



## Convenient Routes to Symmetrical Benzils and Chiral 1,2-Diaryl-1,2-diaminoethanes, Useful Controllers and Probes for Enantioselective Synthesis

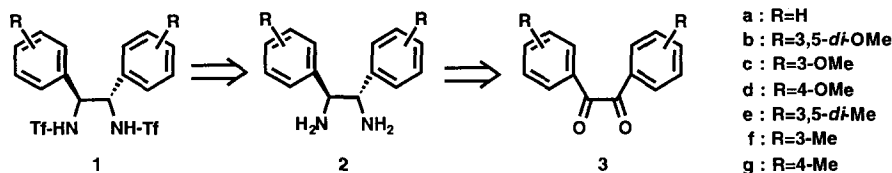
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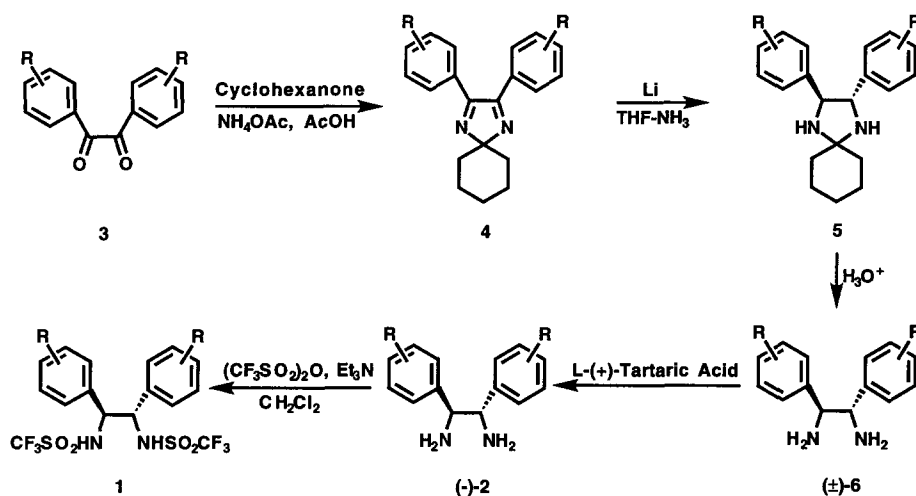
**Summary:** Pathways for the diastereoselective preparation of chiral 1,2-diaryl-1,2-diaminoethanes from ArCOOH, ArCHO or ArBr are described.

The chiral 1,2-diphenyl-1,2-diaminoethane (*stien*) controller system has recently been applied to the development of highly enantioselective versions of key synthetic reactions such as Diels-Alder addition,<sup>1,2</sup> ester-aldehyde aldol coupling,<sup>1,3,4</sup> carbonyl allylation,<sup>5</sup> propargylation and allenylation,<sup>6</sup> ester Claisen rearrangement,<sup>7</sup> Darzens coupling,<sup>8</sup> ester Mannich coupling,<sup>9</sup> olefin bis-hydroxylation,<sup>10</sup> and olefin epoxidation.<sup>11</sup> In certain of these reactions the origin of high enantioselectivity has been traced to neighboring  $\pi$ -donor aromatic substituents on the controller.<sup>2</sup> For this reason and also because of their value in probing possible transition states, we have developed facile synthetic routes to a series of chiral C<sub>2</sub>-symmetric 1,2-diaryl-1,2-diaminoethanes. In view of the increasing interest in these diamines, we describe herein the most convenient of these preparative options.

Scheme 1



Our studies indicate that in general the preparation of substituted *stien* ligands proceeds very satisfactorily using the sequence of reactions introduced earlier for the parent diamine,<sup>1,12</sup> starting with benzil as outlined in Scheme 1 and also in Table 1. The conversion of substituted benzil **3** to the corresponding 2,2-spirocyclohexane-4,5-diaryl-2*H*-imidazole **4** occurred in nearly quantitative yield regardless of substituents (heating at reflux in AcOH for 1 h with 1 equiv of cyclohexanone and excess NH<sub>4</sub>OAc). Birch reduction of **4** to **5** was stereospecific for the *trans* product (4 - 4.4 equiv of Li in 4:5 THF-liq NH<sub>3</sub> at -78 °C) in all cases, and the yields for the reduction **4** → **5** and acidic hydrolysis (2*N* aqueous HCl, ether extraction, basification of the aqueous layer, and CH<sub>2</sub>Cl<sub>2</sub> extraction) **5** → **6** were uniformly high. In each case complete resolution was accomplished satisfactorily

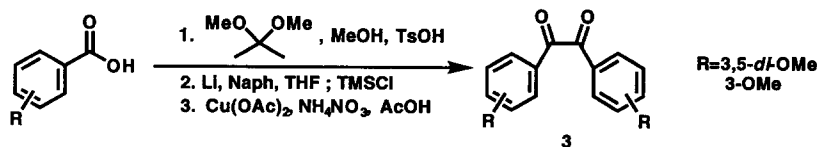
**Table 1. Preparation of Chiral Diamines (2) and Bis-Sulfonamides (1) from Benzils (3)**

R	% yield 4	% yield 4 → 6	% yield 2	% yield 1
H	95	89	64	97
3,5- <i>di</i> -OMe	98	98	57	88
3-OMe	97	100	45	94
4-OMe	100	100	36	88
3,5- <i>di</i> -Me	100	100	57	85
3-Me	100	97	57	73
4-Me	100	92	50	84

using tartaric acid for salt formation and separation of diastereomers by recrystallization.<sup>13,14</sup> The bis-trifluoromethanesulfonyl derivatives<sup>15</sup> of the various diamines, useful predecessors of chiral Lewis acids, were also prepared in good yields, as indicated in Table 1.

The most convenient synthesis of the required substituted benzil depends on the available starting material. In cases where the corresponding benzoic acid is commercially available the sequence outlined in Scheme 2 has been utilized to advantage. Thus, 3,5-dimethoxy- and 3-methoxybenzoic acid were treated with 2,2-dimethoxypropane (1.5 equiv) and a catalytic amount of TsOH in MeOH at 60 °C for 2 days to produce the corresponding methyl esters after quenching with triethylamine and filtration through silica gel in 97% and 93% yield, respectively. Reductive homo coupling of each methyl ester with lithium naphthalenide (3.0 equiv)<sup>16</sup> in THF at -78 °C for 1 h and quenching with TMSCl at -78 °C gave mixtures of the corresponding benzil and

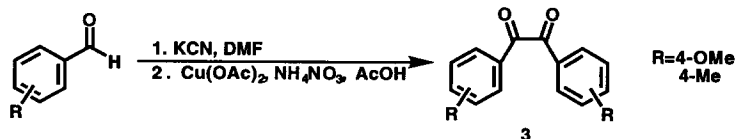
Scheme 2



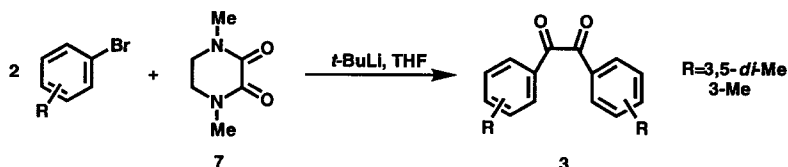
benzoin. Subsequent oxidation of each crude product with Cu(OAc)<sub>2</sub> and NH<sub>4</sub>NO<sub>3</sub><sup>17</sup> in refluxing aqueous acetic acid for 1.5 h afforded benzils **3b** and **3c** in 42% and 43% yields.

4,4'-Dimethoxy and 4,4'-dimethyl-substituted benzils **3d** and **3g** were prepared from the commercially available aldehydes (Scheme 3) by benzoin condensation<sup>17</sup> with potassium cyanide in aqueous EtOH (95 °C, 24 h for R=4-OMe) or DMF (rt, 48 h for R=4-Me) followed by Cu(OAc)<sub>2</sub> oxidation of crude benzoin to benzils **3d** and **3g** as described previously.<sup>18</sup>

Scheme 3



3,3',5,5'-Tetramethyl and 3,3'-dimethyl-substituted benzils (**3e** and **3f**) were synthesized from the readily available aryl bromides via the aryllithium reagents (2 equiv) (readily prepared by reaction of *t*-butyllithium with the aryl bromide in THF at -78 °C for 2.5 h) and *N,N*-dimethylpiperazine-2,3-dione (**7**) at -78 °C for 2 h and at rt overnight using the excellent method of Mueller-Westerhoff.<sup>19</sup>



If, during the course of research on the development of enantioselective synthetic methods, the use of chiral 1,2-diaryl-1,2-diaminoethanes is required, the preparative sequences described herein can be recommended as convenient, expeditious, and reliable.<sup>20</sup>

### References and Notes

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13. The 1 : 1 salt of diamine and tartaric acid was formed by adding hot aqueous tartaric acid solution (1 equiv) to a hot ethanolic solution of the diamine, allowing the resulting mixture to cool slowly to room temperature, and collecting the crystalline solid by filtration. Recrystallization was carried out by suspending the salt in boiling water and adding just the right amount of boiling ethanol to effect solution. Two or in some cases three recrystallizations afforded fully resolved diamine salt.
14. The absolute configuration of **2e/1e** could be assigned by X-ray crystallographic analysis of the crystalline diazaaluminolidine<sup>2</sup> prepared from the reaction of **1e** with Me<sub>3</sub>Al. In the case of diamines **2b**, **2c**, **2d**, **2f** and **2e**, resolution with L-(+)-tartaric acid afforded the levorotatory diamine, as was found with diamines **2a** and **2e** for which absolute configurations are established. It seems likely that all the levorotatory diamines have the same absolute configuration, as expressed by formula **2a**. The mp and optical rotation data are as follows: **2a** (R=H), mp 80-82 °C,  $[\alpha]_D^{23} = -109.2$  (c 0.75, CHCl<sub>3</sub>); **2b** (R=3,5-di-OMe), mp 89-90 °C,  $[\alpha]_D^{23} = -61.6$  (c 1.55, CHCl<sub>3</sub>); **2c** (R=3-OMe), mp 64-66 °C,  $[\alpha]_D^{23} = -61.9$  (c 0.47, CHCl<sub>3</sub>); **2d** (R=4-OMe), mp 86-88 °C,  $[\alpha]_D^{23} = -75.4$  (c 0.74, CHCl<sub>3</sub>); **2e** (R=3,5-di-Me), mp 66-68 °C,  $[\alpha]_D^{23} = -43.4$  (c 0.82, CHCl<sub>3</sub>); **2f** (R=3-Me),  $[\alpha]_D^{23} = -61.8$  (c 0.62, CHCl<sub>3</sub>); **2g** (R=4-Me), mp 80-82 °C,  $[\alpha]_D^{23} = -73.4$  (c 0.45, CHCl<sub>3</sub>).
15. The mp and optical rotation data are as follows: **1a** (R=H), mp 205-206 °C,  $[\alpha]_D^{23} = -8.6$  (c 1.42, CHCl<sub>3</sub>); **1b** (R=3,5-di-OMe), mp 193-195 °C,  $[\alpha]_D^{23} = -9.9$  (c 0.96, CHCl<sub>3</sub>); **1c** (R=3-OMe), mp 120-121 °C,  $[\alpha]_D^{23} = -9.84$  (c 0.43, CHCl<sub>3</sub>); **1d** (R=4-OMe), mp 135-136 °C,  $[\alpha]_D^{23} = -12.0$  (c 0.91, CHCl<sub>3</sub>); **1e** (R=3,5-di-Me), mp 201-203 °C,  $[\alpha]_D^{23} = -4.45$  (c 0.58, CHCl<sub>3</sub>); **1f** (R=3-Me), mp 172-173 °C,  $[\alpha]_D^{23} = -9.95$  (c 0.66, CHCl<sub>3</sub>); **1g** (R=4-Me), mp 188-189 °C,  $[\alpha]_D^{23} = -12.4$  (c 0.60, CHCl<sub>3</sub>).
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20. This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

(Received in USA 13 July 1994)