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A concise synthesis of honokiol

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ABSTRACT

A simple synthesis of the natural product honokiol **1** has been developed which proceeds in four steps and provides a 32% overall yield. Suzuki coupling of 4-allyl-2-bromoanisole **3** with 4-hydroxyphenyl boronic acid, followed by allylation, gave **5**-allyl-4′-allyloxy-2-methoxy-biphenyl **5**. This compound 5 underwent Lewis acid-catalyzed Claisen rearrangement and demethylation in a one-pot reaction which yielded honokiol.

Honokiol **1** is one of the significant bioactive constituents isolated from the bark of *Magnoliae officinalis*, or *Magnoliae obovata* that has been used in traditional Chinese medicine for the relief of flu symptoms, and in the treatment of anxiety and strokes. Recently, honokiol **1** has been demonstrated to possess potent anticancer[1], anti-inflammatory[2], anti-viral,[3] and anxiolytic[4] activities.

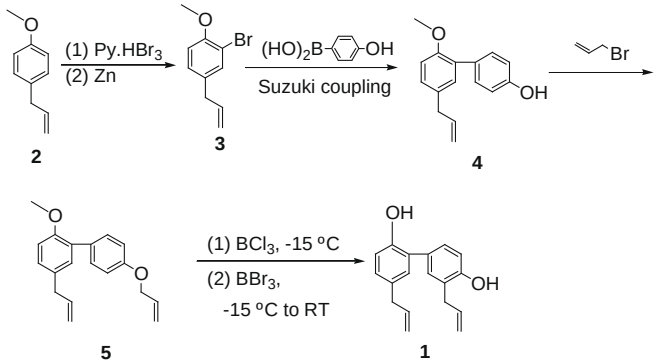
The structure of honokiol 1 consists of *para*-allyl-phenol and an *ortho*-allyl-phenol joined together through *ortho, para*-C,C-coupling. Although the structure of **1** has been identified and its bioactivities have been confirmed for decades, there were only two total syntheses that have been reported. The first approach[5] to synthesize **1** was developed by Tobinaga et al., which employed Grignard reaction with quinol acetate to provide biphenyl compound in a 29% yield. After the Claisen rearrangement, honokiol could be obtained with a 15.6% overall yield. The second approach was developed by Fukuyama,[4b] in which the Suzuki–Miyaura coupling was used as a key step to provide biphenyl compound, and subsequently Grignard reaction was used to provide allyl side chains. Honokiol could be obtained in 21% yield over 14 steps.

The method described herein provides a shorter and higher yielding route to **1**, which employed the Suzuki–Miyaura coupling[6] and the Claisen rearrangement[7] as key steps (Scheme 1). The Suzuki–Miyaura coupling is a powerful and efficient synthetic tool of carbon–carbon bond formation, which utilized aryl halides or triflates and boronic acids or boronate esters in the presence of Pd(0)-based catalyst.

The key intermediate of the present study, 4-allyl-2-bromoanisole **3**, was successfully obtained according to the literature with a minor modification.[8] By employing 2.8 equiv of pyridinium hydrobromide perbromide instead of 2.4 equiv as previously reported, 4-allyl-2-bromoanisole **3** could be obtained with a 68% yield after further debromination by zinc.

It was well known that haloarenes having a steric hindrance of *ortho*-substituent were less reactive than those without *ortho*-substituent in the Suzuki–Miyaura cross-coupling reaction.[6] Indeed, by employing the most commonly used condition of Suzuki coupling (catalyzed by $Pd(Ph_3)_4$ with different bases in different solvents, such as Na_2CO_3 in 2-propanol–H_2O[9] or 1,2-DME–H_2O,[10] or 1,4-dioxane–H_2O,[10] DME–THF–H_2O[11]), the yields of cross-coupling product were negligible with the sterically demanding substrate **3** (Table 1). Different catalysts and conditions of the Suzuki coupling reported in the literature which had shown better yields of palladium-catalyzed unreactive aryl halides have been tried for examples, catalyzed with $PdCl_2$ and K_3PO_4 in toluene[12], $Pd(OAc)_2$–dppf and K_2CO_3,[3] $Pd_2(dba)_3$–P(*t*-Bu)$_3$ and Cs_2CO_3 in 1,4-dioxane,[13] $Pd_2(dba)_3$–PCy_3 and K_3PO_4 in 1,4-dioxane–H_2O[14] (Table 1). Finally, it was found that by employing a catalyst composed of Pd2dba$_3$ and ligand, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, developed by Buchwald et al.[15] yielded promising results.

Since the base was known to accelerate the transmetallation step of the Suzuki–Miyaura coupling,[6] different bases have been tried, and the results were summarized in Table 2. The results have



Scheme 1. Synthesis of honokiol.

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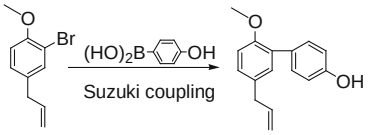
Table 1
Different reaction conditions of the Suzuki coupling



	Catalyst and ligand	Solvent (base)	Temp. (time)	yield
1	$Pd(PPh_3)_4$	*i*PrOH–H_2O (Na_2CO_3)	100 °C 24 h	Trace
2	$Pd(PPh_3)_4$	DME/–H_2O (Na_2CO_3)	90 °C 24 h	Trace
3	$Pd(PPh_3)_4$	Dioxane–H_2O (Na_2CO_3)	90 °C 24 h	Trace
4	$Pd(OAc)_2PPh_3$	DME –THF–H_2O (K_2CO_3)	85 °C 15 h	Trace
5	$Pd(OAc)_2$dppf	THF (K_2CO_3)	85 °C 18 h	Trace
6	$PdCl_2$	K_3PO_4 (Toluene)	100 °C 12 h	Trace
7	$Pd_2(dba)_3P(t\text{-}Bu)_3$	1,4-Dioxane (Cs_2CO_3)	100 °C 48 h	12%
8	$Pd_2(dba)_3PCy_3$	K_3PO_4 (Dioxane/H_2O)	100 °C 15 h	7%
9	$Pd_2(dba)_3$	K_3PO_4 (Dioxane/H_2O)	110 °C 15 h	22%

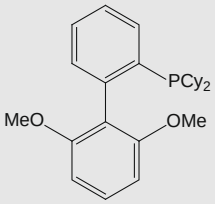
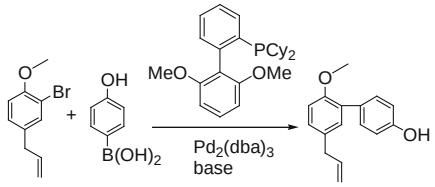


Table 2
Different base effects on the yields of the Suzuki coupling[a]



Entry	Base	Yield[b] (%)
1	K_3PO_4 (5 equiv)	22
2	$CsCO_3$ (3 equiv)	Trace
3	KOAc (3 equiv)	10
4	K_2CO_3 (3 equiv)	12
5	CsF (5 equiv)	49
6[16]	KF (5 equiv)	83

[a] Reaction condition: **3** (30 mg) and 4-hydroxyboronic acid (1.2 equiv) were dissolved in 1,4-dioxane/water (10:1). After addition of base, $Pd_2(bda)_3$, and ligand, the reaction mixture was stirred at 110 °C for 15 h under nitrogen atmosphere.
[b] Isolated yields.

shown that KF could be used to generate a good yield of the desired cross-coupling product **4**.

Allyl ether **5** could be obtained in high yield (90%) by allylation of biaryl **4** with allyl bromide in the presence of K_2CO_3. Compound **5** was treated with boron trichloride (2 equiv) at −15 °C for 1 h. The resulting mixture of BCl_3-catalyzed Claisen's rearrangement was submitted demethylation with BBr_3 (2.5 equiv) without work-up. After 1 h at −15 °C, the reaction was warmed to room temperature and stirred overnight. The reaction mixture was quenched with water. The mixture was purified by silica gel chromatography to provide honokiol **1** with satisfactory yield (63.8%).

In summary, a new synthesis of honokiol **1** has been developed, which proceeded from **2** in five steps (bromination, Suzuki coupling, allylation, one-pot Claisen's rearrangement, and demethylation) and provides a 32% overall yield.

Acknowledgments

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16. Synthesis of 5-allyl-2-methoxybiphenyl-4′-ol **4**: To the solution of 4-allyl-2-bromoanisole (30 mg, 0.1320 mmol) and 1,4-dioxane–water (10:1, 2.2 mL) were added potassium fluoride (5 equiv, 38.4 mg) and 4-hydroxybenzeneboronic acid (1.2 equiv, 21.9 mg). The mixture was ultrasonated for 1 min (in ultrasonic water bath) under nitrogen atmosphere. After 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (16 mol %, 8.7 mg) and $Pd_2(dba)_3$ (2 mol %, 2.4 mg) were added into the reaction mixture, the reaction mixture was heated to 110 °C for 15 h under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (10 mL) and was washed with dilute HCl (0.1 M, 10 mL) and brine. The organic solution was dried over sodium sulfate and concentrated under reduced pressure, the desired product was purified with TLC (hexane/ethyl acetate 3:1, developed twice, R_f 0.45). The desired product, 5-allyl-2-methoxybiphenyl-4′-ol, was obtained as oil (26 mg, 83%).