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Organocatalytic Aryl–Aryl Bond Formation: An Atroposelective [3,3]-Rearrangement Approach to BINAM Derivatives

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Supporting Information

ABSTRACT: Herein we disclose an organocatalytic aryl–aryl bond-forming process for the regio- and atroposelective synthesis of 2,2′-diamino-1,1′-binaphthalenes (BINAMs). In the presence of catalytic amounts of axially chiral phosphoric acids, achiral *N,N′*-binaphthyl hydrazines undergo a facile [3,3]-sigmatropic rearrangement to afford enantiomerically enriched BINAM derivatives in good to excellent yield. This transformation represents the first example of a metal-free, catalytic C(sp^2)–C(sp^2) bond formation between two aromatic rings with concomitant *de novo* atroposelective installation of an axis of chirality. Density functional calculations reveal that, in the transition state for C–C bond formation, the phosphoric acid proton of the catalyst is fully transferred to one of the N-atoms of the substrate, and the resulting phosphate acts as a chiral counterion.

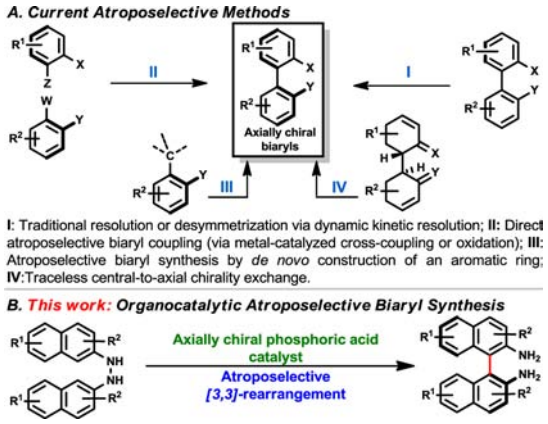

Figure 1. Organocatalytic atroposelective aryl–aryl bond formation utilizing a facile [3,3]-sigmatropic rearrangement.

During the past 20 years, axially chiral biaryl compounds[1] have played a key role as ligands in the development of many catalytic enantioselective transformations, including transition-metal-catalyzed cross-coupling reactions.[2] Without exaggeration it can be stated that axially chiral nonracemic biaryls (e.g., BINAP, BINOL, and their derivatives) have become the most successful class of ligands in history, with a wide range of catalytic enantioselective processes, including several on an industrial scale.[2b,3] Axial chirality is also widespread in nature. More than 1000 axially chiral natural products have so far been isolated. and many of them exhibit remarkable biological activities (e.g., vancomycin, streptonigrin, michellamines); it is not uncommon that opposite enantiomers display completely different biological profiles (e.g., gossypol).[1c] Recently it was recognized that the phenomenon of atropisomerism has enormous implications in the development of pharmaceuticals.[4] Given the abundance of axially chiral biaryl compounds in nature as well as their importance in asymmetric catalysis and materials science, it is surprising that relatively few methods are available for their atroposelective synthesis.[1c,5] Current strategies[6] for the synthesis of axially chiral nonracemic biaryls include resolution of racemic biaryls, desymmetrization of preformed prochiral biaryls, dynamic kinetic resolution of rapidly racemizing preformed chiral biaryls,[6c,g] transition-metal-catalyzed aryl–aryl coupling,[5b,6d] *de novo* construction of an aromatic ring,[6b] and traceless central-to-axial chirality exchange[6f] (Figure 1).

While the methods outlined in Figure 1 are influential, they all have limited scope; new and powerful synthetic strategies are needed to complement existing methods. Recently, we became intrigued by the possibility of achieving the first organocatalytic atroposelective biaryl synthesis using *N,N′*-diaryl hydrazines as substrates (Figure 1B).[7]

The thermal or acid-mediated [3,3]-rearrangement of *N,N′*-diaryl hydrazines, a process known for nearly 110 years, leads to the formation of a new C(sp^2)–C(sp^2) bond between two aromatic rings.[8] This remarkable transformation does not require the use of transition metals, halogen atoms, or other replaceable substituents, the two reacting C(sp^2)–H bonds are not activated in any way, and reactive intermediates (e.g., carbenes, carbon-centered radicals, carbanions, or carbocations) are not involved in the process.

A thorough literature search yielded a single report in 1985 by Sannicolo[9] in which an attempted noncatalytic enantioselective rearrangement of 2,2′-hydrazonaphthalene (**1a**) to BINAM (**2a**), requiring a large excess (3–6 equiv) of (+)-camphor-10-sulfonic acid (CSA), is described (Scheme 1). The observed enantiomeric ratio (*er*) for **2a** was very low (57.5:42.5).[10] No further studies to render this transformation, or any other closely related transformation that furnish biaryls, catalytic and/or highly enantioselective have been reported.[11]

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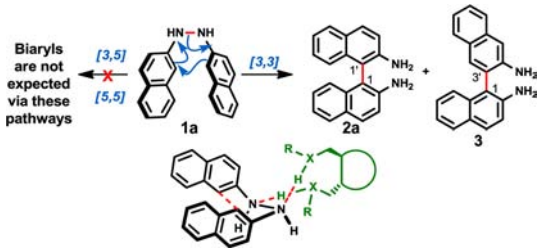
Scheme 1. Regiochemical Considerations and the Initial Model for the Hypothetical Transition State



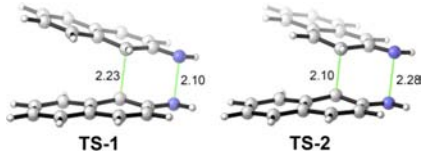


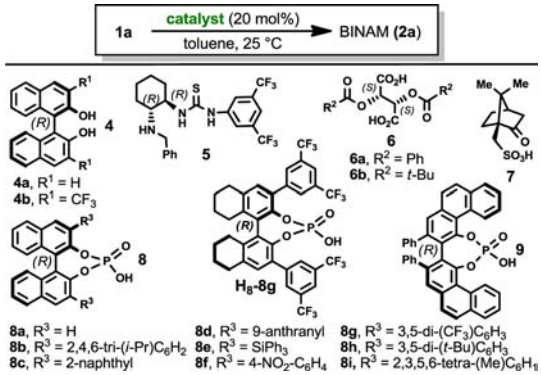
Figure 2. M06-2X transition states for the thermal (i.e., uncatalyzed) rearrangement of **1a**. Distances reported in Å.

We surmised that via the careful screening of catalysts, solvents, and temperature, a set of ideal conditions could be identified that would facilitate the catalytic and highly atroposelective rearrangement of *N,N′*-biaryl hydrazines to biaryl amines. We chose **1a** as our preferred substrate over other *N,N′*-biaryl hydrazines since its substitution pattern allows the formation of only two possible regioisomeric [3,3]-rearrangement products (**2a** and **3**, Scheme 1); the [5,5]- and [3,5]-pathways were not expected to compete.[12]

In addition, density functional calculations at the M06-2X/6-31G(d,p)[13] level of theory with CPCM toluene solvent confirmed that, for the uncatalyzed concerted rearrangement of **1a**, the lowest energy transition state (**TS-1**, Figure 2) provides the expected [3,3] peri- and regioselectivity as well as the potential exclusive formation of **2a** over **3**. The free energy barrier ($\Delta G^{\ddagger}$) for **1a**→**2a** via **TS-1** is 34.2 kcal/mol and for **1a**→**3** via **TS-2** is 48.9 kcal/mol. The dearomatized intermediate along the pathway for **1a**→**2a** is endergonic, with ΔG = 11.9 kcal/mol. The overall rearrangement **1a**→**2a** is exergonic by 30.5 kcal/mol.

Our initial hypothesis was that the ideal catalyst would activate **1a** by engaging both N-atoms (Scheme 1). To maximize H-bonding between **1a** and the catalyst, toluene was chosen as the solvent and a catalyst loading of 20% was used (Table 1). First, we evaluated BINOL (**4a**) and thiourea **5**, but these catalysts did not promote the rearrangement (**1a**→**2a**) even after 2 days (entries 1 and 3). However, the 3,3′-di-CF_3 derivative of BINOL (**4b**) gave rise to **2a** in good yield but with very low enantioselectivity (51.5:48.5 *er*). Presumably, the greater acidity of catalyst **4b** relative to **4a** is why **4b** is able to catalyze the rearrangement as opposed to **4a**.[14] Next, we chose tartaric acid derivatives and (+)-CSA (entries 4−6) as catalysts; formation of **2a** was fast and the yield was high, but the enantioselectivity remained low. At this point we reasoned that it was unlikely that the rearrangement could be catalyzed by H-bond donors, but rather would require full proton transfer from the catalyst to one of the N-atoms of **1a**. If so, enantioselectivity could still be induced via a chiral counterion strategy. Thus we turned our attention to BINOL-derived chiral phosphoric acids as catalysts.[3d,15] Indeed, catalyst **8a** led to rapid product formation with 56.5:43.5 *er*. This result encouraged us to continue the evaluation of axially chiral Brønsted acids for the rearrangement

Table 1. Catalyst Screen for Atroposelective Synthesis of 2a from 1a



Entry[a]	Catalyst	Time[b] (h)	Yield[c] (%)	*er*[d]	*ee* (%)
1	(*R*)-**4a**	48	0	N/A	N/A
2	(*R*)-**4b**	72	70	51.5:48.5	3
3	(*R,R*)-**5**	48	0	N/A	N/A
4	(*S,S*)-**6a**	1	70	51.5:48.5	3
5	(*S,S*)-**6b**	1	83	52.5:47.5	5
6	(+)-CSA (**7**)	1	81	52:48	4
7	(*R*)-**8a**	1	88	56.5:43.5	13
8	(*R*)-**8b**	144	64	54:46	8
9	(*R*)-**8c**	48	86	67:33	34
10	(*R*)-**8d**	72	82	67.5:32.5	35
11	(*R*)-**8e**	144	89	80.5:19.5	61
12	(*R*)-**8f**	48	87	74.5:25.5	49
13	(*R*)-**8g**	2	89	84.5:15.5	69
14	(*R*)-**8h**	6	80	70.5:29.5	41
15	(*R*)-**8i**	24	70	76:24	52
16	(*R*)-**H$_8$-8g**	1	90	90.5:9.5	81
17	(*R*)-**9**	72	84	77:23	54

[a]Reactions were performed on 0.05 mmol scale (0.025 M solution in toluene) using 20 mol% catalyst loading. [b]Time required for the reaction to reach completion (except for entries 1 and 3, in which **1a** did not react). [c]Isolated yield. [d]Enantiomeric ratio determined using Chiralpak IA column (dimensions: 4.6 × 250 mm, 5 μm, flow rate 1 mL/min, hexane:IPA = 50:50).

of **1a**. Variation of the steric bulk and electronic properties of substituents at the 3- and 3′-positions (catalysts **8b**−**i**) resulted in dramatic changes in both the reaction rate and the level of asymmetric induction. For example, catalysts **8b** and **8e** (entries 8 and 11) afforded **2a** in 54:46 and 80.5:19.5 *er*, respectively, but the reaction was very slow (6 days) in both cases. Catalysts bearing fused aromatic rings (**8c** and **8d**) or aromatic rings with electron-withdrawing groups (**8f**, **8g**, and (*R*)-**H$_8$-8g**) as substituents led to faster rearrangement; the presence of CF_3 groups (catalysts **8g** and **H$_8$-8g**) led to the highest observed *er* (84.5:15.5 and 90.5:9.5) in the shortest amount of time (entries 13 and 16). Use of the vaulted type catalyst **9** (entry 17) nearly doubled the *er* values when compared to catalysts **8c** and **8d**, although the reaction rate did not improve (72 h).

Next, we investigated the effect of solvent using catalyst (*R*)-**8g** (Table 2). Among nonpolar solvents (entries 1−7), benzene was the most effective at 25 °C (entry 6). Polar solvents containing highly electronegative heteroatoms (i.e., O and N, entries 8−11) generally furnished **2a** in lower isolated yields and in significantly diminished *er*; presumably the heteroatoms disrupted the proton transfer from the catalyst to **1a**. On the basis of these findings, it was reasonable to assume that traces of water will likely erode the *er*; indeed, addition of molecular sieves (3, 4, or 5 Å MS) resulted in a slight improvement of the *er* (85.5:14.5→87.5:12.5). In benzene, using 4 Å MS and lowering the temperature (25→7 °C) improved the enantioselectivity (87.5:12.5→90.5:9.5 *er*). However, due to the high freezing point of benzene (+5.5 °C), we had to switch back to toluene which has a much lower freezing point

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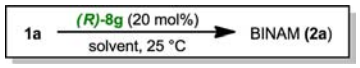
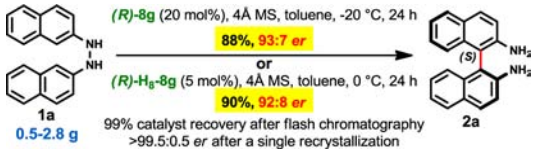
Table 2. Solvent Screen for Atroposelective Synthesis of 2a



Entry[a]	Solvent	Time[b] (h)	Yield[c] (%)	er[d]	ee (%)
1	CH_2Cl_2	2	99	83:17	66
2	$(CH_2Cl)_2$	1	90	83:17	66
3	C_6F_6	8	86	80:20	60
4	$PhCF_3$	0.5	85	83:17	66
5	PhCl	3	85	83:17	66
6	benzene	1	84	85:5:14.5	71
7	pentane	48	77[e]	77.5:22.5[e]	55[e]
8	Et_2O	48	68	74.5:25.5	49
9	THF	48	53	63:37	26
10	MeCN	0.5	96	60.5:39.5	21
11	EtCN	2	75	60:40	20

[a−d]Reaction conditions were the same as in Table 1. [e]Substrate **1a** has poor solubility in this solvent.

Scheme 2. Practical Atroposelective Synthesis of (*S*)-2a on a 0.5−2.8 g Scale Using Catalysts (*R*)-8g and (*R*)-H_8-8g



(−95 °C). The highest *er* (93:7) and an excellent yield (89%) of **2a** were achieved in toluene at −20 °C in the presence of 4 Å MS. Surprisingly, further lowering of the temperature (−20→−40 °C) in toluene decreased both the yield (89→80%) and *er* (93:7→90:10).

The practicality of this powerful catalytic atroposelective method could also be convincingly demonstrated (Scheme 2). The optimized procedure performed well on a 2−10 mmol (up to 2.8 g) scale, affording 88−90% isolated yield of **2a** with up to 93:7 *er*.[16] Remarkably, the catalysts could be recovered in nearly quantitative yield (99%) after flash chromatography, and a single recrystallization of the enantiomerically enriched **2a** from toluene yielded optically pure (>99.5:0.5 *er*) material.

To understand the role of the chiral phosphoric acid catalyst and stereoselectivity, we have used M06-2X/6-31G(d,p) density functional calculations in CPCM-toluene solvent to model the rearrangement **1a**→**2a** catalyzed by (*R*)-H_8-**8g**. Figure 3 shows **TS-3S** and **TS-3R**, which are the lowest energy enantiomeric C−C bond-forming transition states leading to the dearomatized intermediate from **1a**. **TS-3S** has $\Delta G^{\ddagger}$ = 20.0 kcal/mol and **TS-3R** has $\Delta G^{\ddagger}$ = 22.2 kcal/mol at 253 K relative to free catalyst and substrate. These $\Delta G^{\ddagger}$ values are ∼14 kcal/mol lower than for uncatalyzed **TS-1**. **TS-3S** and **TS-3R** feature the phosphoric acid proton fully transferred from the catalyst to one of the N-atoms of **1a**, and the phosphate acts as a chiral counterion.[17] This protonation lowers the barrier by charge polarization to create a more asynchronous, but still concerted, transition state. Transition states without proton transfer were found to be several kcal/mol higher in energy. After proton transfer, the phosphate counterion interacts with protonated **1H**$^+$ in a bidentate fashion involving two H-bonding interactions. However, the H-bonding interactions are not equivalent. In **TS-3S**/**3R**, the phosphate O-atom that was involved in proton transfer has a short H-bonding distance of ∼1.6 Å due to the enhanced electrostatic attraction, while the second H-bonding interaction has a distance of 2.4−2.7 Å.

The free energy difference between **TS-3S** and **TS-3R** is 2.2 kcal/mol at 253 K. We have also modeled the similar (*R*)-**8g** catalyst. The $\Delta\Delta G^{\ddagger}$ for (*R*)-**8g** transition states is 1.4 kcal/mol. We have confirmed the in silico predicted preferential formation of the (*S*)-enantiomer using chiral HPLC (see SI). The C−C bond-forming step in **1a**→**2a** is likely stereodetermining because re-aromatization via phosphate anion deprotonation and proton shuttling to set the axial chirality occurs via amino groups twisting past each other while avoiding naphthyl groups twisting past each other. See the SI for further explanation. Stereoselectivity in the C−C bond-forming transition states is the result of both steric and electronic effects. The chiral counterion creates a spatial chiral pocket to house **1H**$^+$. In addition, the electron-deficient CF_3 groups of catalyst (*R*)-H_8-**8g** (and (*R*)-**8g**) induce significant C−H bond and π−π-aryl interactions that favor **TS-3S** over **TS-3R**. Indeed, modeling of the C−C bond-forming transition states with catalysts **8a** and **8g** with aryl CH_3 groups rather than aryl CF_3 groups showed the expected decrease in stereoselectivity.

The investigated range of substrates include mostly symmetrical *N*,*N*′-biaryl hydrazines (entries 1−7, Table 3) that are substituted in their 3,3′-, 5,5′-, 6,6′-, and 7,7′-positions.[8b,18] Both

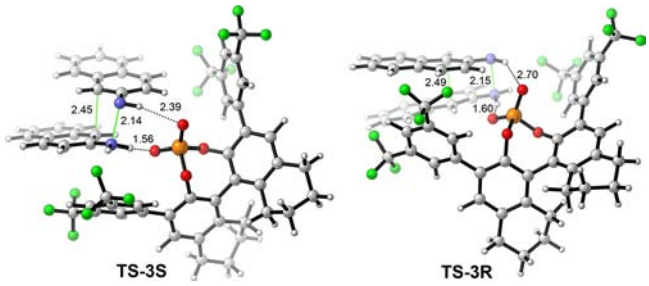
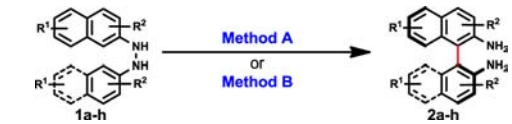


Figure 3. Enantiomeric C−C bond-forming transition states.

Table 3. Exploration of the Substrate Scope for 1→2



Entry[a]	Product	Yield[d] (%), er[e] A	B
1	(−)-2a	89 93:7[a]	86 92:8[a]
		88 93:7[b] (S) [86]	90 92:8[c] (S) [84]
2	(+)-2b	70 87.5 : 12.5 [75]	90 91.5 : 8.5 [83]
3	(−)-2c	81 81.5 : 18.5 [63]	87 82 : 18 [64]
4	(−)-2d	83 65.5 : 34.5 [31]	80 51.5 : 48.5 [3]
5	(−)-2e	85 51 : 49 [2]	83 52 : 48 [4]
6	(−)-2f	85 85 : 15 [70]	82 72.5 : 27.5 [45]
7	(−)-2g	69 85.5 : 14.5 [71]	67 54.5 : 45.5 [9]
8	2h	89 50 : 50 [0]	86 50 : 50 [0]

Method A: catalyst (*R*)-**8g** (20 mol %), 4 Å MS, −20 °C, 24 h (0.025 M solution). Method B: catalyst (*R*)-H_8-**8g** (5 mol %), 4 Å MS, 0 °C, 24 h (0.025 M solution). [a]Reactions were performed on 0.05 mmol scale (0.025 M solution) unless indicated otherwise. [b]Performed on a 2.8 g scale. [c]Performed on a 0.5 g scale. [d]Isolated yield. [e]The *er* was determined using Chiralpak IA column. [ee] values are in %.

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catalysts (*R*)-**8g** and (*R*)-**H$_8$-8g** were tested for each substrate, and in the case of 3,3′-disubstituted hydrazines the observed *er* values were substantially different (entries 4, 6, and 7). Methoxy substituents in the 3,3′-position significantly lowered the observed *er* values (entries 4 and 5), while 5,5′- and 7,7′-dimethoxy hydrazines afforded the corresponding biaryls with good *er* values (entries 2 and 3). It is noteworthy that the rearrangement of unsymmetrical hydrazine **2h** did not result in any enantioselectivity, in agreement with the predicted TS.

In conclusion, we have successfully developed the first organocatalytic atroposelective synthesis of biaryl amines, exploiting a facile [3,3]-rearrangement. Using density functional calculations of the C−C bond-forming step, we can predict the absolute configuration of the axially chiral biaryl products. This approach also allows us to engage in the rational design of more effective catalysts and explore related rearrangements. We are in the process of expanding the scope of this powerful atroposelective method to unsymmetrical biaryl hydrazines.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and charactetization data; complete ref 13b. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) One likely explanation for the observed low enantioselectivity (57.5:42.5 or 1.35:1 er) is that a simple optical resolution occurred due to the presence of large quantities of (+)-CSA.[9]

(11) List et al. recently reported a SPINOL-phosphoric acid-catalyzed asymmetric Fisher indolization reaction: Muller, S.; Webber, M. J.; List, B. *J. Am. Chem. Soc.* **2011**, *133*, 18534.

(12) Upon rearrangement, *N,N′*-biaryl hydrazines that contain only substituted benzene rings can give rise to a mixture of regioisomeric biaryl products featuring 2,2′, 2,4′ and 4,4′-biaryl linkages. The number of possible regioisomers is greatly reduced when the biaryl hydrazines substrates are derived from fused aromatic systems, such as 2-substituted naphthalenes.

(13) (a) Calculations were carried out using Gaussian 09. Transition-state structures were confirmed to be first-order saddle points by vibrational normal mode analysis. (b) Frisch, M. J.; et al. *Gaussian 09*, revision B.01; Gaussian, Inc.: Wallingford, CT, 2009. For M06-2X references see: (c) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215. (d) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.

(14) We found that regular, non-deactivated, silica gel is able to catalyze the rearrangement of **1a** to **2a** in nearly quantitative yield.

(15) (a) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (b) Terada, M. *Synthesis* **2010**, 1929.

(16) In this reaction, 8% of 7*H*-dibenzo[*c,g*]carbazole was also formed which could be easily separated from **2a**.

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(18) These substrates are prepared via reduction of the corresponding symmetrical azo compounds.[8b] We found that the solubility of 6,6′-disubstituted azo compounds is generally very poor compared to azo compounds that bear substituents in any other position. This limited solubility hinders their reduction to the corresponding *N,N′*-biaryl hydrazines.