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ARTICLE TYPE

Asymmetric addition of arylboronic acids to glyoxylate catalyzed by ruthenium/Me-BIPAM complex

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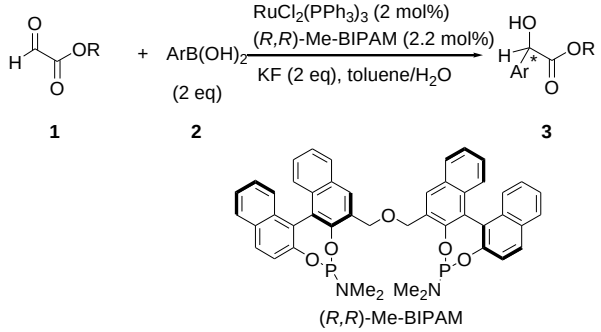
The enantioselective synthesis of α-hydroxy esters by ruthenium-catalyzed 1,2-addition of arylboronic acids to *tert*-butyl glyoxylate is described. The use of $RuCl_2(PPh_3)_3$ with (*R,R*)-Me-BIPAM gave optically active mandelic acids of up to 99% ee. Addition of a fluoride salt such as potassium fluoride KF or cesium fluoride CsF was effective for achieving high enantioselectivities.

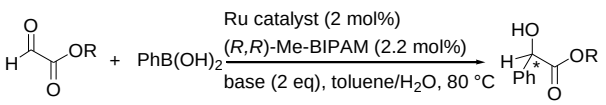
Optically active mandelic acid derivatives are very important chiral building blocks for the synthesis of various bioactive products.[1] Several synthetic methods for these compounds have been developed, including enzymatic methods,[2] Cannizzaro reaction,[3] enantioselective reduction[4] and hydrogenation[5] of α-ketoester, Friedel-Crafts reaction[6,7] and kinetic resolution.[8] Recently, catalytic enantioselective arylation of glyoxylate has been reported.[9] We have already reported a new catalytic cycle starting from transmetalation to give an organorhodium(I),[10] -palladium(II)[11] or -ruthenium(II)[12] intermediate for 1,4-addition of organoboronic acids to electron-deficient alkenes and arylation of the carbon-heteroatom double bond of aldehydes or *N*-sulfonyl imines. In addition, we have developed new bidentate chiral phosphoramidites (Me-BIPAM,[12-14] *N*-Me-BIPAM[15]) on the basis of linked-BINOL for enantioselective 1,4-addition of arylboronic acids to enones,[13] arylation of aldimines[15] and hydrogenation of γ-dehydroamino esters[14] with rhodium catalysts. These ligands were also found to be highly efficient for ruthenium-catalyzed enantioselective arylation of aldehydes and α-ketoesters.[12] Herein, we report asymmetric arylation of glyoxylate (**1**) with arylboronic acids (**2**) catalyzed by a chiral ruthenium complex, generated in situ from $RuCl_2(PPh_3)_3$ and (*R,R*)-Me-BIPAM (Scheme 1).

Our initial investigation began by screening catalysts to evaluate their ability to promote the enantioselective arylation of ethyl glyoxylate with phenylboronic acid. As shown in Table 1, since the rhodium complex was inefficient, the use of ruthenium as the central metal is critical for achieving enantioselectivities. We have already reported $[RuCl_2(p\text{-cymene})]_2$/(*R,R*)-Me-BIPAM complex-catalyzed highly enantioselective arylation of aldehydes.[12] As an initial experiment under similar conditions, the reaction in the presence of 2 mol% of $[RuCl_2(p\text{-cymene})]_2$ and 2.2 mol% of (*R,R*)-Me-BIPAM resulted in 25% yield and 2% ee (entry 2). Several combinations of ruthenium(II) precursors, bases and ester alkyl groups revealed the high efficiency of $RuCl_2(PPh_3)_3$ and KF in toluene for the addition of $PhB(OH)_2$ to *t*-butyl glyoxylate (entry 7). Since hydrolysis of the ester is suppressed, the yield of the product was dependent on the bulkiness of the ester moiety of the substrate, as ethyl (59% yield), *i*-propyl (79% yield), and *t*-butyl (90% yield).



Scheme 1 Asymmetric addition of arylboronic acids to glyoxylate.

Table 1 Reaction conditions.[a]



entry	R =	catalyst	base	solvent	yield/%	ee/%
1	Et	$Rh(nbd)_2BF_4$	KF	toluene	36	4
2	Et	$[RuCl_2(p\text{-cymene})]_2$	KF	toluene	25	2
3	Et	$RuCl_2(nbd)(MeCN)_2$	KF	toluene	39	84
4	Et	$RuCl(p\text{-cymene})(MeCN)_2PF_6$	KF	toluene	17	0
5	Et	$RuCl_2(PPh_3)_3$	KF	toluene	59	93
6	*i*-Pr	$RuCl_2(PPh_3)_3$	KF	toluene	79	94
7	***t*-Bu**	**$RuCl_2(PPh_3)_3$**	**KF**	**toluene**	**90**	**96**
8	*t*-Bu	$RuCl_2(PPh_3)_3$	CsF	toluene	61	92
9	*t*-Bu	$RuCl_2(PPh_3)_3$	K_2CO_3	toluene	52	55
10	*t*-Bu	$RuCl_2(PPh_3)_3$	K_3PO_4	toluene	26	71
11	*t*-Bu	$RuCl_2(PPh_3)_3$	KF	toluene[b]	33	91
12	*t*-Bu	$RuCl_2(PPh_3)_3$	KF	CH_2Cl_2	23	13
13	*t*-Bu	$RuCl_2(PPh_3)_3$	KF	THF	trace	-

[a] Reaction conditions: A mixture of glyoxylates (0.5 mmol), phenylboronic acid (1.0 mmol), base (1.0 mmol), Ru catalyst (2 mol%), and (*R,R*)-Me-BIPAM (2.2 mol%) in toluene (3 ml) and H_2O (0.3 ml) was stirred at 80 ˚C for 16 h. [b] toluene/H_2O = 5/1

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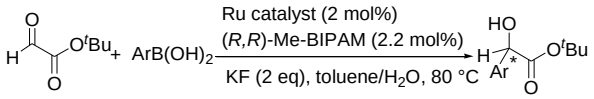
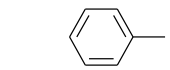
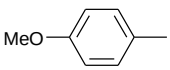
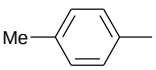
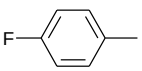
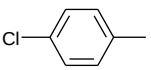
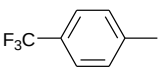
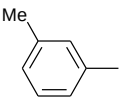
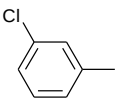
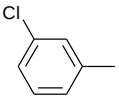
On the other hand, other bases such as K_2CO_3 and K_3PO_4 previously used for addition to aldehydes were not effective (entries 9 and 10). It is interesting that increase of water resulted in lower yield (entry 11). The reaction also failed when other solvents such as CH_2Cl_2 and THF were used. Finally, the desired product was selectively afforded in 90% yield and 96% ee when the reaction was carried out at 80 ºC in toluene/H_2O (10/1) in the presence of a $RuCl_2(PPh_3)_3$/(*R*,*R*)-Me-BIPAM catalyst (2/2.2 mol%). Results of arylation of *tert*-butyl glyoxylate with representative arylboronic acids are summarized in Table 2. Representative *para*- and *meta*-substituted arylboronic acids with electron-donating or electron-withdrawing substituents afforded mandelic acid derivatives in good yields with high enantioselectivities in the range of 76-99% ee. 3-Chlorophenylboronic acid resulted in 16% ee when $RuCl_2(PPh_3)_3$ was used as a catalyst precursor, and the ee was increased to 88% ee with 54% yield to reduce the steric hindrance than that of PPh_3 when $PMePh_2$ was added as a ligand (entries 8 and 9).

Table 2 Arylation of *tert*-butyl glyoxylate.[a]



entry	Ar =	yield/%	ee/%[b]
1		90	96 (S)
2		84	76
3		81	90
4		83	90
5		47	99
6		70	88
7		79	93
8		69	16
9		54	88[c]

[a] Reaction conditions: A mixture of glyoxylates (0.5 mmol), aryl boronic acid (1.0 mmol), KF (1.0 mmol), $RuCl_2(PPh_3)_3$ (2 mol%), and (*R*,*R*)-Me-BIPAM (2.2 mol%) in toluene (3 ml) and H_2O (0.3 ml) was stirred at 80 ˚C for 16 h. [b] The letter within the parentheses indicates the absolute configuration of the chiral center within the product. [c] $PMePh_2$ (2.2 mol%) was added

We propose a possible catalytic cycle of this reaction (Figure 1). The reaction may proceed through transmetalation of $[ArBF_n(OH)_{(3-n)}]K$ to a ruthenium(II) complex giving Ar–[Ru]. Insertion of the C–O double bond into the C–Ru bond, giving [Ru](OCH(Ar)$CO_2{}^t$Bu)Cl, can then undergo hydrolysis.[12]

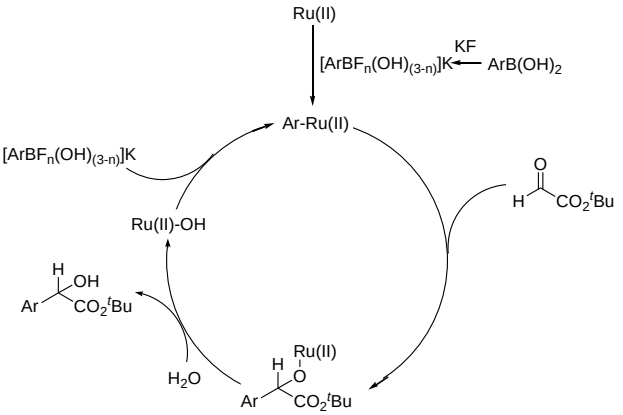
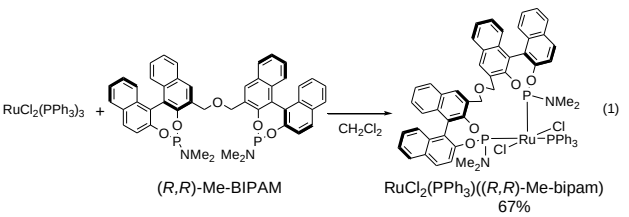


Figure 1 Proposed catalytic cycle

To determine the structure of the catalyst, we reacted $RuCl_2(PPh_3)_3$ with (*R*,*R*)-Me-BIPAM in CH_2Cl_2. This provided $RuCl_2(PPh_3)$((*R*,*R*)-Me-bipam) in 67% yield (eqn (1)). The ^{31}P NMR spectrum of this complex in toluene-d_8 showed an ABX pattern. The spectrum is consistent with two *cis*-phosphorus-phosphorus interactions and one *trans*-phosphorus-phosphorus interaction, the *trans* J_{pp} coupling constant being much greater than the *cis* J_{pp} coupling constant (29 ppm (*dd*, *J* = 30, 495 Hz), 153 ppm (*dd*, *J* = 73, 495 Hz), 170 ppm (*dd*, *J* = 30, 73 Hz)) (Figure 2).[16]



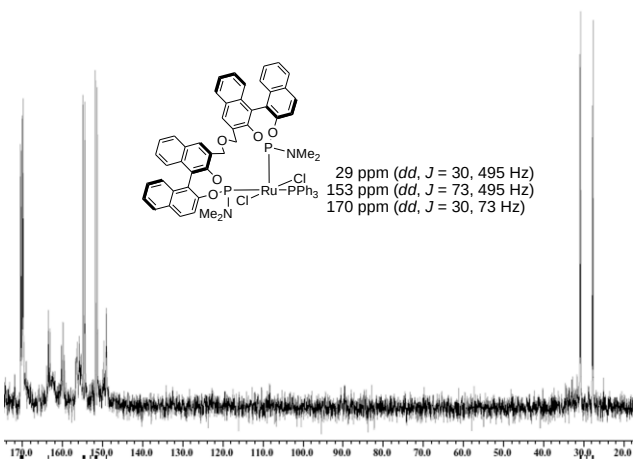
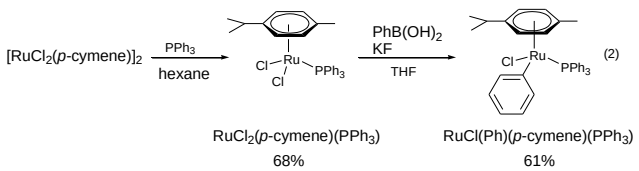


Figure 2 ^{31}P NMR of $RuCl_2(PPh_3)$((*R*,*R*)-Me-bipam)

The transmetalation between $RuCl_2(PPh_3)((R,R)$-Me-bipam) and $ArBF_n(OH)_{(3-n)}$ generated by the reaction of $ArB(OH)_2$ and KF may provide the arylruthenium(II) intermediate $RuCl(Ar)(PPh_3)((R,R)$-Me-bipam), which is analogous to a Ph–Cl exchange between $PhB(OH)_2$ and $[RuCl_2(p\text{-cymene})(PPh_3)]$.[17] Although isolation of the intermediate $RuCl(Ph)(PPh_3)((R,R)$-Me-bipam) failed, the reaction of phenylboronic acid and $RuCl_2(p$-cymene$)(PPh_3)$[18] in the presence of KF gave $RuCl(Ph)(p$-cymene$)(PPh_3)$ in 61% yield (eqn (2)).[17b,19] The enantioselectivity is determined at insertion of the C–O double bond into the C–Ru bond of $RuCl(Ar)(PPh_3)((R,R)$-Me-bipam) complex.



In conclusion, we have developed a $RuCl_2(PPh_3)_3/(R,R)$-Me-BIPAM catalyst as an efficient catalytic system for asymmetric addition of arylboronic acids to glyoxylate. With this catalyst system, optically active mandelic acids were easily prepared in up to 99% ee. To elucidate the enantioselection in the mechanism, characterization of the catalyst and the intermediate is in progress.

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