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

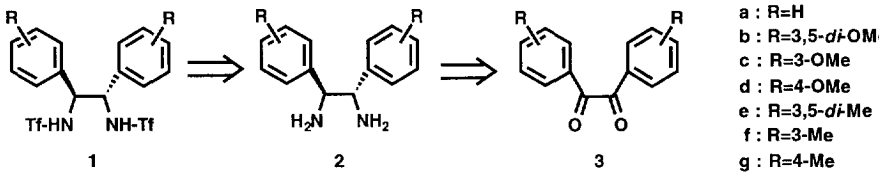
E. J. Corey,* Duck-Hyung Lee and Sepehr Sarshar

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

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

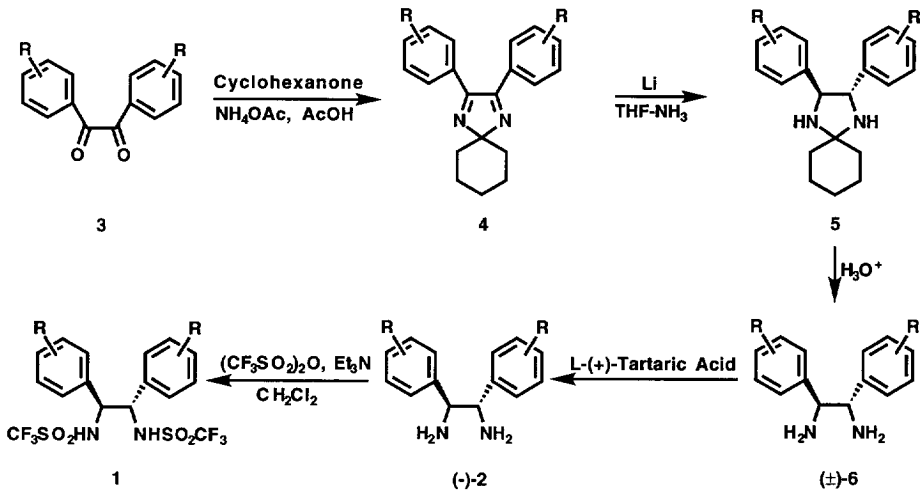
The chiral 1,2-diphenyl-1,2-diaminoethane (*stien*) controller system has recently been applied to the development of highly enantioselective versions of key synthetic reactions such as Diels-Alder addition,[1,2] ester–aldehyde aldol coupling,[1,3,4] carbonyl allylation,[5] propargylation and allenylation,[6] ester Claisen rearrangement,[7] Darzens coupling,[8] ester Mannich coupling,[9] olefin bis-hydroxylation,[10] and olefin epoxidation.[11] In certain of these reactions the origin of high enantioselectivity has been traced to neighboring π-donor aromatic substituents on the controller.[2] 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 $C_2$-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,[1,12] 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 $NH_4OAc$). Birch reduction of **4** to **5** was stereospecific for the *trans* product (4 - 4.4 equiv of Li in 4 : 5 THF-liq $NH_3$ at -78 °C) in all cases, and the yields for the reduction **4** → **5** and acidic hydrolysis (2N aqueous HCl, ether extraction, basification of the aqueous layer, and $CH_2Cl_2$ 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)**

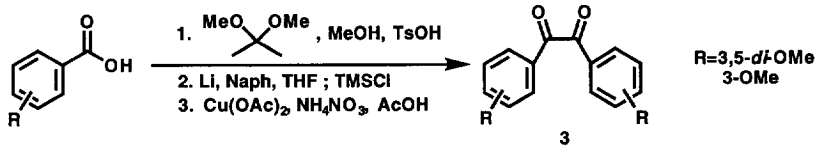



| R | % yield 4 | % yield 4 → 6 | % yield 2 | % yield 1 |
|---|---|---|---|---|
| H | 95 | 89 | 64 | 97 |
| 3,5-*di*-OMe | 98 | 98 | 57 | 88 |
| 3-OMe | 97 | 100 | 45 | 94 |
| 4-OMe | 100 | 100 | 36 | 88 |
| 3,5-*di*-Me | 100 | 100 | 57 | 85 |
| 3-Me | 100 | 97 | 57 | 73 |
| 4-Me | 100 | 92 | 50 | 84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

using tartaric acid for salt formation and separation of diastereomers by recrystallization.[13,14] The bis-trifluoromethanesulfonyl derivatives[15] 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)[16] in THF at -78 °C for 1 h and quenching with TMSCl at -78 °C gave mixtures of the corresponding benzil and

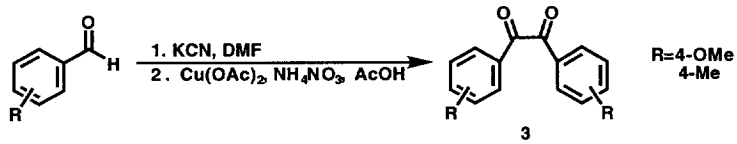
**Scheme 2**



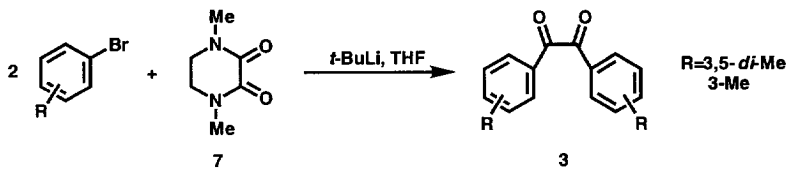

benzoin. Subsequent oxidation of each crude product with $Cu(OAc)_2$ and $NH_4NO_3$[17] in refluxing aqueous acetic acid for 1.5 h afforded benzils **3b** and **3c** in 42% and 43% yields.

4,4'-Dimethoxy and 4,4'-dimethyl-substituted benzils **3d** and **3g** were prepared from the commercially available aldehydes (Scheme 3) by benzoin condensation[17] 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 $Cu(OAc)_2$ oxidation of crude benzoins to benzils **3d** and **3g** as described previously.[18]

**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.[19]




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.[20]

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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[2] prepared from the reaction of **1e** with $Me_3Al$. 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, $CHCl_3$); **2b** (R=3,5-*di*-OMe), mp 89-90 °C, $[\alpha]_D^{23}$ = - 61.6 (c 1.55, $CHCl_3$); **2c** (R=3-OMe), mp 64-66 °C, $[\alpha]_D^{23}$ = - 61.9 (c 0.47, $CHCl_3$); **2d** (R=4-OMe), mp 86-88 °C, $[\alpha]_D^{23}$ = - 75.4 (c 0.74, $CHCl_3$); **2e** (R=3,5-*di*-Me), mp 66-68 °C, $[\alpha]_D^{23}$ = - 43.4 (c 0.82, $CHCl_3$); **2f** (R=3-Me), $[\alpha]_D^{23}$ = - 61.8 (c 0.62, $CHCl_3$); **2g** (R=4-Me), mp 80-82 °C, $[\alpha]_D^{23}$ = - 73.4 (c 0.45, $CHCl_3$).
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, $CHCl_3$); **1b** (R=3,5-*di*-OMe), mp 193-195 °C, $[\alpha]_D^{23}$ = - 9.9 (c 0.96, $CHCl_3$); **1c** (R=3-OMe), mp 120-121 °C, $[\alpha]_D^{23}$ = - 9.84 (c 0.43, $CHCl_3$); **1d** (R=4-OMe), mp 135-136 °C, $[\alpha]_D^{23}$ = - 12.0 (c 0.91, $CHCl_3$); **1e** (R=3,5-*di*-Me), mp 201-203 °C, $[\alpha]_D^{23}$ = - 4.45 (c 0.58, $CHCl_3$); **1f** (R=3-Me), mp 172-173 °C, $[\alpha]_D^{23}$ = - 9.95 (c 0.66, $CHCl_3$); **1g** (R=4-Me), mp 188-189 °C, $[\alpha]_D^{23}$ = - 12.4 (c 0.60, $CHCl_3$).
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