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2-Iodoethanols from aldehydes, diiodomethane and isopropylmagnesium chloride

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Abstract—Diiodomethane and iodoform react with *i*-PrMgCl by halogen–metal exchange. The resulting magnesium reagents tolerate several functional groups, but aldehydes are converted selectively into iodoethanols in good to high yields. These mild reagents preserve racemization prone centres. The substrate controlled diastereoselectivity provides straightforward access to important intermediates of peptidomimetics.

Amino acid derived epoxides and 2-haloethanols are extremely versatile intermediates for the synthesis of protease inhibitors.[1–3] Several synthetic strategies are known, but they are either lengthy, require diazomethane or harsh conditions. Most organic chemists have rather mixed feelings using diazomethane for the synthesis of the intermediate α-chloroketones. The less hazardous siladiazomethane is significantly more expensive and therefore limited to small scale reactions. However, it can be replaced by dimethylsulfoxonium methylide.[4] Nevertheless, a reliable, straightforward and inexpensive approach is still very desirable. Some of these requirements are fulfilled by lithium organyls,[5] their strong basicity impedes the conversion of di- and oligopeptides, yet they provide access to α-chloroketones from *N*,*N*-dibenzylated amino acid esters.[15] The umpolung of $ClCH_2I$ or CH_2I_2 and subsequent addition to aldehydes provides access to epoxides,[6] but requires methyllithium at −78 °C. The deprotonation of CH_2Cl_2 by *n*-BuLi and addition to ketones furnished tertiary β-dichloroalcohols.[7] A more recent approach to the respective iodo species utilized diiodomethane or iodoform and air-sensitive and expensive SmI_2, which can be replaced by metallic samarium and iodoform.[8,9]

Here we report the efficient synthesis of 2-iodoethanols and 2,2-diiodoethanols from safe and convenient precursors. Seeking a safer replacement of methyllithium, we decided to investigate *i*-PrMgCl, which has a remarkable potential for iodine–magnesium exchanges. The late G. Köbrich already reported the halogen–metal exchange of bromoform and dibromomethane with *n*-BuLi. On the contrary, the analogous chloro compounds react by deprotonation.[10] The former reactivity continues in diiodomethane and iodoform, and may be improved by magnesium alkyls. We expected these magnesium reagents to favour late transition states, to tolerate a wide range of functional groups, to display reduced basicity, and thus allow stereoselective conversion of polyfunctional peptides.[11] The rate of the halogen–metal exchange depends on the electron density to a great extent that the stepwise activation of geminal diiodides is feasible. The detailed kinetics and energetics were reported by Hoffmann and the potential of this reaction was revealed in a number of publications already.[12–14] The activation of iodoform or diiodomethane by *i*-PrMgCl proceeded rapidly in tetrahydrofuran at −78 °C (Scheme 1).

The addition of *i*-PrMgCl to aldehydes was considerably slower at this temperature. Addition of an aldehyde after complete iodo-magnesium exchange (15 min) resulted in similar yields and selectivities as obtained for the simultaneous addition (Table 1). Both C1 nucleophiles, which are derived from long-lived ate complexes,[12] reacted with aldehydes (**1a–d**) at −78 °C

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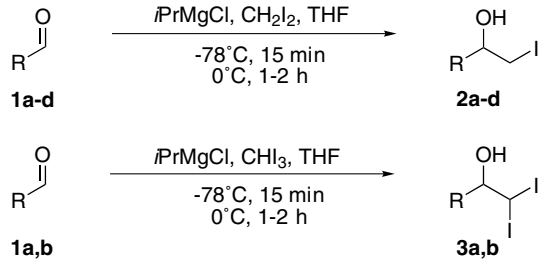
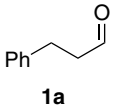
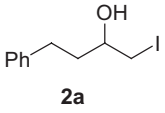
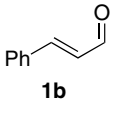
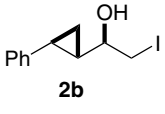
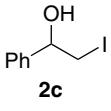
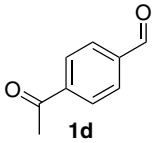
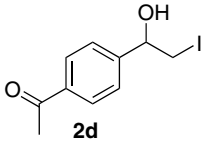
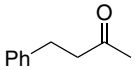
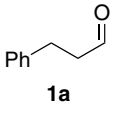
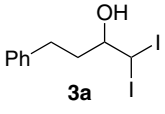
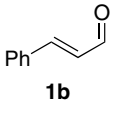
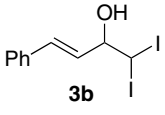
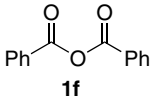
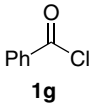


Scheme 1.

Table 1. Reactions of aldehydes, ketones and carboxylic acid derivatives according to Scheme 1 with 2.0 equiv of CH_2I_2 or CHI_3 and *i*-PrMgCl

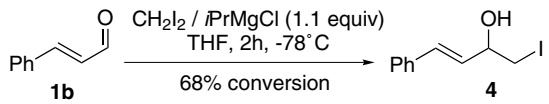
Reagent	Aldehyde	Product	Yield[a] [%]
CH_2I_2/*i*-PrMgCl	 **1a**	 **2a**	96
CH_2I_2/*i*-PrMgCl	 **1b**	 **2b**	91[b]
CH_2I_2/*i*-PrMgCl	 **1c**	 **2c**	73
CH_2I_2/*i*-PrMgCl	 **1d**	 **2d**	69
CH_2I_2/*i*-PrMgCl	 **1e**	Conversion < 10[c]	
CHI_3/*i*-PrMgCl	 **1a**	 **3a**	91
CHI_3/*i*-PrMgCl	 **1b**	 **3b**	82[d]
CH_2I_2/*i*-PrMgCl	 **1f**	Sluggish reaction	
CH_2I_2/*i*PrMgCl	 **1g**	No reaction	

[a] Isolated yields.
[b] Diastereomeric mixture: *syn*/*anti* 96:4, assigned by NMR.[17]
[c] Determined by HPLC.
[d] Contains 4% of 2,2-diiodo-1-(2-iodo-3-phenylcyclopropyl)ethanol (mixture of diastereomers, d.r. > 3:1) and 3% of 2,2-diiodo-1-(2-phenylcyclopropyl)ethanol.

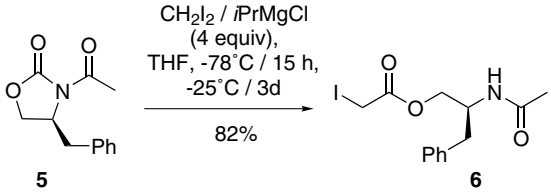
to the β-iodo-(**2a**–**d**) and β-diiodo compounds (**3a** and **b**). The formation of epoxides was not observed even at 0 °C for 2 h. These results are similar to the samarium methodology,[8] but complement the diiodomethane derived lithium reagents, which provide epoxides.[6]

The turnover of **1e** was remarkably slow, it reacted just marginally under these conditions. Consequently, the formylacetophenone **1d** underwent iodomethylation at the aldehyde only. The benzoic anhydride **1f** underwent rapid conversion into a multitude of unidentified products. The conversion of the acid chloride **1g** did not take place, but reactivity could have been enhanced by either chelation assistance or the reported *trans*-metallation into a copper reagent.[15] The differences between the two nucleophilic reagents (Scheme 1) became apparent in the reaction with cinnamic aldehyde, which was converted into the cyclopropyl-methanol **2b** by diiodomethane and into the anticipated diiodinated allyl alcohol **3b** by CHI_3. Two pathways lead to the cyclopropane **2b**: (a) an initial Michael addition is followed by cyclization and iodomethylation,[16] or (b) an iodomethylation of the aldehyde is followed by a Simmons–Smith-like cyclopropanation, which is reported to occur with high *syn*-stereoselectivity, but modest yields for CH_2I_2/*i*-PrMgCl and allyl alcohols.[17] Therefore, we have monitored the reaction at different ratios of aldehyde and CH_2I_2/*i*-PrMgCl to establish the mode of action. The allyl alcohol **4** (Scheme 2) was identified as the dominant intermediate, which was converted into **2b** by a second equivalent of CH_2I_2/*i*-PrMgCl. The exclusive *anti* configuration of the cyclopropane was determined by NMR spectroscopy and revealed the dormant carbenoid reactivity. The relative configuration of the alcohol was tentatively assigned in analogy to the results of Bolm and Pupowicz.[17]

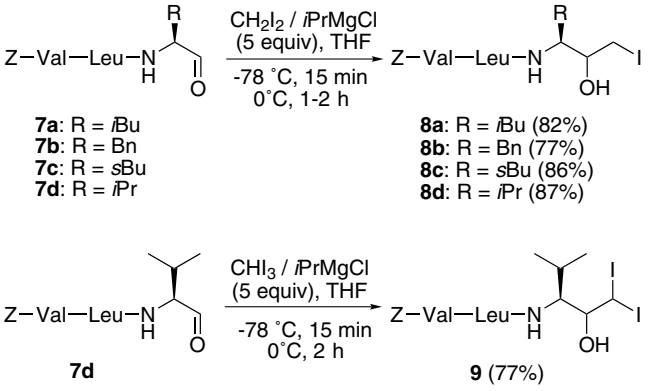
The reaction of the Evans imide **5** with CH_2I_2/*i*-PrMgCl (Scheme 3) resulted in the unexpected, selective iodomethylation of the urethane to furnish the iodoacetate **6**, initially in low yield. However, when the reaction mixture was kept at −25 °C for three days we obtained **6** as a single product. There is precedence for this reactivity of Evans imides.[18] Vinylmagnesium chloride reacted in a similar fashion to result in vinylation of the urethane. A tetrahedral intermediate, similar to Weinreb-amides, was suggested for this monoalkylation.



Scheme 2.



Scheme 3.

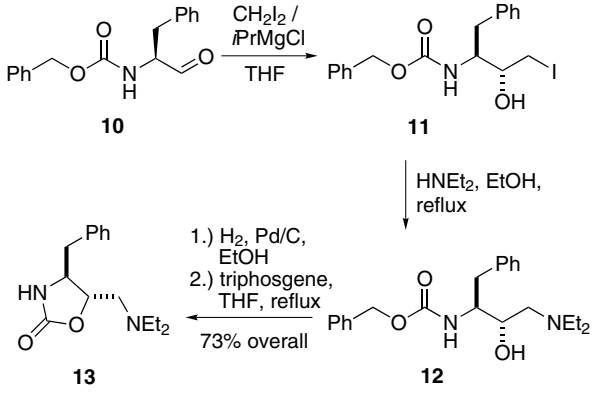


Scheme 4.

After these initial experiments we addressed the iodomethylation of peptide aldehydes, which are important intermediates for the synthesis of protease inhibitors. The deprotonation of the acidic amides required 5-fold excess of the reagent. This was not a nuisance, because the deprotonation froze the configuration of the P1–P3 positions of the tripeptide mimetics **7a**–**d**. The aldehydes were used as 3:1 mixtures of diastereomers, as obtained from the oxidation of alcohols by IBX in DMSO, followed by aqueous work up. The iodomethylation and diiodomethylation provided the compounds **8a**–**d** and **9** (Scheme 4), apparently without epimerization of the P1 position as judged by HPLC. The diastereoselectivity of the reaction was always better than 2:1 as judged by HPLC.

The diastereoselectivity of the iodomethylation was investigated for the phenylalanine derived aldehyde **10** (Scheme 5). The conversion into β-iodoalcohol **11** was followed by substitution of the iodide with diethylamine. The product **12** was deprotected and the resulting amino alcohol was treated with triphosgene to give oxazolidinone **13** and care was taken not to separate the diastereomers.

NMR spectroscopy (^{13}C NMR: γ-effect,[19] NOE) confirmed the relative configuration (*anti*/*syn* d.r. = 86:14). This is in accordance with a chelation controlled Cram transition state and complements the samarium methodology[20] which provides access to the diastereomer when the nitrogen is dibenzylated. The substrate controlled diastereoselectivity provides straightforward access to important intermediates of peptidomimetics. The chiral induction by additional ligands is subject to ongoing investigations.



Scheme 5.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.02.093.

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