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Rhodium-catalyzed Michael addition of arylboronic acids to 3-alkylenyloxindoles: asymmetric synthesis of functionalized oxindoles

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ABSTRACT

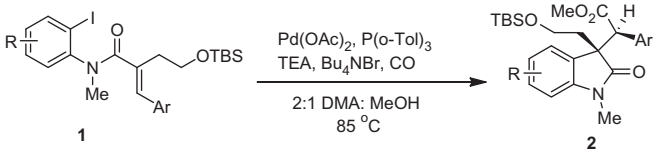
The rhodium-catalyzed diastereo- and enantioselective Michael addition of arylboronic acids to 3-alkylenyloxindoles has been developed with (*R*)-binap as a ligand. A wide variety of the desired functionalized oxindoles are smoothly obtained in high yields (up to 99%) with high enantioselectivities (up to 92% ee) and good diastereoselectivities (up to 82:18).

Introduction

3-Substituted oxindoles constitute one of the most important building blocks in organic synthesis, and this structural unit is encountered in many biologically active compounds.[1] Owing to its importance, many efficient approaches for their construction have been developed.[2–5] Among these available methods, 3-alkylenyloxindoles as Michael acceptors have been widely used in the synthesis of functionalized oxindoles in asymmetric organocatalysis.[4] However, the transition-metal catalyzed conjugated addition of 3-alkylenyloxindoles has been less studied.[5]

In 2003, Weinreb and co-workers reported the synthesis of some special functionalized oxindoles **2** via a halogen-selective tandem intramolecular Heck/carbonylation reaction (Scheme 1).[6] These compounds are valuable intermediates in the synthesis of the marine ascidian metabolite perophoramidine and fungal metabolite communesin F.[6,7] However, racemic oxindoles **2** limited the opportunity to obtain those optically pure natural products. Thus, the exploration of efficient approaches to access enantioenriched oxindoles **2** and their similar structures is desirable.

Pioneered by Miyaura and Hayashi,[8] asymmetric rhodium catalyzed conjugate addition of organometallic reagents to Michael acceptors has become a fascinating tool for the construction of many useful heterocycles.[9e–i] Several Michael acceptors such as α,β-unsaturated ketones, esters, amides, 1-alkenylphosphonates, nitroalkenes and other electron deficient olefins have been extensively investigated in rhodium-catalyzed asymmetric conjugate reaction.[9] To the best of our knowledge, the use of 3-alkylenyloxindoles as Michael acceptors in Rh-catalyzed 1,4-addition is still unexplored. As a part of our continuing interests in the construction of useful chiral building blocks via transition metal-catalyzed asymmetric reactions,[10] and to develop a new strategy to access oxindole **2** analogues, herein we would like to report a rhodium-catalyzed diastereo- and enantioselective Michael addition of arylboronic acids to 3-alkylenyloxindoles.



Scheme 1. The catalytic synthesis of functionalized oxindoles.

Result and discussion

Initially, (*E*)-ethyl 2-(1-benzyl-2-oxoindolin -3-ylidene) acetate **3a**[11] was employed as the starting substrate to examine the reaction conditions. In the presence of KOH at 100 °C, 5 mol % of (*R*)-binap-Rh complex could efficiently catalyze the addition of phenyl boronic acid to **3a**. The desired product **5a** was obtained in a 92%

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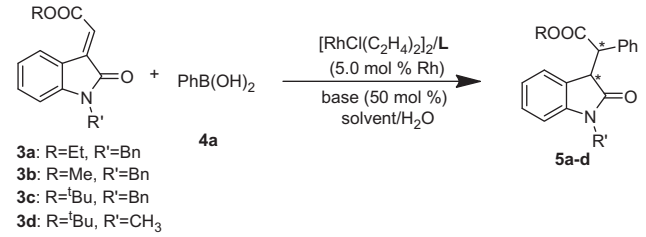
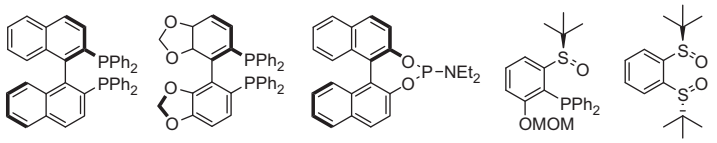
Table 1
Screening of various reaction conditions[a]





Entry	Substrate	Ligand	Solvent	Base	Temp (°C)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**3a**	**L1**	Dioxane	KOH	100	92	77/23	78/83
2	**3a**	**L2**	Dioxane	KOH	100	89	77/23	77/77
3	**3a**	**L3**	Dioxane	KOH	100	90	77/23	78/83
4	**3a**	**L4**	CH_2Cl_2	KOH	40	40	53/47	37/80
5	**3a**	**L5**	CH_2Cl_2	KOH	40	Trace	n.d.	n.d.
6	**3b**	**L1**	Dioxane	KOH	100	95	77/23	76/77
7	**3c**	**L1**	Dioxane	KOH	100	95	71/29	83/82
8	**3d**	**L1**	Dioxane	KOH	100	92	66/34	80/76
9	**3c**	**L1**	Toluene	KOH	100	Trace	n.d.	n.d.
10	**3c**	**L1**	THF	KOH	65	40	87/13	83/82
11	**3c**	**L1**	DMF	KOH	75	10	68/32	70/74
12	**3c**	**L1**	$ClCH_2CH_2Cl$	KOH	75	15	66/34	78/85
13	**3c**	**L1**	^tBuOH	KOH	75	80	74/26	72/76
14	**3c**	**L1**	EtOH	KOH	75	83	89/11	80/74
15	**3c**	**L1**	Dioxane	K_2CO_3	100	95	71/29	82/82
16	**3c**	**L1**	Dioxane	KF	100	90	70/30	81/81
17	**3c**	**L1**	Dioxane	K_3PO_4	100	94	73/27	83/82
18	**3c**	**L1**	Dioxane	Et_3N	100	56	79/21	81/86
19	**3c**	**L1**	Dioxane	KOH	40	98	76/24	88/89
20	**3c**	**L1**	Dioxane	KOH	25	93	75/25	88/89
21[e]	**3c**	**L1**	Dioxane	KOH	40	96	75/25	88/89

[a] Reaction conditions: **3** (0.2 mmol), $PhB(OH)_2$ (0.6 mmol), $[Rh(C_2H_4)_2Cl]_2$ (5.0 mol %), ligand (6.0 mol %), and base (1.0 M, 0.1 mL) in 1.0 mL solvent, 10 h.
[b] Isolated yield.
[c] Determined by chiral HPLC or ^1H NMR of the crude material.
[d] The ee values were determined by chiral HPLC.
[e] 2.5 mol % of Rh was used.

yield with a 77:23 diastereomeric ratio, as well as 78% and 83% ee for each isomer (Table 1, entry 1). Other chiral phosphorus ligands like (*R*)-segphos **L2** or **(***R***)-**phosphoramidite **L3** could get the similar results, but there was no improvement of the yield or stereoselectivities (Table 1, entry 2 and 3). Considering chiral sulfoxides were promising ligands in Rh-catalyzed 1,4-addition reactions, chiral *tert*-butanesulfinylphosphine (*R*)-**L4**[10a] and (*R,R*)-1,2-bis(*tert*-butylsulfinyl)benzene (*R,R*)-**L5**[10b] were also evaluated, but turned out to be the great loss of the activities (Table 1, entries 4 and 5). As a whole, (*R*)-binap was the best ligand we tested for this reaction. In the following, the influence of substituent *R* on the ester group of **3** was investigated. Methyl ester **3b** afforded the corresponding product in a 95% yield with a 77: 23 diastereomeric ratio, and a slightly decreased ee of 76% and 77%, respectively (Table 1, entry 6). Meanwhile, for the *tert*-butyl ester **3c**, the corresponding adduct was obtained with a 95% yield, 71:29 *dr*, and 83% ee of the major diastereomer (Table 1, entry 7). Furthermore, when the N-protecting group was changed to methyl from Bn group, the diastereoselectivity and the ees were slightly decreased (Table 1, entry 8, a 92% yield, 66:34 *dr*, 80% ee for the major diastereomer and 76% ee for minor diastereomer). Various solvents were surveyed (Table 1, entries 9–14) and dioxane was the best solvent for this reaction. Inorganic bases such as K_2CO_3, KF and K_3PO_4 showed no significant difference compared with KOH (Table 1, entries 14–16), and obviously, organic base (triethylamine) is harmful to the reaction (Table 1, entry 18). We found that enantioselectivities can be promoted to 88% and 89% ee when the temperature was decreased to 40 °C, and no additional advantage under lower temperature at 25 °C. In addition, reducing the catalyst loading to 2.5% of Rh showed no influence on ee and the yield decreased slightly (Table 1, entries 19–21).

With the optimal reaction conditions in hand, the substrate scope was next investigated and the results are summarized in Table 2.[12] Arylboronic acids with different substituents, including electron-rich and electron-poor, as well as *meta*- and *para*-groups, reacted smoothly with 3-alkylenyloxindoles **3c** to generate products **5c**–**5k** with high yields (96–99%), high enantioselectivities (83–92%) and moderate *dr* values (up to 76: 24 *dr*, Table 2, entries 1–8). Disappointingly, the *ortho*-substituted arylboronic acids (such as 1-methyl- and 1-methoxy-phenylboronic acid) failed to react with **3c**. On the other hand, 3-alkylenyloxindoles bearing substituents on 5-position could also be phenylated efficiently under these conditions, indicating traceless electronic influences of oxindole block (Table 2, entries 9-10). However, 4-Br- 3-alkylenyloxindole demonstrated moderate *dr* and ee (Table 2, entry 11). In the end, when the substituent R^3 on **3** was not ester but methyl