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Efficient Syntheses of 2-Isopinocampheyl- and Related 2-Terpenyl-1,3,2-dioxaboroles from 1,2-Dicarbonyls and 2-Hydroxyketones

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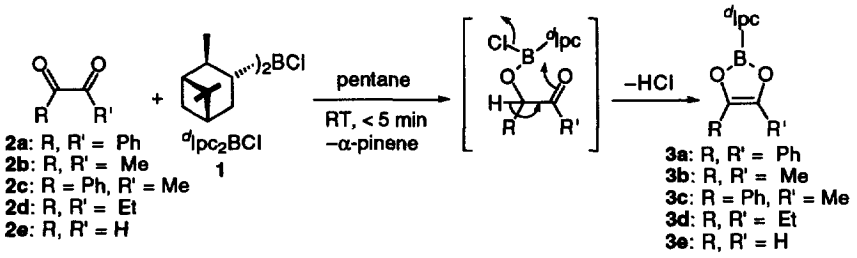
Abstract: Efficient syntheses of synthetically important chiral 1,3,2-dioxaboroles have been developed. The reduction of 1,2-dicarbonyls with *B*-chlorodiisopinocampheylborane, or a reaction of α-hydroxyketones with isopinocampheyldichloroborane, provides rapid, convenient syntheses of chiral enediolboronates of the type, 2-isopinocampheyl-1,3,2-dioxaboroles. The latter procedure has been utilized to synthesize a series of 2-terpenyl-1,3,2-dioxaboroles from terpenyldichloroboranes. © 1997 Elsevier Science Ltd.

While carrying out a study of the asymmetric reduction of 1,2-diketones (**2**) with our versatile chiral reducing agent, *B*-chlorodiisopinocampheylborane[2] (Ipc_2BCl, Aldrich: DIP-Chloride™, **1**), with the aim of synthesizing optically active α-hydroxy ketones and α,β-diols, we encountered an unexpected reaction, the first direct synthesis of boron enediolates from 1,2-dicarbonyls.

On the basis of the reduction of isobutyrophenone with (–)-**1** providing the corresponding *S*-alcohol in 92% ee,[2] we expected the reduction of benzil (**2a**) with one equiv of (–)-**3** would provide benzoin in very high ee. The tentative reaction mechanism suggested that the α-carbonyl group would enhance the reduction rate by activating the second carbonyl for the hydride transfer.[3] However, the ^{11}B NMR spectrum of the intermediate of the reaction of benzil with one equiv of **1** showed a singlet at δ 36 ppm. This is ~6 ppm upfield compared to the value, δ 42 ppm, normally observed for the RBCl(OR) species formed in the usual reduction. The methanolysis of this intermediate, expected to produce an upfield shift in the ^{11}B NMR spectrum to δ 32 ppm, corresponding to $RB(OMe)_2$, showed no change in the spectrum. The usual diethanolamine or alkaline H_2O_2 workup yielded 78% of benzoin. Analysis of this product as the α-methoxy-α-(trifluoromethyl)phenylacetate derivative (MTPA)[4] by capillary gas chromatography, revealed it to be racemic.

The reduction of **2a** with two equiv of **1** afforded the same result as above. None of the expected hydrobenzoin was realized.

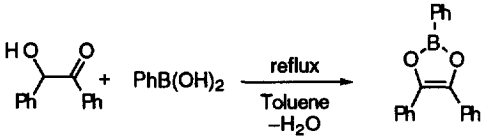
Intrigued by these observations, we conducted this reaction in $CDCl_3$, monitoring it by ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum revealed that both of the phenyl groups are magnetically similar and the proton corresponding to –C<u>H</u>-OB, from an expected reduction, is absent. The ^{13}C NMR disclosed the absence of a carbonyl carbon and the presence of a symmetric >C=C<. We account for the observed spectra by the formation of 4,5-diphenyl-2-isopinocampheyl-1,3,2-dioxaborole (**3a**) by the reaction path shown (eq 1).



(1)

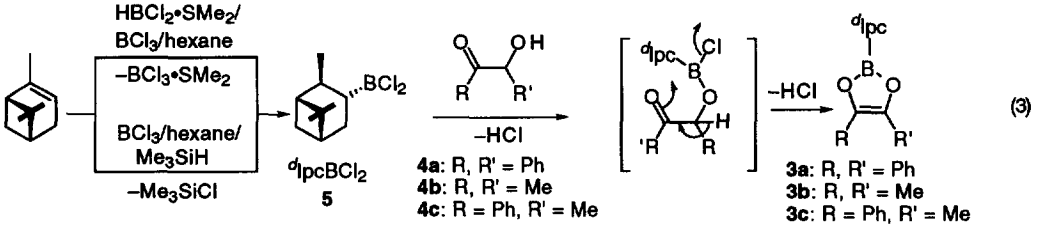
The structure of **3a** was confirmed by preparing it from benzoin and isopinocampheylboronic acid, via a dehydration in the presence of 4Å molecular sieves in THF, at room temperature (RT).[5] The spectral characteristics are identical to those of the reduction intermediate.

The generality of this reaction was demonstrated by preparing the corresponding 2-isopinocampheyl-1,3,2-dioxaboroles from 2,3-butanedione, 2-oxopropiophenone, and 3,4-hexanedione. The parent dioxaborole (**3e**) was readily synthesized from glyoxal. Thus, we have achieved a facile synthesis of 1,3,2-dioxaboroles under very mild reaction conditions. The earlier synthesis of these types of intermediates involved azeotropic dehydration, at elevated temperatures, of a mixture of the corresponding α-hydroxy ketones and alkyl (or aryl) boronic acids (eq 2).[6]



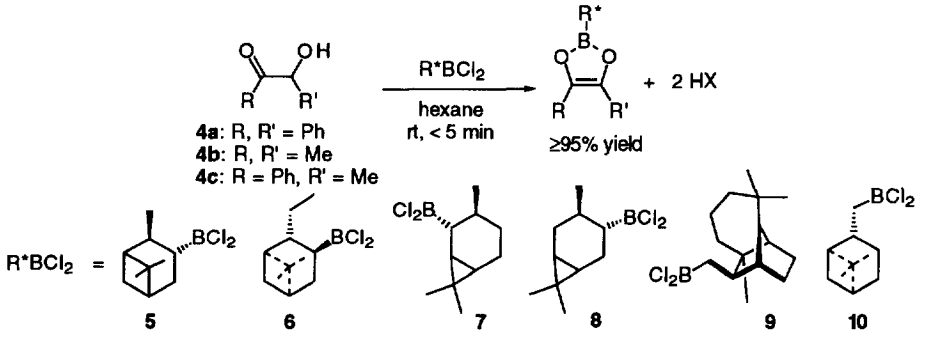
(2)

The fact that the reaction proceeds via the intermediate indicated above was further confirmed by treating benzoin with isopinocampheyldichloroborane (IpcBCl$_2$, **4**)[7] in pentane at rt, when the instantaneous, quantitative formation of **3** was observed (eq 3). This provides an improved general procedure for the synthesis of **3** under very mild reaction conditions. The product is obtained in a very pure form without any need for further purification. Since **5** can be conveniently synthesized using the trimethylsilane procedure,[7b] all of the reactions can be carried out by a one-pot operation.



(3)

Although the reaction illustrated in eq 1 is limited only to R$_2$BCl reagents where one of the R group should be an an alkyl group containing a β-hydrogen atom appropriately placed for the reduction of a carbonyl group, there is no such limitation for the reaction depicted in eq 3. A series of chiral 1,3,2-dioxaboroles were synthesized from the dichloroboranes prepared from 2-ethylapopinene (EapBCl$_2$, **6**), 2-carene (2-IcrBCl$_2$, **7**), 3-carene (4-IcrBCl$_2$, **8**), longifolene (LgfBCl$_2$, **9**) and β-pinene (*cis*-MyrBCl$_2$, **10**) (eq 4).



(4)

α,β-Dihydroxy-α-ketone moieties are present in a number of natural products, including the antifungal antibiotics, oligomycins.[8] A disconnection analysis shows that this fragment may be produced by the aldol reaction of metal enediolates. However, investigations of such reactions are sparse. Although "potentially aromatic" 1,3,2-dioxaboroles have been prepared from α-hydroxy ketones (eq 2)[6] and studied in detail[9] more than three decades ago, the methods are somewhat tedious and not general.[10] To the best of our knowledge, there is only one report involving a borane-mediated aldol reaction of such dioxaboroles, due to Mukaiyama and Yamaguchi.[11] Moreover, there is no report of the synthesis of an optically active 1,3,2-dioxaborole. We have achieved efficient syntheses of 2-isopinocampheyl-1,3,2-dioxaboroles, either from 1,2-dicarbonyl compounds by reaction with *B*-chlorodiisopinocampheylborane, or from α-hydroxy-ketones by a reaction with isopinocampheyldichloroborane. The latter is a more convenient procedure to obtain the dioxaboroles which can be directly used for further condensations with aldehydes in the same pot. The reactions of these chiral dioxaboroles with a representative series of aldehydes for the diastereo- and enantioselective synthesis of α,β-dihydroxy ketones are in progress.

The syntheses of 4,5-diphenyl-2-isopinocampheyl-1,3,2-dioxaborole using Ipc_2BCl and $IpcBCl_2$ are described below. All of the operations were carried out under nitrogen.[12] An oven-dried, 50 mL round-bottom flask, equipped with a side-arm, a magnetic stirring bar, and a connecting tube, was brought to rt in a stream of nitrogen. (–)-DIP-Chloride™ (4.8 g, 15 mmol) was transferred to the flask in a glove bag and dissolved in pentane[13] (15 mL), followed by the addition of benzil (15 mmol) dissolved in a minimum amount of THF using a cannula. The mixture was stirred at this temperature and the reaction was followed using ^{11}B NMR spectroscopy of an aliquot. The spectrum plotted after 15 min showed a singlet at δ 36 ppm. The solvents were removed and the residue was chromatographed using silica to separate **3a** from α-pinene (4.24 g, 80%).

Isopinocampheyldichloroborane (3.3 g, 15 mmol) dissolved in pentane (15 mL) was added in drops to benzoin (3.18 g,15 mmol) suspended in 5 mL pentane with the rapid evolution of two equiv of HCl and the formation of **3a** (^{11}B NMR: δ 36 ppm). The solvent was removed and concentrated using a high vacuum pump to obtain 5.30 g (99%) of *B*-isopinocampheyl-4,5-diphenyl-1,3,2-dioxaborole. ^1H NMR δ ($CDCl_3$) (ppm): 7.60 (m, 4H, Ph); 7.4-7.25 (m, 6H, Ph); 2.45-1.60 (m, 7H); 1.22 (s, 3H. Me); 1.19 (d, J = 7.14 Hz, 3H, Me); 1.13 (s, 3H, Me); 0.95 (d, J = 9.6 Hz, 1H). ^{13}C NMR δ ($CDCl_3$) (ppm): 138.94, 130.65, 128.44, 128.14, 126.54, 47.94, 41.23, 38.72, 38.83, 34.19, 28.98, 28.43, 23.13, 22.88.

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