Titanium(IV) bromide promoted diastereoselective reactions of arylaldehydes with optically active propiolates

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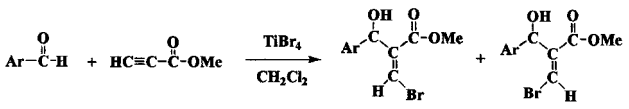
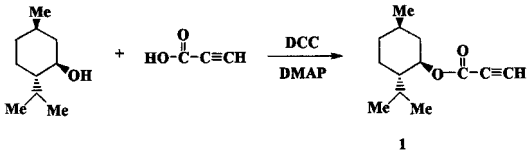
The diastereoselective condensation reaction of arylaldehydes with optically active derivatives of propynoic acid has been examined in the presence of the Lewis acid titanium(IV) bromide ($TiBr_4$); we have found that moderate to excellent diastereomeric excess (de) can be achieved in this $TiBr_4$-promoted reaction.

Keywords: Baylis-Hillman reaction, arylaldehydes, methyl propiolate, titanium(IV) bromide, bromination, condensation

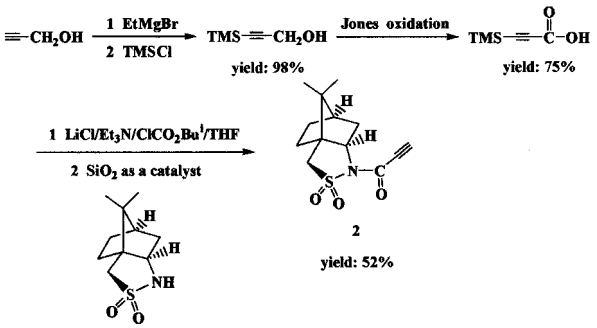
The Baylis-Hillman reaction, notorious for its poor reaction rate, is an important carbon-carbon bond-forming process which affords densely functionalised products.[1] Several methods to accelerate the rate of this useful and simple reaction have been explored so far.[2] Recently, we reported that the reaction of arylaldehydes with methyl propiolate can produce brominated products in the presence of titanium(IV) bromide ($TiBr_4$) under mild reaction conditions (Scheme 1).[3] Although these reactions were in general slow at room temperature (20 °C), the brominated products were obtained in moderate yields as *E/Z* mixtures. Due to the fact that methyl propiolate was reactive in this reaction, we attempted a diastereoselective version of this interesting reaction using a Michael acceptor having a chiral auxiliary such as (–)–*L*–menthol or (–)–(1*S*)–2, 10–camphorsultam. The preparation of optically active starting materials **1** and **2** is shown in Schemes 2 and 3, respectively. The chiral Michael acceptor **1** was prepared simply by reaction of propynoic acid with (–)–*L*–menthol in the presence of 1,3–dicyclohexylcarbodiimide (DCC) and catalytic amounts of 4–*N*,*N*–dimethylaminopyridine (DMAP) (Scheme 2).[4] The chiral reactant **2** was prepared according to the literature (Scheme 3).[5] The two optically active starting materials were directly used for the diastereoselective condensation reactions with arylaldehydes in the presence of $TiBr_4$ under mild reaction conditions.



Scheme 1



Scheme 2



Scheme 3

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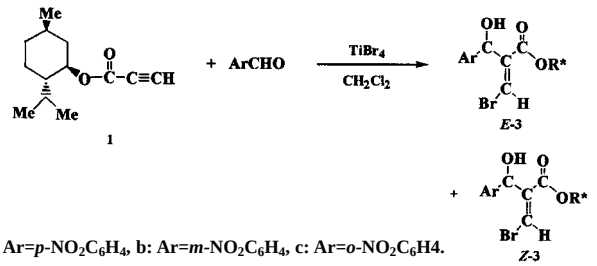
Results and discussion

The reactions of 1 (1.0 equiv) with arylaldehydes (2.0 equiv) were carried out in dichloromethane in the presence of $TiBr_4$ (1.4 equiv) at room temperature. We found that only when the arylaldehydes have strongly electron-withdrawing groups such as NO_2 could the $TiBr_4$ promoted condensation reaction of **1** with arylaldehydes take place to give the corresponding brominated products **3** in moderate yields (Scheme 4). The formed *E*–and *Z*-isomers can be separated by silica gel column chromatography and the diastereoisomeric excess (de) for each double bond isomer can be determined directly by ^1H NMR spectroscopy. The results are summarised in Table 1. The reaction temperature can effect the chemical yields and de to some extent (Table 1, entry 1–4). When the reaction was carried out at 0 °C for *p*-nitrobenzaldehyde, *E*–**3a** was obtained in 7% chemical yield with 73% de and *Z*–**3a** in 50% chemical yield with 43% de (Table 1, entry1). At room temperature (20 °C), we found that *E*–**3a** was formed in 17% yield with 20% de and *Z*–**3a** in 55% yield with 45% de (Table 1, entry 2). The major double–bond isomer was formed in higher yield with similar de as that at 0 °C. Thus, we carried out the reaction of **1** with other nitrobenzaldehydes at room temperature (20 °C). Similar results were obtained (Table 1, entries 2–4). Using (–)–*L*–menthyl moiety as a chiral auxiliary, moderate de can be achieved. This is the first attempt to achieve diastereoselective $TiBr_4$-promoted condensation reactions of arylaldehydes with a propiolate, although only moderate de has been realised. In order to get higher de in this novel condensation reaction, we carried out the reactions of **2** with *p*-nitrobenzaldehyde in the presence of $TiBr_4$ under the same conditions (Scheme 5). We found that the reaction is fairly fast. The product *E*–**4a** was obtained in 10–15% chemical yield with >99% de and *Z*–**4a** in 40–52% chemical yield with 40–63% de (Table 2). Changing the ratio of the substrates did not affect the chemical yields and de of **4a**. The compound *E*–**4a** was obtained with excellent de, although it is the minor isomer. The relative and absolute configuration of *E*–**4a** was unambiguously determined by an X-ray crystal-structure diffraction (Fig. 1). The crystallographic data are reported in the experimental section. Using $TiCl_4$ as a Lewis acid in this case, the reaction also proceeded very well to give the corresponding chlorinated Baylis-Hillman adducts *E*–**4b** and *Z*–**4b** in similar chemical yields and diastereoselectivities (Table 2, entry 5).



a: Ar=*p*-$NO_2C_6H_4$, **b**: Ar=*m*-$NO_2C_6H_4$, **c**: Ar=*o*-NO_2C_6H4.

Scheme 4

Table 1 The enantioselective reactions of 1 with arylaldehydes in the presence of $TiBr_4$ in dichloromethane

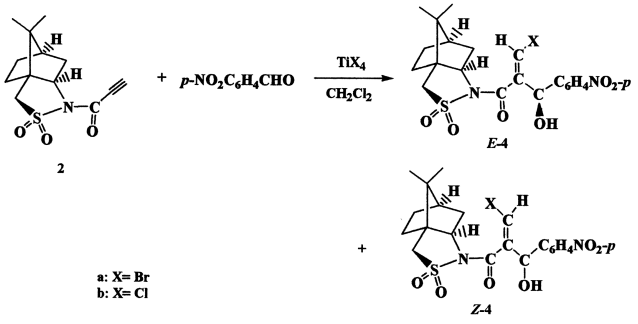
Ar	Reaction conditions		*E : Z*	*E–3*		*Z–3*	
	Temp/°C	Time/h		Yield/%[a]	de/%[b]	Yield/%[a]	de/%[b]
p-$NO_2C_6H_4$	0	48	1 :7.2	7	73	50	43
p-$NO_2C_6H_4$	20	24	1 : 3.2	17	20	55	45
m-$NO_2C_6H_4$	20	24	1 : 3.2	16	2	51	62
o-$NO_2C_6H_4$	20	24	1 : 3.2	16	2	50	40
p-ClC_6H_4	20	48	–	–	–	–	–

[a]Isolated yields. [b]Determined by ^1H NMR spectral data.

Table 2 The enantioselective reactions of 2 with *p*–nitrobenzaldehydes in the presence of TiX_4 in dichloromethane

Entry	Reaction conditions		*E : Z*	*E–4*		*Z–4*	
	Temp/°C	Time/h		Yield/%[a]	de/%[b]	Yield/%[a]	de/%[b]
1	20[c]	12	1 : 4.7	11	>99	52	54
2	20[d]	12	1 : 4.8	10	>99	48	40
3	20[e]	28	1 : 5.6	10	>99	56	56
4	–20[e]	48	1 : 4	10	>99	40	63
5	20[f]	12	1 : 2.7	15	>99	40	38

[a]Isolated yields. [b]Determined by ^1H NMR spectral data. [c]2 : *p*–$NO_2C_6H_4CHO$: $TiBr_4$=2 : 1 : 1.4. [d]2 : *p*–$NO_2C_6H_4CHO$: $TiBr_4$=1 : 2 : 1.4. [e]*p*–$NO_2C_6H_4CHO$: $TiBr_4$=1 : 1 : 1.4. [f] 2 : *p*–$NO_2C_6H_4CHO$: $TiCl_4$=1 : 1 : 1.4.



Scheme 5

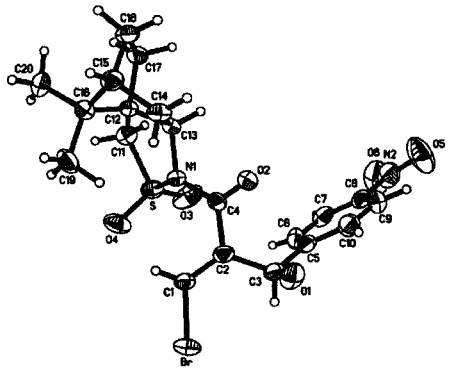


Fig. 1 The crystal structure of *E*–**4a**.

In conclusion, we have demonstrated an unprecedented diastereoselective condensation of arylaldehydes with propiolates promoted by $TiBr_4$ although this reaction is strictly limited to arylaldehydes with strongly electron-withdrawing groups such as NO_2. Efforts are underway to expand significantly the scope and limitations of this novel enantioselective condensation reaction.

Experimental

General. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Mass spectra were recorded by EI methods, and HRMS was measured on a Finnigan MA+ mass spectrometer. Organic solvents used were dried by standard methods when necessary. All solid compounds reported in this paper gave satisfactory CHN microanalyses. All reactions were monitored by TLC with Huanghai GF254 silica gel coated plates. Commercially obtained reagents were used without further purification. Standard chemicals and solvents were employed in all cases without further purification. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure. Alkenes were freshly distilled prior to use. *L*–(–)–Menthol and (1*S*)–(–)–2,10–camphorsultam were obtained from Aldrich (Milwaukee, WI). The menthyl propiolate **1** is a known compound which was prepared according to the literature.[4]

Preparation of 3–trimethylsilyl–2–propyn–1–ol:[6] Mg turnings (5.15 g, 0.21 mol) were placed in a dry, three–necked flask equipped with a condenser, a dropping funnel, and a stirring bar. Anhydrous ether (150 ml) and a crystal of I2 were added to the flask. Ethyl bromide (21.5 g, 0.2 mol) was added dropwise over a 25 min period during which the reaction mixture was kept under reflux. After stirring for 20 min, the solution was cooled to 0 °C, and propargyl alcohol (3.79 g, 68 mmol) in anhydrous ether (4.0 ml) was added dropwise over 30 min. The reaction mixture was warmed to room temperature and the solution was stirred continuously for 45 min. TMSCl (16.8 g, 154 mmol) was added to the flask and the reaction mixture was stirred continuously under nitrogen atmosphere for 18 h. The reaction was quenched at 0 °C with 4 M H_2SO_4 (100 ml) and the solution was extracted with ether 2 × 50 ml). The combined organic layers were washed with water and brine dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled under reduced pressure to give the pure alcohol 8.5 g (98%) as a pale yellow oil. b.p. 95–96 °C/22 mmHg. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 0.22 (s, 9H, $SiMe_3$), 1.67 (br, 1H, OH), 4.32 (s, 2H, CH_2).

Preparation of 3-trimethylsilyl-2-propynoic acid: The chromic acid solution (45 ml), which was made by diluting a mixture of chromium trioxide (9 g, 89 mmol) and concentrated sulfuric acid (14 g, 143 mmol) with H_2O, was added to a stirred and cooled solution of 3-trimethylsilyl-2-propyn-1-ol (8.5 g, 66 mmol) in acetone (50 ml) during 1 h, the temperature being kept at about 20 °C. After stirring for about 48 h, brine was added and the solution was extracted with ether (2 × 20 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled under reduced pressure to give the desired product 7 g (75 %) as a white solid b.p. 108–110 °C/10 mmHg. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 0.27 (s, 9H, $SiMe_3$), 11.2 (br, 1H, C(O)OG).

Preparation of the new compound (1S, 5R, 7R)-1-(10,10-dimethyl-3, 3-dioxo-3-thia-4-aza-tricyclo[5.2.1.0^{1,5}] decane-4-yl)-2-propyn-1-one **2**: To a solution containing 3–trimethylsilyl–2–propynoic acid (1 g, 7.04 mmol) dissolved in dry THF (17 ml) at –20 °C was added Et_3N (1.9 ml, 13.55 mmol), followed by addition of freshly distilled isobutyl chloroformate (0.85 ml, 6.50 mmol). The mixture was stirred at –20 °C for 2 h. Then, LiCl (0.25 g, 5.16 mmol) and a solution containing (–)–bornane–10,2–sultam (1.16 g, 5.42 mmol) in dry THF (10 ml) were added at –20 °C, respectively. The mixture was warmed slowly to room temperature until TLC analysis showed the reaction was completed. The reaction was quenched with 0.2 M HCl and extracted with EtOAc (2 × 20 ml). The combined organic layers were washed with brine, saturated $NaHCO_3$ and brine. After drying over $MgSO_4$, the solvent was removed *in vacuo*. The residue was purified by column chromatography to give the compound **2** (698 mg, 52%) as a yellowish solid (eluent: ethyl

acetate/petroleum ether = 1/8). m.p. 115–116 °C; $[\alpha]^{20}_D$ = +147.6 (c 2.0, $CHCl_3$); IR ($CHCl_3$): ν 1663 cm^{-1} (C–O), 3310 cm^{-1} (≡C–H); ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 0.98 (s, 3H, Me), 1.17 (s, 3H, Me), 1.32–1.45 (m, 2H), 1.82–2.1 (m, 5H), 3.29 (s, acetylene H), 3.45 (d, *J* = 13.8 Hz, 1H), 3.54 (d, *J* = 13.8 Hz, 1H), 3.92 (m, 1H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 19.7, 20.7, 26.2, 32.7, 38.1, 44.7, 48.6, 52.8, 64.8, 74.5, 80.8, 148.7; EI–MS: *m/e* 214 (M^+–53, 0.52); Anal. Calcd for $C_{13}H_{17}NO_3S$ requires C 58.43, H 6.37, N 5.24%; found: C 58.34, H 6.36, N 5.16%.

Typical reaction procedure of arylaldehydes with methyl propiolate in the presence of $TiBr_4$ (at 20 °C): To a solution of $TiBr_4$ (129 mg, 0.35 mmol) in freshly distilled dichloromethane (0.5 ml) was added a solution of *p*-nitrobenzaldehyde (38 mg, 0.25 mmol) in dichloromethane (0.5 ml) at room temperature. After stirring for 5 min, menthyl propiolate **1** (63 mg, 0.3 mmol) was added. The reaction mixture was kept for 24 h at 20 °C. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (2.0 ml). After filtration, the filtrate was extracted with dichloromethane (5.0 ml × 2) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by a flash silica gel column chromatography to give the compound *E*–**3a** (*E*-isomer isolated, 8 mg, 7%) and *Z*–**3a** (*Z*–isomer isolated, 55 mg, 50% as yellowish oily products (eluent: ethyl acetate/petroleum ether = 1/8). *E*–**3a**: (diastereomeric mixture): $[\alpha]^{20}_D$ = –23.3 (c 0.75, $CHCl_3$); de = 73%; IR ($CHCl_3$): ν 1687 cm^{-1} (C = O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ major isomer 0.5–2.0 (m, 18H), 4.37 (d, *J* = 11.2 Hz, 1H, OH), 4.64–4.75 (m, 1H), 6.05 (d, *J* = 11.2 Hz, 1H, benzylic H), 7.55 (d, *J* = 8.5 Hz, 2H, ArH), 7.72 (s, 1H, vinyl H), 8.20 (d, *J* = 8.5 Hz, 2H, ArH); minor isomer 0.5–2.0 (m, 18H), 4.22 (d, *J* = 11.2 Hz, 1H, OH), 4.64–4.75 (m, 1H), 6.05 (d, *J* = 11.2 Hz, 1H, benzylic H), 7.55 (d, *J* = 8.5 Hz, 2H, ArH), 7.72 (s, 1H, vinyl H), 8.20 (d, *J* = 8.5 Hz, 2H, ArH); EI–MS: *m/e* 440 (M^+, 3.76), 301 (M^+–139, 70.26), 283 (M^+–157, 40.400; HRMS calcd for $C_{20}H_{26}BrNO_5$ (M^+ for Br^{79}) requires 439.0994, found: 439.1014.

Z–**3a**: (diastereomeric mixture): $[\alpha]^{20}_D$ = –42.2 (c 0.65, $CHCl_3$); de = 43%; IR ($CHCl_3$): ν 1709 cm^{-1} (C = O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ major isomer 0.45–2.0 (m, 18H), 3.51 (d, *J* = 6.2 Hz, 1H, OH), 4.68–4.77 (m, 1H), 5.5.8 (d, *J* = 6.2 Hz, benzylic H), 7.0 (s, 1H, vinyl H), 7.56 (d, *J* = 8.7 Hz, 2H, ArH), 8.22 (d, *J* = 8.7 Hz, 2H, ArH); minor isomer 0.45–2.0 (m, 18H), 3.75 (d, *J* = 7.2 Hz, 1H, OH), 4.65–4.77 (m, 1H), 5.54 (d, *J* = 7.2 Hz, 1H benzylic H), 7.0 (s, 1H, vinyl H), 7.56 (d, *J* = 8.7 Hz, 2H, ArH), 8.22 (d, *J* = 8.7 Hz, 2H, ArH); EI–MS: *m/e* 440 (M^+, 1.60), 301(M^+–139, 32.20), 283 (M^+–157, 20.77); HRMS calcd for $C_{20}H_{26}BrNO_5$ (M^+ for Br^{79}) requires 439.0994, found: 439.1021.

E–**3b**: (diastereomeric mixture): a yellowish oily product (*E*–isomer isolated, 18 mg, 16%); $[\alpha]^{20}_D$ = –19.8 (c 0.9, $CHCl_3$); de = 2%; IR ($CHCl_3$): ν 1731 cm^{-1} (C = O); ^1H NMR ($CDCl_3$), TMS, 300 MHz) δ major isomer 0.45–2.0 (m, 18H), 4.40 (d, *J* = 11.7 Hz, 1H, OH), 4.62–4.8 (m, 1H), 6.01 (d, *J* = 11.7 Hz,1H benzylic H), 7.46 (m, 1H, ArH), 7.68 (d, *J* = 7.4 Hz, 1H, ArH), 7.82 (s, 1H, vinyl H), 8.17 (d, *J* = 7.4 Hz, 1H, ArH), 8.29 (s, 1H, ArH); minor isomer 0.45–2.0 (m, 18H), 4.21 (d, *J* = 11.7 Hz, 1H, OH), 4.62–4.8 (m, 1H), 6.01 (d, *J* = 11.7 Hz, 1H, benzylic H), 7.46 (m, 1H, ArH), 7.68 (d, *J* = 7.4 Hz, 1N, ArH), 7.82 (s, 1H vinyl H), 8.17 (d, *J* = 7.4 Hz, 1H, ArH), 8.24 (s, 1H, ArH); EI–MS:*m/e* 440 (M^+, 1.60), 301 (M^+ –139, 1.43), 283 (M^+ –157, 17.17), 204 (M^+ –236, 14.32); HRMS calcd for $C_{10}H_8BrNO_5$ (M^+ –$C_{10}H_{18}$) requires 300.9586, found 300.9589.

Z–**3b**: (diastereomeric mixture):a yellowish oily product (*Z*–isomer isolated, 55 mg, 51%); $[\alpha]^{20}_D$ = –4.4 (c 2.75, $CHCl_3$); de = 62%; IR ($CHCl_3$): ν 1729 cm^{-1} (C = O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ major isomer 0.45–2.0 (m, 18H), 3.09 (d, *J* = 5.9 Hz, 1H, OH), 4.64–4.8 (m, 1H), 5.60 (d, *J* = 5.9 Hz, 1H, benzylic H), 7.03 (s, 1H, vinyl H), 7.47 (m, 1H, ArH), 7.66 (d, *J* = 7.4 Hz, 1H, ArH), 8.19 (d, *J* = 7.4 Hz, 1H, ArH), 8.27 (s, 1H, ArH); minor isomer 0.45–2.0 (m, 18H), 3.61 (d, *J* = 7.4 Hz, 1H, OH), 4.64–4.8 (m, 1H), 5.45 (d, *J* = 7.4 Hz, 1H, benzylic H), 7.03 (s, 1H vinyl H), 7.47 (m, 1H, ArH), 7.66 (d, *J* = 7.4 Hz, 1H, ArH), 8.19 (d, *J* = 7.4 Hz, 1H, ArH), 8.27 (s, 1H, ArH); EI–MS: *m/e* 301 (M^+ –139, 2.33), 283 (M^+ –157, 6.56), 204 (M^+ –236, 2.50); HRMS calcd for $C_{10}H_8BrNO_5$ (M^+ –$C_{10}H_{18}$) requires 300.9586, found: 300.9598.

E–**3c**: (diastereomeric mixture): a yellowish oily product (*E*–isomer isolated, 18 mg, 16%); $[\alpha]^{20}_D$ = –54.6 (c, 0.5, $CHCl_3$); de = 2%; IR ($CHCl_3$): ν 1730 cm^{-1} (C = O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) ν major isomer 0.5–2.0 (m, 18H), 3.98 (d, *J* = 73 Hz, 1H, OH), 4.61–4.8 (m, 1H), 6.41 (d, *J* = 7.3 Hz, 1H, benzylic H), 7.2–8.2 (M, 5H, ARH and vinyl H); minor isomer 0.5–2.0 (m, 18H), 4.02 (d, *J* = 5.9 Hz, 1H, OH), 4.61–4.8 (m, 1H), 6.44 (d, *J* = 5.9 Hz, 1H, benzylic H), 7.2–8.2 (m, 5H, ArH and vinyl H); EI–MS: *m/e* 303 (M+ –137, 4.22), 283 (M+ –157, 19.78), 204 (M+ –236, 28.15); HRMS calcd for $C_{10}H_6BrNO_4$ (M+ –$C_{10}H_{20}O$) requires 282.9479, found: 282.9477.

Z–**3c**: (diastereomeric mixture): a yellowish oily product (*Z*–isomer isolated, 62 mg, 56%); $[\alpha]^{20}_D$ = +8.3 (c, 3.1, $CHCl_3$); de = 40%; IR ($CHCl_3$): ν 1726 cm–1 (C = O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ major isomer 0.5–2.0 (m, 18H), 3.60 (br, 1H, OH), 4.62–4.68 (m, 1H), 6.02 (s, 1H, benzylic H), 7.0–8.0 (m, 5H, ArH and vinyl H); minor isomer 0.5–2.0 (m, 18H), 3.68 (br, 1H, OH), 4.62–4.68 (m, 1H), 6.02 (s, 1H, benzylic H), 7.0–8.0 (m, 5H, ArH and vinyl H); EI–MS: *m/e* 404 (M^+, 4.95), 301 (M^+ –139, 30.62), 283 (M^+ –157, 81.88), 204 (M^+ –236, 28.99); HRMS calcd for $C_{10}H_6BrNO_4$ (M^+ –$C_{10}H_{20}O$) requires 282.9479, found: 282.9486.

*Typical reaction procedure of arylaldehyde with (1S, 5R, 7R)-1-(10,10-Dimethyl-3,3-dioxo-3-thia-4-aza-tricyclo[5.2.1.0^{1,5}]decane-4-yl)-2-propyn-1-one **2** in the presence of $TiBr_4$ (at 20 °C)*: To a solution of $TiBr_4$ (129 mg, 0.35 mmol) in freshly distilled dichloromethane (0.5 ml) was added a solution of *p*-nitrobenzaldehyde (38 mg, 0.25 mmol) in dichloromethane (0.5 ml) at room temperature. After stirring for 5 min, 1*S*, 5*R*, 7*R*)-1-(10,10-dimethyl-3,3-dioxo-3-thia-4-aza-tricyclo[5.2.1.0^{1,5}]decane-4-yl)-2-propyn-1-one **2** (67 mg, 0.25 mmol) was added. The reaction mixture was kept for 12 h at 20°C. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (2.0 ml). After filtration, the filtrate was extracted with dichloromethane (2 × 5.0 ml) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by a flash silica gel column chromatography to give the compound *E*–**4** (*E*–isomer isolated, 12 mg, 10%) and *Z*–**4** (*Z*–isomer isolated, 60 mg, 48%) as yellowish solids (eluent: ethyl acetate/petroleum ether = 1/8).

E–**4a**: m.p. 153–154 °C; $[\alpha]^{20}_D$ = +27.1 (c, 0.6, $CHCl_3$); de > 99%; IR ($CHCl_3$): ν 1649 cm^{-1} (C = O); ^1H NMR ($CDCl_3$, TMS, 300 MHz): ν 0.95 (s, 3H, Me), 1.15 (s, 3H, Me), 1.32–147 (m, 2H), 1.82–2.05 (m, 5H), 3.38 (d, *J* = 13.7Hz, 1H), 3.52 (d, *J* = 13.7Hz, 1H), 3.88 (m, 1H), 4.31 (d, *J* = 7.7 Hz, 1H, OH), 6.09 (d, *J* = 7.7 Hz, 1H, benzylic H), 7.46 (s, 1H vinyl H), 7.63 (d, *J* = 8.4 Hz, 2H, ArH), 8.18 (d, *J* = 8.4 Hz, 2H, ArH); EI–MS: *m/e* 481 (M^+ –18, 6.68), 419 (M^+ –80, 6.99), 355 (M^+ –144. 35.06); HRMS calcd for $C_{20}H_{23}N_2O_6S$ (M^+ –Br^{79}) requires 419.1276, found 419.1229.

Z–**4a**: (diastereomeric mixture): $[\alpha]^{20}_D$ = –309.5 (c 3, $CHCl_3$); de = 40%; IR ($CHCl_3$) δ 1678 cm^{-1} (C = O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) ν major isomer 1.01 (s, 3H, Me), 1.25 (s, 3H, Me), 1.30–1.47 (m, 2H), 1.80–2.2 (m, 5H), 3.4–3.5 (m, 2H), 5.61 (s, 1H, benzylic H), 6.60 (s, 1H, vinyl H), 7.68 (d, *J* = 8.7 Hz, 2H, ArH), 8.20 (d, *J* = 8.7 Hz, 2H, ArH); minor isomer 1.16 (s, 3H, Me), 1.28 (s, 3H, Me), 1.30–1.47 (m, 2H), 1.80–2.2 (m, 5H), 3.88 (m, 1H), 4.03 (m, 1H), 6.17 (s, 1H, benzylic H), 7.12 (s, 1H, vinyl H), 7.71 (d, *J* = 8.6 Hz, 2H, ArH), 8.18 (d, *J* = 8.6 Hz, 2H, ArH); EI–MS: *m/e* 419 (M^+ –80, 13.57), 355 (M^+ –144, 34.28); HRMS calcd for $C_{20}H_{23}N_2O_6S$ (M^+ –Br^{79}) requires 419.1276, found: 419.1254.

E–**4b**: (*E*–isomer isolated, 17 mg, 15%): m.p. 141–142 °C; $[\alpha]^{20}_D$ = –4.9 (c, 0.4, $CHCl_3$); de > 99%; IR ($CHCl_3$): ν 1648 cm^{-1} (C = O); ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 0.98 (s, 3H, Me), 1.17 (s, 3H, Me), 1.34–1.46 (m, 2H), 1.80–2.06 (m, 5H), 3.37 (d, *J* = 13.7 Hz, 1H), 3.51 (d, *J* = 13.7 Hz, 1H), 3.88 (m, 1H), 4.30 (d, *J* = 8.0 Hz, 1H, OH), 6.10 (d, *J* = 8.0 Hz, 1H, benzylic H), 7.22 (s, 1H, vinyl H), 7.60 (d, *J* = 8.7 Hz, 2H, ArH), 8.19 (d, *J* = 8.7 Hz, 2H, ArH); EI–MS: *m/e* 437 (M^+ –18, 52.12), 419 (M^+ –35, 11.4), 355 (M^+ –99, 56.84); HRMS calcd for $C_{20}H_{23}N_2O_6S$ (M^+ –Cl^{35}) requires 419.1276, found: 419.1263.

Z–**4b**: (diastereomeric mixture, *Z*–isomer isolated, 45 mg, 40%): $[\alpha]^{20}_D$ = –22.9 (c, 0.35, $CHCl_3$); de = 38%; IR ($CHCl_3$): ν 1648 cm^{-1} (C = O); ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ major isomer 1.01 (s, 3H, Me), 1.17 (s, 3H, Me), 1.31–1.47 (m, 2H), 1.82–2.1 (m, 5H), 3.4–3.5 (m, 2H), 5.64 (s, 1H, benzylic H), 6.42 (s, 1H, vinyl H), 7.69 (d, *J* = 8.8 Hz, 2H, ArH), 8.24 (d, *J* = 8.7 Hz, 2H, ArH); minor isomer 1.15 (s, 3H, Me), 1.20 (s, 3H, Me), 1.31–1.47 (m, 2H), 1.82–2.1 (m, 5H), 3.81–3.90 (m, 1H), 4.0–4.1 (m, 1H), 6.14 (s, 1H, benzylic H), 6.92 (s, 1H, vinyl H), 7.93 (d, *J* = 8.7 Hz, 2H, ArH), 8.22 (d, *J* = 8.8 Hz, 2H, ArH); EI–MS: 437 (M^+ –18, 46.04), 419 (M^+ –35, 15.62), 355 (M^+ –99, 48.99); HRMS calcd for $C_{20}H_{23}N_2O_6S$ (M^+ –Cl^{35}) requires 419.1276, found: 419.1255.

The crystal data of *E*–**4a**: empirical formula: $C_{20}H_{22}BrN_2O_6S$, formula weight: 498.37, temperature 293(2)K, wavelength: 0.71073 Å, crystal system: orthorhombic, space group: P2(1)2(1)2(1), unit cell dimension: *a* = 7.5566(5)Å, *b* = 11.0074(7)Å, *c* = 25.0074(7)Å, α = 90°, β = 90°, γ = 90°, V = 2121.6(2)Å^3, *Z* = 4, calculated density: 1.560 mg/m^3, absorption coefficient: 2.076 mm^{-1}, F(000): 1020, final R indices [*I*>2σ(I)] R_1 = 0.0443, R_W = 0.0911. Its crystal structure

has been deposited at the Cambridge Crystallographic Data Centre and has been allocated the deposition number: CCDC 172328.

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