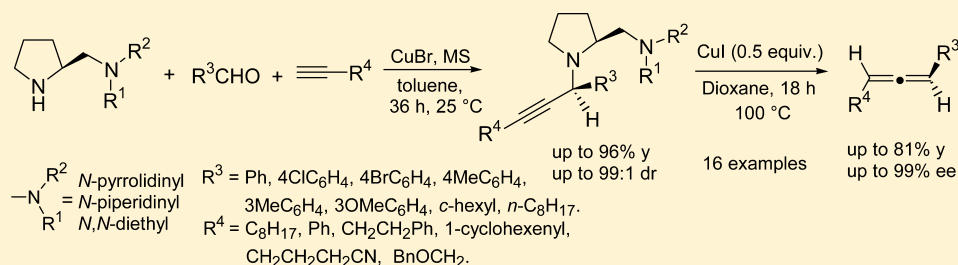


# Copper(I) Halide Promoted Diastereoselective Synthesis of Chiral Propargylamines and Chiral Allenes using 2-Dialkylaminomethylpyrrolidine, Aldehydes, and 1-Alkynes

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**S** Supporting Information

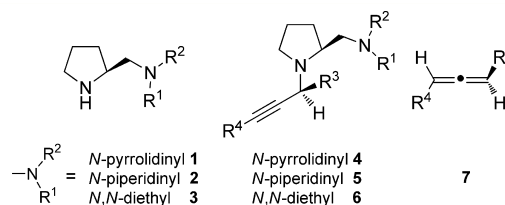


**ABSTRACT:** Copper bromide promoted reactions of aldehydes, 1-alkynes, and chiral 2-dialkylaminomethylpyrrolidine at 25 °C give the corresponding chiral propargylamine derivatives in up to 96% yield and 99:1 dr that are readily converted to the corresponding disubstituted chiral allenenes in up to 81% yield and 99% ee upon reaction with CuI in dioxane at 100 °C.

## INTRODUCTION

Chiral propargylamines are useful synthons for synthesis of biological active skeletons, natural products, and polyfunctional amino derivatives.<sup>1–4</sup> Copper–chiral ligand catalyzed enantioselective propargylamines have been accessed using the chiral auxiliaries quinap,<sup>5–8</sup> pinap,<sup>9–11</sup> pybox,<sup>12–15</sup> and binam diimine.<sup>16,17</sup> Also, chiral amino acid promoted enantioselective synthesis of propargylamines has been reported.<sup>18–20</sup> Recently, Che et al. reported the chiral prolinol derived propargylamines using gold(III) salen complexes.<sup>21,22</sup> The chiral allene structural motifs are also present in several biologically active natural products and pharmaceuticals.<sup>23–25</sup> Also, chiral allenenes are versatile synthons with the potential to provide excellent axis-to-center chirality transfer in organic synthesis.<sup>23,26,27</sup>

Over the years, several synthetic methods were developed to access allenenes.<sup>28–35</sup> Recently, zinc halide promoted conversion of 1-alkynes, aldehydes, and morpholine to racemic 1,3-disubstituted allenenes<sup>36</sup> and to enantiopure allenenes using certain chiral cyclic secondary amines were reported.<sup>37</sup> Also, a two-step synthesis involving preparation of chiral propargylamines and conversion to chiral allenenes in a ZnI<sub>2</sub>-promoted reaction was reported.<sup>38</sup> Copper(I) bromide promoted reactions of 1-alkynes, paraformaldehyde, or substituted aldehydes and diisopropylamine or *N,N*-dicyclohexylamine were reported to give 1-substituted allenenes<sup>39–41</sup> or racemic 1,3-disubstituted allenenes.<sup>42,43</sup> Herein, we report the results of detailed studies on the CuBr-promoted diastereoselective synthesis of chiral propargylamines (4–6) using 1-alkynes, aldehydes, and 2-dialkylaminomethylpyrrolidines (1–3) and their conversion to chiral allenenes 7 in a CuI-promoted reaction (Figure 1).



**Figure 1.** Chiral 2-dialkylaminomethylpyrrolidine derivatives, propargylamines, and allenenes.

## RESULTS AND DISCUSSION

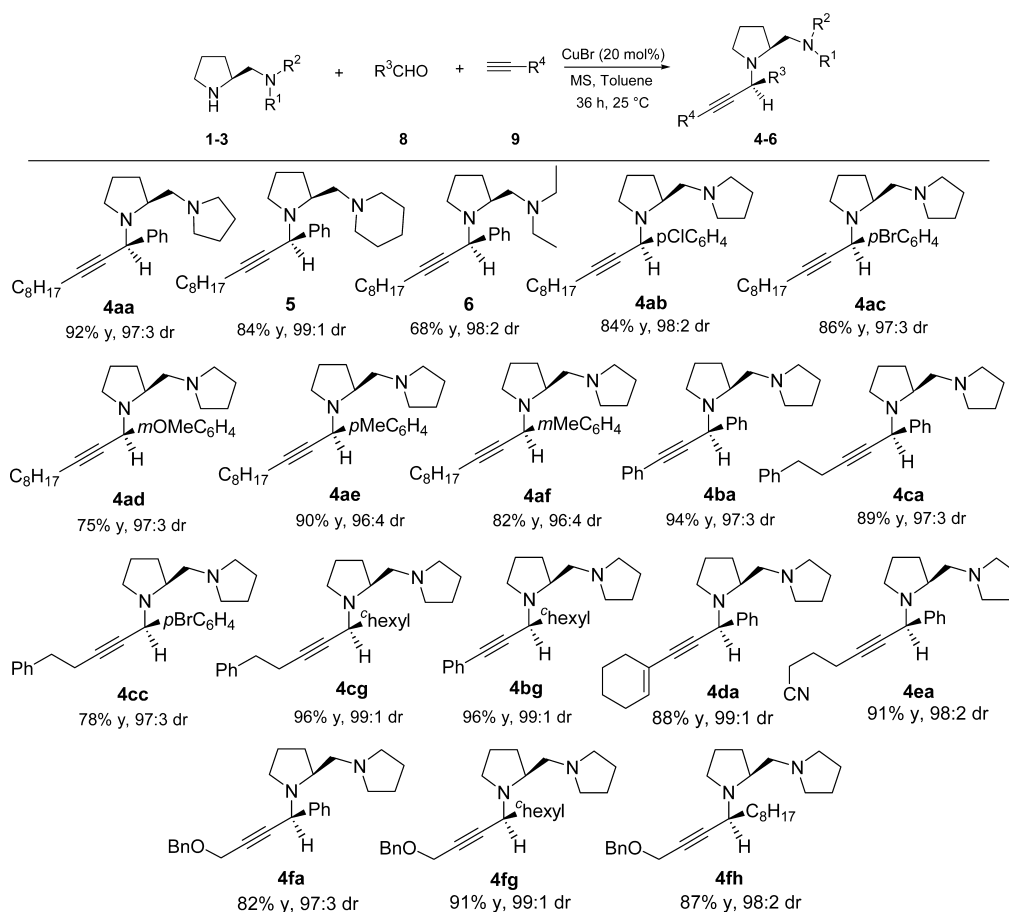
Recently, we have reported that the chiral (2*S*)-phenylpyrrolidine (10) and (S)-diphenylpyrrolidinemethanol (11; (S)-DPP) gave the chiral (R)-allene 7 in 66% and 98% ee, respectively, in a ZnX<sub>2</sub>-promoted one-pot, three-component allene transformation (Scheme 1).<sup>37</sup>

Presumably, better selectivity is observed in the case of (S)-DPP (11) due to coordination of the hydroxyl group with the ZnBr<sub>2</sub> during the formation of the chiral propargylamine intermediate and also during the conversion of the propargylamine into the chiral allene.<sup>37</sup> It was of interest to us to examine the use of the readily accessible and commercially available (S)-2-(1-pyrrolidinylmethyl)pyrrolidine (1) in this one-pot, three-component chiral allene transformation using ZnI<sub>2</sub>. We have observed that in this reaction the (R)-allene 7aa was obtained with 94% ee but only in 4% yield in addition to the corresponding propargylamine intermediate 4aa (88% yield, 96:4 dr).

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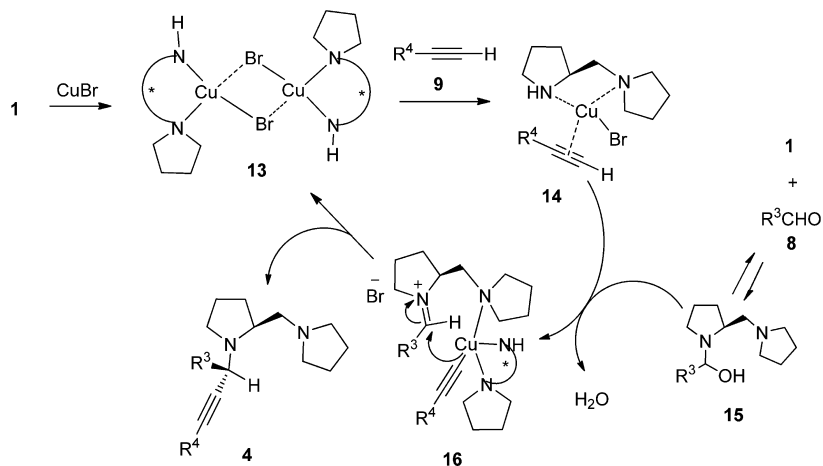
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Table 1. Diastereoselective Synthesis of Propargylamines Using Chiral Amine, Aldehyde, and 1-Alkyne and Copper Bromide<sup>a-c</sup>

<sup>a</sup>The reactions were carried out by taking amine **1-3** (2.0 mmol), 1-alkyne (2.2 mmol), and aldehyde (2.0 mmol) in toluene (3 mL) with CuBr (0.4 mmol) and MS (1.0 g, 4 Å) at 25 °C for 36 h. <sup>b</sup>dr ratio based on crude <sup>1</sup>H NMR. <sup>c</sup>Isolated yield.

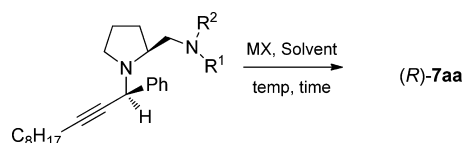
## Scheme 3. Tentative Mechanism for Copper-Catalyzed Propargylamine Formation



from phenylacetylene (**9b**) and benzaldehyde (**8a**) gave the chiral allene **7ba** in 56% yield and 85% ee. The other propargylamines **4ca-fh** prepared from different alkynes and aldehydes afforded the corresponding chiral allenes **7ca-fh** in 58–81% yields with good enantioselectivities (94–99%, Table 3).

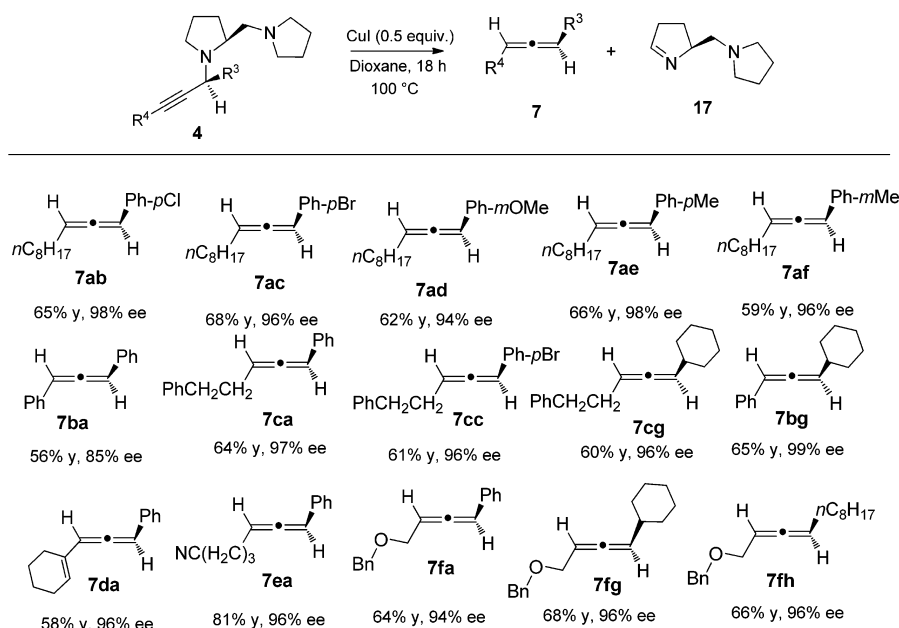
The mechanism outlined in Scheme 4 may be considered for this transformation.<sup>43,48</sup> The triple bond of propargylamine **4** would complex with CuI to give the intermediate **18**, which could

undergo a 1,5-hydride shift to give the alkenyl copper species **19**. Antiperiplanar elimination of the CuI and the imine would then give the chiral allene (*R*)-**7**. A similar mechanism was previously proposed for the Ag(I)-catalyzed conversion of a chiral propargyl-amino alcohol to chiral allenes (Scheme 4). The optimum results obtained using dioxane may be due to its interaction with CuI in the transition states for the formation of the intermediate **18**, **19**, and allene (*R*)-**7**.

Table 2. Reaction of Propargylamines 4aa, 5, and 6 with ZnI<sub>2</sub>, AgNO<sub>3</sub>, and CuX<sup>a</sup>

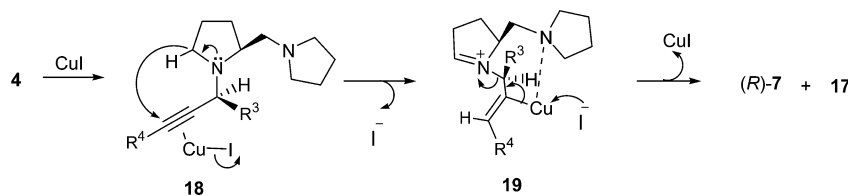
entry	diamine	solvent	temp (°C)	MX	amt of MX (equiv)	time (h)	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	4aa	toluene	120	ZnI <sub>2</sub>	0.5	24	8	98
2	4aa	dioxane	100	ZnI <sub>2</sub>	0.5	18	10	86
3	4aa	CH <sub>3</sub> CN	50	AgNO <sub>3</sub>	0.5	24	14	99
4	4aa	toluene	120	CuI	0.5	2	18	92
5	4aa	toluene	120	CuI	0.5	5	35	76
6	4aa	dioxane	100	CuI	0.25	18	33	99
7	4aa	dioxane	100	CuI	0.5	18	62	99
8	4aa	dioxane	100	CuI	0.5	24	68	98
9	4aa	dioxane	100	CuI	0.75	18	65	99
10	4aa	dioxane	100	CuI	1.0	18	70	98
11	4aa	dioxane	100	CuCl	0.5	18	22	92
12	4aa	dioxane	100	CuBr	0.5	18	30	90
13	5	dioxane	100	CuI	0.5	18	54	99
14	6	dioxane	100	CuI	0.5	18	42	96

<sup>a</sup>The reactions were carried out by taking up amines 4aa, 5, and 6 (0.5 mmol) in solvent (2 mL). <sup>b</sup>Isolated yields. <sup>c</sup>The % ee was confirmed by HPLC analysis on Chiralcel OD-H.

Table 3. Copper Iodide Promoted Chiral Allene Transformation Using Corresponding Propargylamines<sup>a-c</sup>

<sup>a</sup>The reactions were carried out by taking up amines 4 (0.5 mmol) and CuI (0.25 mmol) in dioxane (2 mL). <sup>b</sup>Isolated yield. <sup>c</sup>The % ee was confirmed by HPLC analysis on Chiralcel OD-H, OB-H and OJ-H columns.

Scheme 4. Tentative Mechanism for Copper(I)-Catalyzed Allene Formation

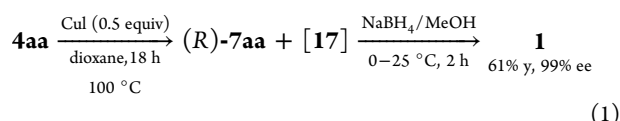


We have made efforts to isolate the imine byproduct 17 but were not successful. However, we have observed that the imine

intermediate 17 formed during the reaction could be readily converted back to the starting (S)-2-(1-pyrrolidinylmethyl)pyrrolidine



**1** by reduction in situ using NaBH<sub>4</sub>/MeOH in 61% yield without loss of its optical purity (eq 1).



We have also examined the utility of chiral diamine **1** in a one-pot chiral allene transformation using CuBr for the preparation of a propargylamine derivative followed by addition of CuI (in dioxane) for chiral (*R*)-allene formation. In this case, we have obtained the chiral (*R*)-allene **7aa** with 48% yield and 90% ee.

## CONCLUSION

We have developed a CuBr-promoted method for diastereoselective synthesis of chiral propargylamine derivatives using (2*S*)-dialkylaminomethylpyrrolidine and transformed them into chiral (*R*)-allenes using copper iodide. Since the chiral propargylamines were obtained in good yields and excellent diastereoselectivities and the chiral allenes synthesized were in high enantiomeric purities, the methods described here have considerable potential for further exploitations in synthesis.

## EXPERIMENTAL SECTION

**General Information.** Chiral proline diamine derivatives **1–3** were synthesized by following the literature reports.<sup>49</sup> CuBr and CuI were purchased from Sigma Aldrich and used without any further purification. Toluene and dioxane were dried on sodium benzophenone ketyl and stored on sodium wire.

**General Procedure for Synthesis of (2*S*)-Dialkylaminomethylpyrrolidine-Derived Chiral Propargylamines.** In an oven-dried 10 mL flask, copper(I) bromide (57 mg, 20 mol %) and chiral diamine **1–3** (2 mmol) in dry toluene (3 mL) were added. Freshly distilled aldehyde **8** (2 mmol), 4 Å MS (1.0 g), and 1-alkyne **9** (2.2 mmol) were added, and the mixture was stirred at 25 °C for 36 h. The 4 Å MS was removed by filtration and washed with Et<sub>2</sub>O. The crude product was concentrated in vacuo and purified by chromatography on basic alumina. The product was eluted in a 98/2 mixture of hexane and ethyl acetate.

**(*S*)-1-((*S*)-1-Phenylundec-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**4aa**).** Light yellow oil. Yield: 0.70 g (92%). IR (neat): 3061, 3028, 2928, 1601, 1493, 1450, 700 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.58 (d, *J* = 7.6 Hz, 2H), 7.31–7.23 (m, 3H), 5.20 (s, 1H), 3.10–3.03 (m, 1H), 2.69 (dd, *J* = 11.9, 5.0 Hz, 1H), 2.62–2.44 (m, 6H), 2.34–2.30 (m, 2H), 2.01–1.94 (m, 1H), 1.81–1.77 (m, 5H), 1.69–1.54 (m, 5H), 1.48–1.44 (m, 2H), 1.31–1.29 (m, 8H), 0.89 (t, *J* = 6.9 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 140.6, 128.2, 127.9, 126.9, 87.6, 76.1, 62.3, 59.5, 56.5, 54.9, 47.5, 31.8, 30.6, 29.3, 29.1, 28.9, 23.5, 22.7, 22.7, 18.8, 14.1. [α]<sub>D</sub><sup>25</sup> = –89.3° (*c* = 0.68, CHCl<sub>3</sub>). LCMS (*m/z*): 381 (M + 1). Anal. Calcd for C<sub>26</sub>H<sub>40</sub>N<sub>2</sub>: C, 82.05; H, 10.59; N, 7.36. Found: C, 82.15; H, 10.59; N, 7.31.

**(*S*)-1-((*S*)-1-(4-Chlorophenyl)undec-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**4ab**).** Light yellow oil. Yield: 0.70 g (84%). IR (neat): 2928, 2785, 1487, 1460, 1089, 1016 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.52 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 5.21 (s, 1H), 3.10–3.05 (m, 1H), 2.70 (dd, *J* = 11.9, 5.4 Hz, 1H), 2.60–2.47 (m, 7H), 2.32 (t, *J* = 6.8 Hz, 2H), 1.99–1.94 (m, 1H), 1.77 (bs, 4H), 1.68–1.53 (m, 5H), 1.47–1.45 (m, 2H), 1.29 (s, 8H), 0.89 (t, *J* = 6.8 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 139.3, 132.6, 129.5, 128.0, 88.0, 75.8, 62.4, 59.4, 55.9, 54.9, 47.5, 31.9, 30.6, 29.3, 29.1, 28.9, 23.5, 22.7, 22.6, 18.8, 14.1. [α]<sub>D</sub><sup>25</sup> = –79.5° (*c* = 0.75, CHCl<sub>3</sub>). LCMS (*m/z*): 415 (M + 1). Anal. Calcd for C<sub>26</sub>H<sub>39</sub>ClN<sub>2</sub>: C, 75.24; H, 9.47; N, 6.75. Found: C, 75.11; H, 9.56; N, 6.68.

**(*S*)-1-((*S*)-1-(4-Bromophenyl)undec-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**4ac**).** Yellow oil. Yield: 0.79 g (86%). IR (neat): 3435, 2926, 2858, 1658, 1587, 1483, 1012, 856, 723 cm<sup>-1</sup>. <sup>1</sup>H NMR

(400 MHz, CDCl<sub>3</sub>): δ 7.47–7.41 (m, 4H), 5.18 (s, 1H), 3.07–3.03 (m, 1H), 2.68 (dd, *J* = 11.9, 5.2 Hz, 1H), 2.58–2.46 (m, 6H), 2.31 (t, *J* = 6.7 Hz, 2H), 1.99–1.93 (m, 2H), 1.77 (s, 4H), 1.68–1.53 (m, 5H), 1.46–1.44 (m, 2H), 1.29 (s, 8H), 0.88 (t, *J* = 6.6 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 139.8, 130.9, 129.9, 120.7, 88.1, 75.6, 62.3, 59.4, 55.9, 54.9, 47.4, 31.8, 30.6, 29.3, 29.1, 28.9, 23.5, 22.7, 22.6, 18.7, 14.1. [α]<sub>D</sub><sup>25</sup> = –64.6° (*c* = 0.85, CHCl<sub>3</sub>). LCMS (*m/z*): 461 (M + 2). Anal. Calcd for C<sub>26</sub>H<sub>39</sub>BrN<sub>2</sub>: C, 67.96; H, 8.55; N, 6.10. Found: C, 67.85; H, 8.51; N, 6.15.

**(*S*)-1-((*S*)-1-(3-Methoxyphenyl)-3-phenylprop-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**4ad**).** Yellow oil. Yield: 0.62 g (75%). IR (neat): 2925, 2448, 2777, 1599, 1484, 1314, 1424, 1045, 755, 689 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.23 (d, *J* = 8.0 Hz, 1H), 7.18–7.17 (m, 2H), 6.78 (d, *J* = 8.1 Hz, 1H), 5.18 (s, 1H), 3.82 (s, 3H), 3.08–3.04 (m, 1H), 2.68 (dd, *J* = 12.0, 5.3 Hz, 1H), 2.62–2.47 (m, 6H), 2.31 (t, *J* = 6.8 Hz, 2H), 1.99–1.97 (m, 1H), 1.77 (s, 4H), 1.68–1.53 (m, 6H), 1.45–1.44 (m, 2H), 1.29 (bs, 8H), 0.89 (t, *J* = 7.1 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 159.4, 142.4, 128.9, 120.7, 114.0, 112.1, 87.5, 76.2, 62.4, 59.5, 56.4, 55.1, 55.0, 47.6, 31.9, 30.6, 29.3, 29.2, 28.9, 23.5, 22.8, 22.7, 18.8, 14.1. [α]<sub>D</sub><sup>25</sup> = –82.1° (*c* = 1.03, CHCl<sub>3</sub>). LCMS (*m/z*): 409 (M – 1). Anal. Calcd for C<sub>25</sub>H<sub>42</sub>N<sub>2</sub>O: C, 78.97; H, 10.31; N, 6.82. Found: C, 78.85; H, 10.38; N, 6.73.

**(*S*)-2-(Pyrrolidin-1-ylmethyl)-1-((*S*)-1-(*p*-tolyl)undec-2-yn-1-yl)pyrrolidine (**4ae**).** Light yellow oil. Yield: 0.71 g (90%). IR (neat): 2928, 2858, 2791, 1510, 1460, 1350, 1141, 831, 765 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 5.17 (s, 1H), 3.09–3.06 (m, 1H), 2.70 (dd, *J* = 11.9, 5.0 Hz, 1H), 2.62–2.46 (m, 7H), 2.34–2.30 (m, 5H), 2.02–1.96 (m, 1H), 1.78 (s, 4H), 1.69–1.55 (m, 5H), 1.49–1.48 (m, 2H), 1.31 (s, 8H), 0.91 (t, *J* = 6.8 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 137.7, 136.5, 128.6, 128.1, 87.4, 76.4, 62.3, 59.5, 56.2, 54.9, 47.6, 31.9, 30.7, 29.3, 29.2, 29.1, 28.9, 23.5, 22.8, 22.7, 21.1, 18.8, 14.1. [α]<sub>D</sub><sup>25</sup> = –81.9° (*c* = 1.19, CHCl<sub>3</sub>). LCMS (*m/z*): 395 (M + 1). Anal. Calcd for C<sub>27</sub>H<sub>42</sub>N<sub>2</sub>: C, 82.17; H, 10.73; N, 7.10. Found: C, 82.21; H, 10.81; N, 7.03.

**(*S*)-2-(Pyrrolidin-1-ylmethyl)-1-((*S*)-1-(*m*-tolyl)undec-2-yn-1-yl)pyrrolidine (**4af**).** Light yellow oil. Yield: 0.65 g (82%). IR (neat): 2926, 2858, 2785, 1608, 1460, 1143, 754 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.39–7.37 (m, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 7.3 Hz, 1H), 5.15 (s, 1H), 3.08–3.05 (m, 1H), 2.69 (dd, *J* = 11.9, 4.9 Hz, 1H), 2.63–2.46 (m, 7H), 2.39–2.30 (m, 5H), 2.02–1.97 (m, 1H), 1.78 (s, 4H), 1.70–1.54 (m, 5H), 1.49–1.47 (m, 2H), 1.31–1.30 (m, 8H), 0.89 (t, *J* = 6.9 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 140.5, 137.5, 128.9, 127.9, 127.7, 125.3, 87.5, 76.3, 62.3, 59.6, 56.5, 55.0, 47.6, 31.9, 30.7, 29.3, 29.2, 28.9, 23.5, 22.73, 22.70, 21.5, 18.8, 14.1. [α]<sub>D</sub><sup>25</sup> = –80.2° (*c* = 0.7, CHCl<sub>3</sub>). LCMS (*m/z*): 395 (M + 1). Anal. Calcd for C<sub>27</sub>H<sub>42</sub>N<sub>2</sub>: C, 82.17; H, 10.73; N, 7.10. Found: C, 82.06; H, 10.65; N, 7.18.

**(*S*)-1-((*S*)-1,3-Diphenylprop-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**4ba**).**<sup>22</sup> Yellow oil. Yield: 0.65 g (94%). IR (neat): 3437, 3061, 3030, 1599, 1489, 1448, 756, 692 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.66 (d, *J* = 7.6 Hz, 2H), 7.54–7.52 (m, 2H), 7.38–7.28 (m, 6H), 5.57 (s, 1H), 3.23–3.18 (m, 1H), 2.79 (dd, *J* = 12.0, 5.6 Hz, 1H), 2.73 (t, *J* = 8.6 Hz, 1H), 2.65–2.52 (m, 6H), 2.05–2.0 (m, 1H), 1.79 (s, 4H), 1.74–1.62 (m, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 140.0, 131.9, 128.4, 128.25, 128.20, 128.1, 127.3, 123.5, 87.6, 86.5, 62.3, 59.5, 57.0, 54.9, 47.9, 30.8, 23.6, 22.9. [α]<sub>D</sub><sup>25</sup> = –120.8° (*c* = 0.91, CHCl<sub>3</sub>). LCMS (*m/z*): 346 (M + 1). Anal. Calcd for C<sub>24</sub>H<sub>28</sub>N<sub>2</sub>: C, 83.68; H, 8.19; N, 8.13. Found: C, 83.56; H, 8.12; N, 8.25.

**(*S*)-1-((*S*)-1,5-Diphenylpent-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**4ca**).** Yellow oil. Yield: 0.66 g (89%). IR (neat): 3057, 3030, 2964, 1600, 1490, 1441, 695 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.52 (d, *J* = 7.3 Hz, 2H), 7.35–7.24 (m, 8H), 5.21 (s, 1H), 3.04–2.97 (m, 1H), 2.93 (t, *J* = 7.3 Hz, 2H), 2.71–2.66 (m, 3H), 2.58–2.42 (m, 8H), 1.98–1.91 (m, 1H), 1.79 (bs, 4H), 1.67–1.57 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 140.8, 140.5, 128.6, 128.4, 128.2, 128.0, 127.0, 126.2, 86.7, 62.4, 59.5, 56.4, 55.0, 47.5, 35.4, 30.6, 23.5, 22.7, 20.8. [α]<sub>D</sub><sup>25</sup> = –87.7° (*c* = 0.12, CHCl<sub>3</sub>). LCMS (*m/z*): 373 (M + 1). Anal. Calcd for C<sub>26</sub>H<sub>32</sub>N<sub>2</sub>: C, 83.82; H, 8.66; N, 7.52. Found: C, 83.91; H, 8.72; N, 7.45.

**(*S*)-1-((*S*)-1-(4-Bromophenyl)-5-phenylpent-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**4cc**).** Yellow oil. Yield: 0.70 g (78%). IR

(neat): 3030, 2962, 2868, 2789, 1604, 1485, 1010, 744, 698  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.41–7.22 (m, 9H), 5.16 (s, 1H), 2.98–2.95 (m, 1H), 2.90 (t,  $J = 7.2$  Hz, 2H), 2.69–2.64 (m, 3H), 2.58–2.43 (m, 6H), 2.39–2.34 (m, 1H), 1.94–1.89 (m, 1H), 1.79–1.75 (m, 4H), 1.63–1.55 (m, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  140.6, 139.6, 130.1, 129.9, 128.6, 128.4, 126.3, 120.7, 87.1, 76.6, 62.4, 59.3, 55.9, 55.0, 47.4, 35.3, 30.5, 23.5, 22.7, 20.7.  $[\alpha]_{\text{D}}^{25} = -56.6^\circ$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ). LCMS ( $m/z$ ): 451 ( $M + 1$ ). Anal. Calcd for  $\text{C}_{26}\text{H}_{31}\text{BrN}_2$ : C, 69.17; H, 6.92; N, 6.21. Found: C, 69.05; H, 6.87; N, 6.28.

(*S*)-1-((*R*)-1-Cyclohexyl-5-phenylpent-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**4cg**). Yellow oil. Yield: 0.73 g (96%). IR (neat): 3063, 3028, 2922, 2851, 2785, 1670, 1604, 1496, 1450, 744, 698  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.32–7.20 (m, 5H), 3.30 (d,  $J = 10.0$  Hz, 1H), 2.85–2.80 (m, 3H), 2.70–2.66 (m, 1H), 2.57–2.48 (m, 7H), 2.43–2.32 (m, 2H), 1.97–1.96 (m, 2H), 1.89–1.85 (m, 1H), 1.76–1.55 (m, 10H), 1.34–1.14 (m, 4H), 0.93–0.85 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  140.9, 128.5, 128.2, 126.1, 84.4, 78.8, 62.1, 59.9, 58.6, 54.9, 46.8, 41.3, 35.7, 31.4, 30.5, 30.4, 26.9, 26.2, 26.0, 23.5, 23.3, 20.8.  $[\alpha]_{\text{D}}^{25} = -94.0^\circ$  ( $c = 1.02$ ,  $\text{CHCl}_3$ ). LCMS ( $m/z$ ): 380 ( $M + 1$ ). Anal. Calcd for  $\text{C}_{26}\text{H}_{38}\text{N}_2$ : C, 82.48; H, 10.12; N, 7.40. Found: C, 82.36; H, 10.18; N, 7.31.

(*S*)-1-((*R*)-1-Cyclohexyl-3-phenylprop-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**4bg**). Yellow oil. Yield: 0.67 g (96%). IR (neat): 3435, 2924, 2787, 1599, 1489, 1446, 754, 690  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.43–7.41 (m, 2H), 7.31–7.27 (m, 3H), 3.61 (d,  $J = 10.0$  Hz, 1H), 3.03–2.96 (m, 1H), 2.84–2.79 (m, 1H), 2.72 (q,  $J = 8.4$  Hz, 1H), 2.53–2.37 (m, 6H), 2.12–1.92 (m, 3H), 1.76–1.48 (m, 13H), 1.30–1.19 (m, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  131.7, 128.2, 127.6, 123.9, 88.5, 85.6, 62.1, 60.2, 59.1, 55.0, 47.2, 41.3, 31.5, 30.6, 30.5, 26.9, 26.2, 26.0, 23.6, 23.5.  $[\alpha]_{\text{D}}^{25} = -142.1^\circ$  ( $c = 0.83$ ,  $\text{CHCl}_3$ ). LCMS ( $m/z$ ): 352 ( $M + 1$ ). Anal. Calcd for  $\text{C}_{24}\text{H}_{34}\text{N}_2$ : C, 82.23; H, 9.78; N, 7.99. Found: C, 82.15; H, 9.86; N, 7.91.

(*S*)-1-((*S*)-3-(Cyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**4da**). Light yellow oil. Yield: 0.61 g (88%). IR (neat): 3061, 3028, 2930, 2785, 1491, 1448, 1136, 702  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.58 (d,  $J = 7.5$  Hz, 2H), 7.34–7.21 (m, 4H), 6.16–6.14 (m, 1H), 5.37 (s, 1H), 3.12–3.07 (m, 1H), 2.72 (dd,  $J = 12.0$ , 5.4 Hz, 1H), 2.65–2.47 (m, 6H), 2.22–2.11 (m, 4H), 2.01–1.96 (m, 1H), 1.77–1.58 (m, 11H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  140.4, 134.0, 128.2, 128.0, 127.0, 120.8, 89.4, 83.3, 62.4, 59.6, 56.9, 55.0, 47.7, 30.6, 29.8, 25.6, 23.6, 22.8, 22.4, 21.6.  $[\alpha]_{\text{D}}^{25} = -115.6^\circ$  ( $c = 1.18$ ,  $\text{CHCl}_3$ ). LCMS ( $m/z$ ): 350 ( $M + 1$ ). Anal. Calcd for  $\text{C}_{24}\text{H}_{32}\text{N}_2$ : C, 82.71; H, 9.25; N, 8.04. Found: C, 82.65; H, 9.21; N, 8.12.

(*S*)-7-Phenyl-7-((*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)hept-5-ynenitrile (**4ea**). Yellow oil. Yield: 0.61 g (91%). IR (neat): 3059, 3030, 2922, 2868, 2797, 2247, 1493, 1450, 702, 665  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.54 (d,  $J = 7.4$  Hz, 2H), 7.35–7.31 (m, 2H), 7.25–7.23 (m, 1H), 5.27 (s, 1H), 3.04–2.99 (m, 1H), 2.71 (dd,  $J = 12.0$ , 5.4 Hz, 1H), 2.57–2.48 (m, 11H), 1.98–1.90 (m, 3H), 1.77 (s, 4H), 1.68–1.61 (m, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  140.1, 128.1, 128.0, 127.2, 119.1, 84.4, 78.6, 62.3, 59.6, 56.4, 55.0, 47.8, 30.6, 25.0, 23.5, 22.8, 18.0, 16.2.  $[\alpha]_{\text{D}}^{25} = -104.2^\circ$  ( $c = 0.96$ ,  $\text{CHCl}_3$ ). LCMS ( $m/z$ ): 336 ( $M + 1$ ). Anal. Calcd for  $\text{C}_{22}\text{H}_{29}\text{N}_3$ : C, 78.76; H, 8.71; N, 12.53. Found: C, 78.85; H, 8.65; N, 12.45.

(*S*)-1-((*S*)-4-(Benzyloxy)-1-phenylbut-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**4fa**). Yellow oil. Yield: 0.64 g (82%). IR (neat): 3061, 3030, 2962, 1602, 1493, 1452, 1201  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.61 (d,  $J = 7.4$  Hz, 2H), 7.41–7.28 (m, 8H), 5.42 (s, 1H), 4.70 (s, 2H), 4.37 (s, 2H), 3.14–3.11 (m, 1H), 2.75 (dd,  $J = 5.5$ , 5.5 Hz, 1H), 2.67–2.51 (m, 7H), 2.03–1.99 (m, 1H), 1.79–1.62 (m, 7H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  139.9, 137.7, 128.5, 128.2, 127.9, 127.3, 83.5, 83.2, 71.3, 62.5, 59.5, 57.6, 56.6, 55.0, 47.9, 30.6, 23.6, 22.8.  $[\alpha]_{\text{D}}^{25} = -86.2^\circ$  ( $c = 0.6$ ,  $\text{CHCl}_3$ ). LCMS ( $m/z$ ): 389 ( $M + 1$ ). Anal. Calcd for  $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}$ : C, 80.37; H, 8.30; N, 7.21. Found: C, 80.25; H, 8.36; N, 7.13.

(*S*)-1-((*S*)-4-(Benzyloxy)-1-cyclohexylbut-2-yn-1-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**4fg**). Yellow oil. Yield: 0.72 g (91%). IR (neat): 3065, 3030, 2928, 1450, 1352  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36–7.29 (m, 5H), 4.62 (s, 2H), 4.24 (d,  $J = 1.6$  Hz, 2H),

3.46 (d,  $J = 9.9$  Hz, 1H), 2.93–2.90 (m, 1H), 2.79–2.74 (m, 1H), 2.64–2.62 (m, 1H), 2.51–2.34 (m, 6H), 2.06–1.88 (m, 2H), 1.75–1.59 (m, 12H), 1.31–1.20 (m, 5H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  137.7, 128.4, 128.1, 127.8, 85.2, 80.9, 71.0, 62.1, 60.1, 58.6, 57.5, 55.0, 47.1, 41.1, 31.4, 30.5, 30.4, 26.8, 26.1, 25.9, 23.5, 23.3.  $[\alpha]_{\text{D}}^{25} = -101.9^\circ$  ( $c = 0.71$ ,  $\text{CHCl}_3$ ). LCMS ( $m/z$ ): 395 ( $M + 1$ ). Anal. Calcd for  $\text{C}_{26}\text{H}_{38}\text{N}_2\text{O}$ : C, 79.14; H, 9.71; N, 7.10. Found: C, 79.25; H, 9.63; N, 7.18.

(*S*)-1-((*S*)-1-(Benzyloxy)dodec-2-yn-4-yl)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**4fh**). Yellow oil. Yield: 0.74 g (87%). IR (neat): 3027, 2925, 2854, 1455, 1350, 1073, 734, 697  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36–7.30 (m, 5H), 4.62 (s, 2H), 4.23 (s, 2H), 3.88 (t,  $J = 7.4$  Hz, 1H), 2.95–2.86 (m, 2H), 2.64 (q,  $J = 8.6$  Hz, 1H), 2.51 (s, 5H), 2.43–2.38 (m, 1H), 1.98–1.93 (m, 1H), 1.75 (s, 6H), 1.65–1.60 (m, 3H), 1.50–1.41 (m, 2H), 1.29–1.27 (m, 10H), 0.88 (t,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  137.6, 128.4, 128.1, 127.8, 85.8, 80.4, 71.1, 62.1, 60.0, 57.5, 55.0, 52.8, 47.4, 35.2, 31.9, 30.5, 29.5, 29.3, 26.8, 23.5, 22.9, 22.7, 14.2.  $[\alpha]_{\text{D}}^{25} = -66.5^\circ$  ( $c = 1.22$ ,  $\text{CHCl}_3$ ). LCMS ( $m/z$ ): 425 ( $M + 1$ ). Anal. Calcd for  $\text{C}_{28}\text{H}_{44}\text{N}_2\text{O}$ : C, 79.19; H, 10.44; N, 6.60. Found: C, 79.32; H, 10.38; N, 6.75.

1-(((*S*)-1-((*S*)-1-Phenylundec-2-yn-1-yl)pyrrolidin-2-yl)methyl)piperidine (**5**). Light yellow oil. Yield: 0.66 g (84%). IR (neat): 3061, 3028, 1726, 1602, 1493, 1450, 1124, 725, 700  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.58 (d,  $J = 7.4$  Hz, 2H), 7.33–7.21 (m, 3H), 5.42 (s, 1H), 3.13–3.08 (m, 1H), 2.62 (dd,  $J = 17.2$ , 8.6 Hz, 1H), 2.65–2.30 (m, 8H), 2.17 (s, 1H), 1.94–1.88 (m, 1H), 1.65–1.43 (m, 13H), 1.30 (s, 8H), 0.89–0.88 (m, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  140.9, 128.2, 127.9, 126.9, 87.4, 76.4, 65.8, 57.4, 56.6, 55.4, 47.7, 31.9, 30.6, 29.3, 29.2, 29.1, 28.9, 26.2, 24.6, 22.73, 22.7, 18.8, 14.1.  $[\alpha]_{\text{D}}^{25} = -76.0^\circ$  ( $c = 0.81$ ,  $\text{CHCl}_3$ ). LCMS ( $m/z$ ): 396 ( $M + 1$ ). Anal. Calcd for  $\text{C}_{27}\text{H}_{42}\text{N}_2$ : C, 82.17; H, 10.73; N, 7.10. Found: C, 82.35; H, 10.62; N, 7.18.

*N*-Ethyl-*N*-((*S*)-1-((*S*)-1-phenylundec-2-yn-1-yl)pyrrolidin-2-yl)methylethanamine (**6**). Yellow oil. Yield: 0.52 g (68%). IR (neat): 3061, 2959, 2928, 1493, 1450, 1383, 1327, 698  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.58 (d,  $J = 7.4$  Hz, 2H), 7.33–7.23 (m, 3H), 5.33 (s, 1H), 3.08–3.06 (m, 1H), 2.61–2.41 (m, 8H), 2.33–2.30 (m, 1H), 1.98–1.91 (m, 1H), 1.66–1.54 (m, 5H), 1.47–1.46 (m, 2H), 1.29 (s, 8H), 1.06 (t,  $J = 6.9$  Hz, 6H), 0.89 (t,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  140.8, 128.2, 127.9, 126.9, 87.5, 76.3, 59.5, 58.4, 56.6, 48.0, 47.9, 31.9, 30.6, 29.4, 29.3, 29.0, 22.8, 22.6, 18.8, 14.2, 12.1.  $[\alpha]_{\text{D}}^{25} = -89.3^\circ$  ( $c = 1.15$ ,  $\text{CHCl}_3$ ). LCMS ( $m/z$ ): 383 ( $M + 1$ ). Anal. Calcd for  $\text{C}_{26}\text{H}_{42}\text{N}_2$ : C, 81.61; H, 11.06; N, 7.32. Found: C, 81.49; H, 11.15; N, 7.21.

**General Procedure for Synthesis of Chiral Allenes from Chiral Proline Derived Propargylamines.** The chiral propargylamine (0.5 mmol) was added to a stirred suspension of  $\text{CuI}$  (48 mg, 0.25 mmol) in dry dioxane (2 mL), and the contents were refluxed for 18 h at  $100^\circ\text{C}$  under a nitrogen atmosphere. Dioxane was removed under reduced pressure, and the crude product was purified on silica gel (100–200) using hexane as eluent to isolate the chiral allene **7**. Characterization data of the chiral allenes **7aa–ea** were identical with our previously reported data.<sup>40</sup>

(*R*)-4-(Benzyloxy)buta-1,2-dien-1-ylbenzene (**7fa**). Colorless liquid. Yield: 0.076 g (64%). IR (neat): 3063, 3032, 1952, 1726, 1599, 1494, 1454  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36–7.20 (m, 10H), 6.29–6.26 (m, 1H), 5.73 (q,  $J = 6.6$  Hz, 1H), 4.63–4.56 (m, 2H), 4.19 (dd,  $J = 6.7$ , 2.3 Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  206.1, 138.1, 133.9, 128.7, 128.4, 127.9, 127.7, 127.1, 126.9, 95.6, 92.6, 72.0, 67.9.  $[\alpha]_{\text{D}}^{25} = -116.5^\circ$  ( $c = 0.55$ ,  $\text{CHCl}_3$ ). LCMS ( $m/z$ ): 237 ( $M + 1$ ). Anal. Calcd for  $\text{C}_{17}\text{H}_{16}\text{O}$ : C, 86.40; H, 6.82. Found: C, 86.18; H, 6.91. HPLC: 94% ee (Daicel Chiralcel OJ-H, hexane/ $i$ PrOH 99/1, flow rate 1.0 mL/min, 254 nm,  $t_{\text{R}}(\text{R}) = 31.9$  min,  $t_{\text{R}}(\text{S}) = 34.7$  min).

(*R*)-(((4-Cyclohexylbuta-2,3-dien-1-yl)oxy)methyl)benzene (**7fg**). Colorless liquid. Yield: 0.082 g (68%). IR (neat): 3030, 2926, 2851, 1961, 1450, 1095  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.37–7.30 (m, 5H), 5.32–5.23 (m, 2H), 4.56 (s, 2H), 4.07 (dd,  $J = 6.8$ , 2.2 Hz, 2H), 2.04–2.00 (m, 1H), 1.79–1.64 (m, 6H), 1.35–1.11 (m, 4H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  204.0, 138.3, 128.4, 127.8, 127.6, 98.0, 89.3, 71.6, 68.8, 37.0, 33.07, 33.03, 26.1, 25.9.  $[\alpha]_{\text{D}}^{25} = -39.7^\circ$  ( $c = 0.58$ ,  $\text{CHCl}_3$ ). LCMS ( $m/z$ ): 243 ( $M + 1$ ). HPLC: 94% ee (Daicel

Chiralcel OB-H, hexane/<sup>i</sup>PrOH 99/1, flow rate 0.5 mL/min, 215 nm,  $t_R(R) = 10.2$  min,  $t_R(S) = 11.2$  min). Anal. Calcd for C<sub>17</sub>H<sub>22</sub>O: C, 84.25; H, 9.15. Found: C, 84.15; H, 9.21.

(*R*)-((Dodeca-2,3-dien-1-yloxy)methyl)benzene (**7fh**). Colorless liquid. Yield: 0.090 g (66%). IR (neat): 3058, 3032, 2925, 2856, 1961, 1453, 1096, 734, 687 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.38–7.28 (m, 5H), 5.25–5.20 (m, 2H), 4.55 (s, 2H), 4.06 (dd, *J* = 6.6, 2.4 Hz, 2H), 2.04–2.0 (m, 2H), 1.44–1.27 (m, 12H), 0.89 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 205.1, 138.3, 128.4, 127.9, 127.6, 92.0, 88.3, 71.6, 68.7, 31.9, 29.4, 29.3, 29.15, 29.10, 28.6, 22.7, 14.1.  $[\alpha]_D^{25} = -15.3^\circ$  (*c* = 0.4, CHCl<sub>3</sub>). LCMS (*m/z*): 273 (*M* + 1). HPLC: 96% ee (Daicel Chiralcel OB-H, hexane/<sup>i</sup>PrOH 100/0, flow rate 0.5 mL/min, 215 nm,  $t_R(R) = 15.2$  min,  $t_R(S) = 17.0$  min). Anal. Calcd for C<sub>19</sub>H<sub>28</sub>O: C, 83.77; H, 10.36. Found: C, 83.65; H, 10.26.

**Reduction of the Imine Intermediate 17 Present in the Product Mixture.** The procedure for the synthesis of chiral allenes from chiral propargylamine (0.5 mmol, 0.190 g) was followed, and this crude mixture was cooled to 0 °C. Methanol (3 mL) and NaBH<sub>4</sub> (0.6 mmol, 0.023 g) were added, and the mixture was stirred further for 2 h at 25 °C. The mixture was then chromatographed on a silica gel (100–200 mesh) column to isolate the allene (*R*)-**7** using *n*-hexane as eluent (yield 0.07 g, 62% *y*, 99% ee). The chiral diamine **1** was recovered using CHCl<sub>3</sub>/MeOH (90/10) as eluent without change in its enantiomeric purity. Yield: 0.047 g (61%).  $[\alpha]_D^{25} = +8.4^\circ$  (*c* = 0.94, EtOH) (lit.<sup>50</sup>  $[\alpha]_D^{25} = +8.5^\circ$  (*c* = 2.4, EtOH)).

**Procedure for the Synthesis of (*S,E*)-Ethyl 3-(2-(Pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)acrylate (**12**).** To the chiral diamine **1** (0.31 g, 2.0 mmol) in dry toluene (3 mL) was added ethyl propiolate (0.2 g, 2.0 mmol) at 25 °C slowly, and the mixture was stirred further for 15 min. Toluene was removed under reduced pressure, and the crude product was purified on basic alumina. The enamine adduct **8** was eluted using hexane/ethyl acetate (80/20).

Yield: 0.44 g (88%). IR (neat): 3503, 2972, 2791, 1685, 1608, 1460, 787, 733 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.73 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.8 Hz, 1H), 4.09 (q, *J* = 8.0 Hz, 2H), 3.64–3.62 (m, 1H), 3.18–3.11 (m, 2H), 2.53–2.42 (m, 6H), 1.96–1.74 (m, 8H), 1.23 (t, *J* = 8.0 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 169.7, 148.6, 84.9, 60.6, 58.7, 54.6, 29.6, 23.5, 23.2, 14.7.  $[\alpha]_D^{25} = -43.9^\circ$  (*c* = 0.58, CHCl<sub>3</sub>). LCMS (*m/z*): 253 (*M* + 1). Anal. Calcd for C<sub>14</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: C, 66.63; H, 9.59; N, 11.10. Found: C, 66.51; H, 9.52; N, 11.21.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

Text giving a representative procedure for the preparation of racemic allenes and figures giving <sup>1</sup>H and <sup>13</sup>C NMR spectra of the products and HPLC analysis profiles. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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