Asymmetric Cyclization

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Synthesis of Chiral 1,4-Benzodioxanes and Chromans by Enantioselective Palladium-Catalyzed Alkene Aryloxyarylation Reactions

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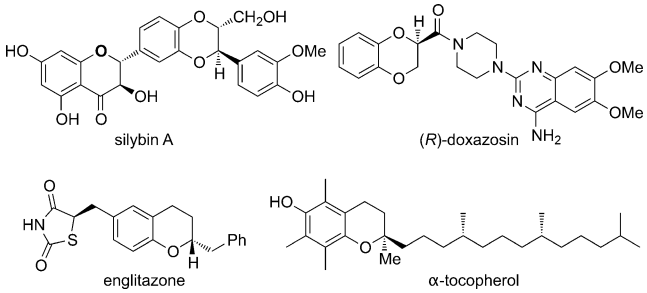
Abstract: *A highly enantioselective alkene aryloxyarylation led to the high-yielding formation of a series of 1,4-benzodioxanes, 1,4-benzooxazines, and chromans containing quaternary stereocenters with excellent enantioselectivity. The sterically bulky and conformationally well defined chiral monophosphorus ligand* ***L4*** *or* ***L5*** *was responsible for the high reactivity and enantioselectivity of these transformations. The application of this method to the synthesis of the chiral chroman backbone of α-tocopherol was demonstrated.*

Many bioactive natural products and drugs contain chiral 1,4-benzodioxane or chroman units (Scheme 1).[1] For example, 1,4-benzodioxane lignans represented by silybin A[2] are a group of natural products that exhibit a wide range of interesting biological activities, such as hepatoprotective,



Scheme 1. Natural products and drugs containing chiral 1,4-benzodioxane and chroman moieties.

anticancer, and antioxidant activity. Doxazosin[3] is a selective α1-adrenoceptor antagonist with a 1,4-benzodioxane moiety that is used to treat high blood pressure and urinary retention associated with benign prostatic hyperplasia. Englitazone[4] is an antidiabetic agent with a chiral chroman structure. α-Tocopherol[5] is the most significant member of the vitamin E family, which features a key chroman ring containing a quaternary stereocenter. The asymmetric synthesis of chiral 1,4-benzodioxanes[6] and chromans[7] has thus gained significant attention over the years. In particular, several excellent metal-catalyzed asymmetric transformations have been developed, including an intramolecular Wacker-type cyclization,[8] allylic substitution,[9] aryl C–O coupling,[10] and allylic C–H oxidation.[11] The palladium-catalyzed alkene aryloxyarylation, involving the coupling of a phenol bearing a pendant alkene with an aryl halide, offered facile access to 2-substituted chromans from readily available starting materials.[12–14] This alkene difunctionalization pioneered by Wolfe and co-workers was best promoted by the use of a sterically bulky monophosphorus ligand. However, in contrast to several excellent examples of enantioselective alkene aminoarylation and alkoxyarylation, an enantioselective variant of alkene aryloxyarylation remains elusive.[15] We believed that an asymmetric version of such transformation would not only provide chiral chroman derivatives, but would also lead to the formation of various chiral benzo-fused six-membered oxygen heterocycles, such as 1,4-benzodioxanes and 1,4-benzooxazines. Herein we report an enantioselective palladium-catalyzed alkene aryloxyarylation that has led to a series of chiral 1,4-benzodioxanes, chromans, and 1,4-benzooxazines bearing quaternary stereocenters in excellent yield with high enantioselectivity.

Over past several years, our research group has focused on the development of efficient chiral monophosphorus ligands for asymmetric catalysis. The success of those conformationally well defined and sterically bulky P-stereogenic monophosphorus ligands based on a dihydrobenzo[*d*][1,3]oxaphosphole framework in various asymmetric carbon–carbon bond-forming reactions[16] prompted us to investigate the alkene aryloxyarylation between 2-((2-methylallyl)oxy)phenol (**1a**) and bromobenzene (**2a**). The reactions were performed in toluene at 110 °C under nitrogen for 18 h with NaO*t*Bu as the base in the presence of $[Pd_2(dba)_3]$ (2 mol %) and a chiral ligand (4 mol %; Table 1, entries 1–8). Previous studies by Wolfe and co-workers[14] on alkene aryloxyarylation between aryl/alkenyl halides and 2-(but-3-en-1-yl)phenols indicated the importance of a suitable monophosphorus ligand for such reactions to proceed in high yield. We were delighted that ligands **L1–L5** were effective for the formation of the desired 1,4-benzodioxane product **3aa**. Interestingly, the ligand structure played a significant role on both reactivity and enantioselectivity.

The use of BI-DIME (**L1**) provided compound **3aa** in low yield with low enantioselectivity, and a major side product was derived from an intermolecular Heck-type reaction (Table 1, entry 1). Encouragingly, ligand **L2** with a methyl substituent at the 2-position effectively inhibited the formation of this side product and dramatically improved both the yield (69 %) and the enantioselectivity (45 % *ee*; Table 1,

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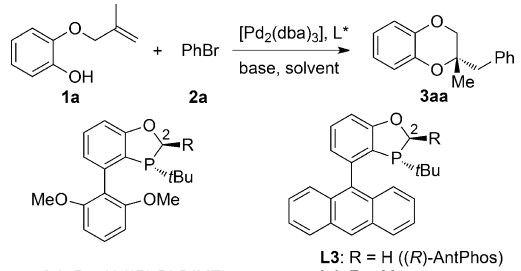
Table 1: Asymmetric alkene aryloxyarylation of 2-((2-methylallyl)oxy)-phenol (**1a**) and bromobenzene (**2a**).



Entry[a]	L*	Solvent	Base	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**L1**	toluene	NaO*t*Bu	110	22	12
2	**L2**	toluene	NaO*t*Bu	110	69	45
3	**L3**	toluene	NaO*t*Bu	110	56	50
4	**L4**	toluene	NaO*t*Bu	110	88	77
5	**L5**	toluene	NaO*t*Bu	110	90	60
6	(*S*)-MonoPhos	toluene	NaO*t*Bu	110	–	–
7	(*S*)-BINAP	toluene	NaO*t*Bu	110	–	–
8	(*S*,*S*)-Me-Duphos	toluene	NaO*t*Bu	110	–	–
9	**L4**	dioxane	NaO*t*Bu	110	60	75
10	**L4**	CPME	NaO*t*Bu	110	45	77
11	**L4**	DMF	NaO*t*Bu	110	10	25
12	**L4**	*c*-C_6H_{12}	NaO*t*Bu	110	82	80
13	**L4**	C_6F_6	NaO*t*Bu	110	88	86
14	**L4**	C_6F_6	NaO*t*Bu	60	88	93
15	**L4**	C_6F_6	K_2CO_3	60	72	92
16	**L4**	C_6F_6	NaOH	60	83	92
17	**L4**	C_6F_6	TEA	60	–	–
18	**L4**	C_6F_6	DABCO	60	–	–

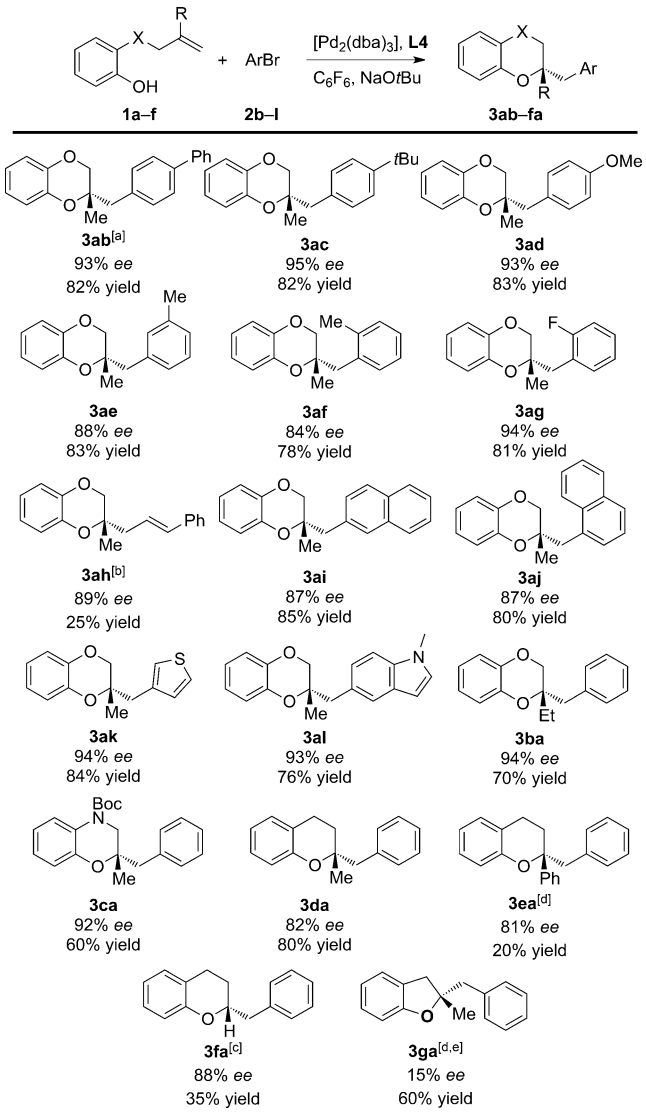
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [$Pd_2(dba)_3$] (0.004 mmol, 2 mol%), ligand (0.008 mmol, 4 mol%), base (0.4 mmol), solvent (1 mL), nitrogen atmosphere, 18 h. The absolute configuration of the products was assigned by analogy according to the absolute configuration of **3fa** and **5b**. [b] Yields of the isolated product. [c] The *ee* value was determined by HPLC on a Chiralcel OJ-H column. CPME = cyclopentyl methyl ether, DABCO = 1,4-diazabicyclo[2.2.2]-octane, dba = dibenzylideneacetone, DMF = *N*,*N*-dimethylformamide, TEA = triethylamine.

entry 2). The low aryl structure of the monophosphorus ligand was also influential. AntPhos (**L3**) provided the product in much higher yield and enantioselectivity than BI-DIME (Table 1, entry 3). In particular, both **L4** and **L5** with substituents at the 2-position provided **3aa** in excellent yield (88 and 90%; Table 1, entries 4 and 5). Good enantioselectivity (77% *ee*) was observed with **L4** (Table 1, entry 4). For comparison, some commercially available chiral mono- or diphosphines, such as monophos, BINAP, and Me-Duphos, were ineffective, thus demonstrating the importance of a sterically bulky monophosphorus ligand in this transformation (Table 1, entries 6–8). We thus chose **L4** as the ligand for further optimization. Screening of the solvent (Table 1, entries 9–13) showed that hexafluorobenzene with an inverted quadrupole moment further enhanced the enantioselectivity to 86% *ee* (Table 1, entry 13). We found that the reaction took place even at 60 °C to give the desired product **3aa** in 88% yield with 93% *ee* (Table 1, entry 14). A strong base was required for this reaction: Potassium carbonate provided a diminished yield (72%; Table 1, entry 15), and no formation of **3aa** was observed when an organic base, such as triethylamine or DABCO, was employed.

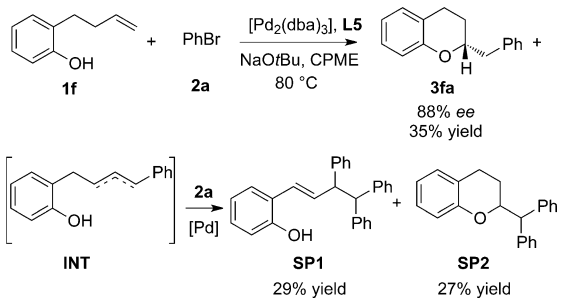
We then investigated the substrate scope of this enantioselective alkene aryloxyarylation. A series of 1,4-benzodioxanes **3ab–al** containing a quaternary stereocenter were formed in good yield with high enantioselectivity (Scheme 2). Various *para*-, *meta*-, and *ortho*-substituted aryl bromides (substrates **2a–g**) were applicable, and the corresponding chiral 1,4-benzodioxanes were obtained in 78–83% yield with 84–95% *ee*. The use of alkenyl bromide **2h** also provided the desired cyclization product **3ah** with 89% *ee*, albeit in low yield (25%). Both 1- and 2-naphthyl bromide could also be employed to form **3ai** and **3aj**, respectively. Heteroaryl bromides, such as **2k** and **2l**, were fully tolerated and converted into the corresponding 1,4-benzodioxanes **3ak** and **3al** containing heterocyclic moieties in high yield with excellent enantioselectivity. The substituent at the quaternary stereocenter was not limited to a methyl group; a 1,4-benzodioxane **3ba** with an ethyl substituent at the stereocenter was also formed with 94% *ee* in 70% yield. Besides 1,4-benzodioxanes, a 1,4-benzooxazine product **3ca** was also formed with 92% *ee* in 60% yield. A chroman product **3da** with a quaternary stereocenter was synthesized with 82% *ee* in 80% yield, and a related chroman product **3ea** with a phenyl substituent at the stereocenter was prepared with good enantioselectivity (81% *ee*), albeit in low yield (20%). The key chiral chroman structure of englitazone,[4] **3fa**, was successfully prepared in 88% *ee*, although a relatively low yield (35%) was observed. A reaction of 2-allylphenol (**1g**) provided the benzofuran compound **3ga** in 60% yield with 15% *ee*, thus indicating that the chiral palladium catalyst was more selective for the preparation of benzo-fused six-membered oxygen heterocycles. A gram-scale reaction between **1a** and 4-bromo-1,1′-biphenyl (**2b**) was conducted, and the desired cyclization product **3ab** was isolated in 75% yield with 91% *ee*, thus demonstrating the practicality of this method.

The high enantioselectivities and yields observed in the formation of 1,4-benzodioxanes, a 1,4-benzooxazine, and chromans prompted us to investigate the reaction mechanism. The reaction between 2-((2-methylallyl)oxy)phenol (**1a**) and bromobenzene (**2a**) with a scalemic composition of **L4** showed a good linear relationship of the *ee* values of the ligand and product **3aa**, thus indicating that this transformation is catalyzed by a palladium catalyst with a single chiral monophosphorus ligand **L4**. Further analysis of the reaction between 2-(but-3-en-1-yl)phenol (**1f**) and bromobenzene (**2a**) revealed the formation of **3fa** as well as two main side products **SP1** and **SP2** (Scheme 3). Presumably, the reaction proceeded via a Heck intermediate **INT**, followed by two more Heck processes to form **SP1** or an alkene aryloxyarylation to form **SP2**. Thus, it was reasonable that an improved yield was observed for the synthesis of **3da** bearing a quaternary stereocenter, in which case the Heck process was inhibited effectively owing to the more hindered nature of its 1,1-disubstituted olefin moiety.

On the basis of the studies by Wolfe and co-workers[17] as well as our own observation, a catalytic cycle for the synthesis



Scheme 2. Enantioselective palladium-catalyzed alkene aryloxyarylation reactions. Unless otherwise specified, all reactions were performed at 60 °C under nitrogen for 18 h with **1** (0.2 mmol), **2** (0.4 mmol), $[Pd_2(dba)_3]$ (0.004 mmol, 2 mol%), **L4** (0.008 mmol, 4 mol%), and NaOtBu (0.4 mmol) in C_6F_6 (1 mL). Product *ee* values were determined by HPLC on a chiral stationary phase. The absolute configuration of **3 fa** was determined by comparing its optical rotation with reported data,[4] and that of the other products was assigned by analogy. [a] Product **3 ab** was isolated from a gram-scale reaction in 75% yield with 91% ee. [b] A mixture of *cis*- and *trans*-β-bromostyrene was employed (*cis*/*trans* 16:84). [c] **L5** was used as the ligand, and cyclohexane was used as the solvent. [d] **L5** was used as the ligand, and toluene was used as the solvent. The reactions were performed at 110 °C. [e] Product **3 ga** was synthesized from the substrates 2-(2-methylallyl)phenol (**1 g**) and **2a**.



Scheme 3. Formation of the main side products **SP1** and **SP2** in the synthesis of chroman **3 fa**.

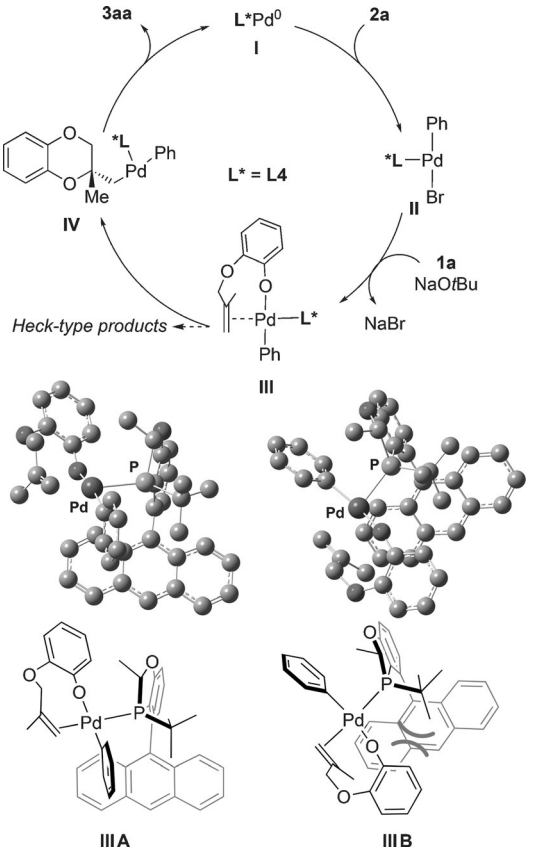
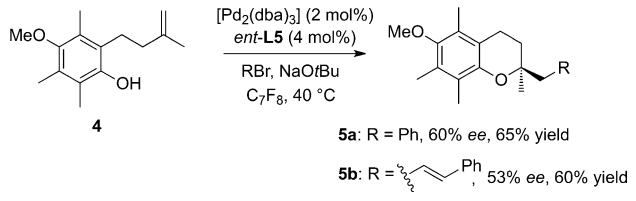


Figure 1. Proposed catalytic cycle and stereochemical model.

of the chiral 1,4-benzodioxane **3 aa** is proposed in Figure 1. Oxidative addition of the Pd^0 species **I** by PhBr (**2 a**) leads to the formation of Pd^{II} complex **II**. With NaO*t*Bu as the base, ligand exchange between the bromide group and the substrate **1 a** takes place to form the Pd complex **III**, which could either lead to the formation of Heck-type products, or a *syn*-oxopalladation[18] could give Pd complex **IV**. Reductive elimination of complex **IV** forms the product **3 aa** and regenerates the Pd^0 species **I** to complete the catalytic cycle. The stereochemical outcome is presumably determined at the *syn*-oxopalladation step. DFT calculations[19] of the Pd species **III** revealed two major conformers **III A** and **III B** for *syn*-oxopalladation. The conformer **III B** is apparently sterically congested between the phenyl group of the substrate **1 a** and the *tert*-butyl group of **L4**, whereas in the energetically more favorable conformer **III A**, **1 a** is coordinated away from the *tert*-butyl group of **L4**, thus leading to the cyclization product **3 aa** with the observed configuration. The anthracenyl moiety, the *tert*-butyl group, and the substituent at the 2-position of **L4** all contribute to this well-defined stereochemical process.

To demonstrate the synthetic utility of this transformation, we investigated the synthesis of the α-tocopherol core structure[7] (Scheme 4). When compound **4**[8c–e] was treated with bromobenzene in the presence of a Pd–*ent*-**L5** catalyst, compound **5a** was obtained with 60% *ee* in 65% yield.



Scheme 4. Synthesis of the chiral chroman unit of α-tocopherol.

Similarly, the reaction between compound **4** and (*E*)-(2-bromovinyl)benzene formed the desired product **5b** with 53% *ee* in 60% yield. The conversion of **5b** into α-tocopherol should be possible through oxidative cleavage of the alkene to afford the corresponding known aldehyde, which has previously been transformed into the natural product.[8c]

In summary, we have developed a highly enantioselective alkene aryloxyarylation that has led to the formation of a series of 1,4-benzodioxanes, a 1,4-benzooxazine, and chromans containing quaternary stereocenters with high enantioselectivity in good yield. The chiral monophosphorus ligands **L4** and **L5** were responsible for the excellent reactivity and enantioselectivity of these transformations. The application of this method to the synthesis of the chiral chroman core structure of α-tocopherol was also demonstrated. The stereochemical model gained from this study will certainly be helpful for the design of better catalytic systems and the further expansion of the scope and synthetic utility of this transformation. Studies along these lines are ongoing.

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