



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

Xiangyang Zhang^{a,b,c}, Guihua Chen^{a,b,c}, Peng Cao^a, Jibing Liu^{a,b,c}, Jian Liao^{a,b,*}

^a Natural Products Research Center, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, PR China

^b Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, PR China

^c Graduate School of Chinese Academy of Sciences, Beijing 100049, PR China

ARTICLE INFO

Article history:

Received 1 July 2011

Revised 4 November 2011

Accepted 15 November 2011

Available online 19 November 2011

Keywords:

3-Alkylenyloxindoles

Functionalized oxindoles

Arylboronic acids

Michael addition

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).

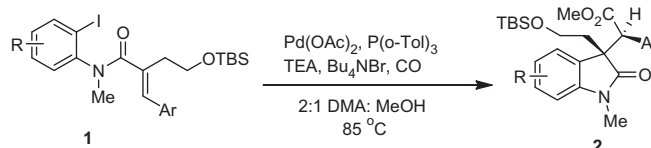
© 2011 Elsevier Ltd. All rights reserved.

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 Miyauchi 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,



Scheme 1. The catalytic synthesis of functionalized oxindoles.

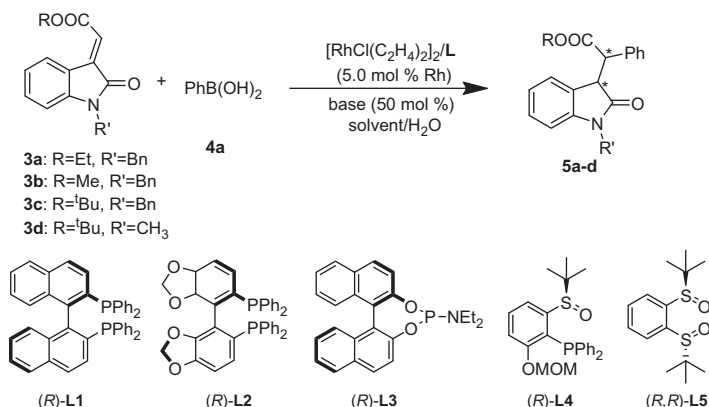
nitroalkenes and other electron deficient olefins have been extensively investigated in rhodium-catalyzed asymmetric conjugate reaction.⁹ To the best of our knowledge, the use of 3-alkylenyloxindoles as Michael acceptors in Rh-catalyzed 1,4-addition is still unexplored. As a part of our continuing interests 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.

Result and discussion

Initially, (*E*)-ethyl 2-(1-benzyl-2-oxindolin-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%

* Corresponding author.

E-mail addresses: jliao10@cioc.ac.cn, jliao@cib.ac.cn (J. Liao).

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 ₂ Cl ₂	KOH	40	40	53/47	37/80
5	3a	L5	CH ₂ Cl 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 ₂ CH ₂ Cl	KOH	75	15	66/34	78/85
13	3c	L1	^t BuOH	KOH	75	80	74/26	72/76
14	3c	L1	EtOH	KOH	75	83	89/11	80/74
15	3c	L1	Dioxane	K ₂ CO ₃	100	95	71/29	82/82
16	3c	L1	Dioxane	KF	100	90	70/30	81/81
17	3c	L1	Dioxane	K ₃ PO ₄	100	94	73/27	83/82
18	3c	L1	Dioxane	Et ₃ N	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(C₂H₄)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 K₂CO₃, KF and K₃PO₄ 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 R³ on **3** was not ester but methyl

Table 2
Asymmetric conjugate addition of arylboronic acids to 3-alkylenyloxindoles^a

Entry	Product	Yield ^b (%)	dr ^c	ee ^d (%)
1		5c 98	76/24	88/89
2		5e 98	70/30	88/87
3		5f 97	70/30	86/83
4		5g 98	67/33	86/83
5		5h 98	75/25	88/89
6		5i 99	71/29	88/88
7		5j 97	69/31	90/92
8		5k 96	75/25	91/91
9		5l 99	78/22	78/81

Table 2 (continued)

Entry	Product	Yield ^b (%)	dr ^c	ee ^d (%)
10		5m 96	82/18	78/84
11 ^e		5n 86	66/34	50/52
12		5o Trace	n.d.	n.d.

^a Reaction conditions: substrate **3** (0.2 mmol), ArB(OH)₂ (0.6 mmol), [Rh(C₂H₄)₂Cl]₂ (5.0 mol % Rh), (R)-BINAP (6.0 mol %), and KOH (1.0 M, 0.1 mL) in 1.0 mL dioxane.

^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 The reaction time is 20 h.

group, only a trace amount of the desired product was obtained (Table 2, entry 12).

Conclusion

In summary, we have disclosed the rhodium-catalyzed diastereo- and enantioselective Michael addition of arylboronic acids to 3-alkylenyloxindoles. The corresponding adducts are obtained in high yields (up to 99%) with high enantioselectivities (up to 92% ee) and good diastereoselectivities (up to 82:18). The present reaction provides a simple approach to synthesize optically active functionalized oxindole derivatives. The further transformations and applications in the key synthetic scaffolds in medicinal chemistry are underway in our laboratory.

Acknowledgments

We are grateful for support from the NSFC (21072186 and 20872139), the West Light Foundation of Chinese Academy of Sciences, and the National Basic Research Program of China (973 Program, 2010CB833300) and Chengdu Institute of Biology, Chinese Academy of Sciences (Y0B1051100).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.071.

References and notes

- For selected examples about the skeleton of oxindoles see: (a) Rasmussen, H. B.; MacLeod, J. K. *J. Nat. Prod.* **1997**, 60, 1152; (b) da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, 12, 273; (c) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2002**, 19, 148; (d) Jensen, B. S. *CNS Drug Rev.* **2002**, 8, 353; (e) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209; (f) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, 42, 36; (g) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, 46, 8748; (h) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, 352, 1381.

2. For selected examples about the preparation of functionalized oxindoles in organocatalytic asymmetric reactions, see: (a) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, 42, 3921; (b) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, 70, 7418; (c) Bella, M.; Kobbelaar, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, 127, 3670; (d) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, 128, 925; (e) Ogawa, S.; Shibata, N.; Inagaki, J.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2007**, 46, 8666; (f) Nakamura, S.; Hara, N.; Nakashima, H.; Kubo, K.; Shibata, N.; Toru, T. *Chem.-Eur. J.* **2008**, 14, 8079; (g) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, 47, 4157; (h) Tian, X.; Jiang, K.; Peng, J.; Du, W.; Chen, Y.-C. *Org. Lett.* **2008**, 10, 3583; (i) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, 10, 1593; (j) Duffey, T. A.; Shaw, S. A.; Vedejs, E. *J. Am. Chem. Soc.* **2009**, 131, 14; (k) Jiang, K.; Peng, J.; Cui, H. L.; Chen, Y.-C. *Chem. Commun.* **2009**, 3955; (l) Qian, Z.-Q.; Zhou, F.; Du, T.-P.; Wang, B.-L.; Ding, M.; Zhao, X.-L.; Zhou, J. *Chem. Commun.* **2009**, 6753; (m) Cheng, L.; Liu, L.; Jia, H.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2009**, 74, 4650; (n) Galzerano, P.; Bencivenni, G.; Pescioli, F.; Mazzanti, A.; Giannichi, B.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem.-Eur. J.* **2009**, 15, 7846; (o) He, R.; Ding, C.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, 48, 4559; (p) Li, X.; Xi, Z.-G.; Luo, S.; Cheng, J.-P. *Org. Biomol. Chem.* **2010**, 8, 77; (q) Li, X.; Zhang, B.; Xi, Z.-G.; Luo, S. Z.; Cheng, J.-P. *Adv. Synth. Catal.* **2010**, 352, 416.
3. For selected examples about the preparation of functionalized oxindoles in transition-metal-catalyzed asymmetric reactions, see: (a) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, 127, 10164; (b) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, 8, 2027; (c) Toullec, P. Y.; Jagt, R. B. C.; De Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2006**, 8, 2715; (d) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, 45, 3353; (e) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, 128, 16488; (f) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kündig, E. P. *Chem. Commun.* **2008**, 4040; (g) Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, 131, 6946; (h) Shintani, R.; Takatsu, K.; Hayashi, T. *Chem. Commun.* **2010**, 46, 6822; (i) Hanhan, N. V.; Sahin, A. H.; Chang, W.; Fetting, J. C.; Franz, A. K. *Angew. Chem., Int. Ed.* **2010**, 49, 744; (j) Trost, B. M.; Czabaniuk, L. C. *J. Am. Chem. Soc.* **2010**, 132, 15534.
4. (a) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, 122, 5666; (b) Bencivenni, G.; Wu, L.; Mazzanti, A.; Giannichi, B.; Pescioli, F.; Song, M.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, 48, 7200; (c) Chen, X.; Wei, Q.; Luo, S.; Xiao, H.; Gong, L. *J. Am. Chem. Soc.* **2009**, 131, 13819; (d) Wei, Q.; Gong, L. *Org. Lett.* **2010**, 12, 1008; (e) Jiang, K.; Jia, Z.; Yin, X.; Wu, L.; Chen, Y. *Org. Lett.* **2010**, 12, 2766; (f) Jiang, K.; Jia, Z.; Chen, S.; Wu, L.; Chen, Y. *Chem. - Eur. J.* **2010**, 16, 2852; (g) Tan, B.; Candeias, N. R.; Barbas, C. F., III *J. Am. Chem. Soc.* **2011**, 133, 4672.
5. (a) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, 129, 12396; (b) Trost, B. M.; Cramer, N.; Bernsmann, H. *J. Am. Chem. Soc.* **2007**, 129, 3086.
6. Artman, G. D., III; Weinreb, S. M. *Org. Lett.* **2003**, 5, 1523.
7. (a) Seo, J. H.; Artman, G. D., III; Weinreb, S. M. *J. Org. Chem.* **2006**, 71, 8891; (b) Evans, M. A.; Sacher, J. R.; Weinreb, S. M. *Tetrahedron* **2009**, 65, 6712; (c) Liu, P.; Seo, J. H.; Weinreb, S. M. *Angew. Chem., Int. Ed.* **2010**, 49, 2000; (d) Seo, J. H.; Liu, P.; Weinreb, S. M. *J. Org. Chem.* **2010**, 75, 2667.
8. Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, 120, 5579.
9. For selected examples about Michael acceptors in the rhodium-catalyzed asymmetric conjugate addition reactions, see: (a) Hayashi, T. *Synlett* **2001**, 879; (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, 103, 2829; (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, 103, 169; (d) Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, 431; (e) Hayashi, T. *Pure Appl. Chem.* **2004**, 76, 465; (f) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, 39, 2093; (g) Wang, Z. G.; Feng, C. G.; Zhang, S. S.; Xu, M. H.; Lin, G. Q. *Angew. Chem., Int. Ed.* **2010**, 49, 5780; (h) Pattison, G.; Piroux, G.; Lam, H. W. *J. Am. Chem. Soc.* **2010**, 132, 14373; (i) Shao, C.; Yu, H. J.; Wu, N. Y.; Tian, P.; Wang, R.; Feng, C. G.; Lin, G. Q. *Org. Lett.* **2011**, 13, 788.
10. (a) Lang, F.; Li, D.; Chen, J. M.; Chen, J.; Li, L. C.; Cun, L. F.; Zhu, J.; Deng, J. G.; Liao, J. *Adv. Synth. Catal.* **2010**, 352, 843; (b) Chen, J.; Chen, J. M.; Lang, F.; Zhang, X. Y.; Cun, L. F.; Zhu, J.; Deng, J. G.; Liao, J. *J. Am. Chem. Soc.* **2010**, 132, 4552; (c) Han, F. Z.; Chen, J.; Zhang, X. Y.; Liu, J. B.; Cun, L. F.; Zhu, J.; Deng, J. G.; Liao, J. *Tetrahedron Lett.* **2011**, 52, 830; (d) Zhang, X. Y.; Chen, J.; Han, F. Z.; Cun, L. F.; Liao, J. *Eur. J. Org. Chem.* **2011**, 1443; (e) Lang, F.; Chen, G. H.; Li, L. C.; Xing, J. W.; Han, F. Z.; Cun, L. F.; Liao, J. *Chem. - Eur. J.* **2011**, 17, 5242.
11. 3-Alkylenyloxindoles **3** were prepared according to the following reported procedure: (a) Ammetto, I.; Gasperi, T.; Antonietta Loreto, M.; Migliorini, A.; Palmarelli, F.; Antonio Tardella, P. *Eur. J. Org. Chem.* **2009**, 6189; (b) Rossiter, S. *Tetrahedron Lett.* **2002**, 43, 4671; (c) López-Alvarado, P.; Avendaño, C. *Synthesis* **2002**, 104.
12. General procedure for enantioselective rhodium-catalyzed addition of arylboronic acids to 3-Alkylenyloxindoles: Under an argon atmosphere and at room temperature, to a 10 mL Schlenk tube with a teflon cap was added ligand (*R*)-binap (7.5 mg, 6.0 mol %), [RhCl(C₂H₄)₂]₂ (1.9 mg, 5.0 mol % Rh) and 1.0 mL dioxane. The mixture was stirred at 25 °C for 40 min, and then arylboronic acids (0.6 mmol, 3.0 equiv), substrate **3** (0.2 mmol) and degassed aq. KOH (1.0 M, 0.1 mL, 0.1 mmol) was added sequentially. The mixture was stirred for appropriate time at 40 °C and directly charged onto a column (silica gel) for flash chromatography with a mixture of Petroleum ether/EtOAc to afford product **5**.