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Applications of Baylis–Hillman chemistry: enantioselective synthesis of (−)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates via chiral leaving group strategy

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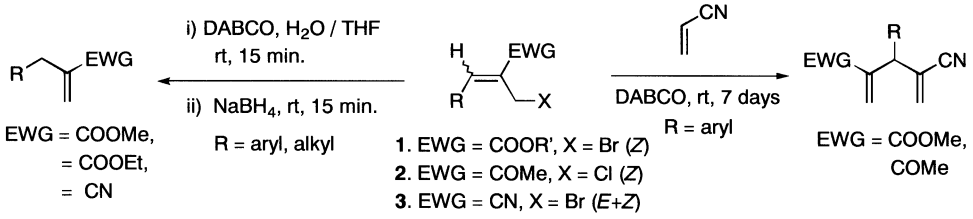
Abstract—Asymmetric synthesis of (−)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates in 25–40% enantiomeric purities via the reaction of methyl (2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates with prop-2-yn-1-ol in the presence of quinidine is described.

Baylis–Hillman chemistry has become one of the important and attractive sources for stereoselective processes in synthetic organic chemistry and is of current interest.[1–9] In continuation of our interest in the applications of the Baylis–Hillman adducts in organic synthesis,[9–11] we herein report chiral leaving group induced enantioselective synthesis of (−)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates via the treatment of methyl (2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates with prop-2-yn-1-ol (propargyl alcohol) in the presence of quinidine.

Recently, we have described applications of (*Z*)-allyl halides (**1** and **2**) obtained from the Baylis–Hillman adducts, as suitable electrophiles in the Baylis–Hillman reaction thus providing a simple synthesis of functionalized 1,4-pentadienes (Scheme 1).[10] We have also successfully used the allyl halides (**1** and **3**) in the synthesis of 2-methylenealkanoates and alkanenitriles via the treatment with $NaBH_4$ in the presence of DABCO in environment friendly aqueous media (Scheme 1).[11]

With a view of understanding the applicability of allyl halides (**1**–**3**), as suitable electrophiles in various organic transformations and also with an objective of expanding the scope of these allyl halides in synthetic organic chemistry, we have directed our studies towards the addition of oxygen nucleophiles from alcohols onto these allyl halides. Literature survey reveals that there are some reports on the nucleophilic addition (S_N2') of certain oxygen nucleophiles such as alkoxides and hydroperoxides to 2-(bromomethyl)alk-2-enoates.[12–14] Recently, intramolecular nucleophilic addition (S_N2') of oxygen nucleophile from oxirane to the allyl bromide moiety of methyl 2-(bromomethyl)-6,7-epoxyhept-2-enoate providing an interesting tetrahydropyran derivative has been reported.[15] However, addition of oxygen nucleophile from prop-2-yn-1-ol (propargyl alcohol) to 2-(bromomethyl)alk-2-enoates has not been studied so far in the literature. Also various allyl propargyl ethers have been successfully employed in a number of interesting organic transformations.[16–20] Therefore, we have selected prop-2-yn-1-ol as a possible



Scheme 1.

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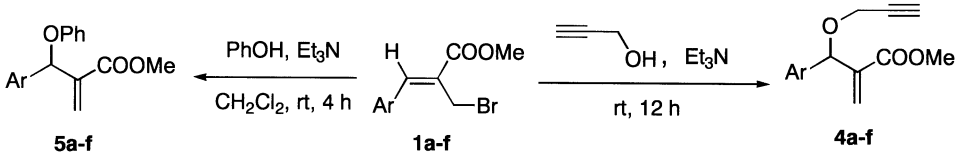
nucleophile for our study with a view that the resulting allyl propargyl ethers might be attractive substrates for useful synthetic transformations. Accordingly, we have carried out the reaction of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**1a**) with prop-2-yn-1-ol in the presence of DABCO under various conditions. The best result was accomplished when methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**1a**) (1 mmol) was treated with prop-2-yn-1-ol (5 mmol) in the presence of DABCO (2 mmol) in dichloromethane at room temperature for 12 h, thus providing methyl 2-methylene-3-phenyl-3-(prop-2-yn-1-yloxy)propanoate (**4a**) in 29% yield. Though the desired product is obtained in pure form, the yield is not encouraging. At this stage, we envisaged that the yield could be possibly improved if we use an appropriate tertiary amine in the place of DABCO. In this search, we have obtained encouraging results when methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**1a**) (1 mmol) was treated with prop-2-yn-1-ol (5 mmol) in the presence of triethylamine (1 mL) at room temperature for 12 h (without any solvent) thus providing the desired methyl 2-methylene-3-phenyl-3-(prop-2-yn-1-yloxy)propanoate (**4a**) in 74% yield after usual work up, followed by column chromatography (silica gel, 2% ethyl acetate in hexanes). We have then extended the same strategy to a representative class of methyl (2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates (**1b–f**) to provide the desired methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)-propanoates (**4b–f**) in high yields (Scheme 2, Table 1).

With a view of expanding the scope of this methodology we have also used phenol as a nucleophile in this study.[21] Thus, we have developed a general synthesis of methyl 3-aryl-2-methylene-3-phenoxypropanoates (**5a–f**) in good yields via the treatment of **1a–f** (1 mmol) with phenol (1 mmol) in the presence of triethylamine (1 mL) in dichloromethane (2 mL) at room temperature for 4 h (Scheme 2, Table 1).

These successful results led us to envisage that if we use an appropriate chiral tertiary amine, which subsequently becomes a leaving group, there might be chiral induction. A literature survey reveals that a number of asymmetric reactions have been reported under the influence of a chiral leaving group.[22–27] We have planned to use various chiral tertiary amines such as sparteine (**6**), cinchonidine (**7**), quinine (**8**) and quinidine (**9**) which are naturally occurring and easily accessible, for our study on the chiral leaving group induced asymmetric synthesis. We have first examined the reaction of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**1a**) with prop-2-yn-1-ol under the influence of a chiral leaving group [tertiary amines (**6–9**)]. Encouraging results were obtained when methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**1a**) (1 mmol) was treated with prop-2-yn-1-ol (5 mmol) in the presence of quinidine (2 mmol) in dichloromethane at room temperature for 24 h thus providing (−)-methyl 2-methylene-3-phenyl-3-(prop-2-yn-1-yloxy)propanoate {(−)-**4a**} in 31% enantioselectivity and in 36% yield. However, other chiral amines **6–8** provided inferior results. We have then extended the same strategy using quinidine to representative allyl bromides (**1b–f**), thus providing a simple synthesis of (−)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates {(−)-**4b–f**} in 25–40% enantiomeric purities and in 32–47% yields (Scheme 3, Table 2).

In order to understand the structure of the allyl bromide–quinidine salt, we have isolated methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate-quinidine salt (**10a**) via the treatment of **1a** (1 mmol) with quinidine (1 mmol) in

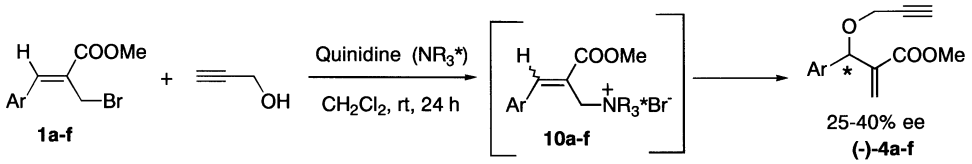


Scheme 2. Ar=phenyl, 4-chlorophenyl, 4-methylphenyl, 4-ethylphenyl, 4-isopropylphenyl, 2-methylphenyl.

Table 1. Synthesis of methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates (**4a–f**) and methyl 3-aryl-2-methylene-3-phenoxypropanoates (**5a–f**)

Allyl bromide	Ar	Propargyl alcohol[a,b]		Phenol[c,d]	
		Product	Yield[e] (%)	Product	Yield[e] (%)
1a	Phenyl	**4a**	74[f]	**5a**	85[f]
1b	4-Chlorophenyl	**4b**	84	**5b**	76
1c	4-Methylphenyl	**4c**	76	**5c**	69
1d	4-Ethylphenyl	**4d**	67	**5d**	64
1e	4-Isopropylphenyl	**4e**	77	**5e**	61
1f	2-Methylphenyl	**4f**	76	**5f**	63

[a] All reactions were carried out on 1 mmol scale of allyl bromides (**1a–f**) with propargyl alcohol (5 mmol) in the presence of Et_3N (1 mL) at room temperature for 12 h.
[b] Products **4a–e** were obtained as colorless viscous liquids and product **4f** was obtained as colorless solid and all the products gave satisfactory IR, ^1H (200 MHz), ^{13}C NMR (50 MHz) spectral data and elemental analyses.
[c] All reactions were carried out on 1 mmol scale of allyl bromide (**1a–f**) with phenol (1 mmol) and Et_3N (1 mL) in dichloromethane (2 mL) at room temperature for 4 h.
[d] All the products **5a–f** were obtained as colorless viscous liquids and gave satisfactory IR, ^1H NMR (200 MHz), ^{13}C NMR (50 MHz) spectral data and elemental analyses.
[e] Isolated yields of the pure products after column chromatography (silica gel, 2% EtOAc in hexanes).
[f] These products were also characterized by mass spectral analysis.



Scheme 3. Ar=phenyl, 4-chlorophenyl, 4-methylphenyl, 4-ethylphenyl, 4-isopropylphenyl, 2-methylphenyl.

Table 2. Enantioselective synthesis of (−)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates {(−)-**4a**–**f**}

Allyl bromide	Ar	Product	Yield (%)[a]	Optical rotation $[\alpha]_D^{20}$ (*c*, $CHCl_3$)	ee (%)[b]
1a	Phenyl	(−)-**4a**	36	−70.24 (1.24)	31
1b	4-Chlorophenyl	(−)-**4b**	47	−83.24 (1.074)	39
1c	4-Methylphenyl	(−)-**4c**	37	−64.19 (0.592)	25
1d	4-Ethylphenyl	(−)-**4d**	32	−74.91 (0.606)	35
1e	4-Isopropylphenyl	(−)-**4e**	36	−81.59 (0.516)	40
1f	2-Methylphenyl	(−)-**4f**	35	−58.06 (0.632)	32

All reactions were carried out on 1 mmol scale of allyl bromides (**1a**–**f**) with propargyl alcohol (5 mmol) in the presence of quinidine (2 mmol) in dichloromethane (4 mL) at room temperature for 24 h.
Products (−)-**4a**–**e** were obtained as colorless viscous liquids and product (−)-**4f** was obtained as colorless solid. All the products gave satisfactory IR, ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz) spectral data which are identical with that of the corresponding racemic molecules.
[a] Isolated yields of the pure products after column chromatography (silica gel, 2% EtOAc in hexanes).
[b] Enantiomeric purity of these molecules was determined by HPLC analysis using chiral column (chiralcel OD column, 5% *i*-PrOH in hexane, 0.5 mL/min) with reference to the corresponding racemic molecules.

dichloromethane at room temperature for 15 h followed by crystallization [of the crude salt from chloroform and hexanes (1:1)] as a crystalline solid in 68% yield. ^{1}H NMR and ^{13}C NMR spectral data confirm the structure of this molecule with exclusive (*E*)-stereochemistry.[28] This crystalline solid on treatment with prop-2-yn-1-ol in the presence of quinidine in dichloromethane at room temperature for 24 h provided the desired product (−)-**4a** in 38% enantiomeric purity and in 37% yield. This indicates that the less enantioselectivity obtained, from the amine salt without crystallization, is presumably due to the presence of (*Z*)-isomer.[29] Since the enantiomeric purities are only moderate, we did not proceed further for obtaining the pure (*E*)-isomer via crystallization in the case of other allyl bromides–quinidine salts (**10b**–**f**). However, our attempts to synthesize methyl 2-methylene-3-phenyl-3-phenoxypropanoate (**5a**) in enantiomerically enriched form via the treatment of **1a** with phenol in the presence of quinidine did not give satisfactory results.

In conclusion, we have developed a simple enantioselective synthesis of (−)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates under the influence of chiral leaving group (quinidine), thus demonstrating the importance of allyl bromides derived from the Baylis–Hillman adducts in organic synthesis.

1. Experimental

Melting points were recorded on a Superfit (India) capillary melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO-FT-IR model 5300 spectrometer using samples as neat liquids or as KBr plates. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in deuterochloroform ($CDCl_3$) on a Bruker-AC-200 spectrometer using tetramethylsilane (TMS, δ=0) as internal standard. Mass spectra were recorded on a micromass VG 7070H instrument. Elemental analyses were recorded on a Perkin–Elmer 240C-CHN analyzer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. HPLC analyses were carried out on Shimadzu LC-10 AD instrument. All the required allyl bromides, i.e. methyl (2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates were obtained via the reaction of the corresponding Baylis–Hillman adducts with HBr/H_2SO_4 according to the literature procedure.[2,3,30].

1.1. General procedure for the preparation of methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates

To a stirred solution of methyl (2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates (1 mmol) in Et_3N (1 mL), was added propargyl alcohol (5 mmol, 0.28 g). After stirring for 12 h at room temperature, the reaction mixture was diluted with ether (15 mL) and washed successively with 2N HCl solution and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product, thus obtained was purified by column chromatography (silica gel, 2% ethyl acetate in hexanes) to provide pure methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates.

1.1.1. Methyl 2-methylene-3-(prop-2-yn-1-yloxy)-3-phenylpropanoate (4a). Colorless viscous liquid. Yield: 74%; IR (neat): 3288, 2118, 1722, 1631 cm^{-1}; ^{1}H NMR: δ 2.45 (t, 1H, *J*=2.4 Hz), 3.70 (s, 3H), 4.01 and 4.18 ($CH_2C{\equiv}C$, d AB q, 2H, *J*=15.6 and 2.4 Hz), 5.51 (s, 1H), 6.00 (d, 1H, *J*=1.2 Hz), 6.37 (s, 1H), 7.28–7.42 (m, 5H); ^{13}C NMR: δ 51.74, 55.93, 74.75, 77.79, 79.50, 125.24, 127.86, 128.17, 128.40, 138.65, 140.72, 166.01; MS (*m/z*):

230 (M^+); Anal. calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13; found: C, 73.40; H, 6.17.

1.1.2. Methyl 3-(4-chlorophenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate (4b). Colorless viscous liquid. Yield: 84%; IR (neat): 3298, 2118, 1722, 1631 cm^{-1}; ^1H NMR: δ 2.44 (t, 1H, J=2.6 Hz), 3.69 (s, 3H), 4.00 and 4.16 ($CH_2C{\equiv}C$, d AB q, 2H, J=15.6 and 2.6 Hz), 5.47 (s, 1H), 6.01 (s, 1H), 6.37 (s, 1H), 7.31 (s, 4H); ^{13}C NMR: δ 51.19, 55.33, 74.36, 76.41, 78.56, 124.82, 127.95, 128.58, 133.33, 136.67, 139.63, 165.15; Anal. calcd for $C_{14}H_{13}O_3Cl$: C, 63.52; H, 4.95; found: C, 63.38; H, 4.97.

1.1.3. Methyl 2-methylene-3-(4-methylphenyl)-3-(prop-2-yn-1-yloxy)propanoate (4c). Colorless viscous liquid. Yield: 76%; IR (neat): 3286, 2124, 1719, 1631 cm^{-1}; ^1H NMR: δ 2.33 (s, 3H), 2.44 (t, 1H, J=1.8 Hz), 3.68 (s, 3H), 3.99 and 4.14 ($CH_2C{\equiv}C$, d AB q, 2H, J=15.5 and 1.8 Hz), 5.47 (s, 1H), 6.00 (d, 1H, J=1.8 Hz), 6.35 (s, 1H), 7.14 (d, 2H, J=7.8 Hz), 7.27 (d, 2H, J=7.8 Hz); ^{13}C NMR: δ 21.12, 51.72, 55.73, 74.62, 77.53, 79.55, 124.96, 127.83, 129.09, 135.50, 137.89, 140.75, 166.03; Anal. calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; found: C, 73.98; H, 6.55.

1.1.4. Methyl 3-(4-ethylphenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate (4d). Colorless viscous liquid. Yield: 67%; IR (neat): 3288, 2118, 1724, 1631 cm^{-1}; ^1H NMR: δ 1.21 (t, 3H, J=7.8 Hz), 2.42 (t, 1H, J=2.2 Hz), 2.63 (q, 2H, J=7.8 Hz), 3.68 (s, 3H), 4.00 and 4.14 ($CH_2C{\equiv}C$, d AB q, 2H, J=15.6 and 2.2 Hz), 5.47 (s, 1H), 5.98 (d, 1H, J=1.8 Hz), 6.34 (s, 1H), 7.15 (d, 2H, J=7.8 Hz), 7.27 (d, 2H, J=7.8 Hz); ^{13}C NMR: δ 15.33, 28.49, 51.66, 55.73, 74.58, 77.53, 79.54, 124.92, 127.83, 135.72, 140.75, 144.14, 166.00; Anal. calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02; found: C, 74.25; H, 7.05.

1.1.5. Methyl 3-(4-isopropylphenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate (4e). Colorless viscous liquid. Yield: 77%; IR (neat): 3289, 2118, 1724, 1632 cm^{-1}; ^1H NMR: δ 1.23 (d, 6H, J=6.8 Hz), 2.43 (t, 1H, J=2.4 Hz), 2.88 (sept. 1H, J=6.8 Hz), 3.69 (s, 3H), 4.01 and 4.14 ($CH_2C{\equiv}C$, d AB q, 2H, J=15.6 and 2.4 Hz), 5.48 (s, 1H), 5.99 (d, 1H, J=2.4 Hz), 6.35 (s, 1H), 7.18 (d, 2H, J=8.0 Hz), 7.28 (d, 2H, J=8.0 Hz); ^{13}C NMR: δ 23.93, 33.84, 51.79, 55.85, 74.61, 77.58, 79.62, 125.10, 126.50, 127.82, 135.85, 140.72, 148.83, 166.13; Anal. calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40; found: C, 75.28; H, 7.36.

1.1.6. Methyl 2-methylene-3-(2-methylphenyl)-3-(prop-2-yn-1-yloxy)propanoate (4f). Colorless solid. Yield: 76%; mp 76–78°C; IR (KBr): 3263, 2114, 1714, 1630 cm^{-1}; ^1H NMR: δ 2.40–2.48 (m, 4H), 3.72 (s, 3H), 4.05 and 4.19 ($CH_2C{\equiv}C$, d AB q, 2H, J=15.6 and 1.8 Hz), 5.76 (s, 1H), 5.81 (s, 1H), 6.39 (s, 1H), 7.15–7.40 (m, 4H); ^{13}C NMR: δ 19.13, 51.80, 56.07, 74.54, 74.59, 79.70, 126.04, 127.29, 128.01, 130.52, 136.25, 136.97, 140.17, 166.25; Analysis calculated for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; found: C, 73.67; H, 6.65.

1.2. General procedure for the preparation of methyl 3-aryl-2-methylene-3-phenoxypropanoates

A solution of methyl (2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates (1 mmol), phenol (1 mmol, 0.094 g) and Et_3N (1 mL) in CH_2Cl_2 (2 mL), was stirred at room temperature for 4 h. Then the reaction mixture was diluted with 2N HCl and extracted with ether (2×10 mL). The combined organic layer was washed with aqueous $NaHCO_3$ solution, water and dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product was purified by column chromatography (silica gel, 2% ethyl acetate in hexanes) to provide the pure methyl 3-aryl-2-methylene-3-phenoxypropanoates.

1.2.1. Methyl 2-methylene-3-phenoxy-3-phenylpropanoate (5a). Colorless viscous liquid. Yield: 85%; IR (neat): 1722, 1631 cm^{-1}; ^1H NMR: δ 3.73 (s, 3H), 5.95 (s, 1H), 6.14 (s, 1H), 6.37 (s, 1H), 6.87–6.98 (m, 3H), 7.15–7.50 (m, 7H); ^{13}C NMR: δ 51.90, 77.38, 116.01, 121.26, 126.15, 127.41, 128.12, 128.50, 129.39, 138.99, 140.41, 157.67, 166.03; MS (m/z): 268 (M^+); Anal. calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01; found: C, 75.91; H, 6.04.

1.2.2. Methyl 3-(4-chlorophenyl)-2-methylene-3-phenoxypropanoate (5b). Colorless viscous liquid. Yield: 76%; IR (neat): 1720, 1633 cm^{-1}; ^1H NMR: δ 3.74 (s, 3H), 5.99 (s, 1H), 6.11 (s, 1H), 6.38 (s, 1H), 6.87–7.01 (m, 3H), 7.16–7.47 (m, 6H); ^{13}C NMR: δ 52.02, 76.81, 116.08, 121.56, 126.28, 128.77, 128.84, 129.51, 134.04, 137.69, 140.13, 157.46, 165.89; Anal. calcd for $C_{17}H_{15}O_3Cl$: C, 67.44; H, 4.99; found: C, 67.71; H, 4.96.

1.2.3. Methyl 2-methylene-3-(4-methylphenyl)-3-phenoxypropanoate (5c). Colorless viscous liquid. Yield: 69%; IR (neat): 1722, 1631 cm^{-1}; ^1H NMR: δ 2.32 (s, 3H), 3.73 (s, 3H), 5.96 (s, 1H), 6.11 (s, 1H), 6.36 (s, 1H), 6.84–6.98 (m, 3H), 7.10–7.37 (m, 6H); ^{13}C NMR: δ 21.15, 51.91, 77.31, 116.06, 121.20, 125.94, 127.43, 129.25, 129.39, 136.02, 137.90, 140.53, 157.79, 166.14; Anal. calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; found: C, 76.39; H, 6.39.

1.2.4. Methyl 3-(4-ethylphenyl)-2-methylene-3-phenoxypropanoate (5d). Colorless viscous liquid. Yield: 64%; IR (neat): 1722, 1631 cm^{-1}; ^1H NMR: δ 1.23 (t, 3H, J=7.8 Hz), 2.64 (q, 2H, J=7.8 Hz), 3.75 (s, 3H), 5.97 (s, 1H), 6.13 (s, 1H), 6.38 (s, 1H), 6.87–7.05 (m, 3H), 7.13–7.47 (m, 6H); ^{13}C NMR: δ 15.34, 28.56, 51.93, 77.26, 116.00, 121.17, 125.98, 127.45, 128.03, 129.39, 136.19, 140.46, 144.19, 157.78, 166.15; Anal. calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80; found: C, 77.29; H, 6.78.

1.2.5. Methyl 3-(4-isopropylphenyl)-2-methylene-3-phenoxypropanoate (5e). Colorless viscous liquid. Yield: 61%; IR (neat): 1722, 1632 cm^{-1}; ^1H NMR: δ 1.24 (d, 6H, J=7.2 Hz), 2.89 (sept. 1H, J=7.2 Hz), 3.76 (s, 3H), 5.98 (s, 1H), 6.14 (s, 1H), 6.38 (s, 1H), 6.87–6.99 (m, 3H), 7.15–7.42 (m, 6H); ^{13}C NMR: δ 23.83, 33.75, 51.83, 77.10, 115.86, 121.06, 125.88, 126.53, 127.34, 129.30, 136.19, 140.34, 148.70, 157.68, 166.05; Anal. calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14; found: C, 77.06; H, 7.20.

1.2.6. Methyl 2-methylene-3-(2-methylphenyl)-3-phenoxypropanoate (5f). Colorless viscous liquid. Yield: 63%; IR (neat): 1724, 1633 cm^{-1}; ^1H NMR: δ 2.35 (s, 3H), 3.74 (s, 3H), 5.73 (s, 1H), 6.32 (s, 1H), 6.42 (s, 1H), 6.82–6.96 (m, 3H), 7.15–7.45 (m, 6H); ^{13}C NMR: δ 19.19, 52.01, 74.78, 115.81, 121.25, 126.20, 127.26, 127.39, 128.23,

129.43, 130.70, 136.32, 136.42, 139.46, 158.09, 166.30; Anal. calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; found: C, 76.79; H, 6.47.

1.3. General procedure for enantioselective synthesis of (−)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)-propanoates

To a stirred solution of methyl (2*Z*)-3-aryl-2-(bromomethyl)prop-2-enoates (**1a**–**f**) (1 mmol) in dichloromethane (4 mL), quinidine (2 mmol, 0.649 g) and propargyl alcohol (5 mmol, 0.28 g) were added. After stirring for 24 h at room temperature, the reaction mixture was diluted with ether (15 mL) and washed successively with 2N HCl solution and water. The ethereal layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, 2% ethyl acetate in hexanes) to provide the pure (−)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates {(−)-(**4a**–**f**)}. The IR, ^{1}H and ^{13}C NMR spectral data of (−)-**4a**–**f** were identical with that of the corresponding racemic molecules.

1.3.1. (−)-Methyl 2-methylene-3-phenyl-3-(prop-2-yn-1-yloxy)propanoate {(−)-4a}. Colorless viscous liquid. Yield: 36%; $[\alpha]_D^{20}=-70.24$ (*c* 1.24, $CHCl_3$); 31% ee; HPLC analysis: chiral column: chiralcel OD; eluent: hexane/*i*-PrOH, 95:05; flow rate: 0.5 mL/min; retention times: 12.38 (major) and 14.02 (minor) min.

1.3.2. (−)-Methyl 3-(4-chlorophenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate {(−)-4b}. Colorless viscous liquid. Yield: 47%; $[\alpha]_D^{20}=-83.24$ (*c* 1.074, $CHCl_3$); 39% ee; HPLC analysis: chiral column: chiralcel OD; eluent: hexane/*i*-PrOH, 95:05; flow rate: 0.5 mL/min; retention times: 10.34 (major) and 12.24 (minor) min.

1.3.3. (−)-Methyl 2-methylene-3-(4-methylphenyl)-3-(prop-2-yn-1-yloxy)propanoate {(−)-4c}. Colorless viscous liquid. Yield: 37%; $[\alpha]_D^{20}=-64.19$ (*c* 0.592, $CHCl_3$); 25% ee; HPLC analysis: chiral column: chiralcel OD; eluent: hexane/*i*-PrOH, 95:05; flow rate: 0.5 mL/min; retention times: 11.68 (major) and 13.29 (minor) min.

1.3.4. (−)-Methyl 3-(4-ethylphenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate {(−)-4d}. Colorless viscous liquid. Yield: 32%; $[\alpha]_D^{20}=-74.91$ (*c* 0.606, $CHCl_3$); 35% ee; HPLC analysis: chiral column: chiralcel OD; eluent: hexane/*i*-PrOH, 95:05; flow rate: 0.5 mL/min; retention times: 9.47 (major) and 11.19 (minor) min.

1.3.5. (−)-Methyl 3-(4-isopropylphenyl)-2-methylene-3-(prop-2-yn-1-yloxy)propanoate {(−)-4e}. Colorless viscous liquid. Yield: 36%; $[\alpha]_D^{20}=-81.59$ (*c* 0.516, $CHCl_3$); 40% ee; HPLC analysis: chiral column: chiralcel OD; eluent: hexane/*i*-PrOH, 95:05; flow rate: 0.5 mL/min; retention times: 9.11 (major) and 11.04 (minor) min.

1.3.6. (−)-Methyl 2-methylene-3-(2-methylphenyl)-3-(prop-2-yn-1-yloxy)propanoate {(−)-4f}. Colorless solid. Yield: 35%; mp 72–73°C; $[\alpha]_D^{20}=-58.06$ (*c* 0.632, $CHCl_3$); 32% ee; HPLC analysis: chiral column: chiralcel OD; eluent: hexane/*i*-PrOH, 95:05; flow rate: 0.5 mL/min; retention times: 10.87 (major) and 12.90 (minor) min.

1.3.7. Methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate-quinidine salt (10a). To a stirred solution of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate (**1a**) (1 mmol, 0.255 g) in dichloromethane (4 mL), quinidine (1 mmol, 0.324 g) was added and stirred at room temperature for 15 h. The solvent was removed under reduced pressure to afford the crude salt (**10a**) as a yellow solid. Careful and selective crystallization of this crude salt (**10a**) from chloroform in hexanes (1:1) provided the stereochemically pure salt (*E*)-**10a** as a colorless crystalline solid. Yield: 68% (0.394 g); mp 146–148°C (dec.); $[\alpha]_D^{20}=+84.76$ (*c* 1.05, $CHCl_3$); IR (KBr): 1697, 1622 cm^{-1}; ^{1}H NMR: δ 0.80–1.04 (m, 1H), 1.60–3.81 (m, 10H), 3.93 (s, 3H), 4.07 (s, 3H), 4.73–5.16 (m, 3H), 5.58–5.98 (m, 2H), 6.61 (d, 1H, *J*=5.4 Hz), 6.85–6.91 (m, 1H), 7.15–8.17 (m, 9H), 8.47 (s, 1H), 8.73 (d, 1H, *J*=4.2 Hz); ^{13}C NMR: δ 21.38, 23.87, 26.12, 37.33, 53.39, 53.83, 55.85, 64.78, 68.97, 100.31, 117.55, 119.69, 120.13, 121.75, 125.44, 129.76, 129.83, 130.62, 131.99, 132.96, 135.22, 143.01, 144.07, 147.54, 152.50, 158.28, 167.67.

1.3.8. (−)-Methyl 2-methylene-3-phenyl-3-(prop-2-yn-1-yloxy)propanoate {(−)-4a}: from (*E*)-10a. This product was obtained as a colorless viscous liquid via the treatment of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate-quinidine salt (*E*)-**10a** (0.5 mmol, 0.289 g) with propargyl alcohol (2.5 mmol, 0.14 g) in the presence of quinidine (0.5 mmol, 0.162 g) in dichloromethane. Reaction time: 24 h, Yield: 37%; $[\alpha]_D^{20}=-85.35$ (*c* 0.284, $CHCl_3$); 38% ee; HPLC analysis: chiral column: chiralcel OD; eluent: hexane/*i*-PrOH, 95:05; flow rate: 0.5 mL/min; retention times: 12.26 (major) and 13.58 (minor) min.

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28. (*E*)-Stereochemistry of this molecule (**10a**) was established by comparison of chemical shift value of β-vinylic proton in ^{1}H NMR spectrum with that of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate-DABCO salt.[11] In the case of methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate-DABCO salt, the β-vinylic proton *cis* to the ester group appears at δ 8.40 (*E*-isomer) whereas the β-vinylic proton *trans* to the ester group appears at δ 7.98 (*Z*-isomer).[31] In the case of **10a**, the β-vinylic proton appears at δ 8.47. Therefore, we have assigned (*E*)-stereochemistry to **10a**. ^{13}C NMR spectrum of this crystallized salt (**10a**) shows the absence of any (*Z*)-isomer.
29. ^{1}H and ^{13}C NMR spectra of crude salt **10a** indicate that the major compound is (*E*)-isomer (≈85%). Spectral analysis also indicates the presence of ≈15% impurities in which presumably (*Z*)-isomer is the major component.
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