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Selective Monoarylation of Aromatic Ketones and Esters via Cleavage of Aromatic Carbon–Heteroatom Bonds by Trialkylphosphine Ruthenium Catalysts

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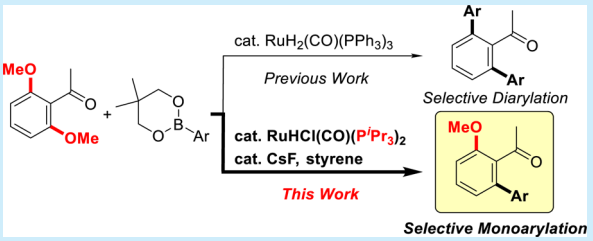
Supporting Information

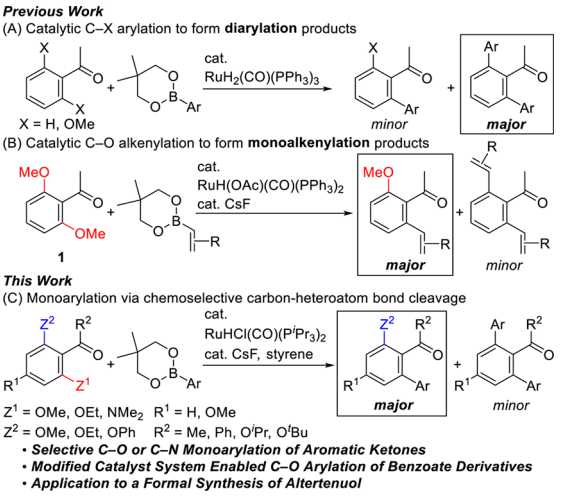
ABSTRACT: We report here the ruthenium-catalyzed selective monoarylation of aromatic ketones bearing two ortho carbon–heteroatom (O or N) bonds. Under the newly developed catalyst system consisting of $RuHCl(CO)(P^iPr_3)_2$, CsF, and styrene, the C–O arylation of 2′,6′-dimethoxyacetophenone with a phenylboronate gave the C–O monoarylation product selectively. The selective C–O monoarylation was applicable to a variety of arylboronates and aromatic ketones and proceeds with high regio- and chemoselectivities. A formal synthesis of altertenuol was also achieved using the C–O monoarylation of an aromatic ester as a key step.



Transition-metal-catalyzed functionalization of unreactive bonds such as C–H and C–Heteroatom bonds have been extensively explored due to its great synthetic utility.[1,2] Chelation-assisted control of the regioselectivity of the bond cleavage has enabled the selective functionalization at the ortho positions of the directing groups. However, there are still limitations in selective monofunctionalizations of arenes possessing multiple reaction sites.[3] Our group has reported ruthenium-catalyzed arylations of aromatic carbonyl compounds with arylboronates via ortho-selective cleavage of carbon–hydrogen or carbon–heteroatom bonds.[1c,3b,4−8] In the reaction of acetophenone derivatives having two ortho C–H or C–OMe bonds, both ortho positions are smoothly arylated, and selective monoarylation was hard to achieve even at low conversion of substrates (Scheme 1A).[5b,6a] In the C–H arylation, the use of styrene as an additive was found effective to some extent to form monoarylation products mostly in moderate yields using 3 equiv of acetophenones to arylboronates.[3b] In the corresponding alkenylation reactions, it was possible to form monoalkenylation products selectively, because coordination of the introduced alkenyl group to the metal center may stabilize the catalytically active low-valent ruthenium complex and may suppress the second C–O bond cleavage. For example, we recently reported selective C–O monoalkenylation of 2′,6′-dimethoxyacetophenone (**1**) with alkenylboronates using the catalyst system consisting of $RuH(OAc)(CO)(PPh_3)_2$ and CsF (Scheme 1B).[6c]

Herein we report the catalytic monoarylation of aromatic ketones and esters possessing two unreactive C–O or C–N bonds at ortho positions (Scheme 1C). A new catalyst system consisting of $RuHCl(CO)(P^iPr_3)_2$, CsF, and styrene was established for the selective monoarylation, and a variety of aryl groups were introduced efficiently at the ortho position. The C–O monoarylation of an aromatic ester was also applied to a formal synthesis of altertenuol.

Scheme 1. Product Selectivities on Ruthenium-Catalyzed Direct Functionalizations of Unreactive Bonds



First, we investigated the ruthenium-catalyzed monophenylation of **1** with phenylboronate **2a** (Table 1). When the reaction of **1** was conducted with 1.2 equiv of **2a** in the presence of 2 mol % of $RuH_2(CO)(PPh_3)_3$ (**5**) at 120 °C for 30 min, diarylation product **4a** was obtained in 45% GC yield along with the desired

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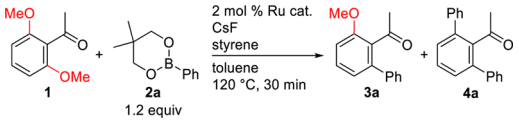
Table 1. Ruthenium-Catalyzed Selective C−O Monoarylation of an Acetophenone Derivative 1 with 2a[a]



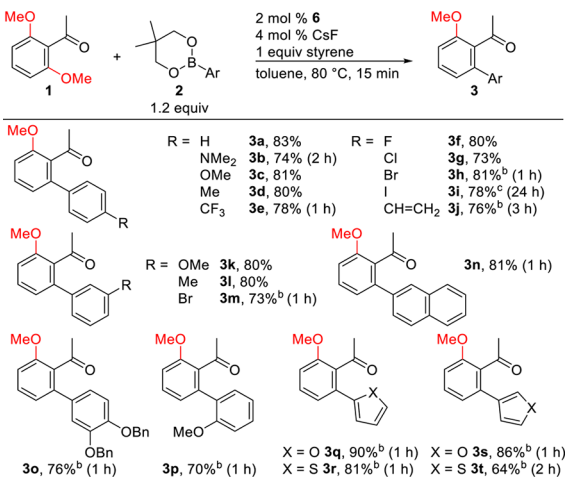
entry	Ru cat.	CsF (mol %)	styrene (equiv)	conversion (%)[b]	yields (%)[b] 3a	4a
1	$RuH_2(CO)(PPh_3)_3$ (**5**)	–	–	47	2	45
2	**5**	–	1	73	10	53
3	$RuH(OAc)(CO)(PPh_3)_2$	4	1	70	19	50
4	$RuH(OAc)(CO)(PCy_3)_2$	4	1	72	61	9
5	$RuH(OAc)(CO)(P^iPr_3)_2$	4	1	92	77	15
6	$RuHCl(CO)(P^iPr_3)_2$ (**6**)	4	1	98	75	22
7[c]	**6**	4	1	96	84	12
8[c]	**6**	–	1	<1	nd[d]	nd[d]
9[c]	**6**	4	–	3	2	nd[d]

[a]Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), Ru cat. (0.01 mmol), CsF (0.02 mmol), styrene (0.5 mmol), 120 °C, 30 min. [b]Determined by GC analysis. [c]Performed at 80 °C for 15 min. [d]Not detected.

monophenylation product **3a** in 2% yield (entry 1). Under these reaction conditions, it is clearly shown that the subsequent second phenylation occurs fast even at low conversion. The use of styrene as an additive led to higher reactivity, and the yield of **3a** was slightly improved to 10% (entry 2).[9] The screening of the ruthenium catalyst was then examined. A combination of $RuH(OAc)(CO)(PPh_3)_2$ with CsF, an effective catalyst system for the C−O monoalkenylation,[6c] gave monoarylation product **3a** with higher selectivity but still in low yield (entry 3). Screening of a series of $RuH(OAc)(CO)(PR_3)_2$-type complexes containing various phosphines revealed that those with trialkylphosphines such as PCy_3 and P^iPr_3 serve as good catalysts[10] for the selective monophenylation reaction (entries 4 and 5), and the reaction using $RuH(OAc)(CO)(P^iPr_3)_2$ gave **3a** in 77% yield. The use of $RuHCl(CO)(P^iPr_3)_2$ (**6**) gave **3a** in high yield with greater catalytic activity (98% conversion) (entry 6). Optimization of the reaction conditions using catalyst **6** further improved the yield of **3a** and the selectivity toward monoarylation over diarylation, and the reaction at 80 °C for 15 min provided **3a** in 84% yield (entry 7). The reactions in the absence of either CsF or styrene were not successful, indicating that both of them are essential for generation of a catalytically active species (entries 8 and 9).

With the optimized reaction conditions in hand, we examined the scope of arylboronates **2** for the C−O monoarylation (Scheme 2). In addition to phenylboronate **2a**, arylboronates bearing various *para*-substituents can be used for the monoarylation. The reaction of **1** proceeded with arylboronates possessing electron-donating (dimethylamino, methoxy, and methyl) and electron-withdrawing (trifluoromethyl, fluoro, and chloro) groups (**2b−g**), and the corresponding monoarylation products **3b−g** were obtained in 73−81% isolated yields.[11] The coupling with arylboronates having bromo, iodo, and vinyl groups (**2h−j**) required higher catalyst loadings, but the corresponding monoarylation products **3h−j** were isolated in 76−81% yields. *Meta*-substituted arylboronates **2k−m** also provided **3k−m** in high yields. The reactions with 2-naphthylboronate **2n** and 3,4-dibenzyloxyphenylboronate **2o** also afforded the corresponding products **3n** and **3o** in 81% and 76% yields, respectively. The monoarylation with *ortho*-methoxyphenylboronate **2p** occurred smoothly without sacrificing the methoxy group on the introduced aryl group. The

Scheme 2. Ruthenium-Catalyzed Selective C−O Monoarylation of 1 with Arylboronates 2[a]

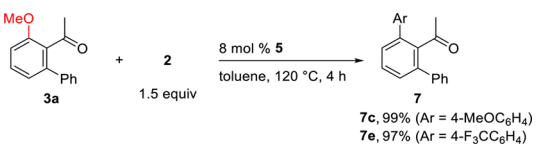


[a]Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), **6** (0.01 mmol), CsF (0.02 mmol), styrene (0.5 mmol), toluene (0.5 mL), 80 °C, 15 min. Isolated yields are shown. [b]Used 4 mol % of **6**, 8 mol % of CsF, and 2 equiv of styrene. [c]Performed at 60 °C and used 10 mol % of **6**, 20 mol % of CsF, and 5 equiv of styrene.

reactions with heteroarylboronates **2q−t** also proceeded using 4 mol % of **6** for 1−2 h to afford **3q−t** in good to excellent yields. Alkylboronates such as benzyl-, neopentyl-, and *β*-phenethylboronates were also examined for this reaction but failed to give the corresponding alkylation products.

Sequential ortho C−O arylation of **1** using two types of arylboronates may provide acetophenone derivatives bearing two different aryl groups at the ortho positions. Therefore, the C−O arylation of monophenylation product **3a** was then investigated. As shown in Scheme 3, when the reaction was conducted using

Scheme 3. Sequential Ortho C−O Arylation



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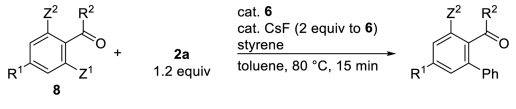
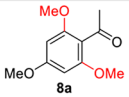
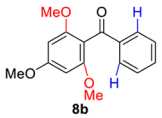
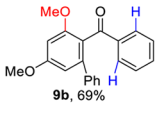
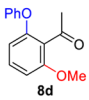
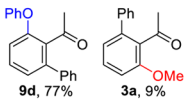
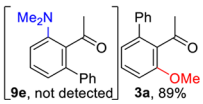
ruthenium catalyst **5**, which is prone to afford the diarylation product, at 120 °C for 4 h, introduction of methoxyphenyl and trifluoromethylphenyl groups proceeded efficiently via cleavage of the remaining ortho C−O bond to afford the unsymmetric diarylation products **7c** and **7e** in excellent yields.

We next investigated the scope of aromatic ketones for the C−O monoarylation (Table 2). The arylation of 2′,4′,6′-trimethoxy-

Table 2. Selective Monoarylation of Various Aromatic Ketones[a]



entry	substrate **8**	**6** (mol %)	styrene (equiv)	product(s)
1	 **8a**	2	1	 **9a**, 74%
2[b]	 **8b**	2	1	 **9b**, 69%
3[c]	 **8c**	4	2	 **9c**, 80%
4[d]	 **8d**	10	2	 **9d**, 77% **3a**, 9%
5[c,e]	 **8e**	4	2	 **9e**, not detected **3a**, 89%

[a]Reaction conditions: **8** (0.5 mmol), **2a** (0.6 mmol), **6** (0.01 mmol), CsF (0.02 mmol), styrene (0.5 mmol), toluene (0.5 mL), 80 °C, 15 min. Isolated yields are shown. [b]Performed at 120 °C for 30 min. [c]Performed for 1 h. [d]Performed at 120 °C for 1 h. [e]1 equiv of **2a** was used.

acetophenone (**8a**) selectively took place at the ortho position and furnished monophenylation product **9a** in 74% yield (entry 1). The reaction of benzophenone derivative **8b**, which has two C−O bonds and two C−H bonds at the positions ortho to the carbonyl group, gave the corresponding C−O monophenylation product **9b** in 69% yield without coupling at the ortho C−H bonds (entry 2). The reaction of 2′,6′-diethoxyacetophenone **8c** also proceeded via cleavage of the C−OEt bond to provide monoarylation product **9c** in 80% yield (entry 3).[12]

The reaction of acetophenones possessing two different functional groups at the ortho positions was then examined. The ruthenium-catalyzed monophenylation of an acetophenone derivative with methoxy and phenoxy groups delivered monophenylation product **9d**, formed via cleavage of the C−OMe bond, in 77% yield as a major product along with 9% of C−OPh bond cleavage product **3a** (entry 4). The reaction of an acetophenone derivative possessing a methoxy and dimethylamino group with 1 equiv of **2a** proceeded efficiently via C−N bond cleavage to give **3a** in 89% yield without generating C−O monophenylation product **9e** (entry 5). The observed chemoselectivity to favor cleavage of more electron-donating groups is opposite to that of the conventional bond cleavage process via oxidative addition but is similar to that of our ruthenium-catalyzed alkenylation of aromatic ketone derivatives via cleavage of C−O or C−N bonds.[6c]

It is unclear why the new catalyst system provides monoarylation products selectively over diarylation products, but the subsequent second arylation can be avoided by stabilizing the ruthenium(0) species formed after the reductive elimination. Coordination of styrene as a π-acid may facilitate the reductive elimination to form the ruthenium(0) species and retard the second oxidative addition of the C−O bond, as suggested for our previously reported C−H monoarylation (Figure 1).[3b] The use

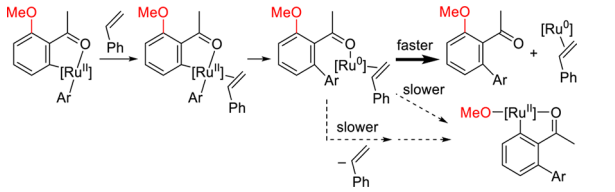
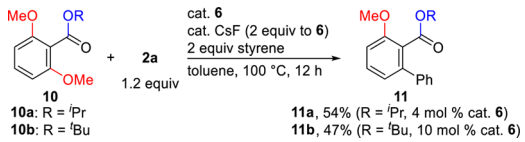


Figure 1. A possible explanation of the mono-/diarylation selectivity.

of highly electron-donating trialkylphosphines may increase the electron density on the ruthenium center and may strengthen the coordination of styrene to prevent the second cleavage of the C−O bond.

The utility of the ruthenium-catalyzed C−O monoarylation reaction was demonstrated further by the reaction of aromatic esters (Scheme 4). Snieckus and Zhao recently reported the

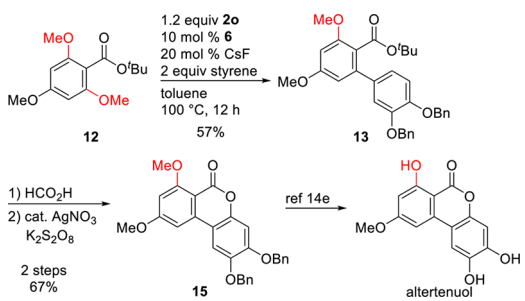
Scheme 4. C−O Monoarylation of Benzoate Derivatives 10



ester-directed C−O arylation of naphthoate derivatives using catalyst **5**, but it was not applicable to simple benzoate derivatives.[13] When our new catalyst system was employed for the phenylation of isopropyl benzoate derivative **10a** at 100 °C for 12 h, monophenylation product **11a** was obtained in 54% yield. The reaction of *tert*-butyl ester **10b** required a higher catalyst loading but gave **11b** in 47% yield.

Finally, we applied the C−O monoarylation to the formal synthesis of altertenuol, a toxin produced by *Alternaria tenuis* (Scheme 5).[14] The reaction of *tert*-butyl 2′,4′,6′-trimethoxybenzoate (**12**), prepared from the commercially available carboxylic acid in 91% yield, with arylboronate **2o** provided monoarylation product **13** in 57% yield. Treatment of **13** with formic acid removed the *tert*-butyl group to deliver carboxylic

Scheme 5. Formal Synthesis of Altertenuol



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acid **14** in 93% yield. Subsequent oxidative cyclization by $K_2S_2O_8$[15] provided biaryl lactone **15** in 72% yield as a single regioisomer. The total synthesis of altertenuol by Abe and co-workers was achieved in one step from compound **15**.[14e]

In summary, we developed the ruthenium-catalyzed selective monoarylation of aromatic ketones and esters via cleavage of unreactive C−O or C−N bonds. The new catalyst system consisting of **6**, CsF, and styrene was particularly effective in the selective monoarylation. Various arylboronates can be used as coupling partners for the reaction, and aromatic ketones bearing two different aryl groups at the ortho positions was synthesized by further C−O arylation of a monoarylation product. The catalytic ortho C−O arylation of simple benzoate derivatives was also achieved for the first time using this catalyst system and applied to the formal synthesis of altertenuol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03761.

Full experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(11) A competition experiment of **1** with equimolar of **2c** and **2e** gave **3c** in lower yield than **3e**. Similar electronic effects of organoboron compounds were also observed in ref 7a, c. See the Supporting Information for details.

(12) The reaction of 2,6-dimethoxy-3-methylbenzophenone with **2a** was examined but provided a complex mixture, and the regioselectivity of the C−O arylation could not be determined. The reaction of 4-methoxy-4-methyl-2-pentanone was also attempted but did not give any arylation product.

(13) Recently, Snieckus and Zhao reported amide- or ester-directed C−O functionalizations using our ruthenium catalyst systems: (a) Zhao, Y.; Snieckus, V. *J. Am. Chem. Soc.* **2014**, *136*, 11224. (b) Zhao, Y.; Snieckus, V. *Org. Lett.* **2015**, *17*, 4674. (c) Zhao, Y.; Snieckus, V. *Chem. Commun.* **2016**, *52*, 1681.

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