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Efficient diastereoselective synthesis of *anti*-α-bromo-β-hydroxyketones

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Abstract

anti-α-Bromo-β-hydroxyketones were synthesized in high diastereoselectivity via the enolboration of a representative series of bromomethylketones using dicyclohexylboron chloride, followed by aldolization with aldehydes.

Keywords: diastereoselective; α-halo ketones; enolboration; aldol reaction.

Diastereoselective synthesis of conformationally nonrigid systems, especially in those C–C bond forming reactions such as aldol additions, has become highly sophisticated in recent years.[1] Since the pioneering report by Mukaiyama and Inoue,[2] diastereo- and enantioselective crossed aldol reactions via boron enolates have been well studied by several groups and applied in several syntheses.[1]

Enolization–aldolization of α-haloketones is an excellent route for the synthesis of α-halo-β-hydroxyketones, which can be used as precursors for the synthesis of useful intermediates, such as α-epoxyketones,[3] α-bromoenones,[4] and α-ynones.[4] These intermediates have found several applications in organic syntheses. Mukaiyama and co-workers reported the synthesis of α-halo-β-hydroxyketones via tin enolates.[3] Shibasaki and co-workers reported cross aldol reactions of α-bromoketones with stoichiometric $Zr(O\text{-}t\text{-}Bu)_4$[5] as well as catalytic $Sm(HMDS)_3$.[6] Shibasaki reported that $n\text{-}Bu_2BOTf$ gave unsatisfactory results for the enolboration–aldolization of 1-bromo-2-heptanone.[5] As part of our ongoing projects in enolboration–aldolization,[7] we undertook to study the enolboration of α-bromoketones. Our successful results with dicyclohexylboron chloride (Chx_2BCl, **1**) are presented below.

Enolboration of 2-bromoacetophenone (**2a**) with 1.1 equiv. of **1** in the presence of triethylamine in Et_2O at 0°C formed the enolborinate as indicated by the ^{11}B NMR spectrum (δ 53 ppm). The by-product $Et_3N{\cdot}HCl$ was removed by filtration and the enolborinate was treated with benzaldehyde at −78°C for 3 h to form the boron aldolate. Subsequent work up with $MeOH/H_2O_2$ provided an 86% yield of the crude product **3a**, the ^1H NMR spectrum of which revealed an *anti*:*syn* ratio of 95:5 (Eq. 1). Purification by flash column chromatography on silica gel yielded the pure product. The observed diastereoselectivity is

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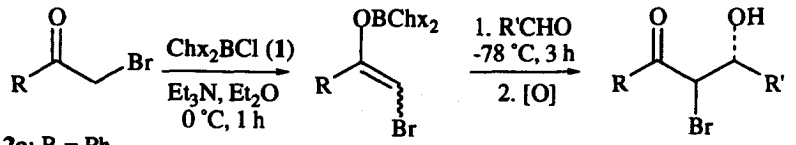
not surprising considering the fact that **1** is an *E*-selective enolizing agent.[7] In fact, the selectivity is better than that realized for the enolboration–aldolization of 3-pentanone with this reagent.[7] The generality of this reaction was demonstrated by enolizing a series of α-bromomethyl ketones, such as 1-bromo-2-butanone (**2b**), 1-bromo-3-methyl-2-butanone (**2c**), and 1-bromo-3,3-dimethyl-2-butanone (**2d**). In all of these cases, we obtained the *anti*-products in ≥93% stereoselectivity. The enolboration of **2d** was slow at 0°C, but was complete in 2 h at room temperature (rt).

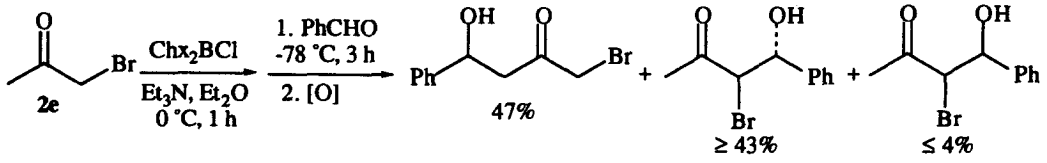


2a: R = Ph
2b: R = Et
2c: R = *i*-Pr
2d: R = *t*-Bu

3a: R = Ph, R' = Ph, 86% yld, 95% *anti*
3b: R = Et, R' = Ph, 88% yld, 93% *anti*
3c: R = *i*-Pr, R' = Ph, 82% yld, 93% *anti*
3d: R = *t*-Bu, R' = Ph, 81% yld, 97% *anti*
4a: R = Ph, R' = Me, 74% yld, 94% *anti*

(1)

It is noteworthy that the enolboration of 1-bromo-2-butanone is very regioselective. We obtained none of the product resulting from the enolboration on the ethyl side of the ketone. However, when bromoacetone (**2e**) was enolized with reagent **1**, we obtained a 1:1 mixture of aldol products resulting from the enolization of the methyl and bromomethyl groups. In this case also, the α-bromo-β-hydroxyketone obtained revealed an *anti*:*syn* ratio of 91:9 (Eq. 2).



2e

(2)

In conclusion, we have achieved the diastereoselective enolboration–aldolization of α-bromomethyl ketones with dicyclohexylboron chloride. The aldol products can be readily converted to α-epoxyketones.[3]

A typical experimental procedure is as follows: All operations were carried out under a nitrogen atmosphere. The α-bromomethylketone (5.0 mmol) was added, dropwise, at 0°C, to a solution of **1** (1.69 g, 5.5 mmol) and Et_3N (0.55 g, 5.5 mmol) in Et_2O (8 mL). The enolborinate was formed instantly with the concurrent formation of solid $Et_3N \cdot HCl$. The mixture was stirred for an additional hour (2 h at rt for **2d**) and the $Et_3N \cdot HCl$ was removed by filtration. The filtrate was cooled to –78°C, the aldehyde (5.0 mmol) was added, and the mixture was stirred for 3 h. Methanol (5 mL) was then added, followed by the addition of H_2O_2 (30%, 2 mL). The mixture was warmed to rt and stirred for 3 h. Water (20 mL) was added and the organics were extracted with Et_2O (3×20 mL), washed with brine, and dried over $MgSO_4$. Removal of solvents provided the crude product which was purified by flash column chromatography over silica gel (hexanes:EtOAc, 8:2).

Acknowledgements

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