)C_6H_4	63	50
3[b]	CN	p-(t-Bu)C_6H_4	73	64
4	Cl	p-(t-Bu)C_6H_4	83	71
5	CO_2Et	p-(t-Bu)C_6H_4	72	59
6	H	p-(t-Bu)C_6H_4	75	76
7	MeO	p-(t-Bu)C_6H_4	33	28
8	CN	p-$MeOC_6H_4$	72	72
9	CN	2-thienyl	76	76
10	Cl	2-thienyl	78	65
11	CO_2Et	2-thienyl	72	64
12	CN	2-furyl	73	72
13	CN	n-C_8H_{17}	73	67
14	Cl	n-C_8H_{17}	65	55
15	CO_2Et	n-C_8H_{17}	59	53
16	H	n-C_8H_{17}	21	18
17[c]	CN	$PhCH_2CH_2$	61	68

[a] Chlorobenzene was used as solvent. [b] *S*-*p*-Tolyl (4-*tert*-butyl)benzothioate was used. [c] $RhH(CO)(PPh_3)_3$ (10 mol %) and dppBz (20 mol %) were used.

The metal-catalyzed ketone CO−C bond cleavage/rearrangement reaction could be applied to aryl esters (Table 3). When 2-(*p*-cyanophenyl)-1-phenylethanone was reacted with 4-chlorophenyl 4-(*tert*-butyl)phenylbenzoate (3 equiv) in the presence of $RhH(CO)(PPh_3)_3$ (10 mol %) and dppBz (20 mol %) in DMI at 150 °C for 6 h, 2-(*p*-cyanophenyl)-1-[4-(1,1-dimethylethyl)phenyl]ethanone and 4-chlorophenyl benzoate were obtained in 66 and 65% yields, respectively. No reaction occurred in the absence of the rhodium complex. 1-Aryl-2-decanones reacted similarly. These reactions can be regarded as the benzylation of thioesters/aryl esters using neutral benzyl ketones as the benzylation reagent, in contrast to the conventional coupling methods using benzylmetal reagents.[8]

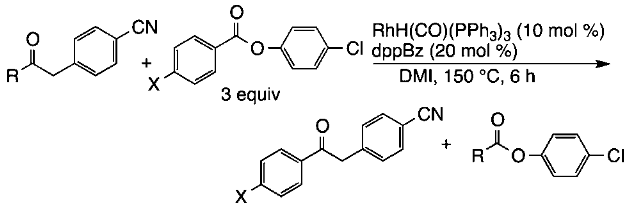
Table 2. Rh-Catalyzed Reaction of 1-Aryl-2-decanones and Thioesters



entry	X	R	yield (%) of benzyl ketone	8
1	CN	p-(t-Bu)C_6H_4	80	72
2	Cl	p-(t-Bu)C_6H_4	59	54
3	CO_2Et	p-(t-Bu)C_6H_4	61	60
4	H	p-(t-Bu)C_6H_4	41	37
5	MeO	p-(t-Bu)C_6H_4	39	34
6	CN	p-$MeOC_6H_4$	76	63
7	CN	3,5-$(MeO)_2C_6H_3$	74	68
8	CN	2-naphthyl	70	64
9	CN	2-thienyl	82	81
10	Cl	2-thienyl	75	70
11	CN	2-furyl	72	69
12[a]	CN	n-C_3H_7	54	54
13[a,b]	CN	n-C_3H_7	59	54
14[a]	CN	*cyclo*-$C_6H_{11}CH_2$	66	58
15[a]	Cl	*cyclo*-$C_6H_{11}CH_2$	50	40

[a] Reaction temperature: 120 °C. [b] Chlorobenzene was used as solvent.

Table 3. Rh-Catalyzed Reaction of Benzyl Ketones and Aryl Esters



entry	R	X	yield (%) of benzyl ketone	ester
1	Ph	t-Bu	66	65
2	Ph	MeO	71	68
3	Ph	Cl	68	72
4	n-C_8H_{17}	t-Bu	65	65
5	n-C_8H_{17}	MeO	46	46
6	n-C_8H_{17}	Cl	39	39

A possible mechanism follows. Oxidative addition of a benzyl ketone to a low-valent rhodium complex provides a C(O)−Rh−C intermediate, which undergoes an exchange reaction with thioester C′(O)−SR forming a C′(O)−Rh−C complex. Then the product is liberated by reductive elimination with the regeneration of the rhodium catalyst. Since the acyl-transfer reaction of a symmetric dibenzyl ketone proceeds in the absence of thioester (Scheme 2), the CO−C bond cleavage of ketone takes place without forming intermediates such as 1,3-diketones, which in fact were not detected in the reaction mixture.

In summary, a rhodium complex catalyzed the acyl-transfer reaction between thioesters/aryl esters and benzyl ketones. It should be emphasized that rhodium catalysis could be used for the transformation involving the cleavage of the CO−C bond in unstrained acyclic ketones and an intermolecular rearrangement. Unsymmetric ketones could also be synthesized by CO−C bond formation with

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catalyzed acyl transfer without forming inorganic waste materials.

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Supporting Information Available. General experimental procedures and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.