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Synthesis of (1*S*,3*R*,4*S*)-1-methyl-3,4-diphenyl-3,4-dihydro-1*H*-isochromene-3,4-diol

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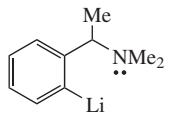
Reaction of dilithiated (*S*)-1-phenylethanol with benzil affords (1*S*,3*R*,4*S*)-1-methyl-3,4-diphenyl-3,4-dihydro-1*H*-isochromene-3,4-diol being a cyclic hemiacetal, whose structure was established by X-ray analysis.

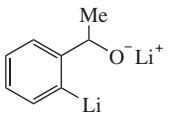
The directed *ortho*-lithiation of substituted arenes followed by reaction with electrophiles is an excellent method for their regiospecific derivatization.[1] We used this method for functionalization of lithiated scalemic *N*,*N*-dimethyl-1-phenylethanamine **1** and 1-phenylethanol **2** (available in both enantiomeric forms) and obtained nonracemic amino alcohols[2] and 1,4-diols[3,4], respectively. Chiral diols are employed as building blocks and auxiliaries in the synthesis of biologically active compounds and as chiral ligands in asymmetric synthesis.[5–7] Diols are known to reveal biological (pharmacological) activity, for example, 1,2-diol derived from (–)-carveol exhibits high anticonvulsant activity.[8] It is worth to note the significance of developing the stereoselective methods for synthesis of diols with known stereochemistry[5,9] as their activity (biological and catalytic) depends on their stereochemical purity.

Previously, we faced a problem of the low diastereoselectivity of chiral diols synthesized from **2**.[3,4] The lithiation of the neutral precursors with BuLi or Bu^{s}Li results in good yields of the lithiated derivatives **1** and **2**, however, coupling of the former with carbonyl compounds proceeds with significantly higher stereoselectivity. Comparison of the lithiated derivatives **1** and **2** shows that **1** has a relatively weak nucleophilic site – tertiary amine, while **2** has a very strong nucleophilic alkoxide ion. We suggest that the presence of such a moiety determines the steric orientation of molecules in reaction complex, and stereoselectivity of the reaction. The preferred orientation of a carbonyl compound may depend not only on its structure, but also on the coordination of its carbonyl carbon with alkoxide oxygen through Li^+ [Figure 1(*a*)]. This coordination occurs at the edges of the reaction complex and is possible from both sides of the CO-plane. Therefore, steric and electronic factors of carbonyl compound do not play decisive role in the complexation with **2** and the formation of the new bond between C_{arom} and $C_{carbonyl}$ leads to two diastereomers. In contrast, the coordination of carbonyl carbon with tertiary amine of **1** is impossible [Figure 1(*b*)]. Thus, stereochemical outcome of the reaction is determined by the structure of carbonyl compound and coordination of C=O with C–Li.

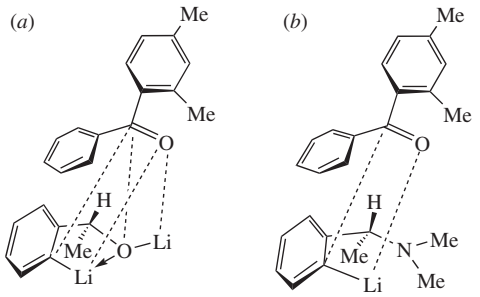
From the inspection of reaction complex **A** (Figure 1) one can see that carbonyl carbon may react with alkoxide oxygen forming



1



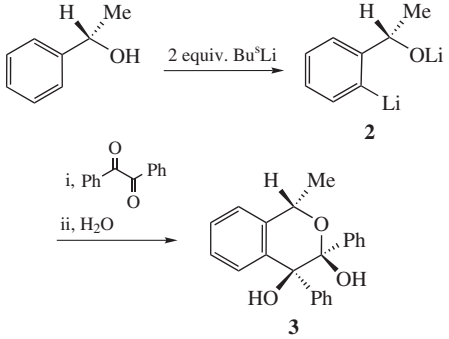
2



A **B**

Figure 1 The possible coordination of carbonyl compounds with **2** (**A**) and **1** (**B**) in reaction complexes.

a hemiketal; however, it was not obtained in our previous experiments with monoketones. To check the possibility of such reaction we decided to use benzil having two carbonyl groups (Scheme 1). The choice of this diketone was also determined by the fact that its condensation with lithiated amine **1** proceeds stereospecifically and affords only one diastereomeric keto amino alcohol – (2*S*)-{(*S*)-2-[1-(*N*,*N*-dimethylamino)ethyl]phenyl}benzoin.[10] The reaction involves only one carbonyl group due to the steric factors. We expected to achieve the same result in the condensation of the lithiated alcohol **2** with benzil. However, the obtained compound did not contain a carbonyl group since its IR and UV spectra manifested no carbonyl absorption. After purification by column chromatography on silica gel and crystallization, the product was obtained in crystalline form and X-ray study gave its structure as **3**† (Figure 2, Scheme 1).‡ (3*R*,4*S*)-Configuration of the new chiral centers was assigned on the basis of the known (1*S*)-configuration of the parent alcohol.



Scheme 1

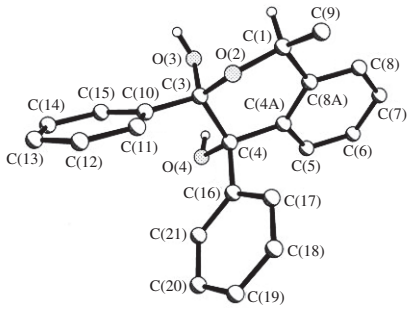
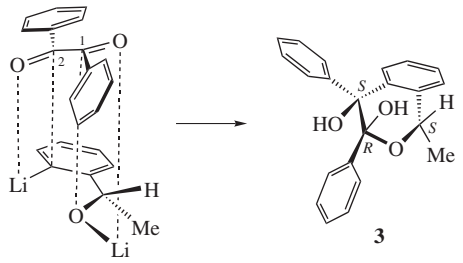


Figure 2 Molecular structure of compound **3**.



Scheme 2

Two nucleophilic centers of compound **2** reacted with two carbonyl groups of benzil with the formation of a hemiketal structure. Two possible mechanisms of the reaction can be considered. According to the first mechanism, the position of benzil molecule relative to **2** in the plausible transition state is fixed due to the simultaneous coordination of one carbonyl group by O–Li and the other carbonyl group by C–Li. As a result only one diastereomer, (1*S*,3*R*,4*S*)-1-methyl-3,4-diphenyl-3,4-dihydro-1*H*-isochromene-3,4-diol,[§] may be formed in the reaction (Scheme 2).

An alternative mechanism, which includes an initial formation of the carbinol center possibly with definite configuration and a further cyclization, is unlikely since it would result in formation of two diastereomers. However, in the ^{1}H NMR spectrum of the reaction mixture we observed only one set of signals which indicated the formation of exclusively one diastereomer. From the inspection of the reaction complex (Scheme 2) it can be seen that the new chiral centers should have the following configurations: carbinol (C-4) – (*S*) and hemiketal (C-3) – (*R*). The agreement with X-ray data gives evidence to the first mechanism: it proves that two nucleophilic centers of the dilithiated alcohol **2** react simultaneously with the formation of the corresponding new O–$C_{carbonyl}$ and C_{arom}–$C_{carbonyl}$ bonds.

The synthesized compound **3** may be of interest not only as a chiral diol, but also as isochroman derivative. Isochromans are the fundamental units of many natural and synthetic compounds that possess a wide spectrum of biological activity. Over past decade significant efforts have been devoted to their design and asymmetric synthesis,[11–14] whereas the isochromans with three chiral centers are not yet well known.

In conclusion, when investigating the condensation of dilithiated alcohol **2** with benzil we found that this reaction gives access to the new unexpected hemiacetal **3**, the formation of which confirms the presence of two reactive centers in **2**. Hemiacetal **3** represents 1,2-diol derivative of isochroman with three chiral centers and is promising in search for new biologically active compounds.

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† *Crystallographic data*. Crystals of **3** ($C_{22}H_{20}O_3$, M = 332.38) are monoclinic, space group C_2, at 100(2) K: a = 8.0578(9), b = 17.077(2) and c = 12.718(2) Å, β = 102.693(3)°, V = 1707.3(3) Å^3, Z = 4, d_{calc} = = 1.293 g cm^{-3}, μ(MoKα) = 0.85 cm^{-1}, F(000) = 704. Intensities of 5337 reflections were measured with a Bruker SMART APEX II CCD diffractometer [λ(MoKα) = 0.71073 Å, ω-scans with a 0.3° step in ω and 10 s per frame exposure, 2θ < 56°] and 3319 independent reflections (R_{int} = 0.023) were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Hydrogen atoms of OH groups were located from the Fourier synthesis of the electron density and refined in the isotropic approximation. The H(C) atom positions were calculated and refined as riding atoms. The refinement converged to wR_2 = 0.0681 and GOF = 1.001 for all independent reflections, R_1 = = 0.0376 was calculated against F for 2785 observed reflections with $I > 2\sigma(I)$. All calculations were performed using SHELXTL program.

CCDC 943841 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2013.

‡ Compound (*S*)-**2** was obtained by treatment of (*S*)-phenylethanol (10 mmol) in diethyl ether (30 ml) with two equivalents of Bu^{s}Li in hexane. Next, a solution of 9.5 mmol of benzil in 20 ml of anhydrous diethyl ether was added dropwise under the dry argon atmosphere at –40 °C. The mixture was stirred for 24 h at room temperature and quenched with water. The water phase was twice extracted with diethyl ether, the organic extracts were washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The ratio of the obtained **3** to the unreacted 1-phenylethanol was estimated from ^{1}H NMR spectrum of the crude material as 1:3. The product was isolated and purified by column chromatography (silica gel 40/60, gradient elution with light petroleum–AcOEt mixture in ratio from 10:1 to 5:1). Yield 0.7 g (100%) as calculated for the reacted 1-phenylethanol; mp 142 °C (light petroleum–diethyl ether), $[\alpha]_D$ –306.1 (*c* 1, ethanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.83 (d, 3H, Me), 3.22 (s, 1H, OH), 3.44 (s, 1H, OH), 5.44 (q, 1H, CH), 6.9–7.5 (m, 14H, arom.). IR (film, ν/cm^{-1}): 3520 (narrow), 3610–3260 (wide). UV [λ_{max}/nm (lgε)]: 256 (0.33).

Racemic **3** was obtained similarly from racemic substrate, mp 141 °C (light petroleum–diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.84 (d, 3H, Me), 3.25 (s, 1H, OH), 3.44 (s, 1H, OH), 5.47 (q, 1H, CH), 6.9–7.6 (m, 14H, arom.). UV [λ_{max}/nm (lgε)]: 254 (0.33).

§ The name of compound **3** is given in accordance with IUPAC rules; however, in literature, such compounds are usually called as 'isochroman' derivatives.