Asymmetric Catalysis

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Palladium-Catalyzed Enantioselective Intramolecular Hydroarylation of Alkynes To Form Axially Chiral 4-Aryl 2-Quinolinones**

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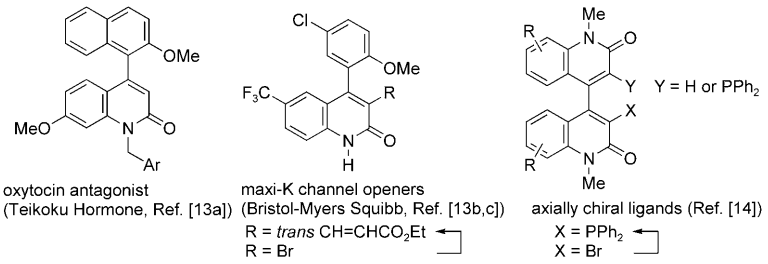
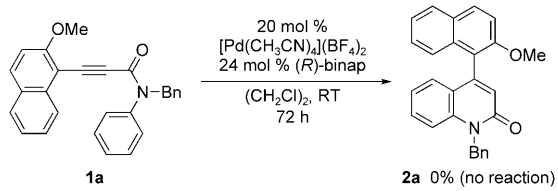
The transition-metal-catalyzed intramolecular hydroarylation of alkynes, which was first reported by Fujiwara and co-workers in 2000,[1] is a useful method for the synthesis of fused aromatic compounds.[2] A large number of transition-metal catalysts have been developed to date for this transformation.[3] Research efforts have been focused on catalytic efficiency, substrate scope, and regioselectivity (6-*endo*-dig versus 5-*exo*-dig[4]), whereas no enantioselective variant of this transformation has been reported.[5–7] On the other hand, recent significant advances in atroposelective biaryl synthesis[8] through transition-metal-catalyzed enantioselective [2+2+2] cycloaddition reactions clearly demonstrate the utility of the asymmetric cyclization strategy for the synthesis of chiral aromatic compounds.[9–11] As an alternative asymmetric annulation method for atroposelective biaryl synthesis, we recently reported an enantioselective cycloisomerization of *N*-alkenyl aryl ethynylamides under the catalysis of a cationic palladium(II)/xyl-segphos complex to give axially chiral 4-aryl 2-pyridones.[12] However, axially chiral 4-aryl 2-quinolinones rather than 4-aryl 2-pyridones have been found as core structures of pharmaceutically active compounds[13] and chiral ligands[14] (Scheme 1).

Therefore, the development of a method for the catalytic enantioselective synthesis of 4-aryl-2-quinolinones that would enable facile access to new synthetic analogues of this class of compounds in enantiomerically enriched form is an important topic. Herein, we disclose the first catalytic enantioselective intramolecular hydroarylation of alkynes. The reaction at room temperature with a cationic palladium(II)/(*S*)-xyl-H_8-binap complex as the catalyst furnished axially chiral 4-aryl 2-quinolinones with good *ee* values.



Scheme 1. Axially chiral 4-aryl 2-quinolinone derivatives as pharmaceutically active compounds and chiral ligands.

We first investigated the reaction of *N*-benzyl-*N*-phenylpropiolamide **1a**, which contains a 2-methoxynaphthyl group at the alkyne terminus, in the presence of a cationic palladium(II)/(*R*)-binap complex (20 mol% Pd). Unfortunately, no reaction was observed at room temperature in 72 hours (Scheme 2). At a higher temperature (80°C), a complex mixture was generated.



Scheme 2. Attempted enantioselective intramolecular hydroarylation of **1a** with a cationic palladium(II)/(*R*)-binap complex. Bn = benzyl.

We anticipated that 3-aryl propiolamide **1b** with an electron-rich 2-naphthyl group on the nitrogen atom would be more nucleophilic than 3-aryl *N*-phenylpropiolamide **1a**.[15] Furthermore, the hydroarylation would occur at the electron-rich 1-position of the naphthalene ring[16] to give the axially chiral benzoquinolinone **2b** with a highly configurationally stable biaryl axis owing to the steric demands of the two large ring systems. Gratifyingly, the expected regio- and enantioselective hydroarylation proceeded to completion at room temperature in 40 hours in the presence of a cationic palladium(II)/(*R*)-binap complex[17] (10 mol% Pd) to give **2b** in high yield with moderate enantioselectivity (Table 1, entry 1).

We then investigated the effects of a variety of axially chiral biaryl bisphosphine ligands (Scheme 3) on the yield and enantioselectivity of the reaction. Among the three bis(diphenylphosphine) ligands examined (Table 1, entries 1–3), (*R*)-H_8-binap furnished **2b** with the highest enantioselectivity

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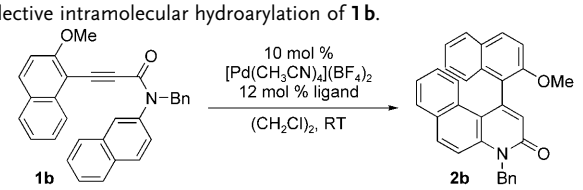
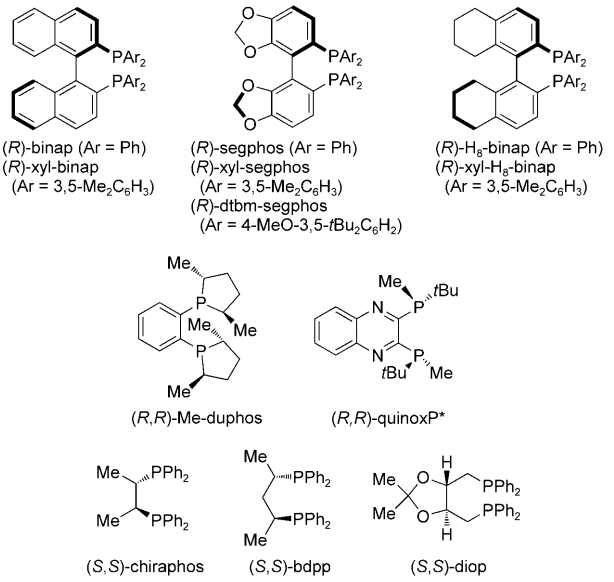
Table 1: Screening of chiral ligands for the palladium-catalyzed enantioselective intramolecular hydroarylation of **1b**.



Entry	Ligand	*t* [h]	Conv. [%][a]	Yield [%][b]	*ee* [%]
1	(*R*)-binap	40	94	93	69 (+)
2	(*R*)-segphos	40	99	64	69 (+)
3	(*R*)-H_8-binap	40	100	76	75 (+)
4	(*R*)-xyl-binap	40	81	73	75 (+)
5	(*R*)-xyl-segphos	40	79	76	72 (+)
6	(*S*)-xyl-H_8-binap	40	100	99	90 (−)
7	(*R*)-dtbm-segphos	40	54	12	< 2
8	(*R*,*R*)-Me-duphos	40	43	25	< 2
9	(*R*,*R*)-quinoxP*	40	55	40	17 (+)
10	(*S*,*S*)-chiraphos	40	39	33	46 (−)
11	(*S*,*S*)-bdpp	40	77	70	50 (−)
12	(*S*,*S*)-diop	40	100	> 99	60 (+)
13[c]	(*S*)-xyl-H_8-binap	72	100	94	92 (−)

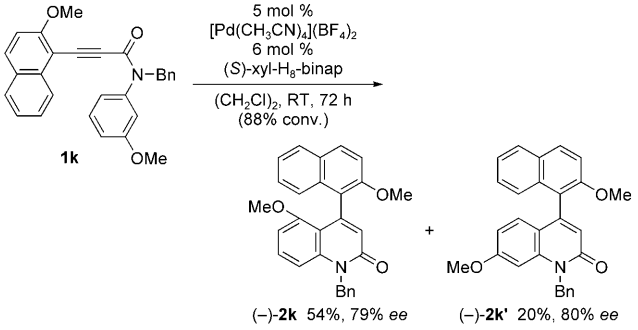
[a] Conversion was determined by ^{1}H NMR spectroscopy. [b] Yield of the isolated product. [c] The reaction was carried out with 5 mol% of $[Pd(CH_3CN)_4](BF_4)_2$ and 6 mol% of (*S*)-xyl-H_8-binap.



Scheme 3. Structures of chiral bisphosphine ligands.

(Table 1, entry 3). When the steric bulk of the aryl substituents on the phosphorus atoms of the biaryl bisphosphine ligands was increased, the enantioselectivity improved (Table 1, entries 4–6), whereby (*S*)-xyl-H_8-binap furnished **2b** in the highest yield with the highest *ee* value (Table 1, entry 6). However, the use of sterically more demanding (*R*)-dtbm-segphos as a ligand furnished racemic **2b** in poor yield (Table 1, entry 7). Chiral non-biaryl bisphosphine ligands (Scheme 3) were also examined (Table 1, entries 8–12); however, the observed *ee* values did not exceed that observed with the (*S*)-xyl-H_8-binap ligand. Finally, a prolonged reaction time (72 h) enabled the amount of palladium required to be decreased to 5 mol%.

We explored the scope of the enantioselective intramolecular hydroarylation of alkynes in the presence of the cationic palladium(II)/(*S*)-xyl-H_8-binap complex for the synthesis of axially chiral 4-aryl 2-quinolinone derivatives (Table 2). With respect to the substituent at the alkyne terminus, 2-methoxynaphthalene (Table 2, entry 1), 2-methoxy-6-methylbenzene (entry 2), and 2-methoxymethoxynaphthalene (entry 3) derivatives **1b–d** all furnished the desired benzoquinolinones **2b–d** in good yields and with good *ee* values. Not only naphthalene derivatives, but also the carbazole derivative **1e**, could be used. The corresponding fused quinolinone **2e** was obtained in good yield with perfect regioselectivity, although the *ee* value was moderate (Table 2, entry 4). 3-Aryl propiolamides bearing various electron-rich aryl groups on the nitrogen atom could also be employed. The reactions of tri- and dimethoxyphenyl derivatives **1f–h** proceeded to give the corresponding axially chiral quinolinones **2f–h** in good yields with good *ee* values (Table 2, entries 5–7). Interestingly, the reactions of 3,4-disubstituted substrates **1i** (Table 2, entry 8) and **1j** (entry 9) proceeded to give the sterically less demanding regioisomers **2i** and **2j**, respectively, with perfect regioselectivity, although the product yields were lower, and the *ee* value of **2j** was moderate. In contrast, the reaction of 3-methoxyphenyl derivative **1k** proceeded to give the sterically more encumbered regioisomer **2k** as the major product, along with the sterically less encumbered minor regioisomer **2k′** (Scheme 4).

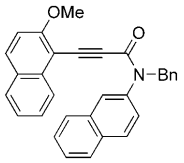
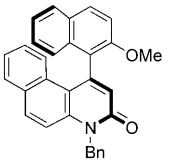
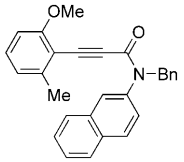
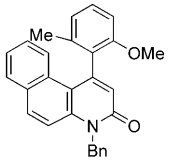
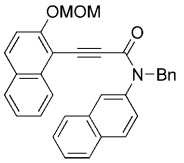
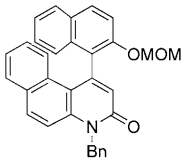
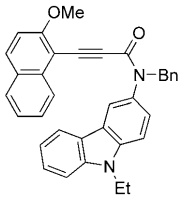
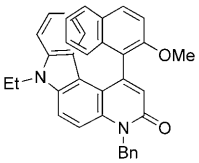
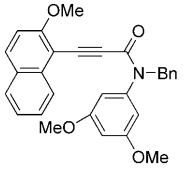
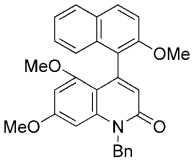
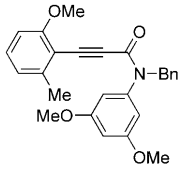
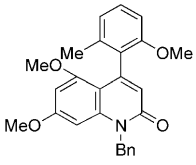
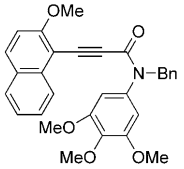
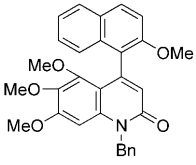
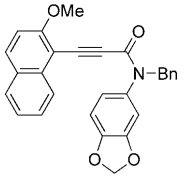
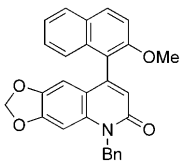
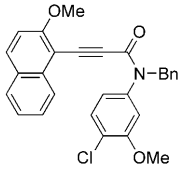
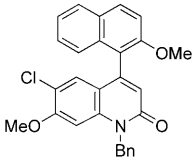


Scheme 4. Palladium-catalyzed enantioselective intramolecular hydroarylation of **1k**.

The presence of the 2-alkoxy-substituted aryl group at the alkyne terminus is important for both reactivity and enantioselectivity. Although the 2-methylnaphthalene derivative **1l** did participate in this reaction, the reaction was sluggish, and the *ee* values observed for the product were moderate (Scheme 5). The effect of the substituents on the nitrogen atom was also examined. Interestingly, the enantioselectivity of the reaction decreased dramatically when the nonmasked NH propiolamide **1m** was used (Scheme 6).

Axially chiral 4-aryl 3-bromo-2-quinolinones have been employed as key intermediates in the synthesis of pharmaceutically important compounds[13c] and chiral ligands[14] (Scheme 1). Therefore, we examined the bromination of the

Table 2: Palladium-catalyzed enantioselective intramolecular hydroarylation of **1b–j** to give axially chiral 4-aryl 2-quinolinones **2b–j**.[a]

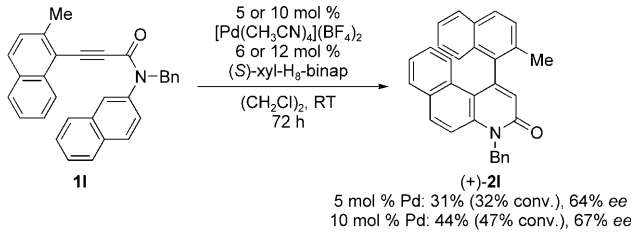
Entry	1	2 (*t* [h], conversion [%][b])		Yield [%][c] (*ee* [%])
1		**1b**	 (*R*)-(−)-**2b** (72, 100)	94 (92)
2		**1c**	 (−)-**2c** (48, 90)	90 (98)
3[d]		**1d**	 (−)-**2d** (72, 74)	65 (84)
4[d]		**1e**	 (−)-**2e** (72, 84)	75 (54)
5		**1f**	 (−)-**2f** (24, 100)	97 (71)
6		**1g**	 (−)-**2g** (24, 100)	90 (87)
7		**1h**	 (−)-**2h** (24, 85)	75 (70)
8		**1i**	 (−)-**2i** (72, 91)	50 (80)
9[e]		**1j**	 (+)-**2j** (72, 54)	44 (55)

[a] Reactions were conducted with $[Pd(CH_3CN)_4](BF_4)_2$ (5 mol%), (*S*)-xyl-H_8-binap (6 mol%), and **1b–j** in $(CH_2Cl)_2$ at room temperature. [b] Conversion was determined by ^1H NMR spectroscopy. [c] Yield of the isolated product. [d] The reaction was carried out with 10 mol% of $[Pd(CH_3CN)_4](BF_4)_2$ and 12 mol% of (*S*)-xyl-H_8-binap. [e] (*R*)-binap was used as the ligand.

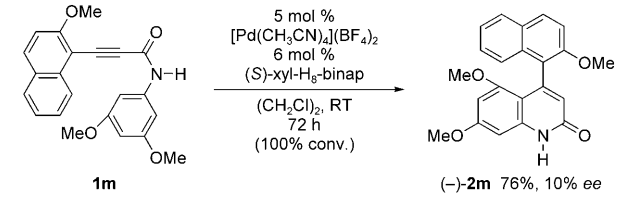
new axially chiral benzoquinolinone (−)-**2b**. The desired reaction proceeded smoothly with NBS as the brominating agent in DMF at room temperature to give the corresponding bromide (−)-**3** in high yield (Scheme 7). The absolute configuration of bromide (−)-**3** was determined unambiguously to be *S* by the anomalous-dispersion method.[18]

A possible mechanism for the enantioselective formation of axially chiral benzoquinolinone (*R*)-**2b** through the enantioselective hydroarylation of **1b** under the catalysis of a cationic palladium(II)/(*S*)-xyl-H_8-binap complex is shown in Scheme 8. The formation of intermediate **A** through bidentate chelation of the alkyne moiety and the alkoxy group of **1b** by the cationic palladium center would induce high reactivity and the rigid chiral environment. The avoidance of steric interaction between the benzyl group of **1b** and the equatorial aryl group on the phosphorus atom of (*S*)-xyl-H_8-binap in the chelation of intermediate **A** would control the axial chirality to give (*R*)-**2b**. Indeed, the reaction rate and enantioselectivity of the reaction of 2-methylnaphthalene derivative **1l** were lower than for the 2-methoxynaphthalene derivative **1b** (Table 2, entry 1 versus Scheme 5). Furthermore, the reaction of the sterically less demanding NH propiolamide **1m** proceeded with significantly lower enantioselectivity than that observed for the sterically demanding *N*-benzylpropiolamide **1b** (Table 2, entry 1 versus Scheme 6).

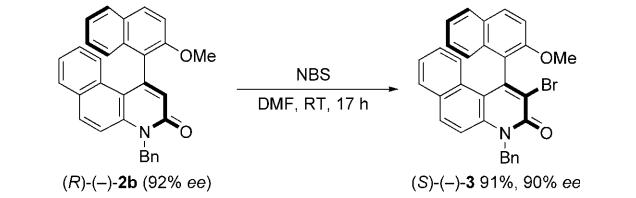
In conclusion, the first enantioselective intramolecular hydroarylation of alkynes to form axially chiral 4-aryl 2-quinolinones was developed by using a cationic palladium(II)/(*S*)-xyl-H_8-binap complex as a catalyst at room temperature. Future studies will focus on the application of this asymmetric annulation strategy to the enantioselective synthesis of various chiral aromatic compounds.



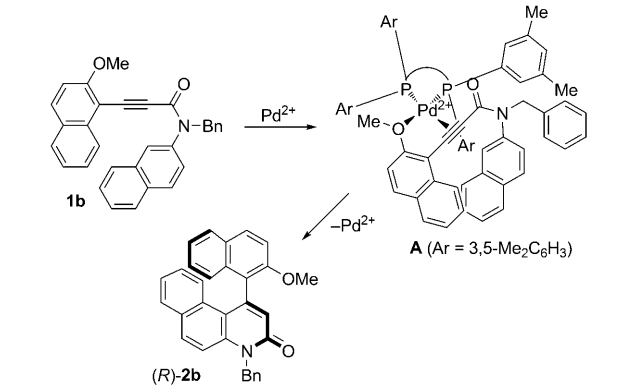
Scheme 5. Palladium-catalyzed enantioselective intramolecular hydroarylation of **1l**.



Scheme 6. Palladium-catalyzed enantioselective intramolecular hydroarylation of **1m**.



Scheme 7. Bromination of 4-aryl 2-quinolinone (*R*)-(−)-**2b** to give bromide (*S*)-(−)-**3**. DMF = *N*,*N*-dimethylformamide, NBS = *N*-bromosuccinimide.



Scheme 8. Possible mechanism for the enantioselective formation of (*R*)-**2b** with a cationic palladium(II)/(*S*)-xyl-H_8-binap catalyst.

Experimental Section

Representative procedure: Under an argon atmosphere, $[Pd(CH_3CN)_4](BF_4)_2$ (3.3 mg, 0.0075 mmol) and (*S*)-xyl-H_8-binap (6.7 mg, 0.0090 mmol) were dissolved in $(CH_2Cl)_2$ (0.4 mL), and the mixture was stirred at room temperature for 5 min. This mixture was then added to a solution of **1b** (66.2 mg, 0.150 mmol) in $(CH_2Cl)_2$ (1.1 mL) at room temperature, and the resulting mixture was stirred at room temperature for 72 h and then concentrated. Purification of the residue by preparative TLC (hexane/EtOAc 1:1) furnished (*R*)-(−)-**2b** (61.9 mg, 0.140 mmol, 94% yield, 92% *ee*).

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[18] CCDC 806596 ((*S*)-(−)-**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

