Pergamon

Tetrahedron Letters 39 (1998) 8203–8206

TETRAHEDRON LETTERS

Lewis Acid-Promoted Carbonyl Addition of Lithium (α-Carbalkoxyvinyl)cuprates to Aldehydes Provides a Novel Asymmetric Synthesis of β,β-Disubstituted α-(Hydroxyalkyl)acrylates

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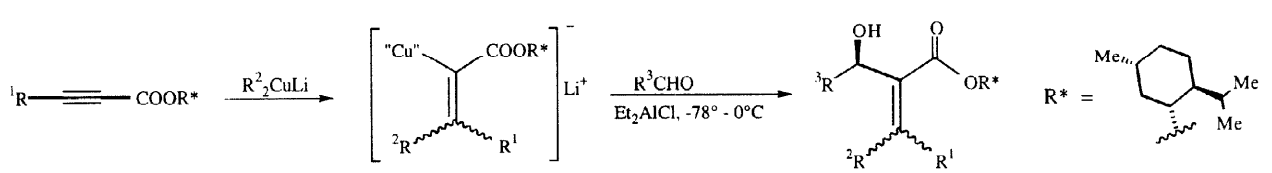
Received 31 July 1998; accepted 1 September 1998

Abstract: A new anionic addition process has been developed for the asymmetric synthesis of unusual Baylis-Hillman adducts, β,β-disubstituted α-(hydroxyalkyl)acrylates. The new process involves conjugate addition of R_2CuLi to β-substituted α,β-acetylenic ester to give lithium (α-carbalkoxyvinyl)cuprate which was then subjected to the carbonyl addition to aldehyde promoted by Et_2AlCl. Modest to good diastereoselectivity (50.0 - 87.7 % de) has been obtained by using (1R,2S,5R)-(-)-menthol as the chiral auxiliary (59.0 - 94.0 % yield). The absolute configuration was unambiguously assigned by transforming the product to methyl (R)-α-methoxyphenylacetate.

The Baylis-Hillman adducts, α-(hydroxyalkyl)acrylates and α-(aminoalkyl)acrylates, are synthetically important precursors having an array of multifunctional groups.[1,2] Even though achiral β-branched α-(hydroxyalkyl)acrylates have been synthesized by use of anionic carbonyl additions of β-branched (α-carbalkoxyvinyl)cuprate or (α-carbalkoxyvinyl)aluminum reagents to carbonyl compounds and their imine derivatives,[3,4] the asymmetric synthesis of β-branched Baylis-Hillman adducts has not been well documented. Recently, (α-carbmenthoxyvinyl)aluminum reagents have been successfully utilized for the asymmetric synthesis of β-unsubstituted Baylis-Hillman adducts.[5] The attempts to apply the β-branched (α-carbmenthoxyvinyl)aluminum reagents for this synthesis have not been successful in our laboratories. Here, we would like to report a new process which involves the carbonyl addition of β-branched (α-carbalkoxyvinyl)cuprates to aldehydes for the synthesis of β-branched α-(hydroxyalkyl)acrylates.

It has been previously shown that addition of β-branched anionic (α-carbalkoxyvinyl)cuprates or Li (α-carbethoxyvinyl)CuHex to aldehydes or ketones can be conducted at -78 °C to room temperature without using any catalyst or promoter.[3] However, we found that the β-branched (α-carbmenthoxyvinyl)cuprates cannot react with aldehydes under the same conditions even at room temperature, which is probably due to the steric effect of the bulky menthyl group. Lewis acids were then employed to activate aldehydes so that the carbonyl additions could proceed. Among various Lewis acids (Et_2AlCl_2, BF_3-Et_2O, *n*-Bu_2BOTf, *etc.*), it was found that diethylaluminum chloride can efficiently promote the present carbon-carbon forming process while other Lewis acids resulted in only a trace amount of addition products. The addition reaction can proceed to completion in



Scheme 1. Asymmetric Carbonyl Addition of Li (α-Carbmenthoxyvinyl)cuprates to Aldehydes

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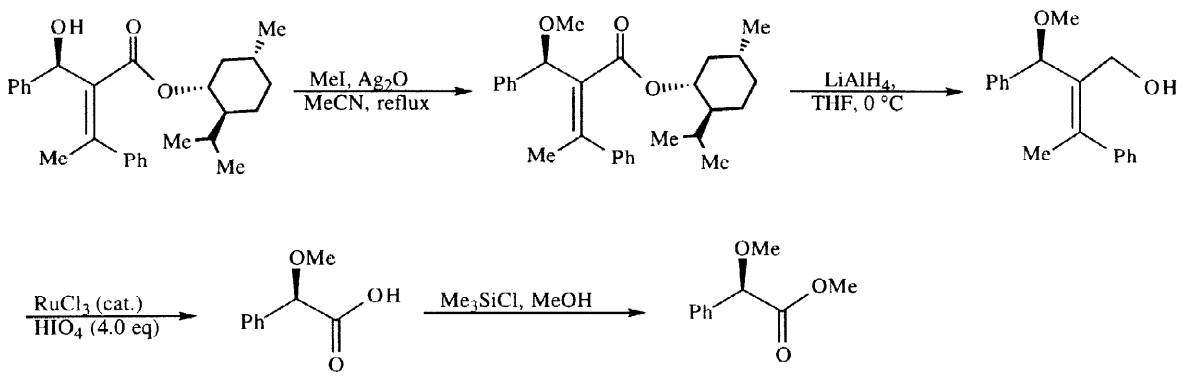
PII: S0040-4039(98)01875-9

the presence of Et_2AlCl (1.0 equivalent) at -78 °C for 3 h and then 0 °C for 0.5 - 1 h (Scheme 1). Recently, we have also found that Et_2AlCl can promote the anionic addition of β-branched (α-carbmenthoxyvinyl)cuprate intermediates to *p*-toluenesulfinimines (thiooxime *S*-oxides).[6]

This Et_2AlCl-promoted addition can proceed in both diethyl ether and THF solvent systems. Lower yields and slower rates were observed in THF than in diethyl ether. It is known that vinylic organocopper intermediates derived from the conjugate addition of dialkylcopper-lithium reagents to α,β-acetylenic esters in diethyl ether solution can coexist with allenoate intermediates in equilibrium.[7-12] The stereochemical interactions of the resulting allenoate with aldehyde control the geometry of the olefinic product, in which the aldehyde approaches the allenoate from the less hindered side.[3] The individual *Z* and *E* olefinic stereoisomers of each product have been completely separated by flash column chromatography. However, the diastereoisomers of each product are not separable by column chromatography. They also cannot be clearly resolved in ^{1}H-NMR spectra, therefore, the diastereoselectivity was determined by HPLC analysis. Modest to good diastereoselectivity and yield have been obtained which are described in Table 1.

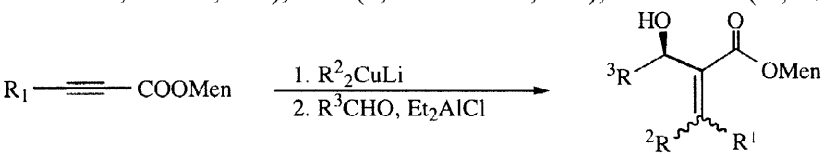
The absolute structure was determined by transforming 4a to methyl (R)-α-methoxyphenylacetate which was derived from (R)-menthyl mandelate (Scheme 2). The transformations started with the reduction of 4a with $LiAlH_4$ in THF and was followed by the ruthenium-catalyzed oxidation using periodic acid.[13] The resulting mandelic acid was then subjected to the carboxyl group protection. The major isomer was proven to be identical to methyl (R)-α-methoxyphenylacetate by ^{1}H-NMR and HPLC analysis.[14]



Scheme 2. Chemical Transformations for Absolute Structure Determination

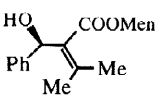
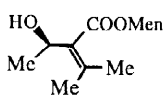
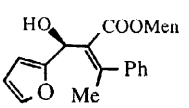
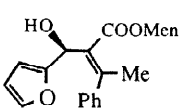
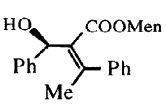
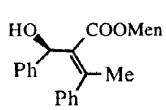
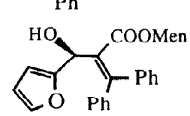
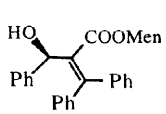
A typical procedure is demonstrated by the coupling reaction for the synthesis of 4a and 4b. A dry flask with a magnetic stirring bar was charged with purified cuprous iodide (218 mg, 1.1 mmol) and freshly distilled diethyl ether (8 mL). The flask was flushed with nitrogen, and cooled to 0 °C before a solution of methyllithium in diethyl ether (1.4 M, 1.46 mL, 2.05 mmol) was added dropwise. The resulting homogeneous gray solution was stirred for 30 min at 0 °C, and then cooled to -23 °C using a carbon tetrachloride-dry ice bath. Into the reaction mixture was added a solution of menthyl phenylpropiolate (284 mg, 1.0 mmol) in diethyl ether (2 mL) via syringe over 10 min. The resulting yellow slurry was stirred at -23 °C for 1.5 h, and then cooled to -78 °C before benzaldehyde (0.128 mL, ca. 1.25 mmol) and Et_2AlCl (1.0 M solution in hexane, 1.25 mL, 1.25 mmol) were added via syringe in order. The reaction mixture was then stirred at -78 °C for 3 h and 0 °C for 1 h. The reaction was finally quenched by dropwise addition of 1N aqueous hydrochloric acid solution. The two phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were then washed with 10 % aqueous amonia and brine, dried over anhydrous magnesium sulfate and

concentrated to dryness. Purification by flash chromatography (EtOAc /hexane, 1/10, v/v) provided two individual *Z/E* isomers of β-methyl β-phenyl α-(hydroxylalkyl)acrylate (4a: 238 mg as a colorless oil, 4b: 34.0 mg as a glassy solid, combined yield 67.0 %). ^{1}H-NMR (200 MHz, $CDCl_3$): 4a, δ 0.27 (d, J = 6.7 Hz, 3 H), 0.54 (d, J = 6.8 Hz, 3 H), 0.69 (d, J = 7.4 Hz, 3 H), 0.70 - 0.88 (m, 3H), 1.15 - 1.49 (m, 5H), 2.29 (s, 3 H), 4.28 (td, J = 6.6 Hz, 1.5 Hz, 1 H), 4.33 (br s, 1 H), 5.84 (br s, 1 H), 7.19 - 7.46 (m, 10 H); 4b, δ 0.46 (d, J = 6.8 Hz, 3 H), 0.75 (d, J = 6.8 Hz, 3 H), 0.84 (d, J = 6.5 Hz, 3 H), 1.22 - 1.78 (m, 8H), 2.33 (s, 3 H), 4.02 (d, J = 10.7 Hz, 1 H), 4.69 (td, J = 10.5 Hz, 4.2 Hz, 1 H), 5.33 (d, J = 10.6 Hz, 1 H), 7.19 - 7.46 (m, 10 H).



Men = (1R,2S,5R)-(-)-menthyl

Table 1. Carbon-Carbon Coupling Results Promoted by Et_2AlCl

R^1	R^2	R^3	Product[a]		^{1}H-NMR (δ) of β-H (C**H**-OH)	% de[b]	Yield (%)[d]
Me	Me	Ph		1	5.73	68.5[c]	71.0
Me	Me	Me		2	4.73	85.2	59.0
Ph	Me			3a	5.77	56.5	68.4[e]
				3b	6.26	87.2	
Ph	Me	Ph		4a	5.84	70.2	67.0[e]
				4b	5.33	87.7	
Ph	Ph			5	5.53	62.7[c]	74.6
Ph	Ph	Ph		6	5.57	50.0	94.0

[a] The stereochemistry was determined by transformations described in Scheme 2. [b] % de was determined by HPLC, chiralcel AD, *i*-PrOH/Hexane (15/85, v/v), 0.5 mL min^{-1}. [c] % de was determined by HPLC, chiralcel OD-H, *i*-PrOH/Hexane (15/85, v/v), 0.7 mL min^{-1}. [d] 1.0 equiv. of Et_2AlCl was used for all cases. However, catalytic amount of Et_2AlCl (less than 30 mol %) also gave complete conversion, but yields were decreased. [e] Combined yields of individual *E* and *Z* isomers after column chromatography (*Z/E* selectivity: 3a/3b = 4.4; 4a/4a = 7.0).

In conclusion, the new asymmetric carbon-carbon bond formation process described in this paper provides a novel approach for the asymmetric synthesis of optically active β,β-disubstituted α-(hydroxyalkyl)acrylates. The Et_2AlCl-promoted system could also be beneficial to the study of asymmetric catalytic addition of vinylcuprate intermediates to aldehydes or ketones. Similar asymmetric C-C forming processes controlled by other chiral auxiliaries are currently being studied in this laboratory so that stereoselectivity can be improved.

Acknowledgments We would like to dedicate this paper to Professor Victor J. Hruby on the occasion of his 60th birthday. We gratefully acknowledge financial support from the Robert A. Welch Foundation (Grant No. D-1361) and the Seed Grant of Texas Tech University. We also would like to thank Sun Hee Kim and Jason Hook for their assistance.

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14. Both isomers of methyl (R)-α-methoxyphenylacetate were synthesized for HPLC co-injection analysis: chiralcel OD-H, *i*PrOH/Hexane (3/17), 0.4 mL min^{-1}, 11.47 min (S), 15.66 min (R).