Transition metal-catalyzed addition reactions of arylboronic acids with alkyl 2-formylbenzoates: efficient access to chiral 3-substituted phthalides†‡

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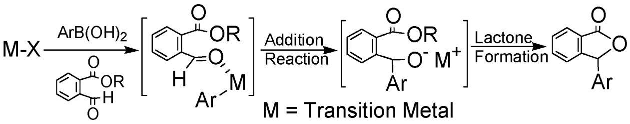
Received (in College Park, MD, USA) 18th January 2010, Accepted 18th February 2010
First published as an Advance Article on the web 25th March 2010
DOI: 10.1039/c001104e

Transition metal-catalyzed addition of arylboronic acids to 2-formylbenzoates afforded 3-substituted phthalides. By using SPINOL-based phosphites as ligands, a Rh(I)-catalyzed asymmetric version of such an addition reaction was achieved.

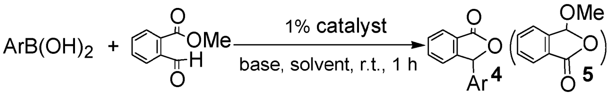
Chiral 3-substituted phthalides (1(3*H*)-isobenzofuranones) are useful molecules as valuable pharmacological compounds and are important building blocks for the synthesis of biologically active compounds.[1,2] Asymmetric synthesis of chiral 3-substituted phthalides have been explored and several methods have been developed.[1–4] Most successful strategies are the asymmetric reduction including catalytic and transfer hydrogenation reduction of the corresponding ketones and most recently reported Rh(I)-catalyzed asymmetric ketone hydroacylation.[4–6] Very recently, Cheng reported the Co-catalyzed asymmetric addition reaction of 2-halobenzoates with aldehydes to access chiral 3-substituted phthalides.[7]

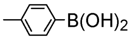
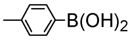
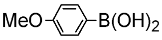
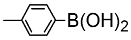
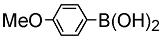
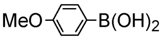
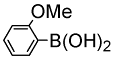
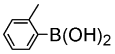
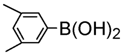
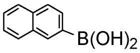
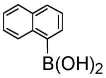
In recent years, transition metal-catalyzed addition reactions of arylboronic acids with aldehydes have become useful tools to access aryl alcohols.[8–11] In this context, we have recently documented Type **I** palladacycle-, platinacycle- and Rh(I)/diene-catalyzed addition reactions of arylboronic acids with carbonyl-containing compounds including aldehydes.[12–14] As 2-nitrobenzaldehyde and 2-methoxybenzaldehyde have been demonstrated to be excellent substrates, we reasoned that 2-formyl benzoates should also be suitable substrates for the addition reaction. Based on the consideration that the addition reactions could be combined with the lactone formation process (Scheme 1), we envisioned that the addition of arylboronic acids to 2-formylbenzoates might provide an efficient way for the preparation of 3-substituted phthalides. In this communication, we report our results, *i. e.*, transition metal-catalyzed addition reactions of arylboronic acids with alkyl 2-formylbenzoates to access 3-substituted phthalides, including an asymmetric version by using optically active Rh(I) catalysts.[15]



Scheme 1 Mechanistic consideration for transition metal-catalyzed addition reactions of arylboronic acids with 2-formylbenzoates to access 3-substituted phthalides.

Table 1 Transition metal-catalyzed addition reactions of phenylboronic acid with methyl 2-formylbenzoate



Entry	Catalyst	ArB(OH)$_2$	Solvent	Conv.[b] (%)
1	**1**	PhB(OH)$_2$	PhMe	100 (81)[c,d]
2	**2**	PhB(OH)$_2$	PhMe	100[d]
3	**3**	PhB(OH)$_2$	PhMe	100 (86)[d]
4	[Rh(C$_2$H$_4$)$_2$Cl]$_2$		THF	<2[e]
5	[Rh(COD)Cl]$_2$	PhB(OH)$_2$	THF	99 (91)
6	**2**		PhMe	(85)
7	**2**		PhMe	(88)
8	**3**		PhMe	(92)[d]
9	**3**		PhMe	(85)[d]
10	[Rh(COD)Cl]$_2$		THF	(93)
11	[Rh(COD)Cl]$_2$		THF	(91)
12	[Rh(COD)Cl]$_2$		THF	(90)
13	[Rh(COD)Cl]$_2$		THF	(81)
14	[Rh(COD)Cl]$_2$		THF	(80)
15	[Rh(COD)Cl]$_2$		THF	(88)

[a] *Reaction conditions*: aldehyde (1.0 equiv.), arylboronic acid (1.5 equiv.), toluene (2 mL)–K$_3$PO$_4$ (3 equiv.) or THF–K$_3$PO$_4$ (5 M) room temperature. [b] Conversion based on ^{1}H NMR. [c] In parenthesis: Isolated yields. [d] Reaction temperature: room temperature for **1** or **2**, and 80–90 °C for **3**, reaction time: 12 h. [e] **4** : **5** was observed in a ratio of 1 : 99.

Our study began with a test of the feasibility of the addition of phenylboronic acid to methyl 2-formylbenzoate by

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† This article is part of a ChemComm 'Catalysis in Organic Synthesis' web-themed issue showcasing high quality research in organic chemistry. Please see our website (http://www.rsc.org/Publishing/Journals/cc/cc09org_web_issue) to access the other papers in this issue.

‡ Electronic supplementary information (ESI) available: Experimental section and spectroscopic data. See DOI: 10.1039/c001104e

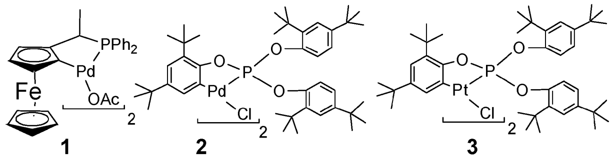
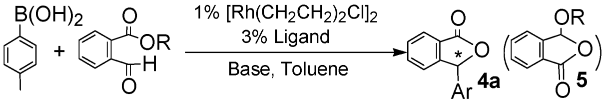


Fig. 1 Type **I** metalacycles.

Table 2 Rh(I)-Catalyzed addition reactions of *p*-tolyboronic acid to 2-formylbenzoates[a]



Entry	Ligand	R	Base	*T*/°C	Conv.[b] (%)	ee[c] (%)
1	**6**	Me	K_3PO_4	0	59[d]	—
2	**7**	Me	K_3PO_4-	0	99[e]	—
3	**8**	Me	K_3PO_4	rt	21[f]	—
4	**9**	Me	K_3PO_4	rt	40[g]	—
5	**10a**	Me	KF	0	5	—
6	**10a**	Me	K_3PO_4	rt	99[h]	56
7	**10b**	Me	K_3PO_4	rt	100[i]	68
8	**10c**	Me	K_3PO_4	rt	96[j]	51
9	**10d**	Me	K_3PO_4	rt	100	6
10	**10b**	Me	K_3PO_4	0	99[j]	77
11	**10b**	Me	K_3PO_4	−5	84[k]	75
12	**10b**	Me	K_3PO_4	−10	24	72
13	**10b**	Et	K_3PO_4	rt	100[l]	67
14	**10b**	CH_2Ph	K_3PO_4	rt	98[m]	—
15	**10b**	*n*-Bu	K_3PO_4	rt	85[n]	65

[a] *Reaction conditions*: aldehyde (1.0 equiv.), *p*-tolylboronic acid (1.5 equiv.), toluene (2 mL), K_3PO_4 (5 M) or KF (1.0–3.0 equiv.). [b] Conversion based on ^{1}H NMR. [c] Determined by HPLC (ChiralCel-OD column). [d] **4a** : **5** in a ratio of 25 : 75. [e] **4a** : **5** in a ratio of 65 : 35. [f] **4a** : **5** in a ratio of 1 : 99. [g] **4a** : **5** in a ratio of 12 : 88. [h] **4a** : **5** in a ratio of 77.5 : 22.5. [i] **4a** : **5** in a ratio of 88.5 : 11.5. [j] **4a** : **5** in a ratio of 91 : 9. [k] **4a** : **5** in a ratio of 88 : 12. [l] **4a** : **5** in a ratio of 86 : 14. [m] **4a** : **5** in a ratio of 17 : 83. [n] **4a** : **5** in a ratio of 96 : 4.

screening a number of transition metal catalysts that were available to us. Our results are listed in Table 1. We found Type **I** palladacycles **1** and **2**, platinacycle **3** (Fig. 1) efficiently catalyzed such addition (Table 1, entries 1–3). While $[Rh(C_2H_4)_2Cl]_2$ was an inefficient catalyst for the addition reaction, it catalyzed the formation of **5** in excellent yield (Table 1, entry 4). On the other hand, $[Rh(COD)Cl]_2$ was found to catalyze the addition reaction efficiently (Table 1, entry 5). We have further briefly employed the palladacycle **2**, platinacycle **3** and $[Rh(COD)Cl]_2$ as catalysts for the addition of different arylboronic acids. We found that high yields were observed for all arylboronic acids tested (Table 1, entries 6–15).

We next turned our attention to the asymmetric version of the addition reaction. We selected Rh(I) complexes for our study because the catalytic activity and enantioselectivity of the catalyst systems could be readily altered by using a number of readily available ligands. Our results are listed in Table 2 for the chiral ligands (Fig. 2). We found ligand **6**[16] and chiral diene **7**[17] gave low yields of the addition products (Table 2, entries 1 and 2). 1,1′-Bi-2-naphthyl-based monodentate ligands **8**[18] and **9** gave low conversions (Table 2, entries 3 and 4). We also tested 1,1′-spirodiindane-7,7′-diol (SPINOL)-based monophosphites. Although Rh(I)/**10a** was not an effective catalyst when using Zhou's protocol (KF, toluene–H_2O 1 : 1),[19] it efficiently catalyzed the addition reaction with K_3PO_4 as base. We have also examined other SPINOL-based phosphites **10b–d** and found **10b** exhibited the highest activity and best enantioselectivity (Table 2, entries 5–9). With **10b** as the ligand, we examined other factors that could influence the enantioselectivity. We found that decreasing the reaction temperature from room temperature to 0 °C improved the enantioselectivity from 68 to 77% (Table 2, entries 6 and 10). Further decreasing the reaction temperature did not affect the enantioselectivity, rather it slowed down the reaction (Table 2, entries 10–12). We have also varied the alkyl groups in the 2-formylbenzoates, finding that methyl formylbenzoate gave the best enantioselectivity (Table 2, entries 12, 13–15).

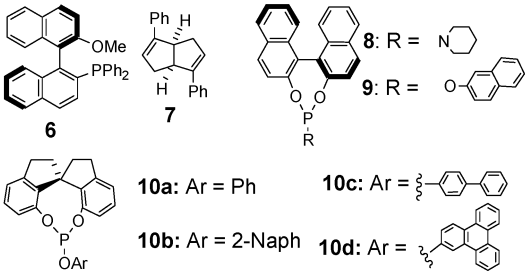
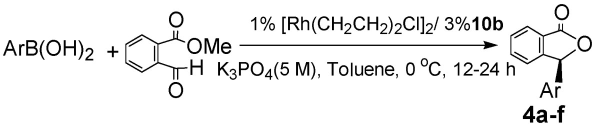
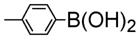
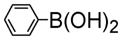
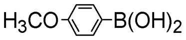
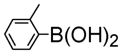
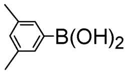
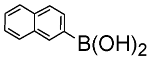


Fig. 2 Chiral ligands.

We have examined different arylboronic acids for the asymmetric addition reaction. We found optically active 3-substituted phthalides were obtained in good yields and enantioselectivity (Table 3). In addition, we found that the enantiopurity of the formed products could be improved by recrystallization. For example, the enantiopurity of **4f** can be improved from 83 to 98% ee after recrystallization.

Table 3 Asymmetric addition reactions of arylboronic acids with methyl 2-formylbenzoate[a]



Entry	$ArB(OH)_2$	Product	Yield[b] (%)	ee[c] (%)
1		**4a**	85	77
2		**4b**	94	71
3		**4c**	93	67
4		**4d**	85	63
5		**4e**	59	66.5
6		**4f**	69	83[d]

[a] *Reaction conditions*: aldehyde (1.0 equiv.), arylboronic acid (1.5 equiv.), toluene (2 mL), K_3PO_4 (1.0–3.0 equiv.), 0 °C. [b] Isolated yields. [c] Determined by HPLC (Chiralcel-OD column). See Supplementary Information for the optical rotation data. [d] CH_2Cl_2 as the solvent.

In summary, we have demonstrated that the addition reaction of arylboronic acids with 2-formylbenzoates to form 3-substituted phthalides can be efficiently catalyzed by transition-metal catalysts including Type **I** palladacycles, platinacycle and Rh(I) catalysts. By using SPINOL-based phosphites as ligands, a Rh(I)-catalyzed asymmetric version of such an addition reaction has been realized and up to 83% ee was achieved. Our study provides an efficient method to synthesize chiral 3-substituted phthalides. Our future work will be directed to improve the enantioselectivity[20] and to explore its application for the preparation of biologically important compounds.

We gratefully thank the NSF (CHE0719311) for funding. Partial support from PSC-CUNY Research Award Program is also gratefully acknowledged. We also thank Frontier Scientific, Inc. for its generous gifts of arylboronic acids.

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