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THE REACTION OF α,β-ACETYLENIC KETONES WITH DICYCLOHEXYLBORANE: STEREOSELECTIVE SYNTHESIS OF FUNCTIONALIZED TRISUBSTITUTED OLEFINS

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Abstract: Allenoxyborinates, easily generated via the 1,4-addition of dicyclohexylborane to α,β-acetylenic ketones, react *in situ* with excess starting ketone to afford stereodefined, functionalized trisubstituted olefins in high yields.

The hydrobortion of functionalized alkenes and alkynes has played an important role in organic synthesis.[1] Recently, we reported that the carbon-carbon double bonds and triple bonds of non-conjugated unsaturated ketones and aldehydes can be selectively hydroborated by dicyclohexylborane.[2] However, reactions of α,β-unsaturated ketones and aldehydes with boron reagents generally proceed in a different manner. For example, Trombini and his coworkers report that conjugated olefinic ketones react stereoselectively with dicyclohexylborane or (-)-diisopinocampheylborane to form boron enolates.[3] The carbonyl group in α,β-olefinic ketones is simply reduced by 9-BBN.[4] Enantioenriched propargylic alcohols are obtained by reduction of α,β-acetylenic ketones using chiral boron reagents, such as β-isopinocampheyl-9-BBN,[5] β-chlorodiisopinocampheylborane[6] and BMS in the presence of chiral β-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine.[7] However, to the best of our knowledge, no report on the reactions of α,β-acetylenic ketones with dialkylboranes has appeared in the literature.

As noted in our earlier reports,[2] dicyclohexylborane reacts preferentially with the triple bond in non-conjugated alkynyl ketones to yield the hydroboration product, whereas 9-BBN is more reactive toward the carbonyl group. However, α,β-acetylenic ketones offer the possibility of a 1,4-addition reaction. 3-Heptyn-2-one was used as a model compound in our study. We verified that the reaction of a molar equivalent of 3-heptyn-2-one with 9-BBN produced 3-heptyn-2-ol in 95% yield but the reaction of a molar equivalent of 3-heptyn-2-one with dicyclohexylborane gave complex results. However, when two molar equivalents of 3-heptyn-2-one were added to a slurry of dicyclohexylborane at 0 °C, the only product isolated was 7-acetyl-6-hydroxy-6-methyl-7-undecen-4-yne (**2a**) (Scheme 1).[8] A variety of α,β-acetylenic ketones were then allowed to react with dicyclohexylborane. In each case, the aldol product was obtained as the major product (Table 1).

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SCHEME 1

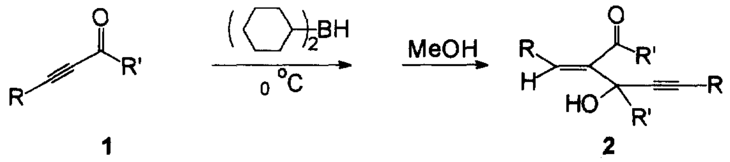


Table 1. Synthesis of Trisubstituted Olefins[a]

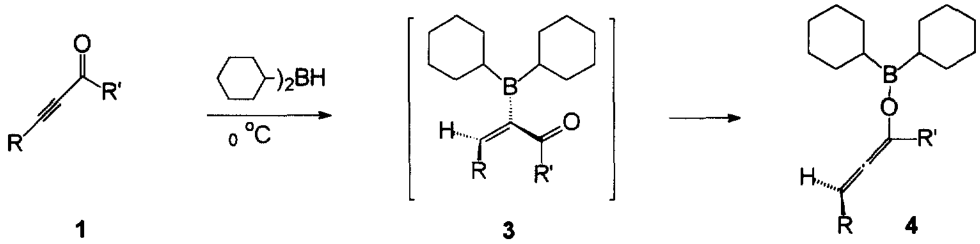
Entry	Product[b]	R	R'	Yield (%)[c]
1	**2a**	$CH_3CH_2CH_2$	CH_3	62
2	**2b**	Ph	CH_3	72
3	**2c**	$CH_3CH_2CH_2$	Ph	78
4	**2d**	Ph	isopropyl	72
5	**2e**	*t*-Bu	Ph	78
6	**2f**	$CH_3CH_2CH_2$	cyclopropyl	66

[a] General procedure for the synthesis of trisubstituted olefins (**2**) is presented in Footnote 8; a 25% excess of dicyclohexylborane was used in all experiments to obtain optimum yields of the desired product. [b] All new compounds were characterized by spectral and elemental analysis or HRMS. [c] Isolated yields.

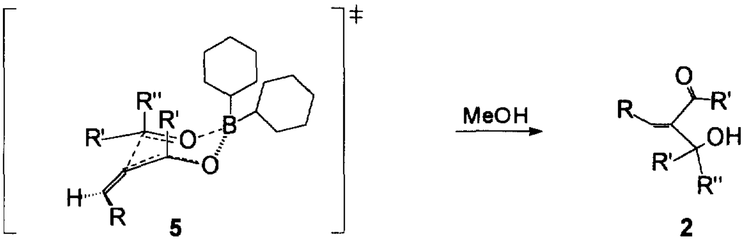
Interestingly, the ^1H NMR and ^{13}C NMR spectrum of all products suggest that only one isomer of each of the trisubstituted olefins is formed. The stereochemistry of the products was determined by NOESY NMR experiments. For example, the NOESY spectrum of 7-acetyl-6-hydroxy-6-methyl-7-undecen-4-yne (**2a**) reveals a NOE cross correlation between the olefinic proton (δ 6.04) and the methyl group (δ 1.63) on the hydroxyl substituted carbon, the olefinic proton does not exhibit a NOE interaction with the methyl group (δ 2.41) of the acetyl group. In addition, the methylene group (δ 2.20) adjacent to carbond-carbon double bond shows no NOE cross correlation with the methyl group on the hydroxyl substituted carbon but exhibits a NOE cross correlation with the methyl of the acetyl group. These results support the *Z* configuration for the trisubstituted olefin.

The mechanism of this reaction is presumed to involve hydroboration of the α,β-acetylenic ketone to form alkenylborane **3** which rearranges to allenoxyborinate **4** (Scheme 2). The allenoxyborinate then reacts with excess α,β-acetylenic ketone via an aldol reaction. Presumably, the reaction of the allenoxyborinate with the ketone occurs via the six-member transition state **5** in which the R group of allenoxyborinates is orientated such that steric interactions are minimized (Scheme 3).

SCHEME 2



SCHEME 3



R'' = RC≡C

In a separate series of experiments, a mixture containing two equivalents of an α,β-acetylenic ketone and one equivalent of an aldehyde was added to the slurry of dicyclohexylborane in THF. The aldol product, formed via reaction of the allenoxyborinate with the aldehyde, as well as the simple aldehyde reduction product were obtained. However, when an alkyl ketone was used in place of the aldehyde, none of the mixed aldol product was produced; only the product of the reaction between the allenoxyborinate and excess α,β-acetylenic ketone was formed. These results suggest that the α,β-acetylenic ketones are less reactive toward allenoxyborinates than aldehydes but are more reactive than alkyl ketones.

In conclusion, the reaction of α,β-acetylenic ketones with dicyclohexylborane produces the 1,4-addition product. Allenoxyborinates are formed as intermediates and undergo an aldol reaction with excess starting ketone. Stereodefined, highly functionalized trisubstituted olefins can be obtained in good yields.

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8. General procedure for the preparation of trisubstituted olefins (**2**): borane-tetrahydrofuran (1.25 mmol, 1.25 mL of a 1.00 M solution in THF) was placed in a dry, argon-flushed, round-bottomed flask which was then immersed in an ice-water bath. Cyclohexene (2.5 mmol, 0.21 g, 0.25 mL) was added dropwise and the mixture stirred at 0 °C for 1 hour. The α,β-acetylenic ketone (2.0 mmol) was then added to the slurry of dicyclohexylborane in THF. The cooling bath was removed and the mixture stirred for 1 hour at room temperature. The reaction was quenched by adding methanol (1 mL) and the trisubstituted olefin was isolated by flash chromatography.