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Chiral *N*-phosphonyl imine chemistry: an efficient asymmetric synthesis of chiral *N*-phosphonyl propargylamines†

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A variety of substituted chiral propargylamines have been synthesized by reacting chiral *N*-phosphonylimines with lithium aryl/alkyl acetylides. Seventeen examples were studied to give excellent yields (>90%) and diastereoselectivities (96 : 4 to 99 : 1). It was found that the types of bases for generating acetylides and solvents are crucial for effectiveness of this asymmetric reaction. In addition, *N*,*N*-isopropyl group on chiral *N*-phosphonylimine auxiliary was proven to be superior to other protecting groups in controlling diastereoselectivity.

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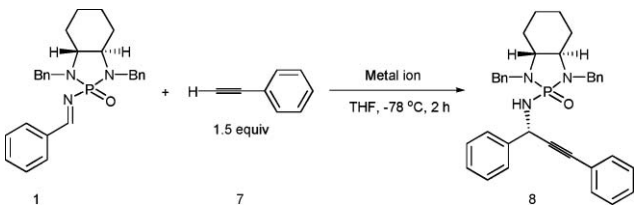
1. Introduction

Chiral propargylamines are versatile building blocks for the synthesis of chemically and biologically important compounds.[1] The addition of terminal alkynes to imines and iminiums has been serving as a common approach to chiral and achiral propargylamines.[2–4] In the past several years, asymmetric catalysis for this synthesis has been actively pursued[5–8] by using various catalysts,[9–14] such as Au(II)salen complex, Cu(I)-*i*-Pr-Pybox-diPh and Cu(I)-PINAP complexes.[14] Although great progress has been made on this asymmetric catalysis, the development of chiral imine-based methodologies is still highly sought after for larger scale synthesis.

The use of chiral sulfinylimines, *N*-*p*-tolylsulfinylimines and *N*-*tert*-butylsulfinylimines offered a practical approach to a series of propargylamines.[15–19] In this synthesis, Lewis acids (*e.g.* $AlMe_3$) are sometimes required to activate sulfinylimine electrophiles for additions by lithium and magnesium acetylides.[17] In the past year, our group reported the design and synthesis of new chiral *N*-phosphonyl imines and has successfully utilized them in a variety of nucleophilic addition reactions to give very useful chiral amino products in good yields and excellent diastereoselectivities.[20] In continuation of our work on chiral *N*-phosphonyl imine chemistry, we would like to report herein the efficient additions of metal aromatic/aliphatic acetylides onto chiral *N*-phosphonyl imines without the use of Lewis acid promoters.

2. Results and discussion

In our initial attempt, the chiral *N*-phosphonyl imine attached with *N*-benzyl group **1** was employed as the electrophile (Scheme 1). The lithium phenyl acetylide was generated by treating phenyl acetylene **7** with LDA in THF at −78 °C for 1 h. Into the resulting mixture was slowly added chiral *N*-phosphonyl imine **1** which was dissolved in THF. The reaction was stirred at −78 °C for 2 h and constantly monitored by TLC (6 : 4 hexane–EtOAc) before it was quenched with saturated ammonium chloride solution. The product **8** was isolated in a good yield (85%) although modest diastereoselectivity (dr = 70 : 30) was observed.

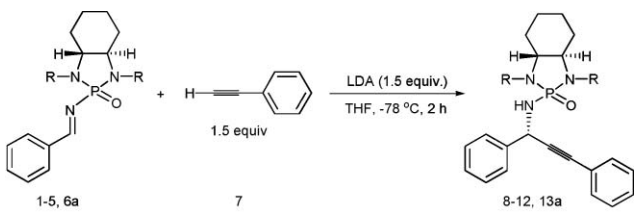


Scheme 1

We next investigated the effects of metal ions of acetylides on the diastereoselectivity by using three other metal cations including sodium, magnesium, aluminium for acetylide formation.

It was found that both sodium and magnesium phenyl acetylides resulted in poor diastereoselectivities of dr = 60 : 40 (for Na) and dr = 65 : 35 (for Mg), respectively. The use of aluminium acetylide did not improve diastereoselectivity (dr = 63 : 37) either. Based on these observations, lithium acetylide was thus chosen as the nucleophile.

We then explored the effects of different *N*,*N*′-R groups on the chiral *N*-phosphonyl auxiliary (Scheme 2). These protecting groups include benzyl, isobutyl, neopentyl, 1-naphthylmethyl, cyclopentylmethyl and isopropyl groups. As shown in Table 1, cyclopentylmethyl and isopropyl group-attached chiral *N*-phosphonyl imines resulted in high chemical yields of 92% and 97%, respectively and excellent diastereoselectivities, dr = 95 : 5 and



Scheme 2

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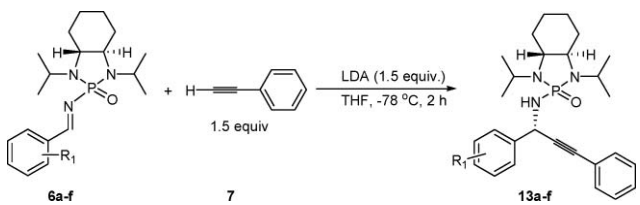
Table 1 Effect of different R groups on asymmetric additions of chiral *N*-phosphonyl imine with lithium phenyl acetylide[a]

Entry	Substrate	R	Product	Yield (%)[b]	dr[c]
1	**1**	Benzyl	**8**	85	70 : 30
2	**2**	Isobutyl	**9**	70	50 : 50
3	**3**	Neopentyl	**10**	60	50 : 50
4	**4**	1-Naphthylmethyl	**11**	90	85 : 15
5	**5**	Cyclopentylmethyl	**12**	92	95 : 5
6	**6a**	Isopropyl	**13a**	97	99 : 1

[a] All reactions were carried out at −78 °C in 0.05 M solution of imine in THF. [b] Combined yields of both isomers. [c] Diastereomeric ratio has been determined by using ^{31}P-NMR and ^{1}H-NMR of crude products.

99 : 1, respectively (Table 1, entries 5 & 6) as determined by ^{31}P and ^{1}H-NMR analysis of crude products. In our previous ketone enolate-based addition to chiral *N*-phosphonyl imines, the 1-naphthylmethyl group gave the highest diastereoselectivity.[20e] However, this group resulted in a modest diastereoselectivity of dr = 85 : 15 in the present system, albeit the yield is still excellent (90%, Table 1, entry 4). Surprisingly, isobutyl and neopentyl groups did not give any diastereoselectivity (Table 1, entries 2 & 3). The isopropyl group was thus proven to be the most efficient one for the present asymmetric induction, which is similar to several of our previous asymmetric reactions using chiral *N*-phosphonyl imines.[20b-d] Obviously, the secondary alkyl substituent (isopropyl) group on chiral *N*-phosphonyl imine (entry 6, Table 1) is superior to its counterparts that are primary alkyl groups (entries 1–5, Table 1), and should be chosen for the present asymmetric control.

After the optimal conditions were realized, the substrate scope was then studied. Several chiral *N*-phosphonyl imines derived from different aldehydes were synthesized and subjected to the addition reaction with lithium phenyl acetylide which was generated by treating with 2.0 M of LDA in THF (Scheme 3). As indicated in Table 2, substitution on the phenyl rings of chiral *N*-phosphonyl imines has no significant effect on either yield or diastereoselectivity. Single isomeric products were obtained in the cases of *ortho*-bromo and *ortho*-methyl chiral *N*-phosphonyl imines (Table 2, entries 4–5).



Scheme 3

Besides the use of lithium phenyl acetylide, two lithium aliphatic acetylides derived from 1-hexyne (**14**) and 3,3-diethoxy-prop-1-yne (**15**) were also employed as the nucleophiles (Scheme 4). The generation of these lithium aliphatic acetylides was conducted by treating aliphatic alkynes with 1.6 M *n*-BuLi in THF at −78 °C. The reaction was stirred for 2 h after it was quenched with saturated solution of NH_4Cl (Scheme 4). Excellent yields (90–98%) and diastereoselectivities (98 : 2 to >99 : 1) were obtained for all cases that were examined as shown in Table 3. In two cases (Table 3, entries 2 and 6), essentially single isomeric products were observed in crude NMR analysis. For all of these cases, the

Table 2 Results of the synthesis of *N*-phosphonyl substituted propargylamines **13a-f** (**7**)[a]

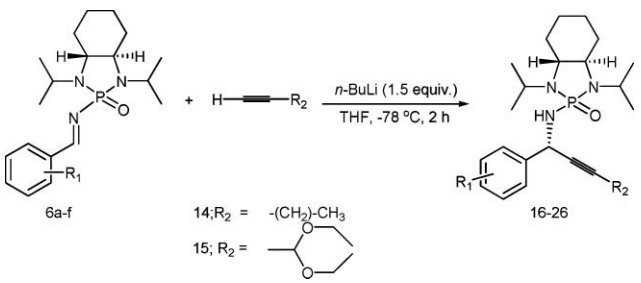
Entry	Substrate	R	Product	Yield (%)[b]	dr[c]
1	**6a**	H	**13a**	97	99 : 1
2	**6b**	*p*-Fluoro	**13b**	95	98 : 2
3	**6c**	*o*-Fluoro	**13c**	96	96 : 4
4	**6d**	*o*-Bromo	**13d**	95	100 : 0
5	**6e**	*o*-Methyl	**13e**	96	100 : 0

[a] All reactions were carried out at −78 °C in 0.06 M solution of imine in THF. [b] Combined yields of both isomers. [c] Diastereomeric ratio has been determined by using ^{31}P-NMR and ^{1}H-NMR of crude products.

Table 3 Results for the synthesis of *N*-phosphonyl-substituted propargylamines **16–26** using lithium aliphatic acetylides **14** and **15**[a]

Entry	Substrate[b]	R_1	R_2	Product	Yield (%)[c]	Dr[d]
1	**6a**	H	*n*-C_4H_9-	**16**	95	98 : 2
2	**6b**	*p*-Fluoro	*n*-C_4H_9-	**17**	97	100 : 0
3	**6c**	*o*-Fluoro	*n*-C_4H_9-	**18**	93	98 : 2
4	**6d**	*o*-Chloro	*n*-C_4H_9-	**19**	95	98 : 2
5	**6e**	*o*-Bromo	*n*-C_4H_9-	**20**	96	98 : 2
6	**6f**	*o*-Methyl	*n*-C_4H_9-	**21**	98	100 : 0
7	**6g**	*o*-Methoxy	*n*-C_4H_9-	**22**	90	99 : 1
8	**6h**	*o*-Nitro	*n*-C_4H_9-	**23**	92	98 : 2
9	**6a**	H		**24**	97	99 : 1
10	**6c**	*o*-Fluoro		**25**	98	99 : 1
11	**6e**	*o*-Bromo		**26**	96	98 : 2

[a] All reactions were carried out at -78 °C in 0.06 M solution of imine in THF. [b] For optical rotation data of these starting materials, see ref. 21 [c] Combined yields of both isomers. [d] Diastereomeric ratio has been determined by using ^{31}P-NMR and ^{1}H-NMR of crude products.



Scheme 4

substitutions on phenyl rings showed no significant effect on yield and diastereoselectivity.

The absolute configuration of asymmetric induction for this asymmetric reaction has been determined by cleaving the phosphonyl group of product **13a** with 3 N aqueous HCl in methanol followed by *N*-acetylation to give acetamide **27** (Scheme 5). The *S* absolute configuration of the isolated acetamide **27** was deduced from its optical rotation, of opposite sign to that of the literature compound which has *R* configuration.[19,22]

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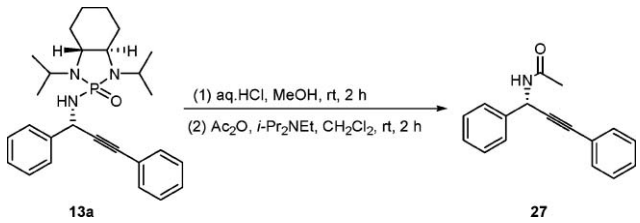

Scheme 5

Conclusions

Chiral *N*-phosphonyl imines were found to react with lithium phenyl and alkyl acetylides smoothly to give substituted chiral propargylamines. Effects on asymmetric induction of different *N*,*N*′-alkyl substituents on chiral *N*-phosphonyl imines and metal ions were carefully investigated; and isopropyl group-attached chiral *N*-phosphonyl imine and metal lithium were found to be highly efficient in terms of yields and diastereoselectivities. The applications of the resulting *N*-phosphonyl-substituted propargylamines will be studied in our laboratories in the future.

Experimental

General methods

All commercially available solvents, unless otherwise mentioned, were used without purification. THF was distilled from sodium–benzophenone ketyl. All the glassware used was dried overnight at 100 °C. All the melting points are uncorrected. The NMR spectra were recorded at 500, 125, 202 MHz for ^{1}H, ^{13}C and ^{31}P respectively. Shifts are reported in ppm based on an internal TMS standard (for ^{1}H/$CDCl_3$) or on residual solvent peaks (for ^{13}C/$CDCl_3$). ^{31}P NMR spectra were referenced to external H_3PO_4 (0.00 ppm). 1.6 M solution of *n*-butyl lithium solution in hexanes, 2 M solution of lithium diisopropylamide in THF, phenyl acetylene, 3,3-diethoxy-prop-1-yne and 1-hexyne were obtained from Aldrich and used as obtained from commercial sources without any further purification.

Typical procedure for the synthesis of *N*-phosphonyl substituted propargylamines using chiral *N*-phosphonyl imines and phenyl acetylene

In a dry vial, under inert gas protection, phenyl acetylene **7** (1.0 mmol) was dissolved in 3 mL THF. The vial was cooled to −78 °C and into the resulting solution lithium diisopropylamide (2.0 M in THF, 1.0 mmol) was added dropwise. The reaction solution was stirred at −78 °C for 1 h and phosphonyl imine **6** (0.50 mmol in 3 ml THF) was added to the reaction mixture. The reaction mixture was stirred for another 2 h before it was quenched by adding saturated ammonium chloride solution followed by 10 mL water. The reaction mixture was then extracted with 2 × 10 mL of diethyl ether. Combined organic layers were washed with water (1 × 20 mL), and dried over anhydrous sodium sulfate. Sodium sulfate was filtered off and the organic layer was evaporated to obtain the desired product as pale yellow solid which on washing with hexanes gave pure product as white solid. In a few cases, a yellow oil was obtained which was further purified by column chromatography (solvent system: EtOAc–hexanes 70 : 30).

Compound 13a. White solid; yield (0.251 g, 97%); mp 164–166 °C; $[\alpha]_D^{25} = -80.5$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 7.5 Hz, 2H), 7.41–7.39 (m, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.31–7.26 (m, 4H), 5.50 (t, J = 10.0 Hz, 1H), 3.68–3.58 (m, 1H), 3.56–3.47 (m, 1H), 2.99 (t, J = 11.5 Hz, 1H), 2.83–2.76 (m, 2H), 2.05 (t, J = 10.5 Hz, 2H), 1.77 (d, J = 11.0 Hz, 2H), 1.38–1.31 (m, 3H), 1.29 (d, J = 7.0 Hz, 3H), 1.23 (d, J = 7.0 Hz, 4H), 1.17 (dd, J = 3.0, 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8 (d, J = 5.3 Hz), 131.4 (2C), 128.5 (2C), 128.2 (2C), 128.1, 127.5, 126.7 (2C), 123.0, 90.6 (d, J = 4.3 Hz), 84.1, 60.0 (d, J = 10.3 Hz), 59.1 (d, J = 10.3 Hz), 48.1 (d, J = 1.5 Hz), 44.4 (d, J = 3.0 Hz), 43.7 (t, J = 4.3 Hz), 30.9, 30.8, 30.6 (d, J = 9.3 Hz), 24.3 23.0 (d, J = 6.5 Hz), 22.8 (d, J = 4.0 Hz), 20.0, 19.8 (d, J = 1.5 Hz); ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.3; LCMS (*m*/*z*): 450 (M + H)$^+$.

Compound 13b. White solid; yield (0.247 g, 95%); mp 186–188 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.56 (m, 2H), 7.41–7.39 (m, 2H), 7.31–7.29 (m, 3H), 7.04 (t, J = 8.5 Hz, 2H), 5.51 (t, J = 10.0 Hz, 1H), 3.66–3.58 (m, 1H), 3.52–3.44 (m, 1H), 2.98 (t, J = 11.0 Hz, 1H), 2.77 (t, J = 10.5 Hz, 2H), 2.06–2.04 (m, 2H), 1.78–1.75 (m, 3H), 1.39–1.29 (m, 3H), 1.26 (t, J = 6.5 Hz, 6H), 1.19 (d, J = 7.0 Hz, 3H), 1.16 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 137.8, 131.4 (2C), 128.4, 128.3, 128.28 (2C), 128.26, 122.8, 115.3, 115.1, 90.2 (d, J = 3.8 Hz), 84.3, 59.9 (d, J = 10.8 Hz), 59.1 (d, J = 9.8 Hz), 47.5, 44.3 (d, J = 3.0 Hz), 43.7 (d, J = 3.8 Hz), 30.9, 30.8, 30.6 (d, J = 9.8 Hz), 24.3, 23.0 (d, J = 5.8 Hz), 22.8 (d, J = 3.8 Hz), 20.0, 19.9 (d, J = 2.0 Hz); ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.2; LCMS: *m*/*z* 468.0 (M + H)$^+$.

Compound 13c. Yellow oil; yield (0.249 g, 96%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 7.5 Hz, 1H), 7.37–7.34 (m, 3H), 7.31–7.21 (m, 5H), 5.65 (t, J = 10.5 Hz, 1H), 3.54–3.39 (m, 3H), 3.00–2.96 (t, J = 10.0 Hz, 1H), 2.85 (t, J = 16.5 Hz, 1H), 2.10–2.02 (m, 3H), 1.38–1.19 (m, 13H), 1.08 (dd, J = 7.0, 14.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3 (d, J = 4.5 Hz), 132.3, 131.55, 131.51 (2C), 129.8, 128.7, 128.4, 128.1 (2C), 127.2, 122.8, 89.2 (d, J = 5.8 Hz), 83.5, 60.1 (d, J = 10.8 Hz), 59.2 (d, J = 10.3 Hz), 46.1, 44.3 (d, J = 2.8 Hz), 43.7 (d, J = 4.3 Hz), 30.8, 30.7 (d, J = 2.8 Hz), 30.6, 24.3, 24.2 (d, J = 2.8 Hz), 22.8 (d, J = 3.5 Hz), 19.9, 19.4 (d, J = 2.0 Hz); ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.4.

Compound 13d. White solid; yield: 0.239 g (95%); mp 174–176 °C; $[\alpha]_D^{25} = -81.3$ (*c* 0.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 7.5 Hz, 1H), 7.56 (d, J = 9.0 Hz, 1H), 7.36–7.33 (m, 3H), 7.27–7.23 (m, 3H), 7.14 (t, J = 8.0 Hz, 1H), 5.64 (t, J = 11.0 Hz, 1H), 3.60–3.50 (m, 2H), 3.44–3.36 (m, 1H), 3.00 (t, J = 10.0 Hz, 1H), 2.86 (t, J = 10.0 Hz, 1H), 2.11 (d, J = 8.5 Hz, 1H), 2.01 (d, J = 7.0 Hz, 1H), 1.77 (m, 2H), 1.33 (d, J = 6.5 Hz, 7H), 1.27 (d, J = 6.5 Hz, 3H), 1.00 (d, J = 6.5 Hz, 3H), 0.953 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9 (d, J = 4.3 Hz), 133.0, 131.4 (2C), 128.9 (2C), 128.5, 128.1 (2C), 127.8, 122.8, 122.2, 89.2 (d, J = 5.5 Hz), 83.7, 60.0 (d, J = 11.3 Hz), 59.2 (d, J = 9.8 Hz), 48.3 (d, J = 2.5 Hz), 44.3 (d, J = 3.0 Hz), 43.7 (d, J = 4.3 Hz), 30.8, 30.7 (d, J = 8.75 Hz), 24.3, 24.2 (d, J = 1.0 Hz), 22.95, 22.92 (d, J = 2.5 Hz), 19.9, 19.3 (d, J = 2.0 Hz); ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.4; LCMS: *m*/*z* 530.0 (M + H)$^+$.

Compound 13e. White solid; yield (0.250 g, 96%); mp 154–156 °C; $[\alpha]_D^{25} = -84.6$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 7.5 Hz, 1H), 7.35–7.32 (m, 2H), 7.26–7.15 (m, 6H),

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5.51 (t, J = 10.0 Hz, 1H), 3.60–3.44 (m, 2H), 3.06–2.96 (m, 2H), 2.76 (t, J = 10.0 Hz, 1H), 2.52 (s, 3H), 2.09–2.01 (m, 2H), 1.77 (d, J = 6.5 Hz, 2H), 1.37–1.23 (m, 7H), 1.21 (d, J = 7.0 Hz, 3H), 1.08 (dd, J = 6.5, 9.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9 (d, J = 4.3 Hz), 134.9, 131.3 (2C), 130.6, 128.1 (2C), 127.9, 127.3, 126.1, 125.9, 123.0, 90.2 (d, J = 5.3 Hz), 83.1, 60.1 (d, J = 11.3 Hz), 59.1 (d, J = 9.8 Hz), 45.6 (d, J = 1.5 Hz), 44.3 (d, J = 3.0 Hz), 43.7 (d, J = 4.5 Hz), 30.9 (d, J = 11.3 Hz), 30.7 (d, J = 9.3 Hz), 24.2 23.0, 22.9, 22.8 (d, J = 3.8 Hz), 19.8, 19.4 (d, J = 2.0 Hz), 19.3; ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.6.

Compound 13f. Colorless oil; yield (0.248 g, 97%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.39 (m, 1H), 7.35–7.32 (m, 2H), 7.27–7.24 (m, 4H), 6.95 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 5.51 (t, J = 10.5 Hz, 1H), 3.90 (s, 3H), 3.53–3.41 (m, 3H), 2.97 (t, J = 11.0 Hz, 1H), 2.83 (t, J = 9.5 Hz, 1H), 2.08-2.01 (m, 3H), 1.78 (d, J = 7.5 Hz, 2H), 1.38-1.29 (m, 2H), 1.28 (d, J = 7.0 Hz, 4H), 1.20 (d, J = 7.0 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H), 1.07 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 131.4 (2C), 130.1, 128.7, 128.0 (2C), 127.9, 127.7, 123.4, 120.7, 111.2, 91.0 (d, J = 3.7 Hz), 82.2, 60.0 (d, J = 10.3 Hz, 3H), 59.2 (d, J = 10.3 Hz, 3H), 55.5, 44.6 (d, J = 1.5 Hz), 44.3 (d, J = 3.3 Hz), 43.7 (t, J = 4.3 Hz), 30.7, 30.6, 30.5, 24.3, 22.8 (d, J = 5.8 Hz), 22.6 (d, J = 3.5 Hz), 19.9, 19.7 (d, J = 1.5 Hz); ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.3.

Typical procedure for the synthesis of *N*-phosphonyl-substituted propargylamines using chiral *N*-phosphonyl imines and aliphatic alkynes

In a dry vial, under inert gas protection, was taken 1-hexyne **14** (1.0 mmol) in 3 mL of THF. The reaction vial was cooled to −78 °C, and into the resulting solution *n*-BuLi (2.0 M in hexanes, 1.0 mmol) was added dropwise. The reaction solution was stirred at −78 °C for 1 h and phosphonyl imine **6** (0.5 mmol in 3 ml THF) was added to the reaction mixture. The reaction mixture was stirred for another 2 h before it was quenched by adding saturated ammonium chloride solution followed by 10 mL water. The reaction mixture was then transferred to the separatory funnel and extracted with 2 × 10 mL of diethyl ether. Combined organic layers were washed with water (1 × 20 mL), dried over anhydrous sodium sulfate which was filtered off and the organic layer was evaporated to obtain the desired product as pale yellow solid which on washing with hexanes gave pure product as white solid in most cases except in few cases where yellow or colorless oil was obtained which was further purified by column chromatography (solvent system: EtOAc–hexanes 70 : 30). A similar procedure was used for the synthesis of compounds **24–26** with the only exception being that 3,3-diethoxy-prop-1-yne **15** was used instead of hexyne **14**.

Compound 16. White solid; yield (0.236 g, 95%); mp 158–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 8.0 Hz, 2H), 7.25 (t, J = 7.0 Hz, 2H), 7.19–7.15 (m, 1H), 5.14 (t, J = 10.0 Hz, 1H), 3.52–3.38 (m, 2H), 2.89 (t, J = 9.0 Hz, 1H), 2.63 (t, J = 10.5 Hz, 1H), 2.12 (t, J = 7.0 Hz, 1H), 1.96 (t, J = 10.5 Hz, 2H), 1.69–1.67 (m, 2H), 1.42–1.37 (m, 2H), 1.34–1.30 (m, 2H), 1.20–1.18 (m, 5H), 1.09 (d, J = 5.5 Hz, 7H), 0.84–0.76 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 128.3 (2C), 127.2, 126.5 (2C), 84.4, 81.3 (d, J = 4.3 Hz), 59.9 (d, J = 10.8 Hz), 59.0 (d, J = 9.8 Hz), 47.7 (d, J = 1.3 Hz), 44.3 (d, J = 3.0 Hz), 43.8 (d, J = 4.5 Hz), 31.5, 30.9 (d, J = 11.3 Hz), 30.7, 30.6 (d, J = 6.8 Hz), 24.3, 23.0 (d, J = 6.3 Hz), 22.7 (d, J = 4.0 Hz), 21.9, 19.9, 19.7 (d, J = 1.5 Hz), 18.4, 13.5; ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.6.

Compound 17. White solid; yield (0.239 g, 97%); mp 164–166 °C; $[\alpha]_D^{25} = -68.1$ (c 0.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.48 (m, 2H), 7.00 (t, J = 5 Hz, 2H), 5.23 (t, J = 9.5 Hz, 1H), 3.61–3.50 (m, 1H), 3.48–3.38 (m, 1H), 2.96 (t, J = 12.5 Hz, 1H), 2.73 (t, J = 10.0 Hz, 1H), 2.63 (t, J = 10.0 Hz, 1H), 2.20 (t, J = 7.0 Hz, 2H), 2.05–2.02 (m, 2H), 1.77–1.75 (m, 2H), 1.50–1.44 (m, 2H), 1.43–1.27 (m, 5H), 1.25 (d, J = 6.5 Hz, 4H), 1.21 (d, J = 7.0 Hz, 3H), 1.15 (dd, J = 7.0, 13.5 Hz, 6H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 161.0, 138.6, 128.3 (d, J = 8.0 Hz), 115.1, 115.0, 84.8, 81.1 (d, J = 4.8 Hz), 59.9 (d, J = 10.7 Hz), 59.0, 58.9, 47.1, 44.3 (d, J = 3.0 Hz), 43.8 (d, J = 4.3 Hz), 31.0 (d, J = 11.3 Hz), 30.7, 30.6 (d, J = 9.8 Hz), 24.3, 23.1 (d, J = 6.5 Hz), 22.6 (d, J = 4.0 Hz), 21.9, 19.9, 19.8 (d, J = 1.5 Hz), 18.4, 13.5; ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.4; LCMS: m/z 448.0 $(M + H)^+$.

Compound 18. White solid; yield (0.235 g, 93%); mp 138–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, J = 7.5 Hz, 1H), 7.25–7.21 (m, 1H), 7.11 (t, J = 6.5 Hz, 1H), 7.02 (t, J = 10.5 Hz, 1H), 5.31 (t, J = 10.5 Hz, 1H), 3.47–3.37 (m, 2H), 3.01 (t, J = 10.5 Hz, 1H), 2.95 (t, J = 11.5 Hz, 1H), 2.77 (t, J = 10.0 Hz, 1H), 2.15 (t, J = 7.0 Hz, 2H), 2.06–2.00 (m, 2H), 1.76 (m, 2H), 1.46–1.41 (m, 2H), 1.40–1.25 (m, 6H), 1.24 (d, J = 6.5 Hz, 3H), 1.17 (d, J = 7.0 Hz, 3H), 1.08 (dd, J = 6.5, 10.0 Hz, 6H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 130.2 (d, J = 3.8 Hz), 128.9 (d, J = 8.3 Hz), 128.2 (d, J = 3.8 Hz), 124.2 (d, J = 3.3 Hz), 115.7 (d, J = 21.2 Hz), 83.9, 80.3 (d, J = 5.8 Hz), 59.99, 59.90, 59.1 (d, J = 9.8 Hz), 44.3 (d, J = 3.0 Hz), 43.7 (d, J = 4.3 Hz), 42.9 (t, J = 2.5 Hz), 30.7 (d, J = 11.2 Hz), 30.6, 30.5, 24.3 (d, J = 5.5 Hz), 22.7 (d, J = 6.5 Hz), 22.5 (d, J = 3.3 Hz), 21.8, 19.8, 19.6 (d, J = 1.5 Hz), 18.3, 13.5; ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.1; LCMS: m/z 448.0 $(M + H)^+$.

Compound 19. Colorless oil; yield (0.232 g, 95%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 7.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 6.5 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 5.38 (t, J = 11.0 Hz, 1H), 3.53–3.45 (m, 1H), 3.39–3.31 (m, 1H), 3.27 (t, J = 9.5 Hz, 1H), 2.96 (t, J = 11.0 Hz, 1H), 2.79 (t, J = 9.5 Hz, 1H), 2.13 (t, J = 7.0 Hz, 2H), 2.09–2.07 (m, 1H), 1.99–1.98 (m, 1H), 1.78–1.76 (m, 2H), 1.45–1.40 (m, 3H), 1.39–1.31 (m, 4H), 1.30 (d, J = 7.0 Hz, 4H), 1.24 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.90–0.85 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2 (d, J = 3.8 Hz), 132.1, 129.6, 128.4, 128.2, 127.1, 84.2, 80.0 (d, J = 6.0 Hz), 60.0 (d, J = 10.8 Hz), 59.2 (d, J = 9.8 Hz), 45.5 (d, J = 1.8 Hz), 44.3 (d, J = 2.8 Hz), 43.6 (t, J = 5.0 Hz), 30.8 (d, J = 4.3 Hz), 30.7 (d, J = 2.3 Hz), 30.5, 24.3 (d, J = 1.0 Hz), 24.2 (d, J = 1.5 Hz), 22.9, 22.8 (d, J = 2.8 Hz), 21.8, 19.8, 19.2 (d, J = 2.0 Hz), 18.3, 13.5; ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.5.

Compound 20. Colorless oil; yield (0.234 g, 96%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (t, J = 6.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 5.38 (t, J = 10.5 Hz, 1H), 3.57–3.49 (m, 1H), 3.39–3.28 (m, 2H), 2.97 (t, J = 10.5 Hz, 1H), 2.84 (t, J = 10.0 Hz, 1H), 2.13 (t, J = 7.0 Hz, 3H), 1.99–1.97 (m, 1H), 1.78–1.73 (m, 2H), 1.45–1.38 (m, 2H), 1.37–1.29 (m, 9H), 1.27 (d, J = 6.5 Hz, 3H), 0.95 (d, J = 6.5 Hz, 3H), 0.88–0.82 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8 (d, J = 4.0 Hz), 132.8, 128.7,

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128.3, 127.8, 122.1, 84.4, 79.9 (d, $J = 6.3$ Hz), 60.0 (d, $J = 10.8$ Hz), 59.2 (d, $J = 9.8$ Hz), 47.7, 44.3 (d, $J = 2.8$ Hz), 43.6 (t, $J = 4.5$ Hz), 30.88, 30.80 (d, $J = 1.3$ Hz), 30.5, 24.3, 24.2, 23.0 (d, $J = 2.8$ Hz), 22.9 (d, $J = 6.5$ Hz), 21.8, 19.9, 19.1 (d, $J = 2.0$ Hz), 18.3, 13.5; ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.6.

Compound 21. White solid; yield (0.242 g, 98%); mp 120–122 °C; $[\alpha]_D^{25} = -73.7$ (c 0.59, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, $J = 7.5$ Hz, 1H), 7.20–7.11 (m, 3H), 5.21 (t, $J = 10.5$ Hz, 1H), 3.51–3.42 (m, 2H), 2.99–2.90 (m, 2H), 2.72 (t, $J = 10.5$ Hz, 1H), 2.45 (s, 3H), 2.13 (t, $J = 7.0$ Hz, 2H), 2.09–2.07 (m, 1H), 2.01–1.99 (m, 1H), 1.78–1.76 (m, 2H), 1.44–1.29 (m, 7H), 1.28 (d, $J = 6.5$ Hz, 4H), 1.21 (d, $J = 6.5$ Hz, 3H), 1.05 (d, $J = 7.0$ Hz, 3H), 0.98 (d, $J = 7.0$ Hz, 3H), 0.87 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8 (d, $J = 4.5$ Hz), 134.7, 130.5, 127.1, 126.1, 125.7, 83.6, 80.0 (d, $J = 6.0$ Hz), 60.0 (d, $J = 10.8$ Hz), 59.2 (d, $J = 9.8$ Hz), 45.2, 44.2 (d, $J = 3.5$ Hz), 43.6 (t, $J = 4.3$ Hz), 31.0, 30.9, 30.8 (d, $J = 8.8$ Hz), 30.6, 24.3 (d, $J = 2.5$ Hz), 23.1, 23.0, 22.9 (d, $J = 3.8$ Hz), 21.8, 19.8, 19.2 (d, $J = 1.5$ Hz), 18.4, 13.5; ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.7; LCMS: m/z 444.0 $(M + H)^+$.

Compound 22. Colorless oil; yield (0.230 g, 95%); $[\alpha]_D^{25} = -80.4$ (c 0.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, $J = 7.5$ Hz, 1H), 7.21 (t, $J = 8.0$ Hz, 1H), 6.90 (t, $J = 7.0$ Hz, 1H), 6.85 (t, $J = 8.0$ Hz, 1H), 5.24 (t, $J = 10.5$ Hz, 1H), 3.85 (s, 3H), 3.49–3.33 (m, 2H), 3.28 (t, $J = 11.0$ Hz, 1H), 2.94 (t, $J = 11.0$ Hz, 1H), 2.78 (t, $J = 10.5$ Hz, 1H), 2.11 (t, $J = 6.5$ Hz, 2H), 2.07–1.98 (m, 2H), 1.74 (m, 2H), 1.42–1.28 (m, 7H), 1.26 (d, $J = 7.0$ Hz, 4H), 1.19 (d, $J = 6.5$ Hz, 3H), 1.01 (t, $J = 7.0$ Hz, 6H), 0.86 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 131.0 (d, $J = 4.5$ Hz), 128.4, 127.8 (d, $J = 15.2$ Hz), 120.6, 111.0, 82.5, 81.5 (d, $J = 5.3$ Hz), 60.0 (d, $J = 10.7$ Hz), 59.1 (d, $J = 9.8$ Hz), 55.4, 44.2 (d, $J = 3.3$ Hz), 43.9, 43.6 (t, $J = 4.5$ Hz), 30.79, 30.72, 30.68, 30.60, 24.3 (d, $J = 1.2$ Hz), 22.8 (d, $J = 6.0$ Hz), 22.7 (d, $J = 3.5$ Hz), 21.7, 19.9, 19.5 (d, $J = 2.0$ Hz), 18.4, 13.5; ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.5; LCMS: m/z 460.0 $(M + H)^+$.

Compound 23. Colorless oil; yield (0.231 g, 92%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 7.5$ Hz, 1H), 7.59 (t, $J = 7.5$ Hz, 1H), 7.41 (t, $J = 7.5$ Hz, 1H), 5.73 (t, $J = 11.0$ Hz, 1H), 3.59–3.32 (m, 3H), 2.95 (t, $J = 11.0$ Hz, 1H), 2.67 (t, $J = 10.0$ Hz, 1H), 2.09 (t, $J = 7.0$ Hz, 2H), 1.76 (m, 2H), 1.42–1.23 (m, 10H), 1.21 (d, $J = 7.0$ Hz, 3H), 1.15 (d, $J = 6.5$ Hz, 3H), 1.09 (d, $J = 6.5$ Hz, 6H), 0.86 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 137.2 (d, $J = 4.5$ Hz), 133.2, 129.8, 128.2, 124.7, 84.2, 78.7 (d, $J = 6.0$ Hz), 59.8 (d, $J = 10.3$ Hz), 59.1 (d, $J = 10.3$ Hz), 45.3 (d, $J = 2.8$ Hz), 44.3 (d, $J = 2.8$ Hz), 43.7 (t, $J = 4.3$ Hz), 30.58, 30.50 (d, $J = 4.8$ Hz), 30.4, 30.3, 24.2 (d, $J = 1.0$ Hz), 24.1 (d, $J = 1.0$ Hz), 22.5 (d, $J = 3.3$ Hz), 21.7, 19.9, 19.2 (d, $J = 2.0$ Hz), 18.1, 13.4; ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.5.

Compound 24. Colorless oil; yield (0.238 g, 97%); $[\alpha]_D^{25} = -78.4$ (c 0.52, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, $J = 7.5$ Hz, 2H), 7.33 (t, $J = 7.5$ Hz, 2H), 7.27 (d, $J = 7.0$ Hz, 1H), 5.35 (t, $J = 9.5$ Hz, 1H), 5.29 (d, $J = 1.5$ Hz, 1H), 3.76–3.68 (m, 3H), 3.61–3.52 (m, 4H), 3.48–3.39 (m, 1H), 2.96 (t, $J = 11.5$ Hz, 1H), 2.77 (t, $J = 10.5$ Hz, 2H), 2.05 (d, $J = 11.5$ Hz, 2H), 1.77 (d, $J = 11.5$ Hz, 2H), 1.25–1.19 (m, 14H), 1.16–1.12 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2 (d, $J = 4.3$ Hz), 128.4 (2C), 127.5, 126.6 (2C), 91.4, 86.4 (d, $J = 5.0$ Hz), 79.5, 60.7, 59.9 (d, $J = 10.3$ Hz), 59.1 (d, $J = 9.8$ Hz), 47.5, 44.3 (d, $J = 3.0$ Hz), 43.8 (d, $J = 4.0$ Hz), 31.1, 30.8, 30.7, 30.6 (d, $J = 9.3$ Hz), 24.2, 22.9, 22.8 (d, $J = 3.3$ Hz), 19.9, 19.7 (d, $J = 1.5$ Hz), 15.0 (2C); ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.2.

Compound 25. Colorless oil; yield (0.237 g, 98%); $[\alpha]_D^{25} = -84.6$ (c 0.52, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, $J = 7.5$ Hz, 1H), 7.22 (q, $J = 7.5$ Hz, 1H), 7.07 (t, $J = 7.5$ Hz, 1H), 6.99 (t, $J = 9.5$ Hz, 1H), 5.41 (t, $J = 10.5$ Hz, 1H), 5.21 (d, $J = 1.0$ Hz, 1H), 3.67–3.61 (m, 2H), 3.53–3.47 (m, 2H), 3.44–3.37 (m, 1H), 3.35–3.29 (m, 1H), 3.03 (t, $J = 10.5$ Hz, 1H), 2.90 (t, $J = 12.0$ Hz, 1H), 2.72 (d, $J = 10.0$ Hz, 1H), 2.01–1.98 (m, 2H), 1.73–1.72 (m, 2H), 1.31–1.24 (m, 2H), 1.17–1.13 (m, 11H), 1.09 (t, $J = 7.0$ Hz, 6H), 1.053 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 159.0, 129.3 (d, $J = 7.8$ Hz), 128.4 (d, $J = 4.0$ Hz), 124.2 (d, $J = 3.3$ Hz), 115.7 (d, $J = 21.2$ Hz), 91.2, 85.2 (d, $J = 5.5$ Hz), 78.7, 60.6 (2C), 59.8 (d, $J = 10.3$ Hz), 59.1 (d, $J = 9.8$ Hz), 44.2 (d, $J = 2.8$ Hz), 43.8 (d, $J = 4.5$ Hz), 42.9, 30.5, 30.4, 24.22, 24.20 (d, $J = 0.8$ Hz), 22.55, 22.52 (d, $J = 2.0$ Hz), 19.8, 19.6 (d, $J = 1.5$ Hz), 15.9 (2C); ^{31}P NMR (202 MHz; $CDCl_3$) δ 21.7; LCMS: m/z 516.0 $(M + Na)^+$.

Compound 26. Colorless oil; yield (0.238 g, 96%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.50 (m, 2H), 7.32 (t, $J = 8.0$ Hz, 1H), 7.13 (t, $J = 9.0$ Hz, 1H), 5.50 (t, $J = 10.5$ Hz, 1H), 5.23 (d, $J = 1.5$ Hz, 1H), 3.70–3.64 (m, 2H), 3.54–3.33 (m, 5H), 2.97 (t, $J = 10.5$ Hz, 1H), 2.82 (t, $J = 7.5$ Hz, 1H), 2.09 (d, $J = 11.0$ Hz, 1H), 2.00 (d, $J = 7.5$ Hz, 1H), 1.78–1.76 (m, 2H), 1.30 (d, $J = 7.0$ Hz, 6H), 1.23 (d, $J = 6.5$ Hz, 4H), 1.17 (t, $J = 7.0$ Hz, 6H), 0.99 (d, $J = 6.5$ Hz, 3H), 0.914 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4 (d, $J = 4.0$ Hz), 133.0, 129.1, 128.6, 127.8, 122.2, 91.2, 84.9 (d, $J = 6.3$ Hz), 79.2, 60.7, 60.0 (d, $J = 10.8$ Hz), 59.1 (d, $J = 10.3$ Hz), 47.7 (d, $J = 2.5$ Hz), 44.3 (d, $J = 3.3$ Hz), 43.6 (d, $J = 4.3$ Hz), 30.8, 30.7 (d, $J = 2.0$ Hz), 30.6, 24.3, 24.2 (d, $J = 1.5$ Hz), 23.0 (d, $J = 3.5$ Hz), 22.8 (d, $J = 5.8$ Hz), 19.9, 19.2 (d, $J = 2.0$ Hz), 14.9 (2C); ^{31}P NMR (202 MHz; $CDCl_3$) δ 22.1.

Procedure for the removal of auxiliary and synthesis of *N*-acetyl derivative

In a 50 mL round bottom flask, 0.438 g of product **10a** was dissolved in 6.0 mL methanol. To this solution was added 3 M HCl (8.0 equiv.) at 0 °C and the reaction was stirred at 0 °C for 30 min and then at room temperature for 2 h. The reaction was monitored by TLC and completion of the reaction was indicated by the disappearance of the starting material on TLC. Volatiles were evaporated under vacuum and then dichloromethane was added to the solid residue. The mixture was stirred at 0 °C and diisopropylethylamine and acetic anhydride were added at the same temperature. The reaction was stirred at 0 °C for 30 min and then at rt for 2 h. After that the resulting mixture was extracted with water and ethyl acetate. The organic layer was dried over sodium sulfate. The sodium sulfate was filtered off and the organic layer was dried under vacuum to get the product which was then triturated with hexanes to get the pure product as a white solid. Mp 174 °C; $[\alpha]_D^{25} = -40.4$ (c 0.50, $CHCl_3$) (reported:[19] +36.1, c 0.86, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, $J = 7.0$ Hz, 2H), 7.48–7.46 (m, 2H), 7.47 (t, $J = 7.5$ Hz, 2H), 7.32 (t, $J = 4.5$ Hz, 4H), 6.24 (s, 2H), 2.03 (s, 3H); ^{13}C NMR (125 MHz,

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$CDCl_3$) δ 168.7, 139.0, 131.7 (2C), 128.6 (2C), 128.5, 128.2 (2C), 128.0, 127.0 (2C), 122.3, 86.9, 84.6, 45.0, 23.1.

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