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Efficient Syntheses of Korupensamines A, B and Michellamine B by Asymmetric Suzuki-Miyaura Coupling Reactions

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Supporting Information

ABSTRACT: Efficient asymmetric Suzuki-Miyaura coupling reactions are employed for the first time in total syntheses of chiral biaryl natural products korupensamine A and B in combination with an effective diastereoselective hydrogenation, allowing ultimately a concise and stereoselective synthesis of michellamine B. Chiral monophosphorus ligands **L1**−**3** are effective for the syntheses of a series of functionalized chiral biaryls by asymmetric Suzuki-Miyaura coupling reactions in excellent yields and enantioselectivities (up to 99% ee). The presence of a polar-π interaction between the highly polarized BOP group and the extended π system of arylboronic acid coupling partner is believed to be important for the high enantioselectivity.

Michellamine B (**1**),[1] originally isolated from tropical liana *Ancistrocladus korupensis* in Cameroon, has gained significant interest as a strong *anti*-HIV-1 and *anti*-HIV-2 agent (Figure 1). Structurally, it derives from heterodimerization of

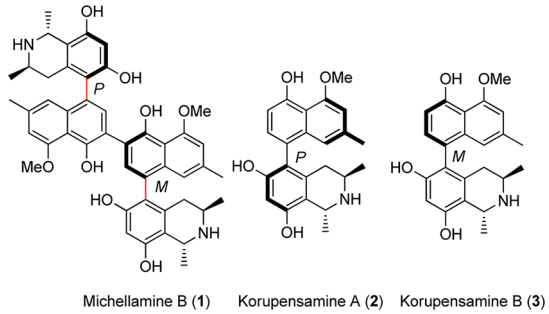

Figure 1. Axially chiral biaryl natural products.

antimalarial atropdiastereomeric natural products korupensamine A (**2**) and korupensamine B (**3**).[2] Due to their interesting biological activities and unique molecular architectures containing both axial and central chirality, there has been considerable study[3] toward diastereoselective syntheses of **2** or **3** led by Bringmann,[4a−c] Lipshutz,[4d,e] Uemura,[4f,g] and Hoye.[4h−k] Notable strategies in constructing the axial chirality include kinetic asymmetric transformation of "lactone",[5] atropselective intermoleculare biaryl coupling,[4e] and chiral chromium complexes.[6] Despite these methods, an efficient route for catalytic asymmetric syntheses of both **2** and **3** is still lacking. Consequently, a concise and stereoselective synthesis of **1** is yet to be reported.

While various methods for constructing chiral biaryls are available including chiral auxiliaries,[7] asymmetric transformations of "pro-chiral" biaryls,[5,8] asymmetric aryl formations,[9] asymmetric oxidative homocouplings,[10] the catalytic asymmetric cross-couplings,[11] particularly Suzuki-Miyaura couplings,[12] remains one of most attractive and versatile methods due to its mild reaction conditions, the ability of tolerating various functionalities, and the availability and nontoxic nature of starting materials. Despite the recent advances in this field, the current substrate scope of asymmetric Suzuki-Miyaura couplings remains very narrow. Limited results were achieved on substrates with synthetically interesting functionalities. To our knowledge, efficient asymmetric Suzuki-Miyaura coupling is yet to be applied in natural product syntheses. In addition, most current methods still suffer from high catalyst loadings and prolonged reaction time. We herein report an asymmetric Suzuki-Miyaura coupling methodology for chiral *ortho*-biaryl-ol derivatives with chiral monophophorus ligands (Figure 2) and applications in total synthesis of **1**−**3**.

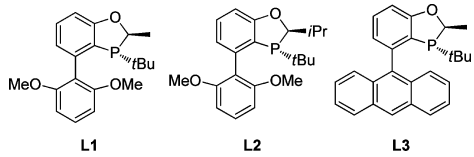

Figure 2. Chiral monophosphorus ligands.

Although enantioselective Suzuki-Miyaura couplings are achieved on a few functionalized substrates with alkoxy,[12e,f] phosphonate,[12a,h,i] bulky amides,[12b] and carbonylbenzooxazolidinone[13] at *ortho* positions, it is particularly important to develop a highly efficient method for synthesizing chiral *ortho*-hydroxyl biaryls because such structures exist ubiquitously in numerous natural products. We thus focused on developing efficient asymmetric Suzuki-Miyaura couplings of aryl halides with an *ortho*-OPG group. Our previous work[13] on asymmetric Suzuki-Miyaura coupling with a Pd-**L1** catalyst showed the importance of a second interaction between two coupling partners for high enantioselectivity. We thus exploited this strategy to explore the enantioselective Suzuki-Miyaura couplings between O-protected

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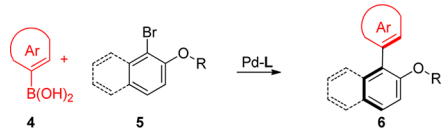
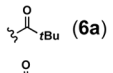
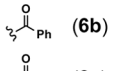
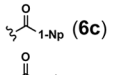
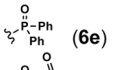
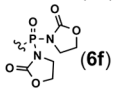
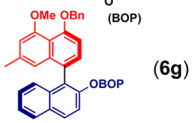
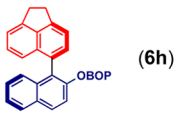
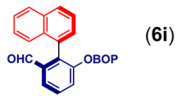
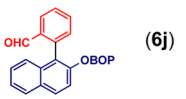
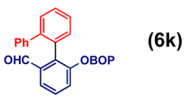
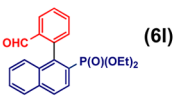
1-bromonaphthalen-2-ol and naphthalen-1-ylboronic acid. The reactions were carried out under nitrogen in toluene/water (5/1 v/v) with K_3PO_4 as the base at 30−35 °C for 12 h (Table 1). It was found that the PG group exerts a significant impact on the enantioselectivity. While excellent yields (90−97% yield) were all obtained with various PG groups, only medium ee's (65−74%) were achieved with -CO*t*Bu, -COPh, -CO(1-Np), and -P(O)Ph_2 groups (entries 1−3, 5). The carbonyl-oxazolidinone protection also led to only 65% ee (entry 4). Interestingly, an excellent enantioselectivity (94% ee) was achieved when a bis(2-oxo-3-oxazolidinyl)phosphinyl (BOP) protection was applied (entry 6). Further employment of the new ligand **L2**, with an isopropyl group on the top aryl ring, led to the coupling product **6f** in an almost perfect ee (99%). Exploration of the substrate scope found that this protocol is tolerable with various substituents and functionalities on both coupling partners (entries 8−13). A variety of chiral functionalized biaryls could be efficiently synthesized in excellent ee's and yields under mild conditions by using these chiral monophosphorus ligands.

Table 1. Asymmetric Suzuki-Miyaura Coupling



4 5 6

entry[a]	product[b]	L*	yield (%)	ee (%)
1	 (**6a**)	**L1**	97	72
2	 (**6b**)	**L1**	95	76
3	 (**6c**)	**L1**	96	76
4	(**6d**)	**L1**	90	65
5	 (**6e**)	**L1**	97	72
6	 (**6f**)	**L1**	95	94
7	(BOP)	**L2**	96	99
8	 (**6g**)	**L2**	95	93
9	 (**6h**)	**L2**	94	92
10	 (**6i**)	**L2**	98	91
11	 (**6j**)	**L1**	95	90[c]
12	 (**6k**)	**L1**	91	90
13	 (**6l**)	**L3**	95	95[d]

[a]Conditions unless otherwise specified: 1.0 equiv of aryl bromide, 1.5 equiv of boronic acid, 1 mol % $Pd(OAc)_2$, 1.2 mol % of chiral ligand, 3 equiv of K_3PO_4, toluene/H_2O (5/1, v/v), rt, 4−12 h, isolated yield, enantiomeric excesses were determined by chiral HPLC on a chiralcel OD-H or chiralPak AD-H column. [b]The absolute configurations of **6a−f** were determined by conversion to 1,1′-binaphthalen-2-ol and by comparison of their optical rotations to reported data. The absolute configurations of **6g−i** were assigned by analogy. The absolute configurations of **6j−l** were not determined. [c]*t*BuOH/H_2O (4/1, v/v) was employed the solvent and K_2CO_3 was used as the base. [d]*t*BuOH/H_2O (4/1, v/v) was employed the solvent.

We attributed to a possible noncovalent interaction between two coupling partners for the high stereoselectivity. The sharp increase of enantioselectivity from OP(O)Ph_2 (entry 5) to OBOP (entry 6) functionality indicated the important effect posed by the oxazolidinone moieties in BOP. Observation from its substrate scope showed the necessity of an extended π system of arylboronic acid for the high enantioselectivity. For example, excellent enantioselectivities were achieved with 1-naphthylboronic acid, 2-formylphenylboronic acid, and *ortho*-phenylphenylboronic acid as shown in Table 1. In contrast, a poor selectivity (20% ee) was observed with 2-methylphenylboronic acid. It was thus proposed the presence of a significant polar-π interaction[14,15] between the highly polarized BOP group and the extended π system of the boronic acid partner during reductive elimination step (Figure 3).

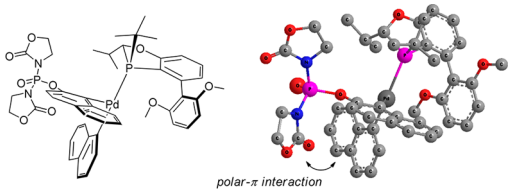


Figure 3. A proposed model of Pd(II)-**L2** catalyst for the synthesis of **6f** during the reductive elimination step.

The facile construction of a series of functionalized chiral biaryls under mild conditions by using this methodology prompted us to pursue the syntheses of both **2** and **3** through catalytic asymmetric Suzuki-Miyaura couplings. Because of the diastereomeric nature of **2** and **3** containing both axial chirality and central carbon chirality, a key challenge is to install the chiral elements in highly selective fashion and without interfering with each other. Our strategy is to construct the axial chirality using the developed asymmetric Suzuki-Miyaura coupling methodology followed by asymmetric hydrogenation to furnish the chiral tetrahydroisoquinoline moiety (Scheme 1).[16] Thus, diol **7** was sequentially protected with TBS and BOP followed by bromination to provide **8**. Asymmetric Suzuki-Miyaura coupling of **8** with arylboronic acid **14**[17] in the presence of 1 mol % $Pd(OAc)_2$ and 1.2 mol % **L2** in toluene/water at 35 °C for 8 h provided the coupling product **9** in 96% yield and 93% ee at a gram scale. Subsequent basic removal of both BOP and TBS groups followed by benzyl protection yielded **10**, which was further transformed to enamide **11** through nitroaldol and reductive acetylation.[18] Asymmetric hydrogenation of **11** with a Rh-WingPhos catalyst developed in our group[19] unfortunately led to the formation of **12** at a low d.r. ratio (2:1). A Rh-MeO-BIBOP catalyst[20] also provided a mediocre ratio (3:1). Further engineering of the hydrogenation catalyst led to the development of **L4**[21] with a chiral bisphosphoindole structure, providing **12** at a good d.r. ratio of 92:8 in 99% overall yield. Subsequent

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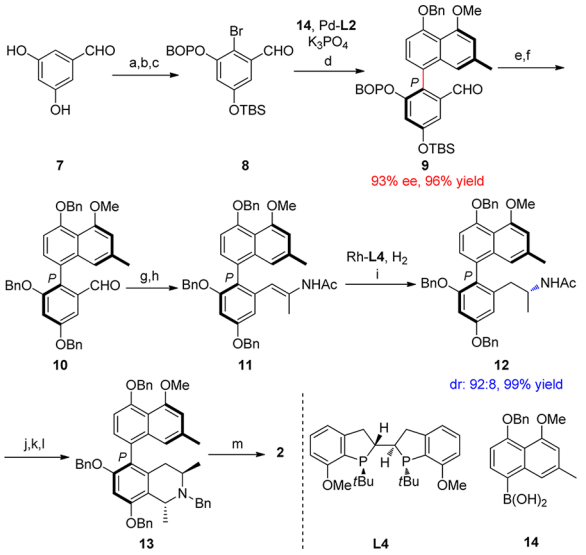
Scheme 1. Syntheses of 2



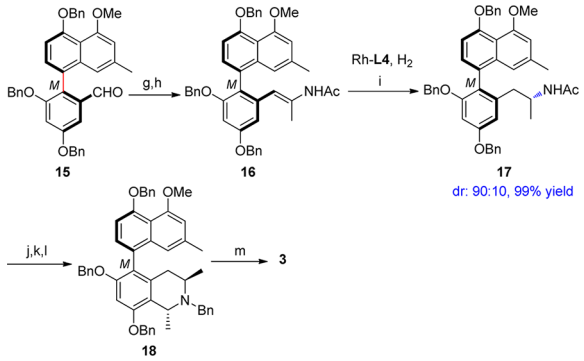
Conditions: (a) TBSCl, TEA, DCM, −78 °C to rt, 59%; (b) NBS, DCM, −15 °C, 86%; (c) BOPCl, TEA, DCM, 98%; (d) **14**, $Pd(OAc)_2$/**L2**, K_3PO_4, toluene/H_2O = 5/1, 96%, 93% ee; (e) NaOH, MeOH, 97%; (f) BnBr, K_2CO_3, DMF, 95%; (g) $EtNO_2$, $HO(CH_2)NH_3^+HCO_2^-$, 60 °C, 92%; (h) Fe, AcOH, Ac_2O, DMF, 70 °C, 60%; (i) 1 mol % $Rh(nbd)_2BF_4$/**L4**, H_2 (20 atm), DCM, 0 °C, 12 h, 99%, d.r. 92/8; (j) BnBr, NaH, DMF, 96%; (k) $POCl_3$, 2,4,6-collidine, toluene, 100 °C, 4 h; (l) $NaBH_4$, EtOH, −78 °C to rt, 85% (over 2 steps, *trans*:*cis* = 6/1); (m) Pd/C (5%), H_2 (1 atm), MeOH/DCM = 2/1, 3 h, 95%.

installation of the tetrahydroquinoline moiety was accomplished through the following transformations: (i) benzyl protection at the amide bond under conditions of NaH/BnBr; (ii) Bischler-Napieralski reaction with $POCl_3$; and (iii) diastereoselective reduction of the resulting imine with $NaBH_4$ (*tans*:*cis* = 6:1). A final global debenzylation by hydrogenolysis provided **2**, whose characterization was identical at every aspects with reported data.[2,4] Thus, **2** was synthesized through an efficient asymmetric Suzuki-Miyaura coupling and an effective diastereoselective hydrogenation as key steps from compound **7** in 24% overall yield and in 13 linear steps

By using a similar route, the synthesis of **3** was also accomplished through asymmetric catalytic technology (Scheme 2). Thus, chiral aldehyde **15** with *M* configuration was synthesized from **8** and **14** with a Pd-*ent*-**L2** catalyst in 96% yield and in 93% ee. After two steps to install the enamide moiety, asymmetric hydrogenation of **16** in the presence of 1 mol % Rh-**L4** catalyst provided **17** with a d.r. ratio of 90:10. The fact that similar diastereoselecitivities were observed in preparation of both **17** and **13** strongly demonstrated the independence of asymmetric hydrogenation with the Rh-**L4** catalyst from the axial chirality of the substrate. **17** underwent installation of the tetrahydroquinoline moiety and global deprotection of the benzyl groups, yielding **3** in equal synthetic efficiency.

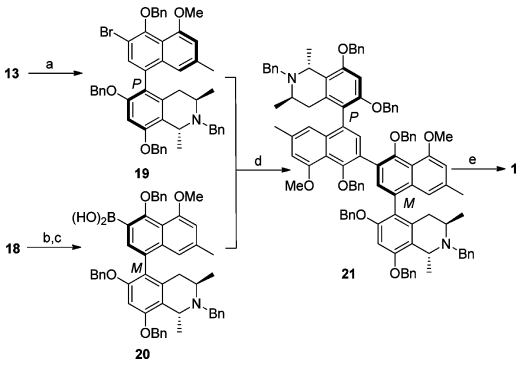
With the syntheses of both korupensamine A and B accomplished, we set out to synthesize michellamine B[22] (**1**) from their advanced intermediates **13** and **18** by a Suzuki-Miyaura coupling (Scheme 3).[22b] Thus, bromide **19** was prepared from **13** under action of $C_5H_5NHBr_3$ as the bromination reagent. Boronic acid **20** was obtained from **18** by bromination followed by metal−halogen exchange to react with $B(OiPr)_3$. Suzuki-Miyaura coupling of **19** and **20** with $Pd(PPh_3)_4$

Scheme 2. Syntheses of 3



Conditions: (g) $EtNO_2$, $HO(CH_2)NH_3^+HCO_2^-$, 60 °C, 93%; (h) Fe, AcOH, Ac_2O, DMF, 70 °C, 61%; (i) 1 mol % $[Rh(NBD)_2]BF_4$/**L4**, H_2 (20 atm), 0 °C, 12 h, 99%, d.r. = 90/10; (j) BnBr, NaH, DMF, 96%; (k) $POCl_3$, 2,4,6-Collidine, toluene, 100 °C, 4 h; (l) $NaBH_4$, EtOH, −78 °C to rt, 78% (over 2 steps, *trans*/*cis* = 4/1); (m) Pd/C (5%), H_2 (1 atm), 3 h, MeOH/DCM = 2/1, 3 h, 86%.

Scheme 3. Syntheses of 1



Conditions: (a) $C_5H_5NHBr_3$, $CHCl_3$, AcOH, 59%; (b) $C_5H_5NHBr_3$, $CHCl_3$, AcOH, 62%; (c) $B(OiPr)_3$, toluene/THF = 2/1, −95 °C, *n*BuLi, −95 °C to −15 °C, aq NH_4Cl (87%); (d) $Pd(PPh_3)_4$, K_3PO_4, DMF, 90 °C, 84%; (e) Pd/C (5%), H_2 (1 atm), MeOH/DCM = 2/1, 7 h, 93%.

as the catalyst led to the formation of the coupling product **21** in 84% yield. Hydrogenolysis of **21** removed all benzyl groups and completed the synthesis of **1** in a concise and highly stereoselective fashion.

In summary, we have developed an efficient and practical asymmetric Suzuki-Miyaura coupling methodology for a series of synthetically useful and functionalized chiral biaryls under mild reaction conditions and at low catalyst loadings. The presence of a polar-π interaction between the highly polarized BOP group and the extended π system of arylboronic acid coupling partner is believed to be essential for the high enantioselectivity. The methodology has been successfully applied in natural product syntheses and allowed for the first time the syntheses of both korupensamine A and B through catalytic asymmetric Suzuki-Miyaura coupling along with an effective diastereoselective hydrogenation. Additionally, the synthesis of their heterodimer **1** is accomplished in a concise and highly stereoselective fashion. Further applications of this methodology in constructing chiral biaryl natural products and analogs are currently underway and progress will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data. This information is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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