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Convenient methods for the synthesis of highly functionalized and naturally occurring chiral allenes

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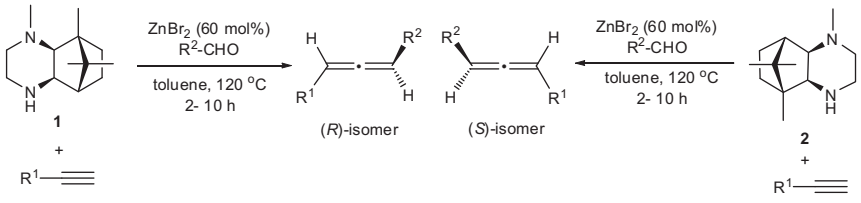
ABSTRACT

A convenient two step procedure to access highly functionalized chiral allenes using chiral *N*-methylcamphanyl piperazine derivatives is described. In this transformation, chiral propargylamines are obtained in 79–96% yields with up to 99:1 dr by the CuBr catalyzed reactions of chiral piperazine derivatives with 1-alkynes and aldehydes containing functional groups, which are converted into chiral allenes in the presence of zinc bromide, affording the chiral allenes in 59–85% yields and with up to 99% ee. The antifungal agent *Sapium japonicum* and an allene precursor intermediate for the synthesis of the pheromone of the male dried bean beetle **15** are obtained in 72–78% yields and with up to 98% ee following this methodology.

1. Introduction

In recent years, allenes have become highly valuable intermediates for target-oriented synthesis because they have proven application in various transformations with high levels of structural diversity.[1] Hence, 1,3-disubstituted chiral allenes containing functional groups play a significant role in organic synthesis, since they can be converted under mild conditions into biologically active compounds.[2] Therefore, the introduction of allene as a functional group into the existing backbone of pharmacologically active compounds could be expected to result in interesting new biological properties.[3] As part of our ongoing research on the synthesis of chiral allenes following the 'chiral amine approach', we have recently reported the enantioselective synthesis of both enantiomers of chiral allenes using chiral *N*-methylcamphanyl piperazine templates (Scheme 1).[4]

Although, this method is useful to access several chiral allenes, the longer reaction time and higher temperature required may pose problems in the synthesis of allenes containing sensitive functional groups. Moreover, methods available for the synthesis of chiral allenes containing sensitive functional groups are still limited and many reported methods involve multistep operations using expensive reagents.[5–8] Therefore, it is highly desirable to develop an efficient and simple method for the synthesis of chiral allenes containing functional groups. Herein, we describe detailed studies on the methods of synthesis of highly functionalized chiral allenes via chiral propargylamine intermediates by using the *N*-methylcamphanyl piperazine templates **1** and **2**.



Scheme 1.

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2. Results and discussion

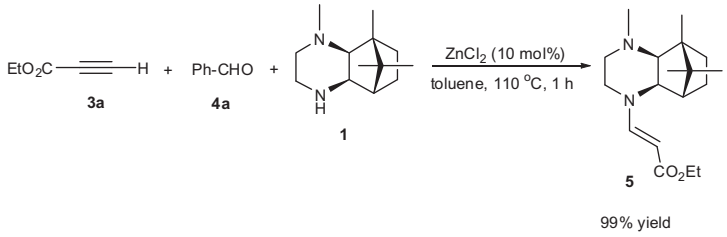
We observed that the reaction between ethyl propiolate **3a** and piperazine **1** gives the Michael addition product **5** in 99% yield (Scheme 2).

Presumably, the formation of the Michael addition product **5** is due to conjugation between the ester group and the triple bond. To examine this, we chose methyl-5-hexynoate as the alkyne **3b** partner in this reaction. However, in this case, we isolated the amide derivative **7** in 28% yields along with the propargylamine **6ba** in 62% yield with 99:1 dr (Scheme 3).

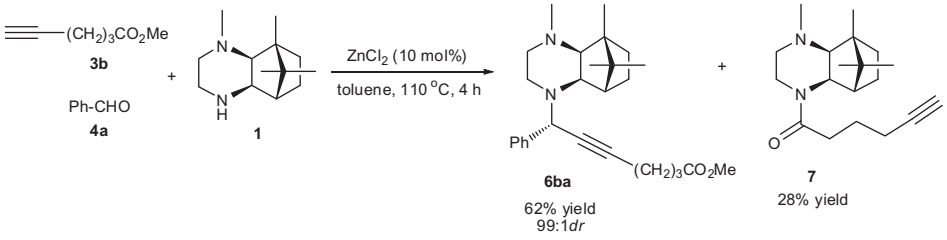
Very recently, a CuBr promoted method has been reported for the diastereoselective synthesis of chiral propargylamines which upon reaction with CuI gave the corresponding chiral allenes.[9] We observed that the reaction between methyl-5-hexynoate **3b**, benzaldehyde **4a**, and chiral camphanylpiperazine **1** using CuBr (10 mol %) gives the corresponding propargylamine **6ba** in 98% yield with 99:1 dr (Scheme 4). The procedure is also useful for chiral propargylamines with other sensitive functional groups (Table 1).

The alkynes containing ester, amide, or alcohol groups are compatible with the present reaction conditions **3c**–**3l**. Chiral piperazine **1** reacted with diethyl 2-(prop-2-ynyl)malonate **3c** and *t*-butyraldehyde **4d** to give the corresponding propargylamine **6cd** in 81% yield and with up to 99:1 dr (Table 1). The reaction of chiral piperazine **1** with *t*-butyraldehyde **4d** and dimethyl propargylmalonate **3d** yielded the product **6dd** in 89% with 97:3 dr. The reaction is also applicable to substituted dimethyl propargylmalonate as illustrated by the reactions using alkynes **3e** and **3f**, which react with aldehydes **4a**, **4c**, **4d**, and **4e** to give the corresponding chiral propargylamines **6ea**, **6ec**, **6ed**, and **6ee** in 86–95% yields with excellent diastereoselectivity (Table 1). Diethyl 2-acetamido-2-propargylmalonate **3g** reacts with aldehydes **4a** and **4d** to give the corresponding propargylamines **6ga**, **6gd** in 86–94% yields and with 96:4, 99:1 dr, respectively. Also, the reaction of *N*-tosyl alkyne **3h** and with the aldehydes **4a** and **4d** gives the corresponding propargylamines **6ha** and **6hd** in 91–96% yields with good diastereoselectivity (Table 1). Similarly, the unprotected 1-alkyne **3k** containing an alcohol functional group reacts with the aldehydes **4a** and **4b** to give the corresponding propargylamines **6ka**, and **6kb** with reasonable yields and with good diastereoselectivity.

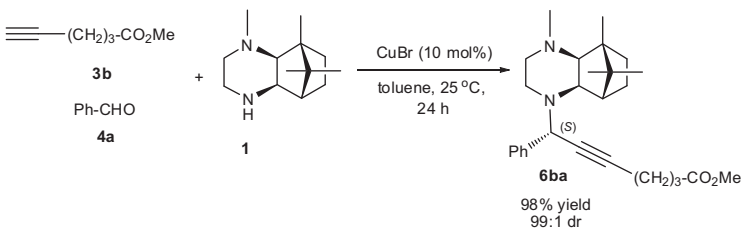
The configuration at the newly formed stereogenic center in propargylamines **6** was assigned as (*S*). We have previously reported that the chiral bispropargylamine **9** obtained using the parent chiral camphanylpiperazine **8**, had an (*R*)-configuration at the new propargyl stereogenic center adjacent to the (*S*)-camphanylamine moiety and an (*S*)-configuration at the other propargyl center adjacent to the (*R*)-camphanylamine moiety, based on single crystal X-ray structure analysis (Fig. 1).[4b] We have also reported that chiral propargylamine **12**, prepared using chiral *N*-methylcamphanyl piperazine **1**, had an (*S*)-configuration at the new propargyl stereogenic center adjacent to the (*R*)-camphanyl amine moiety based on single crystal X-ray structure analysis (Fig. 1).[4b] These structural assignments are in accordance with the expected transition states of alkynylzinc addition to the iminium ion intermediates **10** and **11** (Fig. 1). Therefore, the assignment of the (*S*)-configuration for the new stereogenic center in propargylamines **6** is in accordance with the expected mechanism of alkynyl copper addition to the corresponding iminium ion intermediate as this mode of addition would be similar to the addition



Scheme 2.

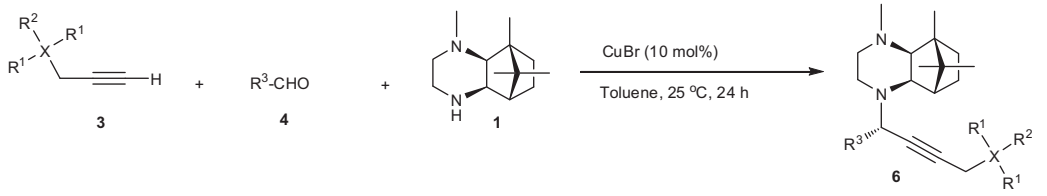


Scheme 3.

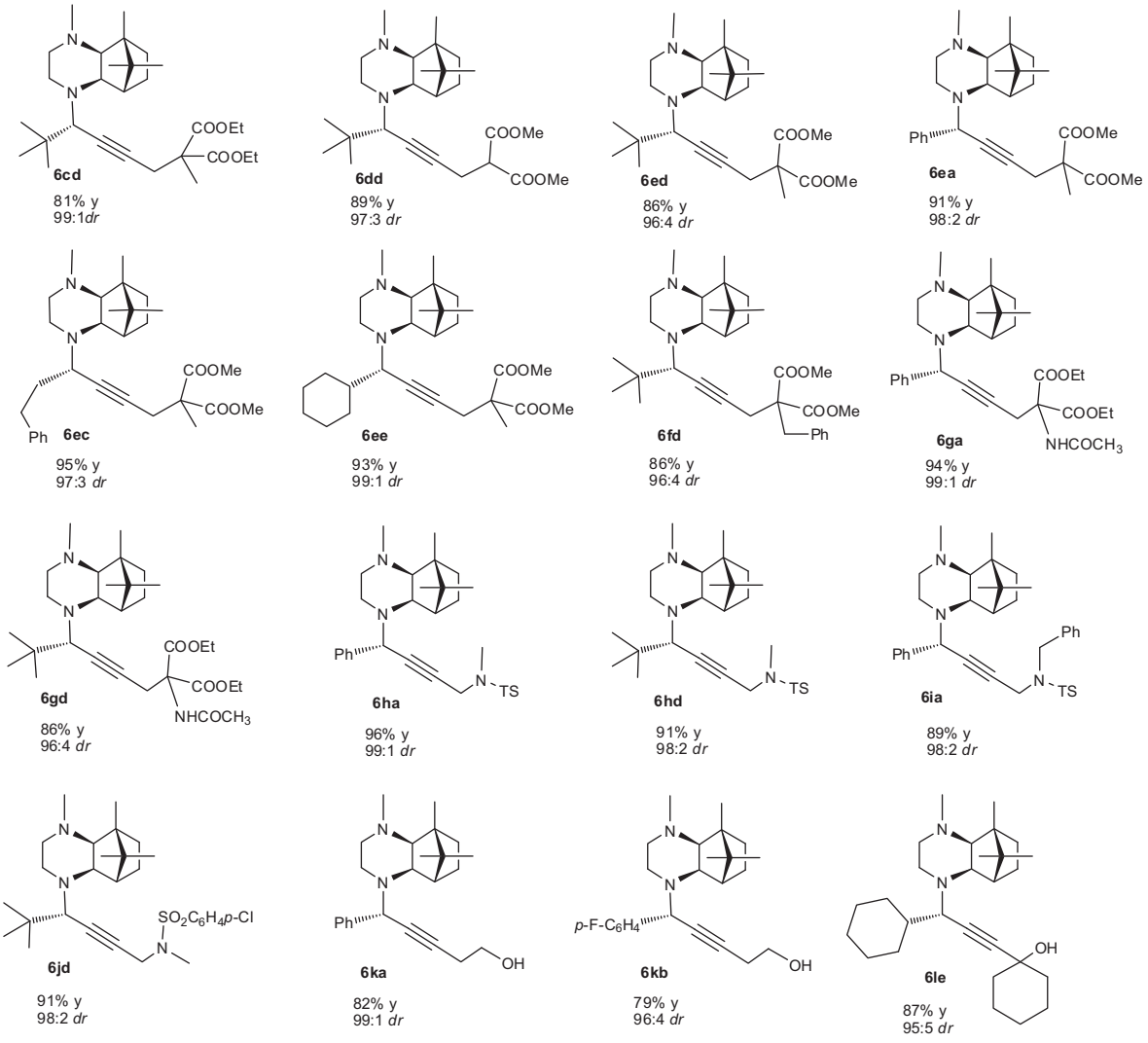


Scheme 4.

Table 1
Diastereoselective synthesis of propargylamines **6** using chiral piperazine **1**, with different 1-alkynes **3** and aldehydes **4** in the presence of copper bromide[a,b,c]



3c = (X= C, R^1 = COOEt, R^2 = Me)
3d= (X= C, R^1 = COOMe, R^2 = H)
3e= (X= C, R^1 = COOMe, R^2 = Me)
3f = (X= C, R^1 = COOMe, R^2 = benzyl)
3g= (X= C, R^1 = COOEt, R^2 = $NHCOCH_3$)
3h= (X= N, R^1 = tosyl, R^2 = Me)
3i= (X= N, R^1 = tosyl, R^2 = benzyl)
3j= (X= N, R^1 = $SO_2C_6H_4$-*p*-Cl, R^2 = Me)
3k= (X= C, R^1 = H, R^2 = OH)
3l = (X= C, R^1 = -$(CH_2)_5$-, R^2 = OH)
4a = PhCHO
4b = *p*-F-C_6H_4CHO
4c = $PhCH_2CH_2CHO$
4d = *t*-BuCHO
4e = *c*-$C_6H_{11}CHO$



[a] The reactions were carried out by using chiral piperazine **1** (1.0 mmol), 1-alkyne (1.1 mmol), and aldehyde (1.0 mmol) in toluene (3 mL) with CuBr (10 mol %) at 25 °C for 24 h.
[b] dr ratio based on ^{1}H NMR crude sample.
[c] Isolated yield.

of alkynylzincs to the iminium intermediate **11**, which gave product **12** with an (*S*)-configuration at the new stereogenic center (Fig. 1).[4b,9,10] It is noteworthy that chiral camphanyl propargylamines **6** and **12**, which have an (*S*)-configuration at the propargyl stereogenic center, gave $[\alpha]_D^{25}$ values in the range of −29 to −55.

We next carried out experiments for the conversion of the chiral propargylamines into the corresponding chiral allenes. When ZnI_2 (50 mol %) was used as the metal salt for the conversion of chiral propargylamine **6ba** in toluene, the expected allene product (*R*)-**13ba** was obtained in 79% yield with 89% ee. We optimized the

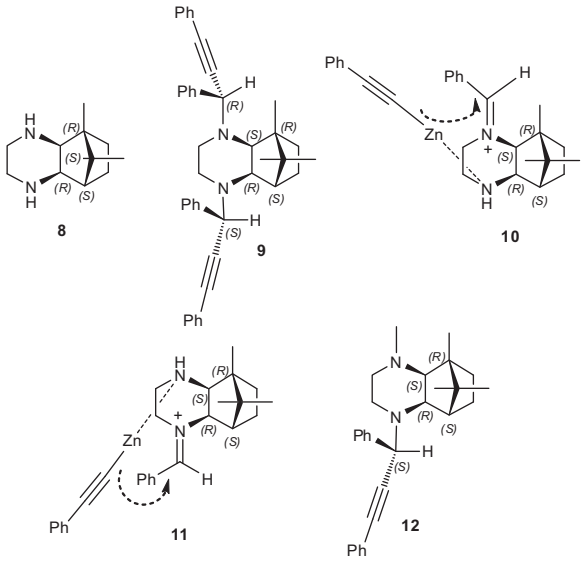
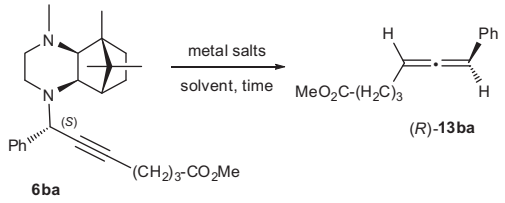


Fig. 1.

Table 2
Conversion of propargylamine **6ba** into chiral allene (*R*)-**13ba** using different metal salts[a]



S. No.	Solvent	Temp	MX_n	Mol (%)	Time (h)	Yield[b] (%)	ee[c] (%)
1	Toluene	120	ZnI_2	50	1	79	89
2	Toluene	120	$ZnBr_2$	50	2	72	99
3	Toluene	120	$ZnCl_2$	50	12	51	99
4	CH_3CN	50	$AgNO_3$	50	24	35	99
5	Toluene	120	CuI	50	12	25	98
6	Toluene	120	CuBr	50	12	19	99
7	Toluene	120	CuCl	50	12	5	99
8	Dioxane	100	CuI	50	18	39	99

[a] The reactions were carried out by using propargylamine **6ba** (1 mmol) in solvent (3 mL).
[b] Yields are isolated.
[c] The % ee was confirmed by HPLC analysis on chiralcel AS-H.

reaction conditions by examining the effect of various metal salts and solvents for the conversion of chiral into chiral allene (*R*)-**13ba** (Table 2).[11]

We observed that the use of CuCl, CuBr, and CuI gave poor results as in these cases, (*R*)-**13ba** allene was obtained in only 5–39% yield with 99% ee (entries 5–8, Table 2). Similarly, allene (*R*)-**13ba** was obtained in only 35% yield with 99% ee when $AgNO_3$ was used (entry 4, Table 2). The zinc halides gave the allene in 51–79% yield with 89–99% ee (entries 1–3, Table 2) while the use of $ZnBr_2$ (0.5 mmol) gave the optimum results (72% yield with 99% ee) in a shorter reaction time of 2 h.

Next, we examined the conversion of propargylamine derivatives into chiral allenes by following the conditions optimized for **6ba** (Table 2, entry 2). We have observed that the reaction of the ester derivatives of propargylamines **6cd**–**6fd** with $ZnBr_2$ gave (*R*)-allenes **13cd**–**13fd** in 65–77% yields with 90–99% ee (Table 3). Similar results were observed with the amide derivatives of propargylamines **6ga** and **6gd** in 73–85% yields and with 99% ee. Moderate yields and ees were realized in the reaction with alcohol derivatives **6ka**, **6kb**, and **6le** (Table 3).

All of the optically active allenes obtained by using *N*-methylcamphanyl piperazine **1** are levorotatory, from which the absolute configurations of the major enantiomer of the allenes were assigned as (*R*) by the Lowe–Brewster rule and also by comparison with the reported $[\alpha]_D^{25}$ values.[12]

When the reaction was performed with isomeric chiral piperazine **2** with diethyl 2-acetamido-2-propargylmalonate **3g** and benzaldehyde **4a**, the desired propargylamine **14ga** was isolated in only 27% yield even after a prolonged reaction time of 48 h. It was noticed that the chiral piperazine **2** reacted with the substituted alkyne **3e** and aldehyde **4a** to give the corresponding propargylamine **14ea** with very low yield (22%). From these observations, it is apparent that the lower reactivity may be due to the steric hindrance between the C_{10} methyl group of camphanyl piperazine **2** and the substituent groups in the alkyne partner. Fortunately, when the reaction mixture was heated at 45 °C for 24 h, the propargylamine product **14ea** was obtained in 89% yield in 99:1 dr (Scheme 5). The configuration at the newly formed stereogenic center in propargylamines **14ea** and **14ga** was assigned as (*R*) since the mechanism of the alkynyl copper addition to the corresponding iminium ion intermediates would be similar to the addition of an alkynylzinc to the iminium intermediate **10** as outlined in Figure 1.[4b,9,10] It is of interest to note that although the propargylamines **6** and **14** are diastereomers, the propargylamines **6** with an (*S*)-configuration at the new propargyl stereogenic center exhibit negative $[\alpha]_D^{25}$ values in the range of −29 to −55, while propargylamines **14ea** and **14ga** with an (*R*)-configuration at the new propargyl stereogenic center gave positive $[\alpha]_D^{25}$ values of +43.6 and +39.1, respectively.

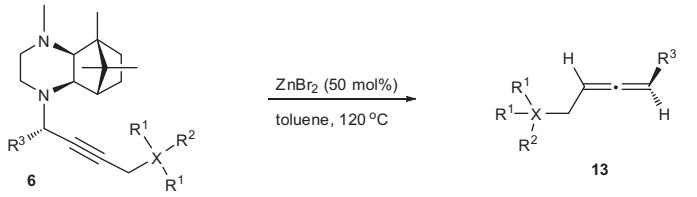
We also carried out the conversion of chiral propargylamine derivatives **14ea** and **14ga** obtained from piperazine **2** into the corresponding chiral allenes (Scheme 5).

The optically active allenes obtained by using *N*-methylcamphanyl piperazine **2** are dextrorotatory from which the absolute configurations of the major enantiomer of the chiral allenes were assigned as (*S*) by the Lowe–Brewster rule and also by comparison with the reported $[\alpha]_D^{25}$ values.[12]

Next, we turned our attention toward the synthesis of naturally occurring allenes by applying this methodology as none of the biologically active allenes were synthesized so far using chiral propargylamine as precursors.[6] We chose the Sapium japonicum **13mf**, a reported antifungal agent containing an allenic moiety as the target. Several synthetic approaches have been reported for the synthesis of this allene in racemic as well as in enantiomerically pure form involving an S_N2 reaction,[6a] Claisen rearrangement,[6b] and 1,2-elimination of alkenyl halides.[6d] We observed that chiral piperazine **1** reacts with 5-oxo-pentanoic acid methyl ester **4f** and TBS alkyne **3m** in the presence of 10 mol % CuBr to give the chiral propargylamine derivate **6mf** in 98% yield with 99:1 dr which upon reaction with $ZnBr_2$ followed by desilylation afforded (*R*)-**13mf** in 78% yield with 98% ee (Scheme 6).[6d] It is noteworthy that compound (*R*)-**13mf** has previously been synthesized by a multistep method with low enantioselectivity.

Compound methyl (*R*,*E*)-2,4,5-tetradecatrienoate **15** is a pheromone component of the male dried bean beetle. We observed that chiral piperazine **1** reacts with 1-decyne **3n** and 4-oxo-butyric acid methyl ester **4g** in the presence of CuBr in toluene to give chiral propargylamine derivative **6ng** in 93% yield with 99:1 dr. This propargylamine intermediate **6ng** reacts with $ZnBr_2$ to give (*R*)-**13ng** allene in 72% yield (Scheme 7). Unfortunately, chiral HPLC columns available to us failed to separate the enantiomers of **13ng**. However, comparison of the specific rotation of

Table 3
$ZnBr_2$ promoted synthesis of chiral allenes from chiral propargylamines[a,b,c]



6cd = (X= C, R^1 = COOEt, R^2 = Me, R^3 = *t*-BuCHO)

6dd = (X= C, R^1 = COOMe, R^2 = H, R^3 = *t*-BuCHO)

6ed = (X= C, R^1 = COOMe, R^2 = Me, R^3 = *t*-BuCHO)

6ea = (X= C, R^1 = COOMe, R^2 = Me, R^3 = PhCHO)

6ec = (X= C, R^1 = COOMe, R^2 = Me, R^3 = $Ph(CH_2)_2CHO$)

6ee = (X= C, R^1 = COOMe, R^2 = Me, R^3 = *c*-$C_6H_{11}CHO$)

6fd = (X= C, R^1 = COOMe, R^2 = benzyl, R^3 = *t*-BuCHO))

6ga = (X= C, R^1 = COOEt, R^2 = $NHCOCH_3$, R^3 = PhCHO)

6gd = (X= C, R^1 = COOEt, R^2 = $NHCOCH_3$, R^3 = *t*-BuCHO)

6ha = (X= N, R^1 = tosyl, R^2 = Me, R^3 = PhCHO)

6hd = (X= N, R^1 = tosyl, R^2 = Me, R^3 = *t*-BuCHO)

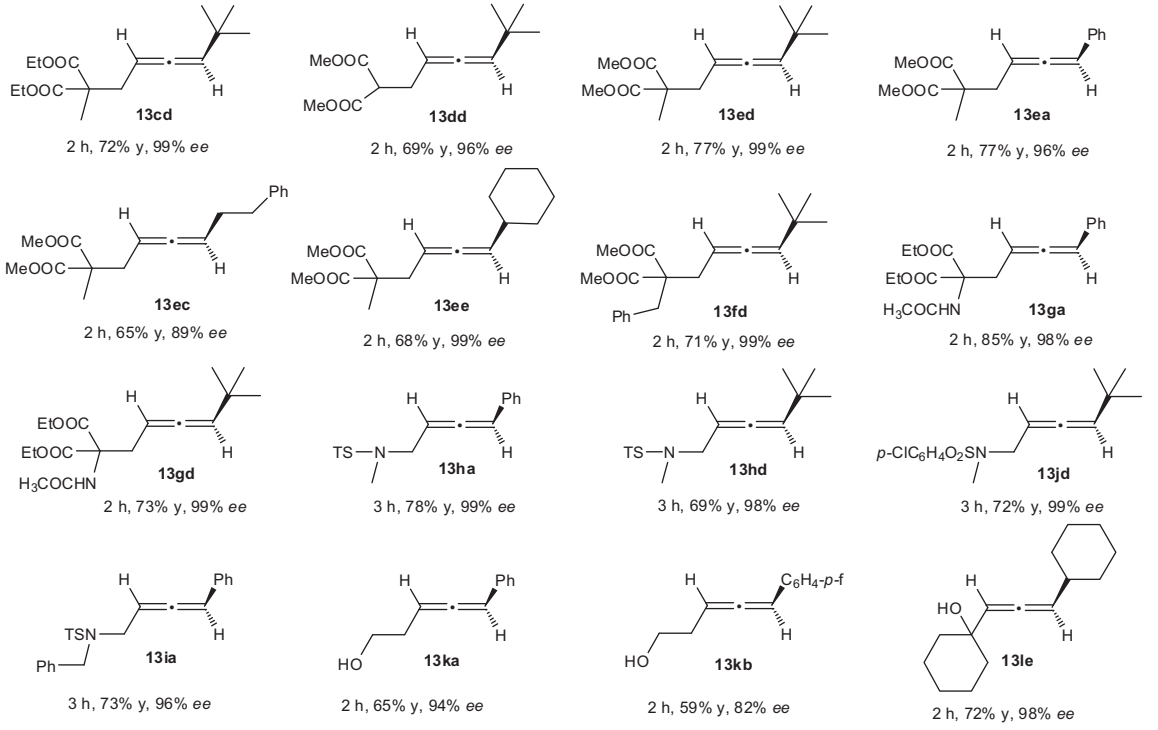
6jd = (X= N, R^1 = $SO_2C_6H_4$-*p*-Cl, R^2 = Me, R^3 = *t*-BuCHO)

6ia = (X= N, R^1 = tosyl, R^2 = benzyl, R^3 = Ph)

6ka = (X= C, R^1 = H, R^2 = CH_2OH, R^3 = PhCHO)

6kb = (X= C, R^1 = H, R^2 = CH_2OH, R^3 = *p*-F-C_6H_4CHO)

6le = (X= C, R^1 = -$(CH_2)_5$-, R^2 = OH, R^3 = *c*-$C_6H_{11}CHO$)



[a] The reactions were carried out by using propargylamine **6** in toluene (3 mL) with $ZnBr_2$ (0.5 mmol).
[b] Isolated yield.
[c] ee was determined by using chiral HPLC.

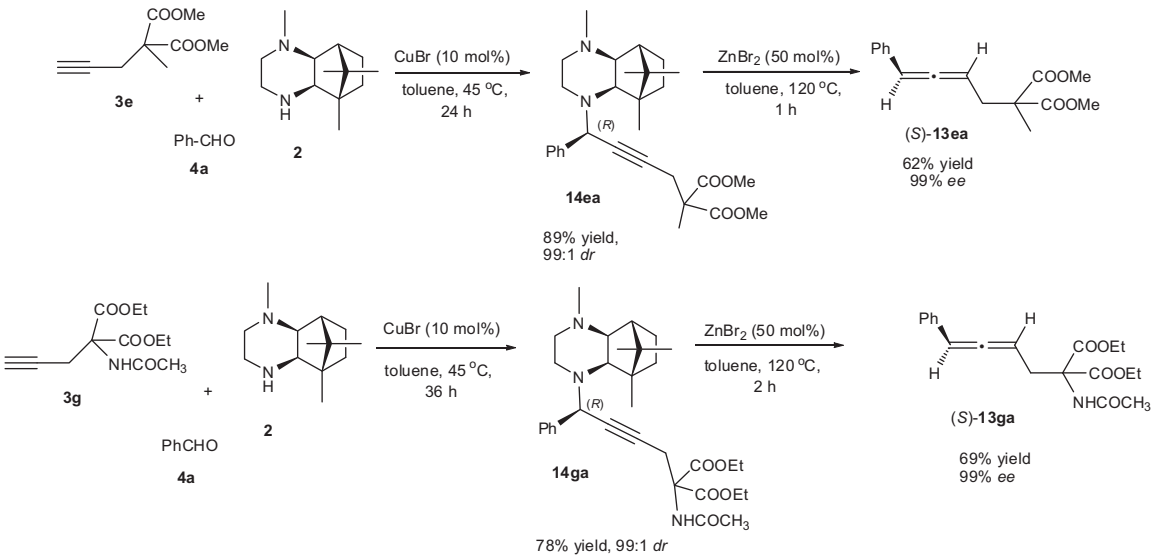
$[\alpha]_D^{25} = -61.5$ (*c* 0.73, hexane) observed for product (*R*)-**13ng** (Scheme 7) with the reported rotation of $[\alpha]_D^{25} = -63.3$ (*c* 2.07, hexane) indicates that its purity was ⩽93% ee. This chiral allene (*R*)-**13ng** precursor has been previously converted into pheromone **15** in two steps (Scheme 7).[6f]

The formation of propargylamines in the reaction of 1-alkynes, aldehydes, and chiral camphanyl piperazines followed by allene transformation can be explained by the mechanism outlined in Scheme 8. Initially chiral piperazine **1** reacts with CuBr to form the dimeric coper complex **16**.[10] Then, reaction with 1-alkyne gives intermediate complex **16**, which in turn reacts with the intermediate imine obtained from the aminal **18**, formed in situ by the reaction of the chiral piperazine and aldehyde to generate the intermediate **19**. Delivery of the alkynyl group from the bottom face of the iminium group would lead to a new (*S*)-stereogenic center at the propargylamine product **20** which could complex with $ZnBr_2$ to give **22** that could then undergo a hydride shift to give chiral allene (*R*)-**8** via the intermediate **23** (Scheme 8).

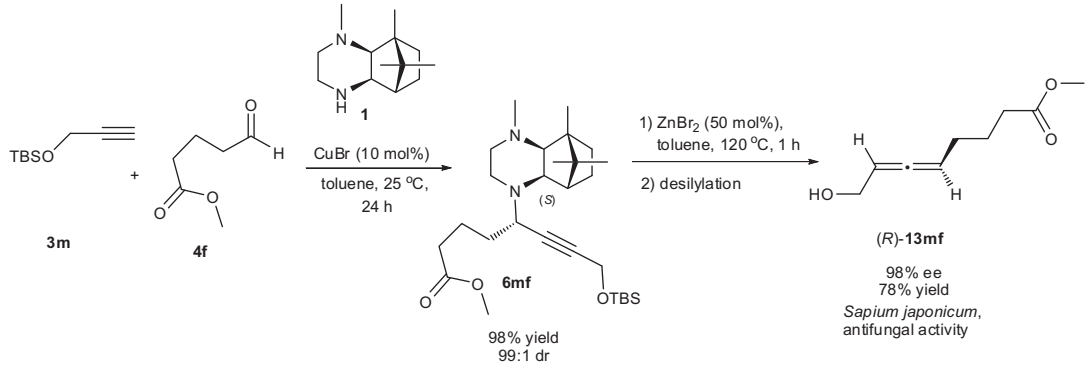
We also found that the imine by-products **24** could be easily converted in situ to the corresponding chiral piperazines in 69% yield by simple sodium borohydride reduction.

3. Conclusion

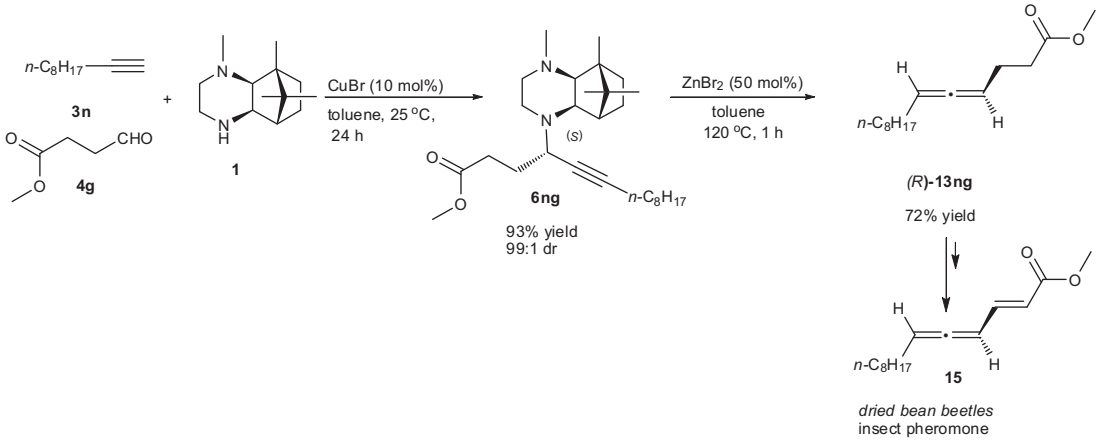
We have developed a method for the synthesis of highly functionalized chiral propargylamine derivatives via the CuBr promoted



Scheme 5.

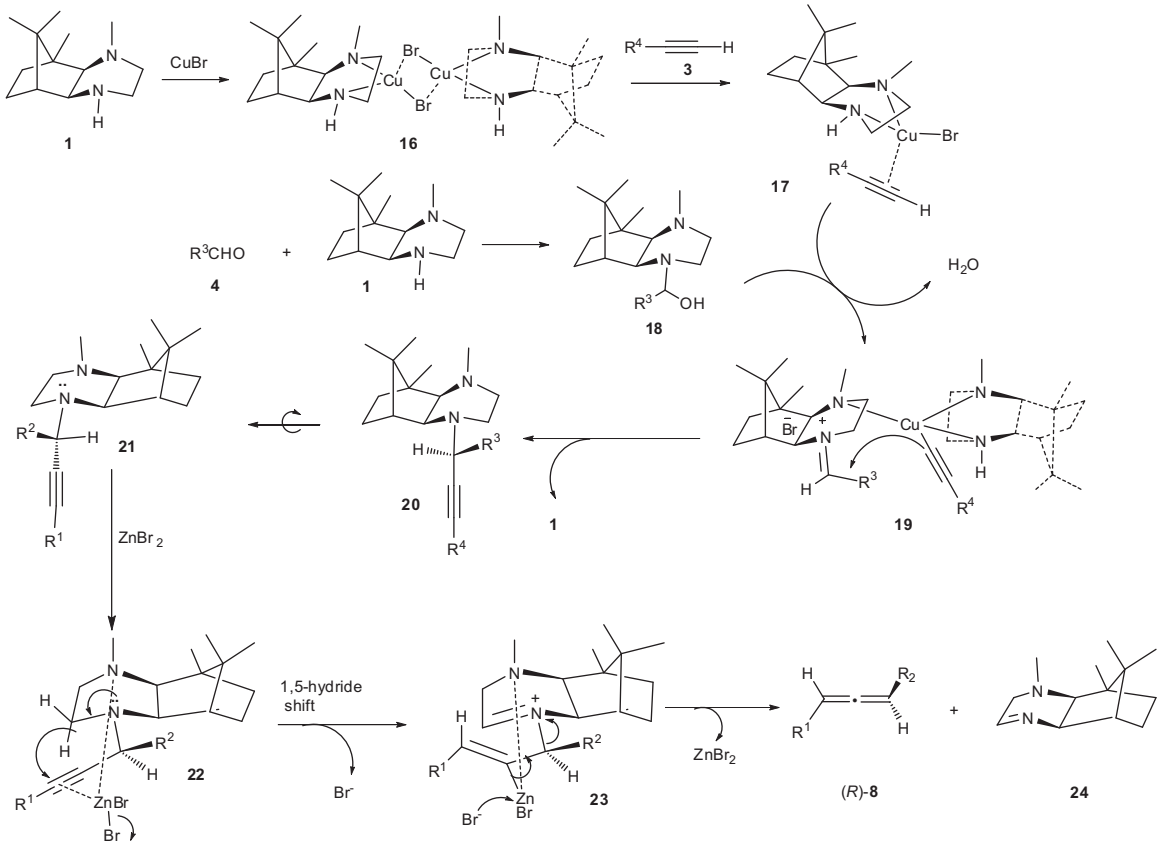


Scheme 6.



Scheme 7.

diastereoselective reaction of 1-alkynes and aldehydes containing sensitive functional groups using the chiral *N*-methylcamphanyl piperazine derivatives **1** and **2**. These chiral propargylamine derivatives are converted into chiral allenes using zinc bromide with high enantiomeric purities. We have also synthesized the naturally occurring chiral allene Sapium japonicum (*R*)-**13mf** and an advanced allene precursor intermediate (*R*)-**13ng** previously used in the synthesis of the pheromone male dried bean beetle **15** by using the 'chiral amine approach'. Accordingly, the methods described here have considerable potential to access biologically active chiral allenes containing sensitive functional groups via the corresponding chiral propargylamines.



Scheme 8.

4. Experimental

4.1. Materials and methods

Melting points were determined using a Superfit capillary point apparatus. IR (KBr) spectra were recorded on JASCO FT-IR spectrophotometer Model 5300. The neat IR spectra were recorded on JASCO FT-IR spectrophotometer Model 5300 and SHIMADZU FT-IR spectrophotometer Model 8300 with polystyrene as reference. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker-AC-200 and Bruker-Avance-400 spectrometers, respectively with chloroform-d as solvent and TMS as reference (δ = 0 ppm). The chemical shifts are expressed in δ downfield from the signal of internal TMS. Liquid chromatography (LC) and mass analysis (LC–MS) were performed on SHIMADZU-LCMS-2010A. The mass spectral analyses were carried out using Chemical Ionization (CI) or Electro spray Ionization (ESI) techniques. Elemental analyses were carried out using a Perkin–Elmer elemental analyzer model-240C and Thermo Finnigan analyzer series Flash EA 1112. Mass spectral analyses for some of the compounds were carried out on VG 7070H mass spectrometer using EI technique at 70 eV. Optical rotations were measured on Rudolph Research Analytical AUTOPOL-II (readability ±0.01°) and AUTOPOL-IV (readability ±0.001°) automatic polarimeters. The conditions of the polarimeter were checked by measuring the specific rotation of standard (*S*)-(−)-diphenyl prolinol, 99% ee (DPP) which was purchased from Gerchem Labs (P) Ltd. Hyderabad. Analytical grade $ZnCl_2$ and $ZnBr_2$ purchased from E-Merck, India and Nice Chemicals Pvt Ltd, Indi, respectively were used. ZnI_2 was purchased from Sigma Aldrich. Powdered zinc halide samples were heated at 120 °C under reduced pressure (0.001 mm Hg) in a vacuum oven and stored under dry nitrogen. Toluene supplied by E-Merck, India was freshly distilled over sodium-benzophenone ketyl before use. Analytical thin layer chromatographic tests were carried out on glass plates (3 × 10 cm) coated with 250 μm acme's silica gel-G and GF_{254} containing 13% calcium sulfate as binder. The spots were visualized by short exposure to iodine vapor or UV light. Column chromatography was carried out using acme's silica gel (100–200 or 230–400 mesh) and neutral alumina.

4.1.1. Reaction of 1-alkyne, aldehyde, and the chiral piperazine 1 with CuBr: synthesis of chiral propargylamine 6

To a stirred suspension of chiral piperazine **1** or **2** (0.210 g, 1 mmol), CuBr (0.014 g, 0.1 mmol), and 1-alkyne **3** (1.1 mmol) in toluene (3 mL), freshly distilled aldehyde **4** (1 mmol) was added at 25 °C. The contents were stirred at 25 °C for 24 h. Toluene was then removed after which water (5 mL) and DCM (15 mL) were added. The DCM layer was washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography using hexane and ethyl acetate (9:1) as eluent to isolate the propargyl amines **6**.

4.1.2. 7-Phenyl-7-(4,5,9,9-tetramethyl-octahydro-5,8-methanoquinazolin-1-yl)-hept-5-ynoic acid ethyl ester 6ba

Yellow oil; R_f = 0.6 (silica gel, hexane/EtOAc 90:10); yield: 0.413 g, 98%, $[\alpha]_D^{25}$ = −51.1 (*c* 0.43, $CHCl_3$); IR(neat) 2951, 2874, 2793, 2762, 2704, 1739, 1660, 1601, 1531, 1493, 1450, 1338, 1367, 996, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.61–7.59 (d, *J* = 7.0 Hz, 2H), 7.32–7.23 (m, 3H), 5.00 (s, 1H), 3.70–3.69 (s, 3H), 3.0–2.98 (d, *J* = 8.0 Hz, 1H), 2.72–2.66 (m, 1H), 2.55–2.41 (m, 5H), 2.27 (s, 3H), 2.14–2.17 (m, 2H), 1.94–1.91 (m, 3H), 1.80–1.73 (m, 2H), 1.43 (s, 3H), 1.26–1.16(m, 3H), 1.03 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 171.4, 139.0, 129.7, 129.0, 128.2, 127.9, 127.1, 82.4, 79.0, 78.2, 65.3, 57.5, 54.3, 53.5, 52.8,

48.1, 47.3, 47.2, 42.5, 37.2, 26.5, 26.1, 22.2, 20.2, 14.7; HRMS (ESI): m/z calcd for $C_{27}H_{38}N_2O_4$: 422.2933 [M+H$^+$]; found: 423.3085.

4.1.3. 2-[5,5-Dimethyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-2-methyl-malonic acid diethyl ester 6cd

Yellow oil; R_f = 0.5 (silica gel, hexane/EtOAc 90:10); yield: 0.396 g, 81%, $[\alpha]_D^{25}$ = −52.0 (c 0.35, $CHCl_3$); IR(neat) 2951, 2879, 2793, 2798, 1738 1599, 1456, 1365, 1294, 1246, 1194, 1107, 1022, 996, 891 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 4.21–4.16 (m, 1H), 3.07 (s, 1H), 2.80–2.58 (m, 6H), 2.24 (s, 3H), 2.18–2.10 (m, 5H), 1.55 (m, 6H), 1.25–1.23 (m, 10H), 0.96 (s, 3H), 0.93 (s, 9H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 171.0, 80.9, 79.9, 66.3, 65.9, 61.7, 61.4, 54.4, 53.4, 49.9, 49.6, 48.8, 47.0, 45.7, 36.9, 36.1, 28.3, 26.2, 25.8, 22.0, 20.6, 19.9, 14.2, 14.0; HRMS (ESI): m/z calcd for $C_{29}H_{48}N_2O_4$: 488.3614 [M+H$^+$]; found: 489.3692.

4.1.4. 2-[5,5-Dimethyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-malonic acid dimethyl ester 6dd

Yellow oil; R_f = 0.6 (silica gel, hexane/EtOAc 90:10); yield: 0.383 g, 89%, $[\alpha]_D^{25}$ = −43.6 (c 0.40, $CHCl_3$); IR(neat) 2953, 2874, 1743, 1437, 1450, 1388, 1365, 1325, 1292, 1211, 1057, 804 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 3.76 (s, 6H), 3.07 (s, 3H) 3.02–3.01 (d, J = 4 Hz, 1H), 2.92–2.80 (m, 2H), 2.79–2.68 (m, 1H), 2.62–2.57 (m, 2H), 2.25 (s, 3H), 2.19–2.13 (m, 2H), 2.04–2.02 (t, J = 5.3 Hz, 1H), 1.58–1.53 (m, 1H), 1.46–1.40 (m, 1H), 1.24 (s, 3H), 0.96 (s, 3H), 0.93 (s, 9H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 169.3, 81.6, 78.9, 78.5,77.7, 71.6, 66.3, 66.0, 56.7, 54.5, 53.0, 49.9, 49.6, 48.8, 47.0, 45.8, 36.9, 36.1, 28.2, 25.8, 23.1, 22.8, 22.0, 20.0, 14.3; HRMS (ESI): m/z calcd for $C_{26}H_{42}N_2O_4$: 446.3145 [M+K$^+$]; found: 485.3374.

4.1.5. 2-Methyl-2-[4-phenyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-ynyl]-malonic acid dimethyl ester 6ea

Yellow oil; R_f = 0.6 (silica gel, hexane/EtOAc 90:10); yield: 0.436 g, 91%, $[\alpha]_D^{25}$ = −50.7 (c 0.52, $CHCl_3$); IR(neat) 2953, 2878, 2798, 2798, 2766, 2704, 1738 1668, 1601, 1537, 1452, 1388, 1292, 1249,1203, 1109, 1028, 997, 856 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.57–7.54 (d, J = 12.0 Hz, 2H), 7.30–7.23 (m, 3H), 4.99 (s, 1H), 3.76–3.70 (s, 6H), 2.98–2.94 (d, J = 16.0 Hz, 3H), 2.48–2.42 (m, 2H), 2.27–2.18 (m, 6H), 1.63 (m, 3H), 1.47–1.43 (m, 6H), 1.20–1.13 (m, 2H), 1.03 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 171.4, 139.0, 129.7, 129.0, 128.1, 127.9, 82.3, 79.0, 78.2, 65.3, 57.5, 54.3, 53.5, 52.8, 50.3, 48.1, 47.3, 47.2, 42.5,37.2, 26.4, 26.1, 22.2, 21.2, 20.2, 14.6; HRMS (ESI): m/z calcd for $C_{29}H_{40}N_2O_4$: 480.2988 [M+H$^+$]; found: 481.3066.

4.1.6. 2-Methyl-2-[6-phenyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-malonic acid dimethyl ester 6ec

Yellow oil; R_f = 0.6 (silica gel, hexane/EtOAc 90:10); yield: 0.482 g, 95%, $[\alpha]_D^{25}$ = −48.1 (c 0.60, $CHCl_3$); IR(neat) 3296, 2951, 2874, 2795, 1743, 1666, 1533, 1454, 1388, 1365, 1288, 1248, 1211, 1132, 1066, 1018, 966 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.29–7.27 (m, 2H), 7.19–7.17 (m, 3H), 3.59–3.55 (t, J = 16.0 Hz, 1H), 2.82 (s, 2H), 2.79–2.57 (m, 5H), 2.28 (s, 3H), 2.19–2.09 (m, 5H), 1.86–1.80 (q, J = 24.0 Hz, 2H), 1.73–1.61 (m, 5H), 1.55 (s, 3H), 1.46–1.39 (m, 2H), 1.26 (s, 3H), 1.15–1.05 (m, 2H), 0.99 (s, 3H) 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 171.4, 142.1, 128.4, 128.3, 125.7, 81.9, 79.1, 78.7, 64.7, 54.5, 53.5,53.3, 52.8, 50.0, 48.2, 47.3, 47.1, 42.0, 37.2, 35.5, 32.8, 26.3, 25.8, 22.1, 20.9, 20.0, 14.6; HRMS (ESI): m/z calcd for $C_{31}H_{44}N_2O_4$: 508.3301 [M+H$^+$]; found: 509.3652.

4.1.7. 2-[5,5-Dimethyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-2-methyl-malonic acid dimethyl ester 6ed

Yellow oil; R_f = 0.6 (silica gel, hexane/EtOAc 90:10); yield: 0.396 g, 86%, $[\alpha]_D^{25}$ = −39.7 (c 0.32, $CHCl_3$); IR(neat) 3306, 2951, 2874, 2795, 2762, 1739, 1666, 1533, 1454, 1388, 1365, 1294, 1249,1203, 1111, 1018, 997, 871 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 3.73 (s, 6H), 3.07 (s, 1H), 2.86 (s, 2H), 2.80–2.70 (m, 3H), 2.63–2.53 (m, 2H), 2.25 (s, 2H), 2.19–2.09 (m, 3H), 1.72–1.69 (m, 2H), 1.57 (s, 3H), 1.25 (s, 3H), 1.08–1.01 (m, 2H), 0.96 (s, 1H), 0.93 (s, 9H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 171.5, 81.0, 79.7, 77.7, 66.3, 65.9, 54.5, 53.5, 52.7, 49.9,49.6 48.8, 47.0, 45.7, 36.9, 36.1, 28.2, 26.4, 25.8, 22.6, 22.0, 20.6, 20.1, 14.2; HRMS (ESI): m/z calcd for $C_{27}H_{44}N_2O_4$: 460.3301 [M+H$^+$]; found: 461.3378.

4.1.8. 2-[4-Cyclohexyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-ynyl]-2-methyl-malonic acid dimethyl ester 6ee

Yellow oil; R_f = 0.6 (silica gel, hexane/EtOAc 90:10); yield: 0.451 g, 93%, $[\alpha]_D^{25}$ = −36.9 (c 0.54, $CHCl_3$); IR(neat) 3302, 2947, 2851, 2795, 2764, 2702, 1739,1657, 1535, 1450, 1388, 1377, 1317, 1292, 1249,1201, 1109, 1022, 997, 817 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 3.72 (s, 6H), 3.13–3.10 (d, J = 12.0 Hz, 1H), 2.82–2.66 (m, 5H), 2.51–2.46 (m, 1H), 2.25 (s, 3H), 2.16–1.88 (m, 3H), 1.72–1.69 (m, 2H), 1.54 (s, 3H), 1.43–1.41 (d, J = 8.0 Hz, 2H), 1.25–1.23 (m, 9H), 1.14–1.08 (m, 3H), 0.97 (s, 1H), 0.89–0.83 (m, 4H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 171.5, 81.7, 79.2, 78.5, 64.6, 60.2, 54.5, 53.5, 52.7, 50.0, 48.4, 47.6, 47.1, 42.2, 40.6, 37.2, 34.6, 31.6, 30.5, 26.7, 26.3, 26.2, 25.9, 22.6, 22.1, 20.9, 20.1, 14.6; HRMS (ESI): m/z calcd for $C_{29}H_{46}N_2O_4$: 486.3458 [M+H$^+$]; found: 487.3536.

4.1.9. 2-Benzyl-2-[5,5-dimethyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-malonic acid dimethyl ester 6fd

Yellow oil; R_f = 0.6 (silica gel, hexane/EtOAc 90:10); yield: 0.469 g, 86%, $[\alpha]_D^{25}$ = −39.7 (c 0.25, $CHCl_3$); IR(neat) , 2951, 2874, 2795, 1743,1666, 1533, 1454, 1388, 1377, 1365, 1288, 1248,1211, 1132, 1066, 1018, 966, 889 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.27–7.24 (t, J = 12.0 Hz, 3H), 7.18–7.16 (d, J = 8.0 Hz, 2H), 3.73 (s, 6H), 3.42 (s, 2H), 3.18 (s, 1H), 3.10–2.93 (dd, J = 24.0 Hz, 1H), 2.83–2.79 (m, 3H), 2.26 (s, 2H), 2.60–2.58 (m, 3H), 2.26 (s, 3H), 1.72–1.53 (m, 3H), 1.47–1.41 (m, 2H), 1.27 (s, 3H), 1.00 (s, 9H) 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 170.2, 135.7, 129.8, 128.4, 127.1, 82.0, 79.9, 77.8, 66.3, 66.0, 58.5, 54.6, 52.6, 50.0, 49.6,48.8, 47.0, 45.8, 37.6, 36.9, 36.2, 28.4, 25.9, 22.6, 22.0, 14.6; HRMS (ESI): m/z calcd for $C_{33}H_{48}N_2O_4$: 536.3614 [M+H$^+$]; found: 537.3691.

4.1.10. 2-Acetylamino-2-[4-phenyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-ynyl]-malonic acid dimethyl ester 6ga

Yellow oil; R_f = 0.7 (silica gel, hexane/EtOAc 70:30); yield: 0.517 g, 94%, $[\alpha]_D^{25}$ = −42.1 (c 0.53, $CHCl_3$); IR(neat) 3420, 3302, 3061, 2951, 2876, 2795, 2760, 1749, 1684, 1601, 1494, 1450, 1388, 1369, 1302, 1205, 1128, 1057, 854, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.53–7.52 (d, J = 4.0 Hz, 2H), 7.32–7.20 (m, 2H), 6.98 (m, 1H), 4.95 (s, 1H), 4.30–4.25 (q, J = 20.0 Hz, 4H), 4.13–4.08 (m, 1H), 2.92–2.90 (d, J = 8.0 Hz, 1H), 2.72–2.62 (m, 1H), 2.47–2.40 (m, 1H), 2.26 (s, 3H), 2.18–2.16 (d, J = 8.0 Hz, 1H), 2.07 (s, 3H), 2.03–2.02 (d, J = 4.0 Hz, 3H), 1.87–1.86 (d, J = 4.0 Hz, 1H), 1.45 (s, 3H), 1.29–1.23 (m, 12H), 1.02 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 169.1, 166.8, 138.8, 129.0, 128.0, 127.9, 127.2, 81.4, 79.2, 78.2, 65.5, 65.3, 62.9, 60.3, 57.5, 54.4, 50.3, 48.2, 47.3, 42.5, 37.2, 26.3, 24.2, 23.0, 22.1,

14.6, 14.2, 14.0; HRMS (ESI): *m*/*z* calcd for $C_{32}H_{45}N_3O_5$: 551.3359 [*M*+H$^+$]; found: 552.3447.

4.1.11. 2-Acetylamino-2-[5,5-dimethyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-malonic acid dimethyl ester 6gd

Yellow oil; R_f = 0.7 (silica gel, hexane/EtOAc 70:30); yield: 0.456 g, 86%, $[\alpha]_D^{25}$ = −36.5 (*c* 0.45, $CHCl_3$); IR(neat) 3498, 3298, 2953, 2874, 2795, 2764, 1736, 1689, 1653, 1535, 1456, 1388, 1377, 1367, 1294, 1246, 1194, 1024, 862 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 6.91 (s, 1H), 4.29–4.25 (m, 4H), 3.15–3.02 (m, 2H), 3.03–3.01 (m, 1H), 2.92–2.82 (m, 1H), 2.76–2.59 (m, 3H), 2.25 (s, 3H), 2.17–2.08 (m, 2H), 2.06 (s, 3H), 1.66–1.60 (m, 1H), 1.57–1.56 (m, 1H), 1.47–143 (m, 1H), 1.29–1.24 (m, 10H), 0.97 (s, 3H), 0.93 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 168.9, 166.9, 81.2, 78.7, 77.7, 66.2, 65.6, 62.9,62.8, 54.6, 49.9, 49.5, 48.8, 47.0, 45.7, 36.9, 36.0, 28.2, 25.8, 24.1, 23.0, 22.1, 20.6, 14.2; HRMS (ESI): *m*/*z* calcd for $C_{30}H_{49}N_3O_5$: 531.3672 [*M*+H$^+$]; found: 532.3750.

4.1.12. *N*-[5,5-Dimethyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-4,*N*-dimethyl-benzenesulfonamide 6hd

Yellow oil; R_f = 0.6 (silica gel, hexane/EtOAc 80:20); yield: 0.454 g, 91%, $[\alpha]_D^{25}$ = −40.8 (*c* 0.40, $CHCl_3$); IR(neat) 2947, 2794, 1600, 1457, 1353, 1167, 926, 821, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.72–7.70 (d, *J* = 8.0 Hz, 2H), 7.30–7.28 (d, *J* = 8.0 Hz, 2H), 4.12 (s, 1H), 2.94 (s, 1H), 2.86 (s, 3H), 2.67–2.65 (d, *J* = 8.0 Hz, 1H), 2.57–2.49 (m, 2H), 2.41 (s, 3H), 2.31 (s, 3H), 2.14–2.11 (d, *J* = 12.0 Hz, 1H), 2.06–1.98 (m, 2H), 1.68–1.59 (m, 1H), 1.51–1.50 (d, *J* = 4.0 Hz, 1H), 1.44–1.40 (m, 1H), 1.21 (s, 3H), 0.82 (s, 9H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 143.4, 134.5, 129.6, 127.7, 84.3, 77.5, 66.2, 66.0, 54.5, 49.5, 49.5, 48.7, 45.7, 40.1, 36.8, 36.0, 34.3, 31.6, 28.2, 25.8, 22.6, 22.0, 21.5, 20.6; HRMS (ESI): *m*/*z* calcd for $C_{29}H_{45}N_3O_2S$: 499.3232[*M*+H$^+$]; found: 500.3302.

4.1.13. 4,*N*-Dimethyl-*N*-[4-phenyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-ynyl]-benzenesulfonamide 6ha

Yellow oil; R_f = 0.6 (silica gel, hexane/EtOAc 80:20); yield: 0.498 g, 96%, $[\alpha]_D^{25}$ = −54.2 (*c* 0.45, $CHCl_3$); IR(neat) 3057, 3030, 2958, 2871, 1665, 1600, 1446, 1446, 1336, 1167, 1084, 1024, 926, 816, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) ; 7.71–7.69 (d, *J* = 8.0 Hz, 2H), 7.36–7.34 (m, 2H), 7.33–7.21 (m, 3H), 7.19–7.17 (d, *J* = 8.0 Hz, 2H), 4.80 (s, 1H), 4.21 (s, 2H), 2.89 (s, 3H), 2.78–2.76 (d, *J* = 8.0 Hz, 1H), 2.71–2.66 (m, 1H), 2.41 (s, 1H), 2.28 (s, 5H), 2.18–2.16 (d, *J* = 8.0 Hz, 1H), 2.06–1.96 (m, 2H), 1.78 (s, 2H), 1.44–142 (m, 6H), 1.24–1.22 (m, 2H), 1.19–1.09 (m, 3H), 1.03 (s, 4H), 0.82 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 143.5, 138.2, 134.3, 129.5, 128.5, 128.0, 127.9, 127.8, 127.2, 126.9, 82.2, 79.8, 78.1, 65.4, 57.5, 54.2, 52.9, 50.3, 48.0, 47.3, 47.1, 46.6, 4.9, 44.8, 42.6, 40.2, 37.1, 34.4, 32.4, 26.2, 24.5, 22.1, 21.5, 21.1, 20.4, 17.5, 14.6; HRMS (ESI): *m*/*z* calcd for $C_{31}H_{41}N_3O_2S$: 519.2919 [*M*+H$^+$]; found: 550.2953.

4.1.14. *N*-Benzyl-4-methyl-*N*-[4-phenyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-ynyl]-benzenesulfonamide 6ia

Yellow oil; R_f = 0.6 (silica gel, hexane/EtOAc 80:20); yield: 0.549 g, 89%, $[\alpha]_D^{25}$ = −42.7 (*c* 0.80, $CHCl_3$); IR(neat) 3063, 3030, 2953, 2876, 1704, 1600, 1493, 1452, 1374, 1167, 1096, 926, 898, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.82–7.80 (d, *J* = 8.0 Hz, 2H), 7.42–7.32 (m, 6H), 7.28–7.26 (m, 3H) 7.18–7.16 (d, *J* = 8.0 Hz, 2H), 4.79 (s, 1H), 4.47–4.45 (d, *J* = 8.0 Hz, 2H), 4.19–4.17 (d, *J* = 8.0 Hz, 2H), 2.82–2.81 (d, *J* = 4.0 Hz, 1H), 2.65–2.58 (m, 1H), 2.36–2.31 (m, 1H), 2.27 (s, 3H), 2.26 (s, 3H), 2.15–2.13 (d, *J* = 8.0 Hz, 1H), 2.03–1.98 (m, 2H), 1.76 (s, 2H), 1.44 (s, 3H), 1.21–1.14 (m, 1H), 1.03 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)143.5, 138.2, 134.3, 129.5, 128.0, 127.9, 127.8, 127.2, 126.9, 82.2, 79.8, 78.1, 65.4, 57.5, 54.2, 52.8, 50.3, 48.0, 47.3, 47.1, 46.6, 44.9, 44.8, 42.6, 37.1, 34.4, 32.0, 26.2, 24.5, 22.1, 21.5, 21.1, 20.4, 14.6; HRMS (ESI): *m*/*z* calcd for $C_{37}H_{45}N_3O_2S$: 595.3232 [*M*+Na$^+$]; found: 618.3133.

4.1.15. 4-Chloro-*N*-[5,5-dimethyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-hex-2-ynyl]-*N*-methyl-benzenesulfonamide 6jd

Yellow oil; R_f = 0.6 (silica gel, hexane/EtOAc 75:25); yield: 0.472 g, 91%, $[\alpha]_D^{25}$ = −31.7 (*c* 0.40, $CHCl_3$); IR(neat) 2942, 2876, 2794, 1589, 1479, 1397, 1353, 1161, 1095, 1013, 980, 926, 767, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.79–7.78 (d, *J* = 4.0 Hz, 2H), 7.49–7.48 (d, *J* = 4.0 Hz, 2H), 4.61 (s, 1H), 4.15 (s, 2H), 2.93 (s, 1H), 2.88 (s, 3H), 2.84–2.79 (m, 1H), 2.66–2.61 (m, 4H), 2.53–2.48 (m, 2H), 2.24 (s, 3H), 2.17 (s, 3H), 2.04–1.98 (m, 2H), 1.72–1.63 (m, 1H), 1.52–1.51 (d, *J* = 4.0 Hz, 2H), 1.48–1.41 (m, 1H), 1.21(s, 3H), 0.97 (s, 4H), 0.82 (s, 9H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 139.2, 137.3, 136.1, 129.4, 129.3, 129.1, 128.7, 77.3, 66.4, 65.9, 54.4, 50.0, 49.4, 48.7, 47.0, 45.7, 40.1, 36.8, 36.0, 34.2, 29.3, 28.2, 25.9, 21.9, 20.6, 14.2; HRMS (ESI): *m*/*z* calcd for $C_{28}H_{42}ClN_3O_2S$: 519.2686 [*M*+H$^+$]; found: 520.2764.

4.1.16. 4-Phenyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-yn-1-ol 6ka

Yellow oil; R_f = 0.7 (silica gel, hexane/EtOAc 80:20); yield: 0.299 g, 82%, $[\alpha]_D^{25}$ = −49.3 (*c* 0.75, $CHCl_3$); IR (neat) 3300, 2953, 2878, 2795, 1893, 1743, 1655, 1604, 1506, 1451, 1368, 1365, 1332, 1222, 1155, 1128, 1095, 1041, 966, 923, 844 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.61–7.59 (d, *J* = 8.0 Hz, 2H), 7.32–7.26 (m, 3H), 5.03 (s, 1H), 3.82–3.79 (t, *J* = 12.0 Hz, 2H), 2.98–2.96 (d, *J* = 8.0 Hz, 1H), 2.73–2.69 (m, 3H), 2.52–2.45 (m, 1H), 2.35–2.30 (m, 1H), 2.27 (s, 3H), 2.22–2.19 (t, *J* = 12.0 Hz, 1H), 2.14–2.07 (m, 1H), 1.93–1.77 (m, 3H), 1.47 (m, 4H), 1.27–1.09 (m, 3H), 1.04(s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 139.1, 128.1, 128.0, 127.2, 84.1, 78.1, 65.6, 61.5, 57.6, 54.4, 50.3, 48.1, 47.4, 47.3, 42.7, 37.2, 26.3, 23.3, 22.2, 21.2, 14.7; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{34}N_2O$: 366.2671 [*M*+H$^+$]; found: 367.2749.

4.1.17. 4-(4-Fluoro-phenyl)-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-yn-1-ol 6kb

Yellow oil; R_f = 0.7 (silica gel, hexane/EtOAc 80:20); yield: 0.303 g, 79%, $[\alpha]_D^{25}$ = −29.9 (*c* 0.80, $CHCl_3$); IR(neat) 3300, 2953, 2878, 2795, 1893, 1743, 1655, 1604, 1506, 1451, 1368, 1365, 1332, 1222, 1155, 1128, 1095, 1041, 966, 923, 844 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.56–7.53 (t, *J* = 12.0 Hz, 2H), 7.02–6.96 (m, 2H), 4.97 (s, 1H), 4.65 (s, 1H), 3.81–3.77 (t, *J* = 16.0 Hz, 2H), 2.95–2.93 (d, *J* = 8.0 Hz, 1H), 2.73–2.61 (m, 3H), 2.31–2.26 (m, 4H), 2.20–2.18 (d, *J* = 8.0 Hz, 1H), 2.14–2.04 (m, 1H), 1.93–1.89 (m, 3H), 1.80–1.73 (m, 1H), 1.45 (s, 3H), 1.27–1.23 (m, 1H), 1.03 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 139.1, 128.1, 128.0, 127.2, 84.1, 78.1, 65.6, 61.5, 57.6, 54.4, 50.3, 48.1, 47.4, 47.3, 42.7, 37.2, 26.3, 23.3, 22.2, 21.2, 14.7; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{33}FN_2O$: 384.2577 [*M*+H$^+$]; found: 385.2654.

4.1.18. 1-[3-Cyclohexyl-3-(5,9,9-trimethyl-octahydro-5,8-methano-quinazolin-1-yl)-prop-1-ynyl]-cyclohexanol 6le

Yellow oil; R_f = 0.7 (silica gel, hexane/EtOAc 80:20); yield: 0.369 g, 87%, $[\alpha]_D^{25}$ = −49.3 (*c* 0.63, $CHCl_3$); IR(neat) 3300, 2953, 2878, 2795, 1893, 1743, 1655, 1604, 1506, 1451, 1368, 1365,

1332, 1222, 1155, 1128, 1095, 1041, 966, 923, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 3.21–3.19 (d, J = 8.0 Hz, 1H), 2.87–2.85 (d, J = 8.0 Hz, 2H), 2.77–2.66 (m, 1H), 2.66–2.55 (m, 1H), 2.25 (s, 3H), 2.14–2.09 (m, 2H), 2.04–1.96 (m, 3H), 1.93–1.80 (m, 2H), 1.74–1.64 (m, 7H), 1.59–1.51 (m, 5H), 1.47–1.37 (m, 3H), 1.24 (s, 6H), 1.17–1.08 (m, 3H), 0.97 (s, 4H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 139.1, 128.1, 128.0, 127.2, 84.1, 78.1, 65.6, 61.5, 57.6, 54.4, 50.3, 48.1, 47.4, 47.3, 42.7, 37.2, 26.3, 23.3, 22.2, 21.2, 14.7; HRMS (ESI): m/z calcd for $C_{27}H_{44}N_2O$: 426.3610 [M+H^+]; found: 427.3688.

4.1.19. 2-Methyl-2-[4-phenyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-ynyl]-malonic acid dimethyl ester 14ea

Yellow oil; R_f = 0.6 (silica gel, hexane/EtOAc 90:10); yield: 0.427 g, 89%, $[\alpha]_D^{25}$ = +43.6 (c 0.31, $CHCl_3$); IR(neat) 2953, 2878, 2798, 2798, 2766, 2704, 1738 1668, 1601, 1537, 1452, 1388, 1292, 1249,1203, 1109, 1028, 997, 856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.62–7.60 (d, J = 12.0 Hz, 2H), 7.33–7.29 (m, 3H), 4.78 (s, 1H), 3.71 (s, 6H), 3.05–3.03 (d, J = 16.0 Hz, 3H), 2.45–2.42 (m, 1H), 2.27–2.18 (m, 6H), 1.79 (m, 3H), 1.62–1.54 (m, 4H), 1.20–1.13 (m, 4H), 1.03 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 171.4, 139.6, 128.0, 127.8, 127.0, 80.1, 77.3, 73.3, 68.0, 61.2, 53.4, 53.0, 52.8, 50.4, 48.0, 46.8, 46.0, 45.2, 36.2, 26.6, 26.5, 22.0, 20.5, 20.2, 13.5; HRMS (ESI): m/z calcd for $C_{29}H_{40}N_2O_4$: 480.2988 [M+H^+]; found: 481.3144.

4.1.20. 2-Acetylamino-2-[4-phenyl-4-(4,5,9,9-tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-but-2-ynyl]-malonic acid dimethyl ester 14ga

Yellow oil; R_f = 0.7 (silica gel, hexane/EtOAc 70:30); yield: 0.429 g, 78%, $[\alpha]_D^{25}$ = +39.1 (c 0.23, $CHCl_3$); IR(neat) 3420, 3302, 3061, 2951, 2876, 2795, 2760, 1749, 1684, 1601, 1494, 1450, 1388, 1369, 1302, 1205, 1128, 1057, 854, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.33–7.31 (m, 2H), 7.09–6.90 (m, 3H), 6.78 (s, 1H), 4.71 (s, 1H), 4.09–4.04 (q, J = 20.0 Hz, 4H), 3.90 (s, 1H), 3.25 (s, 2H), 2.71–2.69 (d, J = 4.0 Hz, 1H), 2.26–2.19 (m, 3H), 2.18–2.16 (d, J = 8.0 Hz, 1H), 2.05 (s, 3H), 1.86–1.82 (m, 6H), 1.24 (s, 3H), 1.08–1.04 (m, 6H), 0.81 (s, 3H), 0.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 169.1, 166.8, 139.6, 129.7, 129.0, 128.0, 127.7, 127.1, 81.8, 79.1, 73.4, 67.9, 65.6, 62.6, 62.8, 61.2, 60.3, 53.1, 50.4, 48.0, 46.8, 46.0, 45.2, 36.1, 26.6, 24.2, 23.0, 22.0, 21.0, 20.4, 14.1, 14.0, 13.4; HRMS (ESI): m/z calcd for $C_{32}H_{45}N_3O_5$: 551.3359 [M+H^+]; found: 552.3437.

4.1.21. 8-(*tert*-Butyl-dimethyl-silanyloxy)-5-(4,5,9,9-etramethyl-octahydro-5,8-methano-quinazolin-1-yl)-oct-6-ynoic acid methyl ester 6mf

Colorless oil; R_f = 0.6 (silica gel, hexane/EtOAc 90:10); yield: 0.480 g, 98%, $[\alpha]_D^{25}$ = −37.4 (c 0.46, $CHCl_3$); IR(neat) 2947, 2931, 2854, 1473, 1391, 1358, 1249, 1090, 1002, 936, 843, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 4.33 (s, 2H), 3.66–3.65 (s, 3H), 2.88–2.83 (m, 2H), 2.78–2.66 (m, 1H), 2.57–2.52 (m, 1H), 2.34–2.57 (m, 5H), 2.18–2.11 (m, 2H), 1.75–1.55 (m, 6H), 1.42–1.41 (m, 1H), 1.23 (s, 2H), 1.06–1.03 (m, 3H), 0.99 (s, 3H), 0.91 (s, 9H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 173.9, 83.6, 83.1, 78.3, 64.7, 54.4, 53.3, 51.8, 51.4, 50.0, 48.2, 47.5, 47.1, 41.9, 37.1, 33.7, 32.7, 25.8, 22.1, 20.8, 18.3, 14.5; HRMS (ESI): m/z calcd for $C_{28}H_{50}N_2O_3Si$: 490.3591, [M+H^+]; found: 491.3669.

4.1.22. 4-(4,5,9,9-Tetramethyl-octahydro-5,8-methano-quinazolin-1-yl)-tetradec-5-ynoic acid methyl ester 6ng

Brown liquid; R_f = 0.6 (silica gel, hexane/EtOAc 90:10); yield: 0.412 g, 93%, $[\alpha]_D^{25}$ = −45.5(c 0.62, $CHCl_3$); IR(neat) 2947, 2931, 2854, 1655, 1473, 1391, 1358, 1249, 1090, 1002, 936, 843, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 3.64 (s, 3H), 3.59–3.57 (t, J = 8.0 Hz, 1H), 2.83–2.80 (m, 2H), 2.74–2.71 (m, 1H), 2.58–2.54 (m, 1H), 2.41–2.38 (t, J = 12.0 Hz, 2H), 2.26 (s, 3H), 1.86–1.81 (q, J = 20.0 Hz, 6H), 1.67–1.59 (m, 2H), 1.48–1.38 (m, 5H), 1.27 (s, 9H), 1.22 (s, 3H), 0.97 (s, 3H), 0.88–0.85 (t, J = 20.0 Hz, 4H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 174.0, 84.8, 78.1, 64.7, 54.4, 52.9, 51.4, 50.0, 48.3, 47.8, 47.0, 41.7, 37.1, 31.8, 30.7, 29.3, 29.0, 28.7, 25.9, 22.6, 22.0, 20.7, 18.5, 14.4, 14.1; HRMS (ESI): m/z calcd for $C_{28}H_{48}N_2O_2$: 444.3716, [M+H^+]; found: 445.3785.

4.2. General procedure for the preparation of chiral allenes from propargylamines

Chiral propargylamines 6 (1 mmol) were added to a stirred suspension of $ZnBr_2$ (0.113 g, 50 mol%) in dry toluene (3 mL) and the contents were refluxed for 1–2 h at 120 °C under a nitrogen atmosphere. Toluene was removed under reduced pressure and the crude product was purified by silica gel (100–200 mesh) column chromatography using hexane as the eluent to isolate the chiral allenes.

4.2.1. (*R*)-8-Phenyl-octa-6,7-dienoic acid ethyl ester 13ba

Colorless liquid, R_f = 0.8 (silica gel, hexane/EtOAc 98:2); yield: 0.262 g, 72%, 99% ee, $[\alpha]_D^{25}$ = −214.5 (c 0.57, $CHCl_3$); HPLC using chiral column, chiralcel OB-H, hexanes:*i*-PrOH/97:3; flow rate 0.5 mL/min, 254 nm, retention times: 28.3 min. (*R*) and 29.7 min. (*S*); IR (neat) 3030, 2951, 2854, 1948, 1738, 1597, 1494, 1437, 1363, 1315, 1242, 1155, 1072, 1026, 991, 912 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.22–7.20 (m, 4H), 7.21–7.17 (m, 1H), 6.18–6.15 (t, J = 12.0 Hz, 1H), 5.59–5.54 (q, J = 20.0 Hz, 1H), 3.67 (s, 3H), 2.42–2.38 (t, J = 16.0 Hz, 2H), 2.22–2.15 (m, 2H), 1.87–1.82 (q, J = 20.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 205.2, 173.9, 134.7, 128.8, 128.5, 126.7, 126.6, 126.2, 95.1, 94.1, 51.5, 33.4, 28.1, 24.2; HRMS (ESI): m/z calcd for $C_{14}H_{16}O_2$: 216.1150 [M+Na^+]; found: 239.0947.

4.2.2. (*R*)-2-(5,5-Dimethyl-hexa-2,3-dienyl)-2-methyl-malonic acid diethyl ester 13cd

Colorless liquid, R_f = 0.8 (silica gel, hexane/EtOAc 98:2); yield: 0.203 g, 72%, 99% ee, $[\alpha]_D^{25}$ = −56.8 (c 0.61, $CHCl_3$); HPLC using chiral column, chiralcel AD-H, heptane:*i*-PrOH/99.5:0.5; flow rate 1.0 mL/min ,210 nm, retention times: 6.7 min. (*R*) and 7.2 min. (*S*); IR (neat) 2962, 2906, 2868, 1961, 1734, 1462, 1377, 1365, 1298, 1242, 1190, 1107, 1026, 946, 862 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 5.20–5.14 (m, 2H), 3.74–3.73 (s, 6H), 3.51–3.47 (t, J = 16.0 Hz, 1H), 2.61–2.57 (m, 2H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 205.9, 171.9, 171.8, 90.7, 85.1, 61.1, 53.8, 35.9, 31.3, 28.4, 22.2, 19.6, 14.0, 13.8; the ^{13}C NMR data were in agreement with the reported data.[5g]

4.2.3. (*R*)-2-(5,5-Dimethyl-hexa-2,3-dienyl)-malonic acid dimethyl ester 13dd

Colorless liquid, R_f = 0.8 (silica gel, hexane/EtOAc 98:2); yield: 0.165 g, 69%, 96% ee, $[\alpha]_D^{25}$ = −80.8 (c 0.70, $CHCl_3$); HPLC using chiral column, chiralcel AS-H, hexanes:*i*-PrOH/99:1; flow rate 0.4 mL/min, 220 nm, retention times: 13.2 min. (*R*) and 14.7 min. (*S*); IR (neat) 2959, 2866, 1961, 1739, 1437, 1388, 1340, 1232, 1078, 1041, 881, 844, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 5.10–5.08 (m, 1H), 5.01–4.96 (q, J = 20.0 Hz, 1H), 3.72 (s, 6H), 2.64–2.53 (m, 2H), 1.64 (s, 1H), 1.44 (s, 3H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 201.1, 169.4, 169.3, 104.8, 89.2, 52.5, 52.5, 51.2, 31.7, 29.9, 28.2; the ^{13}C NMR data were in agreement with the reported data.[5g]

4.2.4. (*R*)-2-Methyl-2-(4-phenyl-buta-2,3-dienyl)-malonic acid dimethyl ester 13ea

Colorless liquid, R_f = 0.9 (silica gel, hexane/EtOAc 98:2); yield: 0.210 g, 77%, 96% ee, $[\alpha]_D^{25}$ = −205.9 (*c* 0.65, $CHCl_3$); HPLC using chiral column, chiralcel AD-H, hexanes:*i*-PrOH/99:1; flow rate 0.5 mL/min, 254 nm, retention times: 20.2 min. (*R*) and 21.5 min. (*S*); IR (neat) 3036, 2997, 2953, 2849, 1950, 1734, 1597, 1494, 1458, 1435, 1379, 1290, 1244, 1203, 1109, 985, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.33–7.25 (m, 4H), 7.21–7.17 (m, 1H), 6.16–6.13 (m, 1H), 5.49–5.43 (q, *J* = 24.0 Hz, 1H), 3.75–3.71 (d, *J* = 16.0 Hz, 6H), 2.73–2.70 (d, *J* = 12.0 Hz, 2H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 206.9, 172.1, 134.1, 128.5, 126.9, 126.8, 94.6, 89.3, 53.7, 52.6, 35.5, 19.9; the ^{13}C NMR data were in agreement with the reported data.[5g]

4.2.5. (*R*)-2-Methyl-2-(6-phenyl-hexa-2,3-dienyl)-malonic acid dimethyl ester 13ec

Colorless liquid, R_f = 0.9 (silica gel, hexane/EtOAc 95:5); yield: 0.196 g, 65%, 89% ee, $[\alpha]_D^{25}$ = −70.1 (*c* 0.45, $CHCl_3$); HPLC using chiral column, chiralcel AD-H, hexanes:*i*-PrOH/99:1; flow rate 0.5 mL/min, 210 nm, retention times: 17.5 min. (*R*) and 18.2 min. (*S*); IR (neat) 3086, 3063, 3026, 2999, 2951, 1963, 1736, 1604, 1531, 1496, 1454, 1435, 1246, 1203, 1156, 1111, 985 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.28–7.26 (m, 1H), 7.21–7.17 (m, 4H), 5.16–5.10 (m, 1H), 5.00–4.93 (m, 1H), 3.72 (s, 6H), 2.71–2.68 (t, *J* = 12.0 Hz, 2H), 2.54–2.52 (m, 2H), 2.32–2.25 (m, 2H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 206.0, 172.2, 141.6, 128.4, 128.3, 125.8, 90.2, 85.6, 53.8, 52.5, 35.8, 35.4, 30.5, 19.7, 14.1; the ^{13}C NMR data were in agreement with the reported data.[5g]

4.2.6. (*R*)-2-(5,5-Dimethyl-hexa-2,3-dienyl)-2-methyl-malonic acid dimethyl ester 13ed

Colorless liquid, R_f = 0.6 (silica gel, hexane/EtOAc 95:5); yield: 0.202 g, 77%, 99% ee, $[\alpha]_D^{25}$ = −61.9 (*c* 0.45, $CHCl_3$); HPLC using chiral column, chiralcel AS-H, heptane:*i*-PrOH/100:0; flow rate 0.25 mL/min, 230 nm, retention times: 37.2 min. (*R*) and 42.7 min. (*S*); IR (neat) 2959, 2868, 1961, 1738, 1458, 1435, 1377, 1363, 1296, 1246, 1201, 1109, 1020, 935, 877 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 5.09–5.08 (m, 1H), 5.01–4.98 (q, *J* = 12.0 Hz, 1H), 3.71 (s, 6H), 2.60–2.56 (m, 2H), 1.44 (s, 3H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 203.1, 172.4, 172.3, 102.9, 86.9, 53.8, 52.8, 52.5, 36.3, 31.7, 30.1, 19.8; the ^{13}C NMR data was in agreement with the reported data.[5g]

4.2.7. ^1H and ^{13}C NMR spectra of (*R*)-2-(4-cyclohexyl-buta-2,3-dienyl)-2-methyl-malonic acid dimethyl ester 13ee

Colorless liquid, R_f = 0.9 (silica gel, hexane/EtOAc 98:2); yield: 0.190 g, 68%, 99% ee, $[\alpha]_D^{25}$ = −57.2 (*c* 0.55, $CHCl_3$); HPLC using chiral column, chiralcel AD-H, hexanes:*i*-PrOH/99.5:0.5; flow rate 0.5 mL/min, 210 nm, retention times: 37.2 min. (*R*) and 42.7 min. (*S*); IR (neat) 2993, 2926, 2852, 1961, 1736, 1618, 1450, 1377, 1290, 1244, 1201, 1159, 1111, 985 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 5.08–5.06 (m, 1H), 4.98–4.96 (q, *J* = 8.0 Hz, 1H), 3.72 (s, 6H), 2.59–2.57 (m, 2H), 1.94–1.93 (m, 1H), 1.72–1.71 (m, 4H), 1.44 (s, 3H), 1.38–1.22 (m, 4H), 1.04–1.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 204.7, 172.3, 96.9, 85.9, 53.8, 52.5, 37.1, 36.2, 33.0, 26.1, 25.9, 22.6, 19.8; the ^{13}C NMR data were in agreement with the reported data.[5g]

4.2.8. (*R*)-2-Benzyl-2-(5,5-dimethyl-hexa-2,3-dienyl)-malonic acid dimethyl ester 13fd

Colorless liquid, R_f = 0.9 (silica gel, hexane/EtOAc 96:4); yield: 0.234 g, 71%, 99% ee, $[\alpha]_D^{25}$ = −64.1 (*c* 0.55, $CHCl_3$); HPLC using chiral column, chiralcel AS-H, hexanes:*i*-PrOH/99.8:0.2; flow rate 0.5 mL/min, 210 nm, retention times: 11.2 min. (*R*) and 12.0 min. (*S*); IR (neat) 3078, 2959, 2906, 2866, 1961, 1738, 1641, 1439, 1361, 1325, 1282, 1246, 1211, 1076, 922 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.28–7.24 (m, 1H), 7.18–7.14 (m, 2H), 5.71–5.61 (m, 1H), 5.13–5.09 (m, 3H), 4.99–4.93 (q, *J* = 24.0 Hz, 1H), 3.72 (s, 6H), 2.71–2.69 (d, *J* = 8.0 Hz, 2H), 2.63–2.60 (m, 2H), 2.36 (s, 2H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 203.1, 171.2, 132.3, 129.1, 128.2, 125.3, 119.2, 103.1, 86.4, 57.9, 52.4, 52.3, 36.7, 32.8, 31.6, 30.1; the ^{13}C NMR data were in agreement with the reported data.[5g]

4.2.9. (*R*)-2-Acetylamino-2-(4-phenyl-buta-2,3-dienyl)-malonic acid dimethyl ester 13ga

Yellow oil, R_f = 0.7 (silica gel, hexane/EtOAc 90:10); yield: 0.293 g, 85%, 98% ee, $[\alpha]_D^{25}$ = −192.3 (*c* 0.55, $CHCl_3$); HPLC using chiral column, chiralcel OD-H, hexanes:*i*-PrOH/100:0; flow rate 1.5 mL/min, 254 nm, retention times: 17.9 min. (*R*) and 28.1 min. (*S*); IR (neat) 3310, 2982, 1950, 1743, 1653, 1518, 1460, 1371, 1309, 1192, 1093, 1062, 1014, 887 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.32–7.28 (m, 2H), 7.25–7.18 (m, 3H), 6.83 (s, 1H), 6.13–6.11 (m, 1H), 5.38–5.32 (q, *J* = 12.0 Hz, 1H), 4.28–4.11 (m, 4H), 3.18–3.15 (dd, *J* = 12.0 Hz, 2H), 1.91 (s, 3H), 1.28–1.25 (t, *J* = 12.0 Hz, 4H), 1.21–1.17 (t, *J* = 16.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 207.1, 169.1, 167.5, 134.0, 128.6, 127.1, 126.7, 94.8, 88.1, 66.3, 62.7, 32.1, 22.9, 14.0, 13.9; the ^{13}C NMR data were in agreement with the reported data.[8c]

4.2.10. 2-Acetylamino-2-(5,5-dimethyl-hexa-2,3-dienyl)-malonic acid dimethyl ester 13gd

Colorless liquid, R_f = 0.6 (silica gel, hexane/EtOAc 90:10); yield: 0.237 g, 73%, 99% ee, $[\alpha]_D^{25}$ = −66.3 (*c* 0.46, $CHCl_3$); HPLC using chiral column, chiralcel AD-H, hexanes:*i*-PrOH/95:5; flow rate 0.5 mL/min, 210 nm, retention times: 22.8 min. (*R*) and 26.2 min. (*S*); IR (neat) 3382, 3312, 2962, 2905, 2868, 1961, 1743, 1682, 1502, 1440, 1367, 1304, 1278, 1201, 1093, 1060, 1018, 946 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 6.79 (s, 1H), 5.06–5.03 (q, *J* = 12.0 Hz, 1H), 4.92–4.85 (q, *J* = 28.0 Hz, 4H), 4.28–4.21 (m, 4H), 3.04–3.01 (d, *J* = 12.0 Hz, 2H), 2.02 (s, 3H), 1.27–1.23 (m, 6H), 0.99 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 203.1, 168.9, 167.7, 167.6, 103.1, 85.6, 66.3, 62.6, 62.5, 33.1, 31.5, 30.1, 23.1, 13.9; the ^{13}C NMR data were in agreement with the reported data.[8c]

4.2.11. (*R*)-*N*-(5,5-Dimethyl-hexa-2,3-dienyl)-4,*N*-dimethyl-benzenesulfonamide 13hd

Colorless liquid, R_f = 0.9 (silica gel, hexane/EtOAc 98:2); yield: 0.202 g, 69%, 98% ee, $[\alpha]_D^{25}$ = −92.8 (*c* 0.46, $CHCl_3$); HPLC using chiral column, chiralcel OJ-H, hexanes:*i*-PrOH/ 90:10; flow rate 0.5 mL/min, 210 nm, retention times: 15.8 min. (*R*) and 16.2 min. (*S*); IR (neat) 2959, 2923, 2897, 2861, 1955, 1593, 1464, 1345, 1303, 1164, 1089, 1086, 977 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.69–7.67 (d, *J* = 12.0 Hz, 2H), 7.33–7.31 (d, *J* = 12.0 Hz, 2H), 5.18–5.16 (m, 1H), 5.05–5.00 (q, *J* = 20.0 Hz, 1H), 3.72–3.56 (m, 2H), 2.73 (s, 3H), 2.43 (s, 3H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 202.7, 143.3, 134.6, 129.7, 127.4, 104.6, 88.3, 50.4, 34.2, 31.9, 30.1, 21.5; the ^{13}C NMR data were in agreement with the reported data.[8d]

4.2.12. (*R*)-*N*-Benzyl-4-methyl-*N*-(4-phenyl-buta-2,3-dienyl)-benzenesulfonamide 13ia

Colorless liquid, R_f = 0.9 (silica gel, hexane/EtOAc 90:10); yield: 0.283 g, 73%, 96% ee, $[\alpha]_D^{25}$ = −220.3 (*c* 0.45, $CHCl_3$); HPLC using chiral column, chiralcel AS-H, hexanes:*i*-PrOH/85:15; flow rate 0.5 mL/min, 254 nm, retention times: 27.8 min. (*R*) and 29.8 min. (*S*); IR (neat) 3058, 3021, 2923, 1955, 1650, 1598, 1490, 1459,

1340, 1091, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.78–7.76 (d, J = 8.0 Hz, 2H), 7.33–7.13 (m, 13H), 6.04–6.02 (m, 1H), 5.28–5.23 (q, J = 20.0 Hz, 1H), 4.41 (s, 2H), 3.90–3.88 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 206.2, 143.4, 137.5, 135.8, 133.4, 129.8, 129.8, 128.7, 128.5, 128.1, 127.9, 127.8, 127.3, 126.9, 95.9, 90.0, 50.3, 45.7, 21.5; HRMS (ESI): m/z calcd for $C_{24}H_{23}NO_2S$: 389.1449 [M+H]; found: 390.1526.

4.2.13. (*R*)-4,*N*-Dimethyl-*N*-(4-phenyl-buta-2,3-dienyl)-benzenesulfonamide 13ha

Colorless liquid, R_f = 0.9 (silica gel, hexane/EtOAc 95:5); yield: 0.244 g, 78%, 99% ee, $[\alpha]_D^{25}$ = −232.2 (c 0.50, $CHCl_3$); HPLC using chiral column, chiralcel AS-H, hexanes:*i*-PrOH/85:15; flow rate 0.5 mL/min, 254 nm, retention times: 30.4 min. (*R*) and 33.6 min. (*S*); IR (neat) 3058, 3021, 2923, 1955, 1650, 1598, 1490, 1459, 1340, 1091, 967, 910, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm); 7.70–7.68 (d, J = 8.0 Hz, 2H), 7.32–7.28 (m, 5H), 7.23–7.21 (m, 2H), 6.19–6.17 (m, 1H), 5.48–5.43 (q, J = 20.0 Hz, 1H), 3.81–3.77 (m, 2H), 2.78 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 206.4, 143.5, 134.6, 133.4, 129.7, 129.1, 128.7, 128.2, 127.3, 127.3, 126.8, 96.1, 90.6, 49.6, 34.4, 21.5; HRMS (ESI): m/z calcd for $C_{24}H_{34}N_2O$: 313.1136 [M+Na^+]; found: 336.1042.

4.2.14. (*R*)-4-Chloro-*N*-(5,5-dimethyl-hexa-2,3-dienyl)-*N*-methyl-benzenesulfonamide 13jd

Colorless liquid, R_f = 0.9 (silica gel, hexane/EtOAc 95:5); yield: 0.225 g, 72%, 99% ee, $[\alpha]_D^{25}$ = −83.2 (c 0.62, $CHCl_3$); HPLC using chiral column, chiralcel OD-H, hexanes:*i*-PrOH/98:2; flow rate 0.5 mL/min, 250 nm, retention times: 16.7 min. (*R*) and 17.3 min. (*S*); IR (neat) 3095, 2958, 2898, 2860, 1961, 1589, 1479, 1402, 1347, 1161, 1013, 987, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.33–7.32 (d, J = 8.0 Hz, 4H), 5.27–5.22 (q, J = 20.0 Hz, 1H), 5.16–5.13 (m, 1H), 3.59–3.50 (q, J = 36.0 Hz, 2H), 3.14–3.01 (m, 2H), 2.24 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 202.8, 139.1, 136.3, 129.4, 128.8, 104.8, 88.1, 50.3, 34.2, 31.9, 30.1; the ^{13}C NMR data was in agreement with the reported data.[8d]

4.2.15. (*R*)-5-Phenyl-penta-3,4-dien-1-ol 13ka

Colorless liquid, R_f = 0.5 (silica gel, hexane/EtOAc 95:5); yield: 0.104 g, 65%, 94% ee, $[\alpha]_D^{25}$ = −219.7 (c 0.59, $CHCl_3$); HPLC using chiral column, chiralcel OD-H, hexanes:*i*-PrOH/97:3; flow rate 0.5 mL/min, 254 nm, retention times: 34.1 min. (*R*) and 38.0 min. (*S*); IR (neat) 3350, 3063, 3030, 2928, 2879, 1950, 1753, 1701, 1597, 1494, 1458, 1311, 1299, 1203, 1049, 912, 877, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.32–7.30 (m, 4H), 7.23–7.18 (m, 1H), 6.22–6.18 (q, J = 16.0 Hz, 1H), 5.63–5.58 (q, J = 20.0 Hz, 2H), 3.80–3.78 (t, J = 8.0 Hz, 2H), 2.44–2.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 205.7, 134.4, 128.6, 126.9, 126.6, 95.1, 91.5, 61.9, 32.1; the ^{13}C NMR data were in agreement with the reported data.[5h]

4.2.16. (*R*)-5-(4-Fluoro-phenyl)-penta-3,4-dien-1-ol 13kb

Colorless liquid, R_f = 0.6 (silica gel, hexane/EtOAc 95:5); yield: 0.105 g, 59%, 82% ee, $[\alpha]_D^{25}$ = −184.6 (c 0.55, $CHCl_3$); HPLC using chiral column, chiralcel OD-H, hexanes:*i*-PrOH/98:2; flow rate 0.6 mL/min, 254 nm, retention times: 24.1 min. (*R*) and 29.0 min. (*S*); IR (neat) 3351, 3043, 2928, 2958, 1951, 1738, 1232, 1203, 1153, 912, 750, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.27–7.24 (m, 2H), 7.01–6.99 (t, J = 8.0 Hz, 2H), 6.18–6.16 (m, 1H), 5.63–5.58 (m, 1H), 3.80–3.76 (t, J = 16.0 Hz, 2H), 2.43–2.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 205.5,160.6, 130.3, 128.1, 128.0, 115.7, 115.9, 94.1, 91.7, 61.9, 32.0; the ^{13}C NMR data were in agreement with the reported data.[5h]

4.2.17. (*R*)-1-(3-Cyclohexyl-propa-1,2-dienyl)-cyclohexanol 13le

Colorless liquid, R_f = 0.4 (silica gel, hexane/EtOAc 95:5); yield: 0.158 g, 72%, 98% ee, $[\alpha]_D^{25}$ = −121.7 (c 0.55, $CHCl_3$); HPLC using chiral column, chiralcel AD-H, hexanes:*i*-PrOH/95:5; flow rate 0.5 mL/min 214 nm, retention times: 10.6 min. (*R*) and 11.2 min. (*S*); IR (neat) 3313, 2923, 2849, 1962, 1446, 1399, 1355, 1320, 1264, 1247, 1144, 1100, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 5.32–5.31 (d, J = 4.0 Hz, 2H), 2.02–1.97 (m, 1H), 1.78–1.71 (m, 2H), 1.65–1.59 (m, 7H), 1.52–1.47 (m, 4H), 1.36–1.26 (m, 4H), 1.10–1.04 (m, 3H), 0.90–0.85 (m, 1H),; ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 199.9, 101.3, 101.0, 70.5, 38.5, 38.3, 37.2, 33.2, 33.1, 25.5, 22.5; the ^{13}C NMR data were in agreement with the reported data.[7c]

4.2.18. (*R*)-8-Hydroxy-octa-5,6-dienoic acid methyl ester 13mf

Colorless liquid, R_f = 0.4 (silica gel, hexane/EtOAc 98:2); yield: 0.132 g, 78%, 98% ee, $[\alpha]_D^{25}$ = −67.7 (c 0.45, $CHCl_3$); HPLC using chiral column, chiralcel AS-H, hexanes:*i*-PrOH/95:5; flow rate 0.8 mL/min 214 nm, retention times: 20.3 min. (*R*) and 23.8 min. (*S*). IR (neat) 3448, 2951, 2869, 1963, 1736, 1439, 1201, 1154, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 5.34–5.32 (m, 1H), 5.25–5.22 (m, 1H), 4.11–4.09 (d, J = 8.0 Hz, 2H), 3.66 (s, 3H), 2.38–2.34 (t, J = 16.0 Hz, 2H), 2.06–2.03 (m, 3H), 1.78–1.73 (m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 203.3, 174.1, 92.5, 92.4, 60.6, 60.4, 51.6, 33.2, 27.8, 24.0. HRMS (ESI): calcd for $C_9H_{14}O_3$: 170.0943 [M+H^+]; found: 171.1022.

4.2.19. (*R*)-Pentadeca-4,5-dienoic acid methyl ester 13ng

Colorless liquid, R_f = 0.4 (silica gel, hexane/EtOAc 98:2); yield: 0.188 g, 72%, $[\alpha]_D^{25}$ = −61.5 (c 0.73, $CHCl_3$); IR (neat) 3008, 2900, 2840, 2644, 1960, 1710, 1430, 1280, 1250, 1210, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 5.25–5.11 (m, 2H), 3.70–3.67 (s, 3H), 2.45–2.41 (t, J = 16.0 Hz, 2H), 2.32–2.28 (m, 2H), 1.97–1.93 (m, 2H), 1.59 (s, 2H), 1.27 (s, 11H), 0.94–0.86 (t, J = 16.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 203.6, 173.6, 92.6, 89.4, 51.5, 33.2, 31.8, 29.6, 29.4, 29.2, 29.1, 28.8, 23.8, 22.6, 14.0; HRMS (ESI): calcd for $C_{15}H_{26}O_2$: 238.1933 [M+H^+]; found: 239.2012. the ^{13}C NMR data were in agreement with the reported data.[6f]

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