Novel Asymmetric C−C Bond Formation Process Promoted by Et_2AlCl and Its Application to the Stereoselective Synthesis of Unusual β-Branched Baylis−Hillman Adducts

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The Baylis−Hillman reaction is an important carbon−carbon bond formation process.[1,2] The resulting enantiomerically enriched α-(hydroxyalkyl)acrylates and α-(aminoalkyl)acrylates can provide numerous chemically and biologically important precursors having an array of multifunctional groups.[3−5] For example, α-(aminoalkyl)-acrylates can be utilized for the synthesis of conformationally constrained taxol and taxotere side chain analogues.[6] Some α-constrained taxotere side chains have resulted in significant potency enhancement in the tests of inhibition activity in microtubule depolymerization and cytotoxicity toward KB-V1 in comparison with the parent drug.[6b,c] Several asymmetric Baylis−Hillman processes have recently been established for the synthesis of optically pure α-(hydroxyalkyl)acrylates by using chiral auxiliaries.[3,7] However, a process for the asymmetric synthesis of β-branched α-(hydroxyalkyl)acrylates and α-(aminoalkyl)acrylates has not been well documented thus far, which is probably due to the fact that β-substituted olefinic substrates do not normally undergo the Baylis−Hillman reaction. Alternative approaches have to be studied to overcome the limitations of the original Baylis−Hillman system.

It is well-known that (α-carbalkoxy)vinyl copper and aluminum anions can react with aldehydes and ketones to give Baylis−Hillman adducts.[8−10] Recently, we reported the stereospecific synthesis of chiral and achiral β-monosubstituted and β,β-disubstituted Baylis−Hillman adducts by using new procedures.[10a−c] These methods involved the conjugate additions of R_2CuLi (or RMgBr−CuBr−DMS)[11−16] and reductive addition of DIBAL−HMPA complex to α,β-acetylenic esters to generate anionic (α-carbalkoxyvinyl)cuprate and (α-carbalkoxyvinyl)aluminum intermediates. These organometalic intermediates were then subjected to nucleophilic additions to aldehydes and ketones (Scheme 1). To develop an asymmetric version of this process, chiral imines can be employed to replace aldehydes as electrophilic acceptors to react with (α-carbalkoxyvinyl)metal anions. Chiral *p*-toluenesulfinimines (thiooxime *S*-oxides)[17,18] pioneered by Davis became attractive choices for this strategy because they have been successfully utilized as electrophilic acceptors to react with various anionic species for the stereoselective synthesis of many organic compounds, such as α- and β-amino acids,[19] *N*-sulfinyl *cis*-aziridine 2-carboxylic acids[20] and amines,[21] etc. Here, we would like to report a novel asymmetric carbon−carbon bond formation by applying Davis-type *p*-toluenesulfinimines to the tandem vicinal difunctionalization process.

In the new system, the direct anionic additions of β-branched (α-carbethoxyvinyl)cuprate and aluminum reagents to *p*-toluenesulfinimines were first attempted, but without success in several solvent systems even at room temperature. Therefore, various Lewis acids (BF_3−Et_2O, *n*-Bu_2BOTf, $ZnCl_2$, Et_2AlCl, etc.) were then employed to activate *p*-toluenesulfinimine electrophiles. It was found that the β-branched (α-carbalkoxyvinyl)-cuprates could react very well with *p*-toluenesulfinimines at low temperature (−23 °C) when diethylaluminum chloride was added into the reaction system (Scheme 2). More interestingly, both diastereoselectivity and *Z*/*E* selectivity were well controlled in this Et_2AlCl-promoted process (Table 1); one isomer was observed by ^1H NMR of the crude products for most cases (**1**, **2**, **4**−**7** in Table 1). Only in two cases (**3** and **8**) were modest *Z*/*E* selectivities observed for which the reason is not clear.

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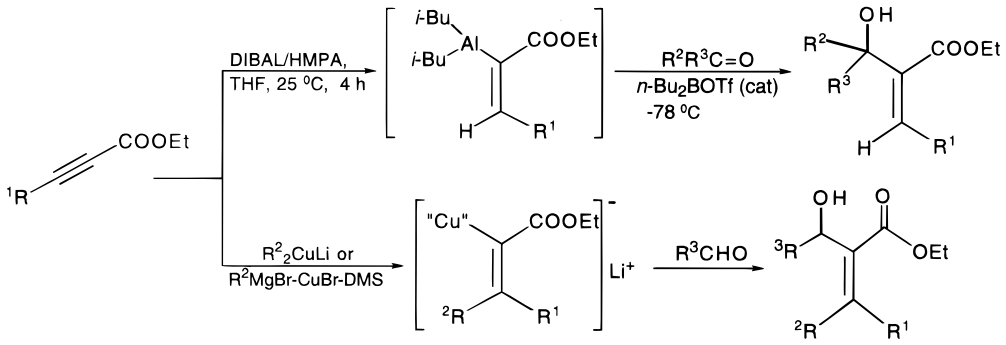
Scheme 1



Scheme 2

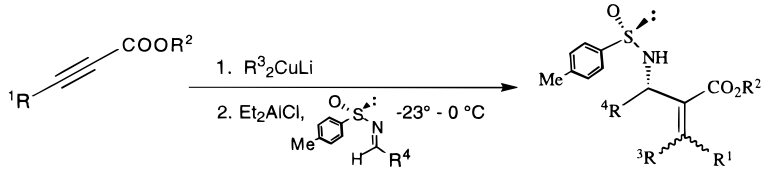
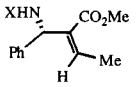
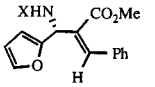
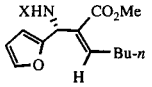
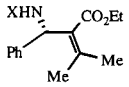
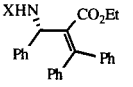
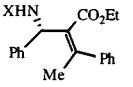
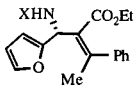
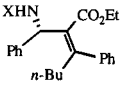


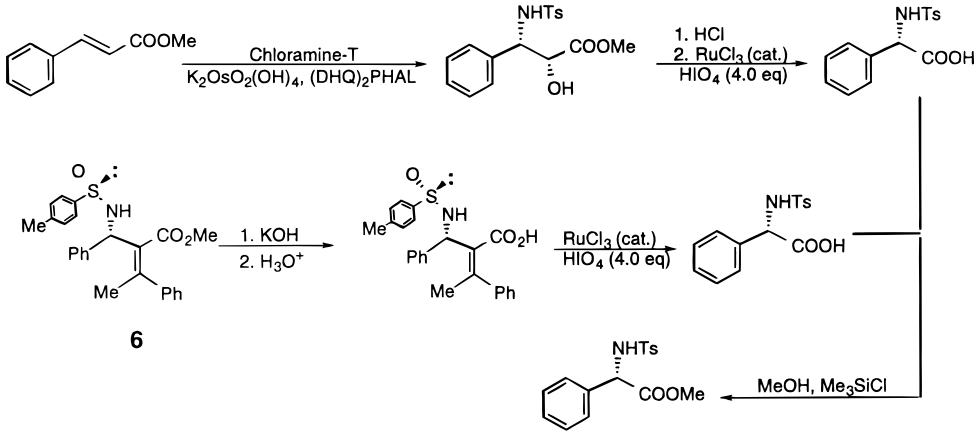
Table 1. Results of Anionic Additions of Vinylcuprates to *p*-Toluenesulfinimines

R^1	R^2	R^3	R^4	Product (= X)		$[\alpha]_D^{25}$ (95 % EtOH)	Yield (%)[a]
H	Me	Me	Ph		**1**	+135.6 (c=0.52)	58.6
H	Me	Ph			**2**	+85.7 (c=0.57)	58.7
H	Me	*n*-Bu			**3**	*Z*/*E* = 1.8:1	54.5[c]
Me	Et	Me	Ph		**4**[b]	+128.9 (c= 1.22)	77.1
Ph	Et	Ph	Ph		**5**	-71.3 (c=0.24)	77.0
Ph	Et	Me	Ph		**6**	+189.3 (c=0.81)	81.0
Ph	Et	Me			**7**	+174.0 (c=0.54)	66.0
Ph	Et	*n*-Bu	Ph		**8**	*Z*/*E* = 2.2:1	65.2[c]

[a] Only one isomer was observed by crude ^{1}H-NMR determination. The purified products (1, 4 and 5) were selectively analyzed by chiral HPLC (OD-H and AD columns) and proven to be optically pure; [b] X-Ray structure was obtained, m.p. 75.1-77.0 °C; [c] The yield of two isomers which were difficult to separate by column chromatography. Only one diastereoisomer was observed for each *Z* and *E* olefinic product by crude ^{1}H-NMR determination.

The reaction also proceeded with a catalytic amount of Et_2AlCl (30 mol %) but gave poor yields (<40% in cases **4** and **6** which were examined). Only a trace amount of adducts was observed by using other Lewis acids (BF_3—Et_2O, *n*-Bu_2BOTf, $ZnCl_2$, etc.) as the nucleophilic addition promoters. It is interesting to point out that this Et_2AlCl-promoted reaction can only proceed in diethyl ether solution; almost no desired products were detected when THF was employed as the solvent. Neither β-non-branched nor β-branched (α-carbalkoxyvinyl)aluminum

Scheme 3



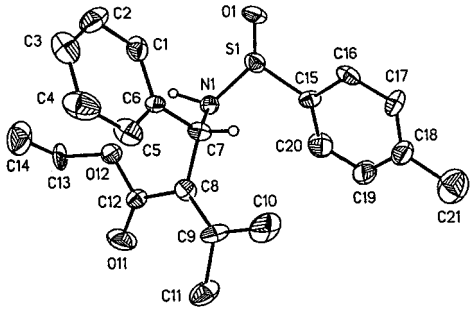


Figure 1. X-ray structure of the product **4**.

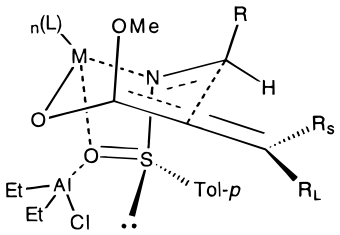


Figure 2. Hypothesis of asymmetric induction pattern.

derived from DIBAL−HMPA reductive additions of α,β-acetylenates could undergo the additions to *p*-toluenesulfinimines even at room temperature with 2 equiv of Et_2AlCl.

Chiral *p*-toluenesulfinimines were prepared following the procedure developed by Davis.[21] Michael addition of R_2CuLi (1.1 equiv) to α,β-acetylenic esters (1.0 equiv) was performed in freshly distilled diethyl ether at −23 °C for 2 h. The resulting β-branched (α-carbalkoxyvinyl)cuprates were reacted with *p*-toluenesulfinimines (1.2 equiv) at −23 °C for 12 h and at 0 °C for 1 h in the presence of Et_2AlCl solution in hexane (1.2 equiv). Most of the products in Table 1 are oils except compound **4,** which was obtained as the only solid product. It was fortunate that we were able to obtain the X-ray structure of compound **4** for the absolute structure determination. The crystals were obtained by using H_2O−MeOH (v/v, 3:7) as the cosolvent for recrystallization (X-ray structure of **4** see Figure 1).

During the effort to grow the crystals, synthetic methods were also employed at the same time for the absolute structure determination. Compound **6** was transformed to a known α-amino acid ester (Scheme 3) synthesized by using Sharpless AA reaction.[22] In this procedure, compound **6** and Sharpless AA product were first hydrolyzed to the carboxylic acid derivatives and then subjected to the ruthenium-catalyzed oxidation using periodic acid.[23] The resulting α-amino acids were then converted into methyl esters[24] for HPLC analysis by co-injection.[25] This carboxylic ester based AA procedure can also serve as a concise method for the synthesis of aromatic and nonaromatic α-amino acids, because the ester functional groups have proven to be strong regioselectivity-directing moieties in the Sharpless AA system. The styrene-based Sharpless AA process has been applied to aromatic α-amino acid synthesis by the Sharpless group very recently.[26]

Given the high diastereoselectivity and *Z*/*E* stereospecificity of the present system, a similar hypothesis of a chairlike transition state proposed by Davis can be employed to understand the asymmetric induction pattern (Figure 2).[20] M can be the lithium cation (from R_2CuLi), which can compete with copper for the coordination with the oxygen atom.[9b] Et_2AlCl coordinates to the oxygen atoms of sulfinimine to activate its eletrophilic reactivity to the anionic addition. It has been observed that an excess amount of Et_2AlCl can promote the addition reaction at a faster rate; therefore, extra Et_2AlCl might also coordinate with the nitrogen atom to further activate sulfinimine.[19a] The anion intermediate approaches the sulfinimine electrophilic carbon center from the less hindered side of the lone pair of electrons so that the newly formed chiral center can be controlled. It is known that vinylic organocopper intermediates coexist with allenoate intermediates in equilibrium in diethyl ether solution. It should be reasonable to predict that allenoate organocopper intermediates dominate the

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(24) Brook, M. A.; Chan, T. H. *Synthesis* **1983**, 201.

(25) Both isomers of *N*-*p*-toluenesulfonyl phenylglycine methyl ester were synthesized for HPLC co-injection: Chiralcel-OD-H, *i*-PrOH/hexane (3/17), 0.7 mL min^{-1}, 11.57 min (*S*), 12.42 min (*R*). Some racemization was observed in these two oxidation procedures.

(26) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207.

nucleophilic additions in which the *Z*/*E* selectivity is controlled by R_s and R_L groups (s = small, L = large).

In conclusion, a novel tandem asymmetric carbon−carbon formation system has been established, providing the first approach to the highly stereoselective synthesis of unusual Baylis−Hillman adducts, β-branched α-(aminoalkyl)acrylates. The absolute structure is unambiguously determined by X-ray analysis and by synthetic conversions to a known sample. The application of this method to the asymmetric synthesis of biologically important compounds will be conducted in this laboratory in the future.

Experimental Section

All reactions were conducted under nitrogen atmosphere in oven-dried glassware with magnetic stirring. Diethyl ether and THF were dried and freshly distilled from sodium and benzophenone under nitrogen protection. Organolithium reagents (MeLi, PhLi, and *n*-BuLi in diethyl ether solutions) and Et_2AlCl in hexane solution were purchased from Aldrich Chemical Co. Other commercial chemicals were used without purification, and their stoichiometries were calculated on the basis of the reported purities from the manufacturers. Flash chromatography was performed on E. Merck silica gel 60 (230−400 mesh). High-resolution mass spectral analysis was conducted by the Scripps Research Institute.

The representative procedure was illustrated by the nucleophilic addition of β,β-dimethyl[α-(alkoxycarbonyl)vinyl]cuprate to *p*-toluenesulfinimines. Into a dry, nitrogen-flushed flask was added purified cuprous iodide (0.210 g, 1.10 mmol) and freshly distilled diethyl ether (9 mL). The resulting solution was cooled to 0 °C, and a solution of methyllithium in diethyl ether (1.4 M, 1.46 mL, 2.05 mmol) was added via syringe. The resulting homogeneous gray solution was stirred for 30 min at 0 °C and then cooled to −23 °C using a CCl_4/dry ice bath before a solution of ethyl 2-butynoate (0.112 g, 1.0 mmol) in Et_2O (2 mL) was added in ca. 10 min. The reaction mixture was stirred at −23 °C for 2 h before a solution of (*S*)-(+)-benzylidene-*p*-toluenesulfinamide (0.292 g, 1.2 mmol) in diethyl ether (2 mL) and an Et_2AlCl solution (1.0 M solution in hexane, 1.2 mL, 1.2 mmol) were added via syringe in order. The resulting mixture was stirred at −23 °C for 12 h and at 0 °C for 1 h. The reaction was finally quenched by dropwise addition of saturated aqueous NH_4Cl solution (2 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with 10% aqueous ammonia and brine, dried over anhydrous magnesium sulfate, and concentrated to dryness, which was determined by ^{1}H NMR. Purification by flash chromatography (EtOAc/hexane, 1/10, v/v) provided product **4** (0.286 g, 77.1% yield) as a colorless solid. Needle crystals were obtained by using H_2O−MeOH (v/v, 3:7) as crystallization solvent (for X-ray structure of **4**, see Figure 1): mp 75.1−77.0 °C; $[\alpha]^{25}_D$ = +128.9 (*c* 1.22, 95% EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66 (d, *J* = 6.52 Hz, 2 H), 7.25−7.63 (m, 7 H), 5.52 (d, *J* = 8.91 Hz, 1 H), 5.38 (d, *J* = 8.92 Hz, 1 H), 4.00 (m, 2 H), 2.43 (s, 3 H), 2.01 (s, 3 H), 1.68 (s, 3 H), 1.02 (t, *J* = 7.07 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 145.3, 141.6, 141.1, 129.3, 128.5, 128.1, 126.9, 126.3, 126.1, 125.9, 60.1, 56.0, 23.4, 21.7, 21.1, 13.8; HRMS (FAB) *m*/*z* (M^+ + 1) found 372.1628, calcd for $C_{21}H_{26}O_3NS$ 372.1633.

1: colorless oil (0.201 g, 58.6% yield); $[\alpha]^{25}_D$ = +135.6 (*c* 0.52, 95% EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62 (d, *J* = 6.54 Hz, 2 H), 7.24−7.39 (m, 7 H), 6.20 (q, *J* = 7.31 Hz, 1 H), 5.31 (d, *J* = 7.58 Hz, 1 H), 5.00 (d, *J* = 7.58 Hz, 1 H), 3.60 (s, 3 H), 2.42 (s, 3 H), 1.99 (d, *J* = 7.31 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 141.7, 141.3, 140.6, 140.5, 133.1, 129.4, 128.4, 127.4, 127.0, 125.7, 60.5, 51.3, 21.4, 15.7; HRMS (FAB) *m*/*z* (M^+ + 1) found 344.1326, calcd for $C_{19}H_{22}O_3NS$ 344.1320.

2: light yellow oil (0.232 g, 58.7% yield); $[\alpha]^{25}_D$ = +85.7 (*c* 0.57, 95% EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.19 Hz, 2 H), 7.26−7.34 (m, 8 H), 6.92 (s, 1 H), 6.26 (m, 2 H), 5.47 (d, *J* = 7.49 Hz, 1 H), 5.05 (d, *J* = 7.49 Hz, 1 H), 3.64 (s, 3 H), 2.40 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 152.0, 142.7, 141.4, 137.1, 134.9, 132.1, 129.5, 128.5, 128.3, 128.2, 125.9, 125.7, 110.6, 108.1, 55.4, 51.8, 21.3; HRMS (FAB) *m*/*z* (M^+ + 1) found 396.1276, calcd for $C_{22}H_{22}O_4NS$ 396.1269.

5: colorless oil (0.381 g, 77.0% yield); $[\alpha]^{25}_D$ = −71.3 (*c* 0.24, 95% EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.23 Hz, 2 H), 7.52 (d, *J* = 6.94 Hz, 2 H), 7.36−7.13 (m, 15 H), 5.82 (d, *J* = 10.36 Hz, 1 H), 5.51 (d, *J* = 10.36 Hz, 1 H), 3.71 (q, *J* = 7.22 Hz, 2 H), 2.37 (s, 3 H), 0.62 (t, *J* = 7.22 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 151.4, 142.8, 142.3, 140.9, 140.7, 139.7, 131.3, 129.4, 128.9, 128.8, 128.4, 128.3, 127.9, 127.8 127.4, 126.5, 125.7, 60.4, 60.3, 21.3, 13.1; HRMS (FAB) *m*/*z* (M^++1) found 496.1929, calcd for $C_{31}H_{30}O_3NS$ 496.1946.

6: colorless oil (0.351 g, 81.0% yield); $[\alpha]^{25}_D$ = +189.3 (*c* 0.81, 95% EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.21 Hz, 2 H), 7.37−7.18 (m, 12 H), 5.93 (d, *J* = 8.40 Hz, 1 H), 5.42 (d, *J* = 8.40 Hz, 1 H), 3.66 (q, *J* = 7.20 Hz, 2 H), 2.36 (s, 3 H), 2.22 (s, 3 H), 0.60 (t, *J* = 7.20 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 145.4, 143.6, 141.2, 141.0, 140.3, 131.4, 129.4, 128.3, 128.0, 127.4, 127.2, 126.9, 126.5, 126.0, 60.2, 55.2, 21.6, 21.3, 13.2; HRMS (FAB) *m*/*z* (M^+ + 1) found 496.1929, calcd for $C_{31}H_{30}O_3NS$ 496.1946.

7: colorless oil (0.279 g, 66.0% yield); $[\alpha]^{25}_D$ = +174.0 (*c* 0.54, 95% EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.72 Hz, 2 H), 7.32−7.18 (m, 8 H), 6.25 (m, 1 H), 6.18 (m, 1 H), 6.02 (d, *J* = 8.40 Hz, 1 H), 5.38 (d, *J* = 8.40 Hz, 1 H), 3.75 (q, *J* = 7.16 Hz, 2 H), 2.40 (s, 3 H), 2.19 (s, 3 H), 0.69 (t, *J* = 7.16 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 153.1, 146.6, 143.4, 142.0, 141.3, 140.8, 129.5, 128.9, 128.0, 127.4, 126.9, 126.3, 110.4, 107.1, 60.4, 50.3, 21.6, 21.2, 13.2; HRMS (FAB) *m*/*z* (M^+ + 1) found 396.1276, calcd for $C_{22}H_{22}O_4NS$ 396.1269.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all pure isomers. This material is available free of charge via the Internet at http://pubs.acs.org.

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