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Enantioselective Synthesis of C_2-Symmetric Spirobilactams via Pd-Catalyzed Intramolecular Double *N*-Arylation

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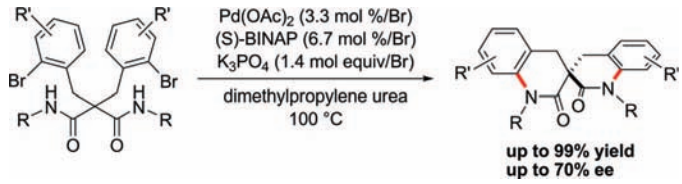
ABSTRACT



A Pd/BINAP-complex-catalyzed enantioselective intramolecular double *N*-arylation of malonamides bearing 2-bromoarylmethyl groups furnished C_2-symmetric spirobi(3,4-dihydro-2-quinolone) derivatives in up to 70% ee.

The demand for C_2-symmetric spiranes has been steadily increasing in synthetic chemistry because they contain an entirely rigid spiro backbone, which creates an effective asymmetric environment.[1] For instance, Zhou and co-workers have demonstrated the practicality of chiral phosphorus ligands based on the spiro skeleton.[2] A novel asymmetric dearomatization of phenol derivatives was recently reported, in which the use of a chiral hypervalent iodine(III) reagent having a spirobiindane scaffold was crucial for the high enantioselectivity.[3] We have also been investigating the utility of chiral spiro compounds as not only ligands[4] but also organocatalysts.[5] Since C_2-symmetric spiro skeletons have been recognized as suitable structural cores for useful materials, it is important to establish efficient protocols for their synthesis. A catalytic asymmetric synthesis would therefore provide a highly practical method for the preparation of optically active spiranes. The first example of this approach was reported by Tamao and co-workers in 1996.[6] They obtained an enantiomerically enriched 5-silaspiro[4.4]-

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(6) Tamao, K.; Nakamura, K.; Ishii, H.; Yamaguchi, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 12469.

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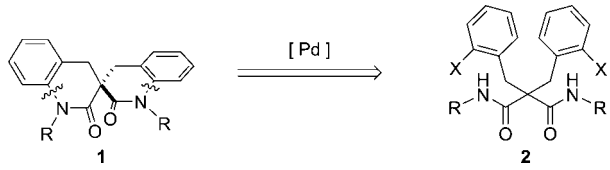
Scheme 1. Synthetic Approach to **1** via *N*-Arylation

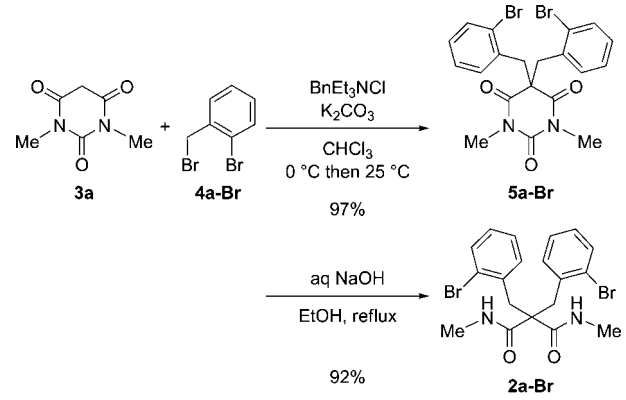


nonane derivative through an intramolecular double hydrosilylation catalyzed by a Rh/chiral diphosphine complex. Since then, asymmetric catalysis has been successfully employed for the synthesis of C_2-symmetric spiro compounds.[7−9] Hence, further development of their catalytic asymmetric synthesis may provide an efficient route to various optically active spiranes. Herein we report an enantioselective synthesis of spirobi(3,4-dihydro-2-quinolone) derivatives **1**[10] utilizing a Pd-catalyzed *N*-arylation (the Buchwald−Hartwig reaction). Such frameworks are expected to be versatile building blocks for functional chiral molecules.[10b] The present study is believed to be the first example of an enantioselective synthesis of C_2-symmetric spiranes using the Buchwald−Hartwig reaction.[11,12]

We hypothesized that optically active spirobilactams **1** would be obtained via a Pd-catalyzed double cyclization of malonamides **2** (Scheme 1). As a model substrate, 2,2-bis(2-bromobenzyl)-*N*,*N*′-dimethylmalonamide (**2a-Br**), in which the bromophenyl group can be reacted intramolecularly with the secondary amide, was designed (Scheme 2). The malonamide **2a-Br** was readily prepared in high yield starting with commercially available *N*,*N*′-dimethylbarbituric acid (**3a**). Thus, dialkylation of **3a** with 2-bromobenzyl bromide (**4a-Br**) under phase transfer catalysis conditions,[13] followed by a hydrolytic ring-opening reaction,[14] gave **2a-Br** in 89% yield (2 steps).

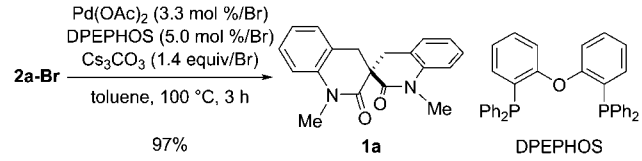
To examine whether the Pd-catalyzed intramolecular double *N*-arylation would be indeed operative, we initially

Scheme 2. Preparation of **2a-Br**



synthesized racemic **1a**.[15] A mixture of **2a-Br** and Cs_2CO_3 (1.4 equiv/Br) in toluene was stirred at 100 °C for 3 h in the presence of $Pd(OAc)_2$ (3.3 mol %/Br) and DPEPHOS (5.0 mol %/Br) to afford **1a** quantitatively (Scheme 3). No special care (e.g., high dilution or slow addition) was needed to prevent possible intermolecular reactions.

Scheme 3. Synthesis of the Racemic Spirobilactam **1a**



This result prompted us to explore an efficient chiral ligand (Table 1). When the reaction was conducted with (*S*)-BINAP in *N*-methyl-2-pyrrolidone (NMP) solvent, **1a** was obtained in 99% yield with 55% ee (entry 1). Other axially chiral diphosphine ligands including (*S*)-Tol-BINAP were less stereoselective (entries 2−7). Pd complexes with chiral monophosphine ligands such as (*R*)-MeO-MOP and (*S*)-QUINAP gave the racemate in 69% and 57% yields, respectively (entries 8 and 9). The reactions with a ferrocene-based chiral phosphine also produced **1a**, albeit with no enantioselectivity (entries 10 and 11). A centrally chiral diphosphine ligand (*R*,*R*)-DIOP, a phosphine-oxazoline hybrid ligand (*R*)-^{i}Pr-PHOX, and a bisoxazoline ligand (*S*,*S*)-^{t}Bu-BOX turned out to be ineffective (entries 12−14). Non-negligible background reactions were observed under the reaction conditions without ligand, resulting in a 19% yield of **1a** (entry 15).

After extensive optimization of reaction conditions (Pd/BINAP ratio, base, solvent, etc.),[16] we were gratified to find

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(10) The preparation of racemic **1** using another route was reported; see: (a) Choi, H.-J.; Park, Y. J.; Kim, M. G.; Park, Y. S. *J. Heterocycl. Chem.* **2000**, *37*, 1305. (b) Choi, H.-J.; Park, Y. S.; Kim, M. G.; Park, Y. J.; Yoon, N. S.; Bell, T. W. *Tetrahedron* **2006**, *62*, 8696.

(11) For the enantioselective Buchwald−Hartwig reaction, see: (a) Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. *J. Am. Chem. Soc.* **2005**, *127*, 3676. (b) Kitagawa, O.; Yoshikawa, M.; Tanabe, H.; Morita, T.; Takahashi, M.; Dobashi, Y.; Taguchi, T. *J. Am. Chem. Soc.* **2006**, *128*, 12923. (c) Kitagawa, O.; Kurihara, D.; Tanabe, H.; Shibuya, T.; Taguchi, T. *Tetrahedron Lett.* **2008**, *49*, 471.

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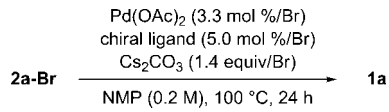
(16) See Supporting Information for details.

Table 1. Ligand Screening in the Asymmetric Intramolecular Double *N*-Arylation of **2a-Br**[a]



entry	chiral ligand	yield (%)[b]	ee (%)[c]
1	(*S*)-BINAP	99	55
2	(*S*)-Tol-BINAP	97	37
3	(*R*)-SYNPHOS	99	−36[d]
4	(*R*)-SEGPHOS	96	−14[d]
5	(*R*)-DIFLUORPHOS	73	−7[d]
6	(*R*)-MeO-BIPHEP	98	−26[d]
7	(*R*)-C_3-TUNEPHOS	97	−14[d]
8	(*R*)-MeO-MOP	69	*rac*
9	(*S*)-QUINAP	57	*rac*
10	(*R*)-(*S*)-JOSIPHOS	99	*rac*
11	(*R*)-(*R*)-WALPHOS	98	*rac*
12	(*R*,*R*)-DIOP	53	*rac*
13	(*R*)-^{i}Pr-PHOX	35	*rac*
14	(*S*,*S*)-^{t}Bu-BOX	3	*rac*
15	none	19	

[a] All reactions were carried out in the presence of 3.3 mol %/Br of $Pd(OAc)_2$, 5.0 mol %/Br of chiral ligand, and 1.4 equiv/Br of Cs_2CO_3 at 100 °C for 24 h in *N*-methyl-2-pyrrolidone (0.2 M) under an argon atmosphere. See Supporting Information for the structures of the chiral ligands. [b] Determined by ^{1}H NMR. [c] Determined by HPLC analysis (Daicel Chiralpak IB). [d] The enantiomer opposite to that in entry 1 was preferentially formed.

an improvement of the enantioselectivity. Thus, the employment of 6.7 mol %/Br of (*S*)-BINAP and 1.4 equiv/Br of K_3PO_4 in *N*,*N*′-dimethylpropylene urea (DMPU) solvent led to quantitative formation of the spirobilactam **1a**, whose enantiomeric excess reached 70% (Table 2, entry 1). The scope of this transformation was next examined with a variety of malonamides **2**. Substrate **2a-Cl** having 2-chlorobenzyl groups was less reactive: **1a** was produced in only 8% yield with 6% ee (entry 2). Although the reaction of the iodide analog **2a-I** took place smoothly to give **1a** in high yield, its enantioselectivity was as low as 38% ee (entry 3). This might reflect on the greater reactivity of the aryl iodide toward the background reaction.[17] Similar to **2a-Br**, the reactions of **2b** (R = Et) and **2c** (R = Bn) furnished the products **1b** and **1c** in excellent yields (99%) and sufficient selectivities (52% ee and 49% ee), respectively (entries 4 and 5). The enantioselectivity is affected by the substituent on the aromatic ring. Thus, moderate optical purity (48% ee) was detected for **1d** possessing Cl groups at the 5-positions, whereas nearly racemic spirobilactams were produced for 5-MeO- and 3-NO_2-substituted malonamides **2e** and **2f** (entries 6−8). It was also feasible to introduce a 1,3-benzodioxole ring to the spirobilactam, leading to quantitative formation of **1g** with 57% ee (entry 9). Unfortunately, no selectivity was observed for the sterically more demanding substrate **2h** (entry 10). It should be emphasized that optically

(17) The conversion of **2a-Br** was 10% in the absence of (*S*)-BINAP after 3 h, whereas that of **2a-I** reached >95% under the same conditions.

Table 2. Pd-Catalyzed Enantioselective Intramolecular Double *N*-Arylation of **2**[a]

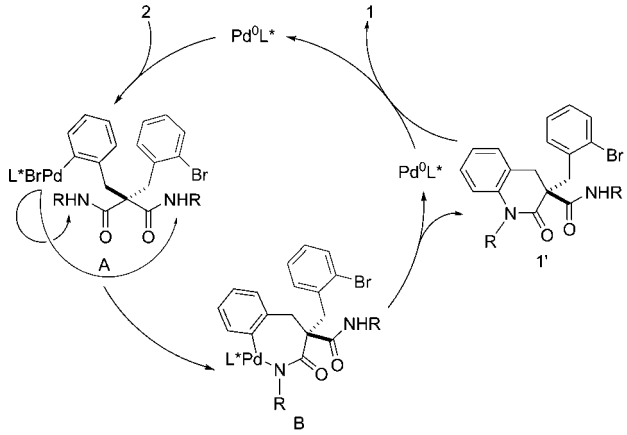
		product (**1**)	
entry	substrate (**2**)	yield (%)[b]	ee (%)[c]
1	X = Br (**2a-Br**)	99 (**1a**)	70
2	X = Cl (**2a-Cl**)	8 (**1a**)	6
3	X = I (**2a-I**)	94 (**1a**)	38
4	R = Et (**2b**)	99 (**1b**)	52
5	R = Bn (**2c**)	99 (**1c**)	49
6[d]	R′ = 5-Cl (**2d**)	85 (**1d**)	48
7[d]	R′ = 5-MeO (**2e**)	90 (**1e**)	6
8	R′ = 3-NO_2 (**2f**)	42 (**1f**)	5
9	(**2g**)	99 (**1g**)	57
10[d]	(**2h**)	95 (**1h**)	*rac*

[a] All reactions were performed at 100 °C under an argon atmosphere for 6−24 h. The ratio of **2** (mol)/$Pd(OAc)_2$ (mol)/(*S*)-BINAP (mol)/K_3PO_4 (mol)/DMPU (L) = 1.0/0.066/0.13/2.8/2.5. [b] Isolated yield. [c] Determined by HPLC analysis. Absolute configuration of the products has not been determined yet. [d] The reactions were performed in toluene using Cs_2CO_3 as the base for 24−72 h.

pure **1a**, **1b**, and **1c** were readily obtained by a single recrystallization of the product. For example, addition of MeOH (ca. 20 mL) to a solution of **1a** (70% ee, 3.37 g) in $CHCl_3$ (ca. 20 mL) at rt afforded 1.18 g of enantiomerically pure **1a**.

A plausible catalytic cycle for the asymmetric *N*-arylation is depicted in Scheme 4. As in the conventional Buchwald−Hartwig reaction,[18] the formation of **1** seems to be initiated by the oxidative addition of one of the bromoarenes in **2** to a catalytically active Pd^0 complex. Desymmetrization of the amide groups in the resulting Pd^{II} complex **A** proceeds to

Scheme 4. Plausible Catalytic Cycle



give palladacycle **B**. The following C−N bond-forming reductive elimination yields monocyclized compound **1′** and regenerates the Pd catalyst. A subsequent intramolecular *N*-arylation of **1′** furnishes the desired spirobilactam **1**.

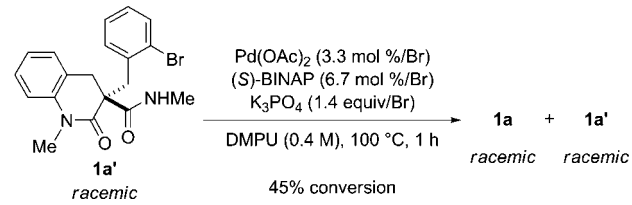
Enantioselectivity is determined in the first cyclization, namely, the formation of the intermediate **1′** by way of **B**. It is accordingly conceivable that a kinetic resolution process would be involved in the second cyclization (**1′** to **1**). To confirm this possibility, racemic intermediate **1a′**, which was prepared by the *N*-arylation of **2a-Br** under milder conditions,[19] was subjected to the Pd catalysis.

Contrary to our expectations, no enantioselectivities were observed for both the formed **1a** and the unreacted **1a′** at

(18) (a) Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 3584. (b) Fujita, K.; Yamashita, M.; Puschmann, F.; Alvarez-Falcon, M. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9044. (c) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001.

(19) Racemic **1a′** was obtained by mixing **2a-Br**, $Pd(OAc)_2$ (3.3 mol %/Br), DPEPHOS (5.0 mol %/Br), and Cs_2CO_3 (1.4 equiv/Br) in toluene at 50 °C for 48 h. For details, see Supporting Information.

Scheme 5. Pd-Catalyzed Enantioselective Intramolecular *N*-Arylation of Racemic Intermediate **1a′**



45% conversion (Scheme 5). However, these results evidently support the postulated reaction pathway shown in Scheme 4.

In summary, we have developed an efficient synthetic method toward spirobilactams **1**, where the Pd-catalyzed enantioselective intramolecular double *N*-arylation of malonamides **2** is included as the key step. Optically active **1a** was obtained in 88% overall yield from the starting material, *N*,*N*′-dimethylbarbituric acid, without chromatographic purification. Further study on the synthetic utility of **1** is currently in progress.

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

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