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Asymmetric Synthesis of 2-Aryl-2,3-dihydro-4-quinolones by Rhodium-Catalyzed 1,4-Addition of Arylzinc Reagents in the Presence of Chlorotrimethylsilane

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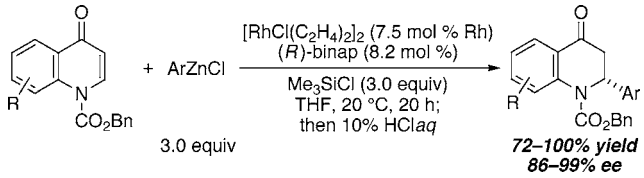
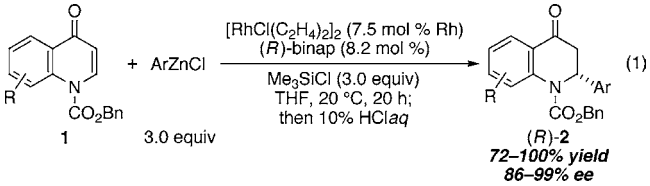
ABSTRACT



The first catalytic asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones has been developed by way of a rhodium-catalyzed 1,4-addition of arylzinc reagents to 4-quinolones. These 1,4-adducts can be obtained with high enantioselectivity by the use of (*R*)-binap as a ligand, and high yields are realized by conducting the reactions in the presence of chlorotrimethylsilane.

Design, synthesis, and evaluation of a series of organic molecules is one of the efficient methods for the identification of biologically active compounds in medicinal chemistry.[1] In this context, there has been a report on the effectiveness of 2-aryl-2,3-dihydro-4-quinolones as a new class of antimitotic antitumor agents.[2] It has also been shown that the activity differs in one enantiomer from the other, indicating the importance of highly enantioselective preparation of these compounds. Unfortunately, however, there are no effective ways of preparing enantio-enriched 2-aryl-2,3-dihydro-4-quinolones, limiting the opportunity for extensive studies of these compounds. Here we describe the first catalytic enantioselective synthesis of these compounds by a rhodium-catalyzed asymmetric 1,4-addition of arylzinc reagents to 4-quinolones (**1**)[3,4] in the presence of chlorotrimethylsilane (eq 1).



(1)

As a starting point, we initially employed 1-benzyloxycarbonyl-4-quinolone (**1a**) as a model substrate and attempted a rhodium-catalyzed asymmetric 1,4-addition of phenylboronic acid in the presence of (*R*)-binap as a ligand at 50 °C (Table 1, entry 1).[5] Under these conditions, only a small

(1) (a) Wermuth, C. G., Ed. *Practice of Medicinal Chemistry*, 2nd ed.; Elsevier: London, 2003. (b) Erhardt, P. W. *Pure Appl. Chem.* **2002**, *74*, 703−785.

(2) (a) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S.-C.; Hamel, E.; Hackl, T.; Lee, K.-H. *J. Med. Chem.* **1998**, *41*, 1155−1162. (b) Zhang, S.-X.; Feng, J.; Kuo, S.-C.; Brossi, A.; Hamel, E.; Tropsha, A.; Lee, K.-H. *J. Med. Chem.* **2000**, *43*, 167−176.

(3) For synthetic methods of 4-quinolones, see: (a) Beifuss, U.; Schniske, U.; Feder, G. *Tetrahedron* **2001**, *57*, 1005−1013. (b) Tois, J.; Vahermo, M.; Koskinen, A. *Tetrahedron Lett.* **2005**, *46*, 735−737.

(4) For examples of nonasymmetric stoichiometric 1,4-addition to 4-quinolones, see: (a) Beifuss, U.; Feder, G.; Bes, T.; Uson, I. *Synlett* **1998**, 649−651. (b) Reference 3a.

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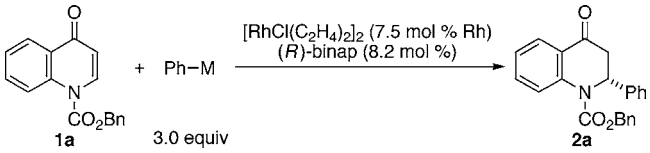
Table 1. Rhodium-Catalyzed Asymmetric 1,4-Addition of Phenylmetal Species to 4-Quinolone **1a**



entry	Ph-M	conditions[a]	yield (%)	ee[b] (%)
1	$PhB(OH)_2$	A	10	99 (*R*)
2	PhZnCl	B	35	99 (*R*)
3	PhZnCl	C	88	98 (*R*)

[a] Conditions A: KOH (30 mol %), 1,4-dioxane/H_2O (10/1), 50 °C, 20 h. Conditions B: THF, 20 °C, 20 h; then H_2O quench. Conditions C: Me_3SiCl (3.0 equiv), THF, 20 °C, 20 h; then 10% HCl(aq) quench. [b] ee was determined by chiral HPLC on a Chiralcel OD-H column with hexane/2-propanol = 90/10.

amount of 1,4-adduct **2a** was obtained (10% yield) with a recovery of unreacted **1a** (72%), although the enantioselectivity of **2a** was very high (99% ee).

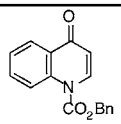
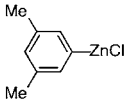
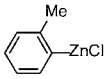
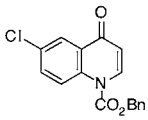
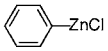
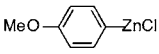
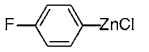
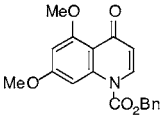
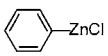
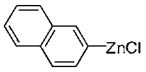
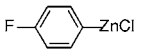
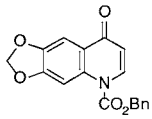
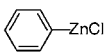
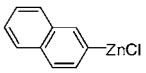
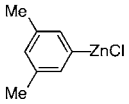
In an attempt to improve the reactivity, we then explored the possibility of catalytic asymmetric 1,4-addition of phenylzinc chloride (entry2), which is known to be an effective nucleophile to structurally similar 2,3-dihydro-4-pyridone substrates under rhodium catalysis, achieving high yield and ee.[6] Although substrate **1a** was completely comsumed by the use of phenylzinc chloride, 1,4-adduct **2a** was obtained only in 35% yield (with 99% ee), and the rest of the starting material was converted to unidentified products.

In the hope that the addition of chlorotrimethylsilane might facilitate the activation of substrate toward 1,4-addition (as a Lewis acid) and/or the stabilization of the product (by forming a silyl enol ether),[7] we then conducted a reaction in the presence of chlorotrimethylsilane under otherwise identical conditions as in entry 2. To our delight, 1,4-adduct **2a** was obtained in 88% yield after hydrolytic workup, and the ee of this product stayed as high (98% ee; entry 3).[8]

As shown in Table 2, several other 4-quinolones bearing substituents on the fused benzene ring can also undergo the 1,4-addition reaction under these conditions, not only with phenylzinc chloride but also with various other arylzinc chlorides, to afford a variety of 2-aryl-2,3-dihydro-4-quinolones in high yield with excellent enantioselectivity (72−100% yield, 86−99% ee). It is worth noting that the reactions are best conducted when a THF solution of arylzinc chloride and a THF solution of chlorotrimethylsilane are simultaneously added to a mixture of 4-quinolones and Rh/(*R*)-binap catalyst in THF.[9]

To determine the absolute configuration of these 1,4-adducts, the benzyloxycarbonyl group of **2a** (98% ee; Table 1, entry 3) was removed under basic aqueous conditions, obtaining known compound **3** in 82% yield with no erosion of ee (98% ee; eq 2). By comparison of the optical rotation

Table 2. Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylzinc Reagents to 4-Quinolones[a]

entry	substrate	ArZnCl	product	yield (%)	ee (%)[b]
1			**2b**	100	98 (*R*)
2			**2c**	74	86 (*R*)[c]
3			**2d**	89	99 (*R*)
4			**2e**	82	88 (*R*)
5			**2f**	72	95 (*R*)
6			**2g**	87	99 (*R*)
7			**2h**	92	98 (*R*)
8			**2i**	87	97 (*R*)
9			**2j**	94	94 (*R*)[c]
10			**2k**	87	90 (*R*)[c]
11			**2l**	96	97 (*R*)

[a] Conditions: $[RhCl(C_2H_4)_2]_2$ (7.5 mol % Rh), (*R*)-binap (8.2 mol %), Me_3SiCl (3.0 equiv), THF, 20 °C, 20 h; then 10% HCl(aq) quench. [b] ee was determined by chiral HPLC on a Chiralcel OD-H column with hexane/2-propanol unless otherwise noted. [c] ee was determined by chiral HPLC on a Chiralpak AD-H column with hexane/2-propanol.

(5) (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579−5580. (b) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052−5058.

(6) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240−6241.

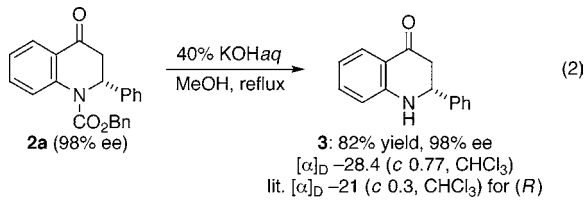
(7) Hayashi, T.; Yamamoto, S.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 4224−4227.

(8) The use of other chlorotrialkylsilanes (e.g., Et_3SiCl and *t*-$BuMe_2SiCl$) is not effective for promoting this 1,4-addition reaction.

(9) **General Procedure.** Compound **1** (0.20 mmol) was added to a solution of $[RhCl(C_2H_4)_2]_2$ (2.9 mg, 15 μmol of Rh) and (*R*)-binap (10.3 mg, 16.5 μmol) in THF (0.46−0.66 mL) at room temperature. ArZnCl (0.77−0.66 mL, 0.60 mmol; 0.78−0.91 M solution in THF) and chlorotrimethylsilane (0.77−0.66 mL, 0.60 mmol; 0.78−0.91 M solution in THF) were simultaneously added dropwise to it over 10 min, and the resulting mixture was stirred for 20 h at 20 °C. The reaction was quenched with HCl (10% aqueous), and the mixture was stirred for 1 h at room temperature. This was extracted with Et_2O, and the organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel preparative TLC with EtOAc/hexane to afford the desired 1,4-adduct **2**.

(10) (a) Antus, S.; Baitz-Gács, E.; Kajtár, J.; Snatzke, G.; Tökés, A. L. *Liebigs Ann. Chem.* **1994**, 497−502. (b) Tökés, A. L.; Szilágyi, L. *Synth. Commun.* **1987**, *17*, 1235−1245.

with the literature value,[10] the absolute configuration was determined to be (*R*).



(2)

The stereochemical outcome of these 1,4-addition reactions catalyzed by Rh/(*R*)-binap can be rationalized by the αre face approach of the substrate to avoid a steric repulsion between the phenyl group on the phosphorus atom of (*R*)-binap and the fused benzene ring of the substrate (Figure 1).[5]

In summary, we have developed the first catalytic asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones by way of a rhodium-catalyzed 1,4-addition of arylzinc reagents to 4-quinolones. These 1,4-adducts can be obtained in high ee by the use of (*R*)-binap as a ligand, and high yields have been realized by conducting the reactions in the presence of chlorotrimethylsilane.

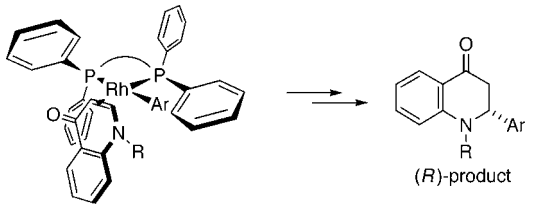


Figure 1. Proposed stereochemical pathway for the asymmetric 1,4-addition to 4-quinolones catalyzed by Rh/(*R*)-binap (R = CO_2Bn).

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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