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Rhodium-Catalyzed Diarylation of Oxalates Using Arylboron Compounds

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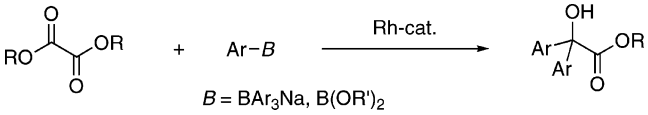
Received December 21, 2006

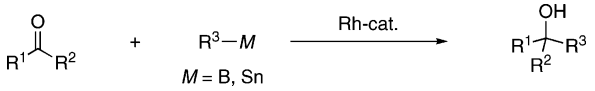


Dialkyl oxalates undergo selective diarylation on one of their carbonyl carbons upon treatment with arylboron reagents in the presence of a rhodium catalyst to give the corresponding α-hydroxydiarylacetates. Under similar conditions, the arylation of benzoylformate and benzil also proceeds efficiently.

The rhodium-catalyzed nucleophilic addition of organoboron and -stannane reagents to carbonyl compounds is now recognized to be a highly useful tool for alcohol synthesis (Scheme 1).[1] The mild, weakly nucleophilic organometallic reagents are effectively activated under rhodium catalysis to react readily with aldehydes (R^1 or $R^2 = H$)[2] and structurally or electronically activated ketones (R^1, $R^2 = -(CH_2)_3-$;[3] R^1 or $R^2 = COR'$;[4] etc.).

Recently, we succeeded in conducting the intermolecular arylation of relatively less reactive electrophiles such as unactivated ketones as well as imines and nitriles under suitable conditions.[5] In the course of our study of rhodium-catalyzed arylation reactions,[6] it has been found that dialkyl oxalates undergo diarylation selectively upon treatment with arylboron reagents to give the corresponding α-hydroxydiarylacetates.[7] This is a rare example of rhodium-catalyzed intermolecular arylation on the carbonyl carbon of esters.[8] α-Hydroxyesters are useful materials as the synthetic intermediates of certain carbo- and heterocyclic compounds, as well as for other applications including delivery systems of cosmetic and pharmaceutical agents.[9] In addition, related α-dicarbonyl compounds, benzoylformate and benzil, have also been found to undergo monophenylation by the rhodium catalysis.

SCHEME 1



In an initial attempt, diethyl oxalate (**1a**) (1 mmol) was treated with sodium tetrakis(4-methylphenyl)borate (**2a**) (0.5 mmol) under conditions similar to those employed for the reaction of ketones.[5] Thus, in the presence of $[RhCl(cod)]_2$ (0.005 mmol) and NH_4Cl (1 mmol) as a catalyst and a proton source, respectively, in refluxing *o*-xylene at 120 °C for 13 h, ethyl 2-hydroxy-2,2-bis(4-methylphenyl)acetate (**3a**) was formed in 75% yield (Table 1, entry 1). The addition of phenol in place of NH_4Cl completely suppressed the reaction (entry 2). The present arylation was found to proceed effectively without any additives to afford **3a** in 87% yield (entry 3). The hydroxy complex $[Rh(OH)(cod)]_2$ was as effective as $[RhCl(cod)]_2$ (entry 4), while the activity of Rh(acac)(cod) was very low (entry 5). It was confirmed that the reaction does not proceed at all without any rhodium catalyst. At a lower or higher temperature, the yield of **3a** decreased (entries 6 and 7). The reaction proceeded with somewhat reduced efficiency in refluxing toluene (entry 8), while a polar solvent, 1,4-dioxane, was found to be unsuitable (entry 9).

Dimethyl- (**1b**) and di(*n*-butyl) oxalate (**1c**) also underwent the diarylation upon treatment with **2a** under the optimized conditions to give the corresponding α-hydroxyacetates in good yields (Scheme 2). In contrast, a sterically hindered ester, di(*tert*-butyl) oxalate (**1d**), did not react with **2a** at all.

Table 2 summarizes the results for the reactions of di(*n*-butyl) oxalate (**1c**) with sodium tetraarylborate **2** or 5,5-dimethyl-2-aryl[1,3,2]dioxaborinane **4**. Tetraphenylborate and tetrakis(4-fluorophenyl)borate reacted efficiently to give **3d** and **3e** in 68 and 137% yields, respectively. In the latter case, the yield exceeding 100% indicates that more than one aryl group in **2** can be utilized. The reactions with arylboronates **4** also proceeded to give the corresponding diarylated products. The addition of KF was essential for the reaction with **4** to occur.

A plausible mechanism for the reaction of oxalates **1** with arylboron reagents **2** or **4** is illustrated in Scheme 3. The reaction may proceed via nucleophilic addition of an arylrhodium

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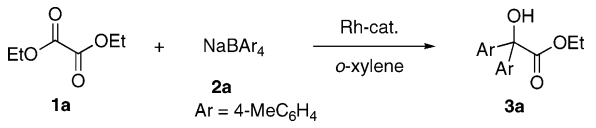
10.1021/jo062628j CCC: $37.00
Published on Web 02/20/2007

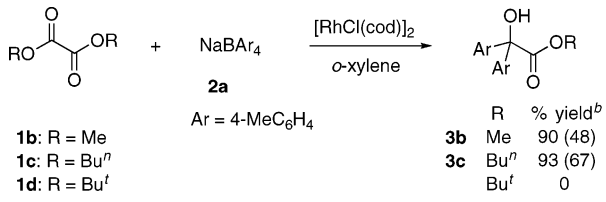
TABLE 1. Reaction of Diethyl Oxalate (1a) with Sodium Tetrakis(4-methylphenyl)borate (2a)[a]



entry	Rh catalyst	temp (°C)	time (h)	% yield of **3a**[b]
1[c]	$[RhCl(cod)]_2$	120	13	75 (51)
2[d]	$[RhCl(cod)]_2$	120	11	0
3	$[RhCl(cod)]_2$	120	13	87 (57)
4	$[Rh(OH)(cod)]_2$	120	11	81
5	Rh(acac)(cod)	120	8	7
6	$[RhCl(cod)]_2$	100	11	45
7	$[RhCl(cod)]_2$	140	11	69
8[e]	$[RhCl(cod)]_2$	120	12	65
9[f]	$[RhCl(cod)]_2$	120	6	9

[a] Reaction conditions: [**1a**]:[**2a**]:[Rh catalyst] = 1:0.5:0.005 (in mmol), in *o*-xylene (5 mL) under N_2. [b] GLC yield based on the amount of **2a** used. Value in parentheses indicates yield after purification. [c] With NH_4Cl (1 mmol). [d] With phenol (1 mmol). [e] In refluxing toluene. [f] In refluxing 1,4-dioxane.

SCHEME 2[a]



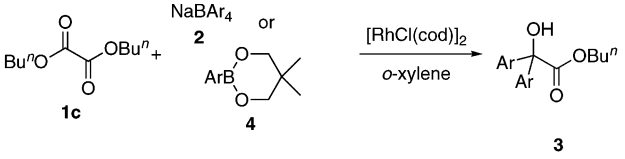
[a] Reaction conditions: [**1**]:[**2a**]:[$[RhCl(cod)]_2$] = 1:0.5:0.005 (in mmol), in *o*-xylene (5 mL) under N_2 at 120 °C for 12 h. [b]GLC yield based on the amount of **2a** used. Value in parentheses indicates yield after purification.

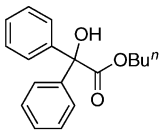
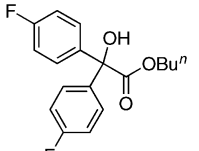
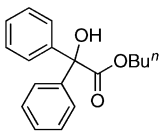
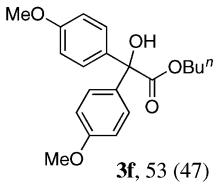
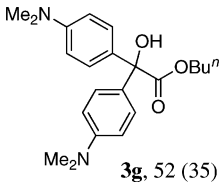
intermediate **A**, which is generated by transmetalation of a Rh(I)X species with **2** or **4**, to one of the carbonyl groups of **1** to give an intermediate **B**. Then, the elimination of alkoxyrhodium **C** from **B** gives α-ketoester **5**. The alkoxyrhodium **C** undergoes transmetalation with **2** or **4** to regenerate **A**. Under the present reaction conditions, α-ketoester **5** may also undergo nucleophilic addition of **A** on its keto carbonyl group to yield **D**,[4a] which releases the borate of the final diarylated product **3** and regenerates **A** via transmetalation. Each transmetalation step with **4** may be promoted by added KF.[1a,10]

On the basis of the consideration described above, the phenylation of an α-ketoester by the present procedure was next attempted. Thus, ethyl benzoylformate (**5a**) was treated with **2b** in the presence of $[RhCl(cod)]_2$ in *o*-xylene at 120 °C for 9 h (Scheme 4). As expected, a monophenylated product, ethyl 2-hydroxy-2,2-diphenylacetate (**7**), was formed in 74% yield. The yield of **7** was significantly enhanced by the addition of NH_4Cl and PhOH. Particularly, using the latter additive, **7** was obtained in 168% yield, which indicates the participation of more than one phenyl group of **2b** in the reaction. In contrast, as described above, the reaction of diethyl oxalate **1a** did not proceed in the presence of PhOH (entry 2 in Table 1). These results indicate that, in the diarylation of oxalates **1**, the additive suppresses the first arylation from **1** to **5**, although it may possess high potential to promote the second step from **5** to **3**. In addition, **5a** was found to react effectively with phenylboronic acid (**6**) in the presence of KF to give **7** in 93% yield within 2 h.[11]

A related α-diketone, benzil (**8**), also underwent the phenylation in the present reaction system using **2b**, $[RhCl(cod)]_2$, and PhOH as the phenylation reagent, catalyst, and promoter, respectively, to give 2-hydroxy-2,2-diphenylacetophenone (**9**) in an excellent yield (Scheme 5).[4a] One of the major roles of

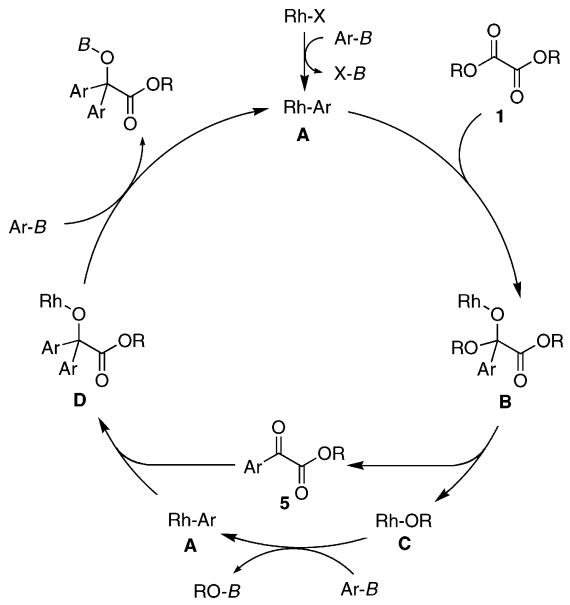
TABLE 2. Reaction of Dibutyl Oxalate (1c) with Tetraarylborates 2 or Arylboronates 4[a]



product, % yield[b]	
with **2**	 **3d**, 68 (54)
	 **3e**, 137 (105)
with **4**[c]	 **3d**, 45
	 **3f**, 53 (47)
	 **3g**, 52 (35)

[a] Reaction conditions: [**1c**]:[**2** or **4**]:[$[RhCl(cod)]_2$] = 1:0.5 or 1:0.005 (in mmol), in *o*-xylene (5 mL) under N_2 at 120 °C. [b] GLC yield based on the amount of **2** or **4** used. Value in parentheses indicates yield after purification. [c] For the reaction with **4**, KF (1 mmol) was added.

SCHEME 3



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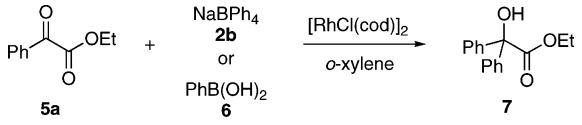
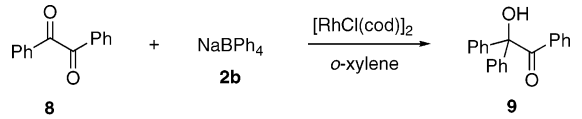
SCHEME 4[a]



	additive	% yield[b]
2b	–	74
2b	NH_4Cl	101
2b	PhOH	168 (138)
6[c]	KF	93

[a] Reaction conditions: [**5a**]:[**2b** or **6**]:[[RhCl(cod)]$_2$]:[additive] = 1:0.5:0.005:1 (in mmol), in *o*-xylene (5 mL) under N_2 at 120 °C for 9 h. [b]GLC yield based on the amount of **2b** or **6** used. Value in parentheses indicates yield after purification. [c]For 2 h.

SCHEME 5[a]



additive	% yield[b]
–	83
NH_4Cl	92
PhOH	199 (157)

[a] Reaction conditions: [**8**]:[**2b**][[RhCl(cod)]$_2$]:[additive] = 1:0.5:0.005:1 (in mmol), in *o*-xylene (5 mL) under N_2 at 140 °C for 6−12 h. [b]GLC yield based on the amount of **2b** used. Value in parentheses indicates yield after purification.

added PhOH would be the protonolysis of intermediary alkoxyrhodium species to make an effective bypath.[5,6e] However, the detrimental effect in the reaction of **1** is not accountable at the present stage.

In summary, we have shown that dialkyl oxalates undergo selective diarylation by treatment with arylboron reagents in the presence of a rhodium catalyst system. This appears to provide a useful, general synthetic route leading to α-hydroxydiarylacetates. It has also been confirmed that benzoylformate as well as benzil also undergoes arylation effectively under similar conditions.

Experimental Section

Ethyl 2-Hydroxy-2,2-bis(4-methylphenyl)acetate (3a). To a 20 mL two-necked flask were added diethyl oxalate (**1a**) (1 mmol, 146 mg), sodium tetrakis(4-methylphenyl)borate (**2a**) (0.5 mmol, 199 mg), [RhCl(cod)]$_2$ (0.005 mmol, 2.5 mg), 1-methylnaphthalene (ca. 60 mg) as internal standard, and *o*-xylene (5 mL). The resulting mixture was stirred under N_2 (balloon) at 120 °C (bath temperature) for 13 h. After cooling, analysis of the mixture by GC confirmed formation of compound **3a** (61 mg, 87%). The product (40 mg, 57%) was also isolated by extraction of the mixture with ether, evaporation of the solvents, and thin-layer chromatography on silica gel using hexane/ethyl acetate (90:10, v/v). Compound **3a**:[12] oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.3 Hz, 3H), 2.33 (s, 6H), 4.15 (s, 1H), 4.31 (q, J = 7.0 Hz, 2H), 7.14 (d, J = 8.4 Hz, 4H), 7.31 (d, J = 8.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.1, 62.8, 80.6, 127.3, 128.7, 137.7, 139.3, 174.7; MS *m*/*z* 284 (M^+).

Acknowledgment. This work was partly supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Standard experimental procedure and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062628J

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