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Enantioselective 6-*endo*-trig Wacker-type cyclization of 2-geranylphenols: application to a facile synthesis of (−)-cordiachromene

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ABSTRACT

An enantioselective intramolecular oxidative cyclization of 2-geranylphenols catalyzed by a Pd(II)-spiro bis(isoxazoline) complex is reported. The reaction proceeds in a 6-*endo*-trig manner to give chromene derivatives in reasonable yields and with moderate enantioselectivities. This transformation can be applied to a protecting-group-free total synthesis of naturally occurring cordiachromene.

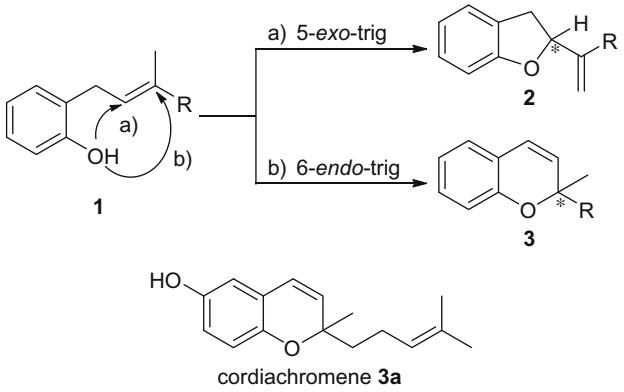
1. Introduction

An intramolecular oxidative cyclization catalyzed by a palladium complex, referred to as the Wacker-type cyclization, is one of the most versatile methods for the preparation of heterocycles.[1] Among them, reactions of 2-allylphenol substrates **1** have been extensively investigated and developed to asymmetric synthesis.[2] Such cyclizations usually proceed in a 5-*exo*-trig fashion to give dihydrobenzofuran derivatives **2** (Scheme 1a). In contrast, there are only a few examples of a 6-*endo*-trig Wacker-type cyclization constructing a benzopyran (chromene) skeleton **3** (Scheme 1b).[3] Chromenes are ubiquitous structural units found in physiologically active compounds[4] and are also useful intermediates in the synthesis of natural products.[5] Although enantioselective 6-*endo*-trig Wacker-type cyclizations are expected to be a powerful tool for the preparation of optically active chromenes, no such reports have been published yet. Herein, we report an enantioselective synthesis of chromene derivatives via a 6-*endo*-trig Wacker-type cyclization of 2-geranylphenols. This transformation can be applied to a protecting-group-free total synthesis[6] of cordiachromene **3a**.

2. Results and discussion

Firstly, we examined several chiral ligands for an enantioselective Wacker-type cyclization using 2-geranylphenol **1b** as a model substrate (Table 1).[7] We were pleased to find the formation of the desired optically active chromene product **3b** with a spiro bis(isoxazoline) ligand (SPRIX).[8,9] Thus, the reaction of **1b** in the presence of 10 mol % of $Pd(OCOCF_3)_2$, 11 mol % of (*P*,*R*,*R*)-*i*-Pr-SPRIX **4**, and 4 equiv of *p*-benzoquinone in $Cl_2CHCHCl_2$ at 60 °C for 24 h afforded **3b** in 55% yield with 54% ee (entry 1). In this reaction, 5-*exo*-trig cyclization product **2b** was also formed in 11% yield, albeit with a lower stereoselectivity. Effective chiral ligands for asymmetric 5-*exo*-trig cyclizations of 2-allylphenols, (*S*,*S*)-*i*-Pr-BOXAX **5**[2b–e] and (−)-sparteine **6**,[2f,g] did not promote the reaction enantioselectively (entries 2 and 3). Pd complex **7**, which is known to be a valuable catalyst for enantioselective Wacker-type cyclizations,[2a] gave a trace amount of racemic **3b** (entry 4). Furthermore, other chiral ligands (*R*,*R*)-Bn-BOX **8** and (*S*)-BINAP **9** did not work under these conditions (entries 5 and 6). When the reaction was conducted without any chiral ligands, only 15% yield of **3b** was obtained (entry 7). This background process would be a major pathway for the formation of racemic **3b** in entries 2–6. These results obviously demonstrate the high utility of SPRIX for the enantioselective 6-*endo*-trig Wacker-type cyclization.

Cordiachromene **3a** was first isolated from an American tree *Cordia alliodora*,[10] and later from *Aplidium constellatum*,[11] *Aplidium antillense*,[12] and *Aplidium multiplicatium*.[13] This chromene displays



Scheme 1. Wacker-type cyclization of 2-allylphenol derivatives.

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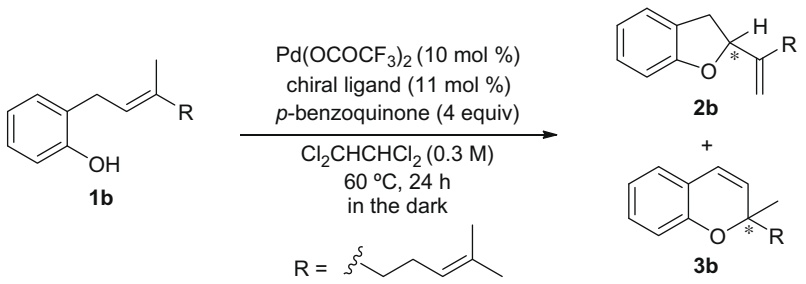
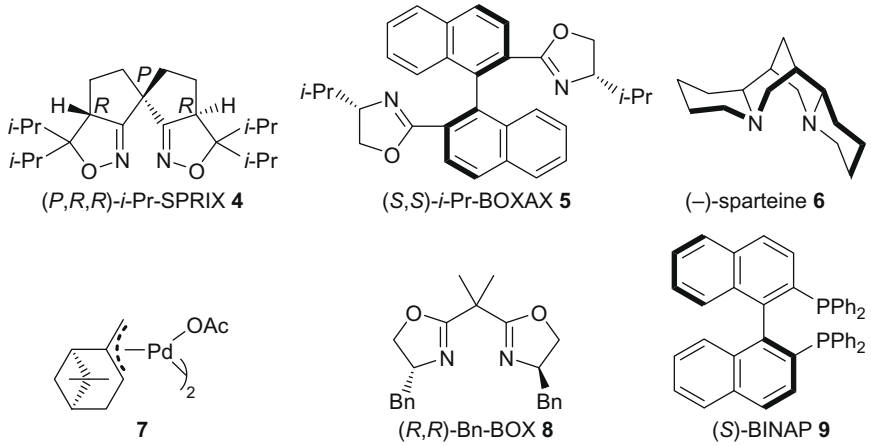
Table 1
Screening of catalyst systems in the enantioselective intramolecular Wacker-type cyclization of **1b**[a]



Entry	Chiral ligand	Conv.[b] (%)	Yield[b] (%)		ee[c] (%)	
			2b	**3b**	**2b**	**3b**
1	**4**	100	11	55	18	54
2	**5**	48	5	19	<5	*rac*
3	**6**	58	7	19	<5	*rac*
4	**7**[d]	79	0	5	–	*rac*
5	**8**	24	0	15	–	*rac*
6	**9**	36	0	17	–	*rac*
7	None	61	0	15	–	–



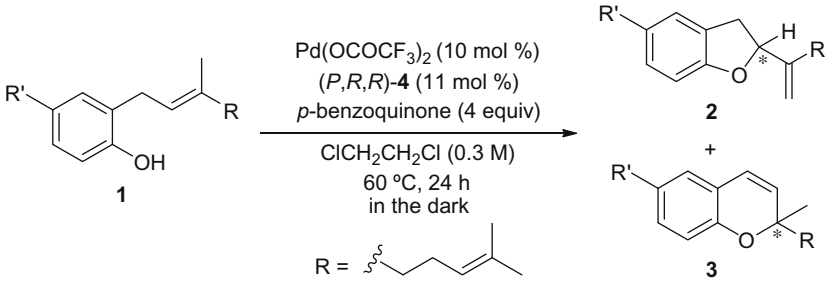
[a] All reactions were carried out in the presence of 10 mol % of $Pd(OCOCF_3)_2$, 11 mol % of chiral ligand, and 4 equiv of *p*-benzoquinone at 60 °C for 24 h in $Cl_2CHCHCl_2$ (0.3 M) under a nitrogen atmosphere in the dark.
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by HPLC analysis.
[d] 10 mol % of chiral complex **7** was used instead of $Pd(OCOCF_3)_2$.

antibacterial activity against *Staphylococcus aureus*[12] and anti-inflammatory activity.[14] The asymmetric total synthesis of **3a** has been achieved by utilizing the Sharpless enantioselective epoxidation[15] or lipase-catalyzed kinetic resolution of racemic acetates.[16] Both of these strategies provided the target product in reasonable yields with high enantiomeric purities, but they required a lengthy synthetic sequence. Toward an application of the Pd-catalyzed oxidative 6-*endo*-trig cyclization for the facile synthesis of **3a**, we examined a variety of hydroquinone substrates protecting one hydroxy group. Representative results are shown in Table 2.[17] In spite of moderate chemical yields and enantioselectivities, products **3c**–**e** having an ether group were obtained (entries 1–3). Acetal functionality was tolerated as a protecting group for the phenol component to produce **3f** (entry 4). Reactions of ester-substituted substrates **1g**–**j** furnished the corresponding chromenes **3g**–**j** in 30–52% yields (entries 5–8). 2-Geranylphenol **1k** bearing a bromo moiety convertible to a hydroxy group[18] also participated in this cyclization to give **3k** in 46% yield with 55% ee (entry 9).

As shown in Table 2, the synthetic precursors **3c–k** of cordiachromene were obtained in an optically active form. Chromenes, however, have proven to racemize under acidic and basic[19] as well as photochemical conditions.[7,20] To avoid such a racemization, we attempted to execute a protecting-group-free asymmetric synthesis of cordiachromene, namely, direct conversion of non-protected substrate **1a** to **3a** (Scheme 2).[21] The precursor **1a** was readily prepared from hydroquinone and geraniol in the presence of $BF_3{\cdot}Et_2O$ in 34% yield.[22] Disappointingly, we could not obtain **3a** in an acceptable yield under the catalytic conditions, due to an inevitable oxidation of **1a** into 2-geranylbenzoquinone.[23] A stoichiometric use of the Pd salt was eventually found to be operative for the cyclization. Thus, **3a** with 54% ee was isolated in 42% yield when **1a** was treated with 1 equiv of $Pd(OCOCF_3)_2$ and 1.1 equiv of (*P*,*R*,*R*)-**4** at 60 °C for 2 h (Scheme 2).[24] The absolute configuration of the resulting **3a** was assigned to be (*R*) by comparison of the sign of the specific rotation with the reported value.[15,16]

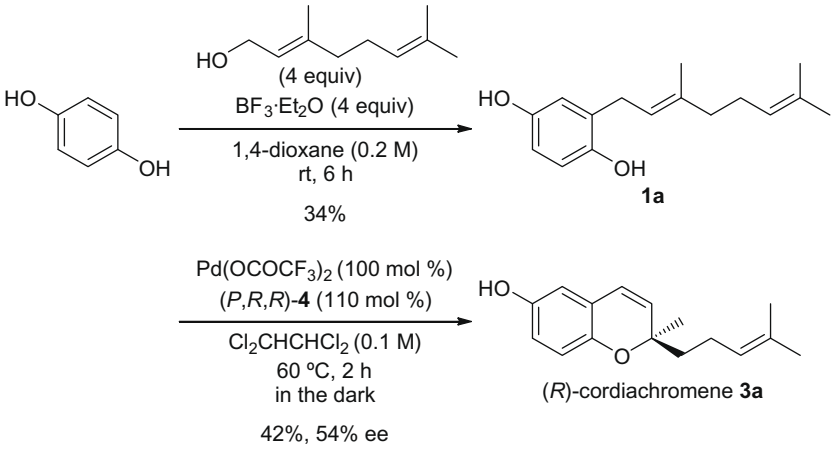
This enantioselective 6-*endo*-trig cyclization of **1** seems to proceed through a general catalytic cycle of Wacker-type reaction, that is, an initial coordination of the olefin to Pd(II), a subsequent intramolecular attack of the nucleophile, and a final β-hydride elimination producing chromenes **3**. From the results shown in

Table 2
Effect of substituents on the aromatic ring in the enantioselective intramolecular Wacker-type cyclization of **1**[a]

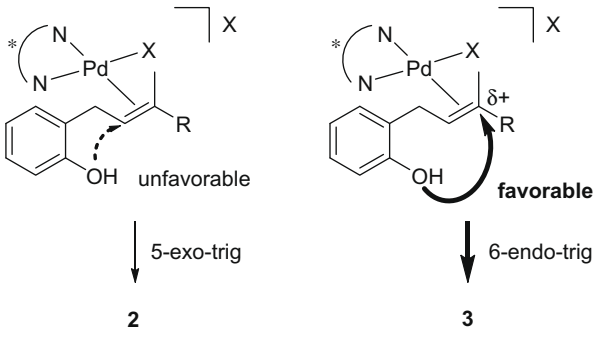


Entry	1	R′	Yield[b] (%)	Ratio 2/3[c]	ee of 3[d] (%)
1	**1c**	BnO	45 (24)	1/1.6	34
2	**1d**	MeO	42 (19)	1/1.5	48
3	**1e**	TBSO	26 (15)	1/1.4	49
4	**1f**	MOMO	61 (33)	1/2.1	37
5	**1g**	PivO	57 (35)	1/2.2	52
6	**1h**	BzO	46 (37)	1/4.1	44
7	**1i**	BocO	68 (52)	1/3.0	47
8	**1j**	TsO	41 (30)	1/4.1	42
9	**1k**	Br	63 (46)	1/4.7	55

[a] All reactions were carried out in the presence of 10 mol % of $Pd(OCOCF_3)_2$, 11 mol % of (*P,R,R*)-**4**, and 4 equiv of *p*-benzoquinone at 60 °C for 24 h in $ClCH_2CH_2Cl$ (0.3 M) under a nitrogen atmosphere in the dark. In each case, the starting material was almost consumed at the end of the reaction.
[b] Combined yield determined by ^1H NMR spectroscopy. Isolated yields for **3** are given in parentheses.
[c] Determined by ^1H NMR.
[d] Determined by HPLC analysis.



Scheme 2. Asymmetric protecting-group-free short total synthesis of **3a**.



Scheme 3. Plausible description of the regioselectivity.

Table 1, the use of ligand **4** is essential for promoting this cyclization. Presumably, the Pd–SPRIX complex activates the olefin significantly because of its strong Lewis acidity.[9c] A positive charge induced on the C–C double bond is more stabilized at the carbon atom possessing the two alkyl chains (Scheme 3). The nucleophilic attack of the phenolic hydroxy group, therefore, takes place preferentially at this carbon, leading to a 6-*endo*-trig cyclization.[3a]

3. Conclusion

In conclusion, we have developed an enantioselective 6-*endo*-trig Wacker-type cyclization of 2-geranylphenols, where the SPRIX ligand plays a crucial role for obtaining optically active chromene derivatives. This reaction can be extended to a protecting-group-free asymmetric synthesis of a natural product. (*R*)-Cordiachromene was prepared in 14% overall yield over two steps from commercially available and cheap reagents. Further improvement of conditions for this enantioselective Wacker-type cyclization is currently ongoing in our group.

Acknowledgment

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17. Typical experimental procedure for the Pd-catalyzed oxidative cyclization of **1** (Table 2): Under a nitrogen atmosphere, a solution of $Pd(OCOCF_3)_2$ (2.5 mg, 10 mol %) and (*P*,*R*,*R*)-**4** (3.1 mg, 11 mol %) in $ClCH_2CH_2Cl$ (0.125 mL) was stirred at 25 °C for 2 h. To the solution was added a solution of *p*-benzoquinone (32.4 mg, 0.30 mmol) and **1** (17.3 mg, 0.075 mmol) in $ClCH_2CH_2Cl$ (0.125 mL). The reaction mixture was stirred at 60 °C for 24 h in the dark. After complete consumption of **1**, the resulting mixture was subjected to short column chromatography on silica gel (eluent: ethyl acetate) and concentrated under vacuum in the dark. Crude yield was determined by ^{1}H NMR spectrum using *p*-hydroxyacetophenone as an internal standard. The residue was purified by preparative TLC in the dark to give dihydrobenzofuran **2** and chromene **3**.
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20. We indeed observed photoracemization of the products **3b–k**: for example, for **3k**, 55% ee was diminished to 45% ee after 24 h upon irradiation with a (room) light.
21. Pd-catalyzed non-enantioselective transformation of **1a** to **3a** has already been reported. Racemic **3a** was obtained in 18% yield by using $PdCl_2$ (3 mol %) and $CuCl_2$ (10 mol %) under an O_2 atmosphere. see: Iyer, M.; Trivedi, G. K. *Synth. Commun.* **1990**, *20*, 1347.
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23. Both stepwise addition of *p*-benzoquinone and the use of a combination of O_2 with Cu co-catalyst as the oxidant were ineffective.
24. Experimental procedure for the synthesis of cordiachromene **3a** (Scheme 2): Under a nitrogen atmosphere, a solution of $Pd(OCOCF_3)_2$ (4.2 mg, 100 mol %) and (*P*,*R*,*R*)-**4** (5.2 mg, 110 mol %) in Cl_2CHCH_2Cl (0.06 mL) was stirred at 25 °C for 6 h. To the solution was added a solution of **1a** (3.1 mg, 0.0125 mmol) in $Cl_2CHCHCl_2$ (0.06 mL). The reaction mixture was stirred at 60 °C for 2 h in the dark. After complete consumption of **1a**, the resulting mixture was directly passed through a short pad of silica gel, which was rinsed with ethyl acetate. The filtrate was evaporated to dryness in the dark. The crude product was purified by preparative TLC (hexane/ethyl acetate = 10/1) in the dark to give 1.3 mg (42%) of (*R*)-**3a** as a yellow oil. The enantiomeric excess was determined to be 54% ee by HPLC analysis using a chiral stationary phase column [Chiralpak AD-H, hexane/*i*-PrOH = 40/1, flow rate = 0.5 mL/min, λ = 335 nm: 52.0 min (minor) and 68.9 min (major)]. Analytical data for **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.57 (s, 3H), 1.66 (s, 3H), 1.61–1.75 (m, 2H), 2.00–2.17 (m, 2H), 4.31 (br, 1H), 5.09 (t, *J* = 6.9 Hz, 1H), 5.60 (d, *J* = 9.9 Hz, 1H), 6.28 (d, *J* = 9.9 Hz, 1H), 6.48 (d, *J* = 2.9 Hz, 1H), 6.57 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.64 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.6, 22.7, 25.7, 26.0, 40.9, 78.1, 112.8, 115.4, 116.7, 122.0, 122.6, 124.1, 131.0, 131.7, 147.0, 149.2. IR (film): 422, 475, 659, 715, 815, 862, 922, 1078, 1200, 1333, 1384, 1456, 1486, 2350, 2863, 2923, 2968, 3359 cm^{-1}. HRMS (ESI): calcd for $C_{32}H_{40}NaO_4$: *m*/*z* 511.2824 ([2 M+Na]$^+$), found: *m*/*z* 511.2838. $[\alpha]_D^{25} = -58.1$ (*c* 0.04, $CHCl_3$) {lit[16] $[\alpha]_D = -109.1$ (*c* 0.95, $CHCl_3$, 95% ee)}.