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Asymmetric synthesis of 1-vinyltetrahydroisoquinoline through Pd-catalyzed intramolecular allylic amination

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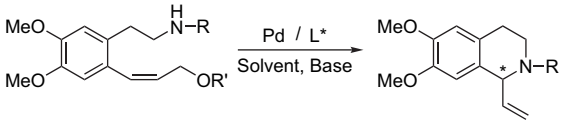
Abstract—Asymmetric synthesis of 6,7-dimethoxy-1-vinyltetrahydroisoquinolines through Pd-catalyzed intramolecular allylic amination of 3-(amidoethylphenyl)prop-2-enyl carbonates was studied, using a library of fine-tunable monodentate phosphoramidite ligands. Under optimized conditions, excellent enantiopurity (up to 96% ee) and 100% product selectivity were achieved. 1-Vinyltetrahydroquinoline thus obtained is a highly versatile intermediate for the synthesis of various biologically active alkaloids of medicinal interest.

1. Introduction

C1-Substituted tetrahydroisoquinolines are abundantly found in nature, especially in a variety of plants, soil, and marine microorganisms, and provide important synthetic targets because of their pharmacological properties.[1] Members of this family have shown diverse activities,[1] e.g., cytotoxicity,[2] antagonist activity to D1 and NMDA receptors,[3] analgesic activity,[4] pathogenesis of Parkinson's disease,[5] and enzyme inhibitory activities for glucosidases[6] and monoamine oxidases.[7] Thus, the synthesis of this class of compounds in optically active forms is very important for the study of their biological and pharmacological activities, hence has attracted much interest in developing efficient methods and methodologies among synthetic organic chemists.[8,9]

Traditionally, the synthesis of optically active C1-substituted tetrahydroisoquinolines relied largely on the diastereoselective reactions to introduce the chirality at the C1 position.[10] Several enantioselective catalytic approaches have recently been developed for the introduction of chirality at the C1 position, e.g., enantioselective Pictet–Spengler reaction,[11] enantioselective alkylation, vinylation, alkynylation or cyanation of 3,4-dihydroisoquinolines,[12–17] enantioselective alkynylation of tetrahydroisoquinolines,[18] asymmetric hydrogenation of 3,4-dihydroisoquinolines[19,20] as well as 1-alkylidenetetrahydroisoquinolines,[21] etc.[8]

In 2003, a Pd-catalyzed intramolecular asymmetric allylic amination approach was reported by Katsuki and coworkers, which was able to construct the heterocycle by introducing the chirality at the C1 position simultaneously in a single step (Scheme 1).[22] The reaction led to a highly versatile C1-substituted tetrahydroisoquinoline, which can be easily transformed into various tetrahydroisoquinoline alkaloids. This could be a highly efficient approach if excellent reaction rate and enantioselectivity were attained. The chiral Pd catalyst system used in this process was, however, not able to achieve high catalytic activity (12–23 days were needed to reach synthetically meaningful conversions) although very good enantioselectivity (82–88% ee under the optimized conditions) was achieved.[22] Accordingly, the development of more efficient chiral Pd catalyst systems is apparently necessary to make this process highly efficient and synthetically useful.



Scheme 1. Pd-catalyzed intramolecular allylic amination approach to 1-vinyltetrahydroisoquinolines.

In order to achieve high efficiency in the reaction rate and enantioselectivity, the development of suitable chiral ligands for this process is crucial. We have been developing a library of novel enantiopure monodentate phosphoramidite and phosphite ligands based on axially chiral biphenols, which can be readily prepared and modified, for a variety of catalytic asymmetric reactions.[23] The salient feature of these ligands is their fine-tuning capability through modification of the R^1, R^2, and R^3 groups (Fig. 1). High catalytic activity and enantioselectivity have been achieved in various transition metal-catalyzed transformations, including asymmetric

Keywords: Asymmetric synthesis; Allylic amination; Palladium; Monodentate phosphoramidite; Alkaloid; Tetrahydroisoquinoline.
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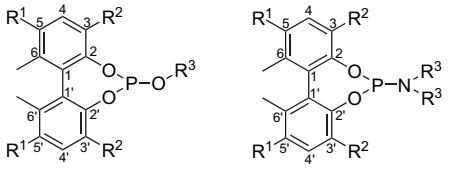


Figure 1. Chiral biphenol-based phosphoramidite and phosphite ligands.

hydrogenation,[24] asymmetric hydroformylation,[23] asymmetric conjugate additions to cycloalkenones and nitroalkenes,[23,25] and asymmetric allylic alkylation as well as its application to the total synthesis of (+)-γ-lycorane.[26,27] Since a couple of these chiral monodentate phosphoramidite ligands were found to be extremely effective (up to 99.7% ee) in the Pd-catalyzed asymmetric allylic alkylation, we thought this type of ligands would be effective for the asymmetric allylic amination process as well and optimization could be done through systematic modifications through library synthesis.

We describe here a successful application of these novel phosphoramidite ligands to the Pd-catalyzed intramolecular allylic amination reaction for the asymmetric synthesis of 1-vinyltetrahydroisoquinolines (Scheme 1), which have been obtained in nearly quantitative yields and excellent enantiopurity up to 96% ee.

2. Results and discussion

2.1. Monodentate phosphoramidite ligand library

A library of enantiopure monodentate phosphoramidite ligands consisting of various biphenol moieties and amine moieties were prepared according to the procedures reported previously by our laboratory[23,24,27] (Fig. 2) and used for the intramolecular allylic amination reactions.

2.2. Preparation of 3-(amidoethylphenyl)prop-2-enyl carbonate substrates

A series of 3-(amidoethylphenyl)prop-2-enyl carbonates **5** were prepared, largely following the procedure reported by Katsuki and co-workers for two substrates,[22] with modifications. Scheme 2 illustrates the syntheses of these substrates **5**, starting from commercially available 3,4-dimethoxyphenylethylamine (**1**). For the preparation of **5a-1** and **5a-2** and **5b-1**–**5b-3**, the amine moiety of **1** was converted to tosylamide and trifluoroacetylamide first and then iodinated to give **2a** and **2b**, respectively. Katsuki and co-workers used HIO_3/I_2 for this iodination for the preparation of **2b** (66% yield). We used ICl in place of HIO_3/I_2 and obtained **2b** in 95% yield. Sonogashira coupling of **2a** and **2b** with propargyl alcohol gave **3a** and **3b**, which were subsequently hydrogenated over P2–Ni to afford the corresponding *Z*-alcohols **4a** and **4b**, respectively, in excellent overall yields. The *Z*-allylic alcohols **4**, thus obtained, were acylated with chloroformates (Me, vinyl, and Ph) to give the carbonates **5a-1** and **5a-2** and **5b-1**–**5a-3** in excellent yields. Katsuki and co-workers used (trifluoroacetylaminoethylphenyl)-prop-2-enyl acetate and pivaloate, but we found that the intramolecular allylic amination reaction using our ligands proceeded much faster when the corresponding carbonates were used in a preliminary feasibility study. Thus, we employed only carbonates in this work. In addition, we used tosyl besides trifluoroacetyl for the amide moiety. The *tert*-butyl carbonate **5a-3** was prepared by using $(t\text{-Boc})_2O$ in the acylation of **4a**. For the preparation of *E*-allylic carbonate **5a-1-t**, **2a** was subjected to the Heck reaction with methyl acrylate to give **6a**, which was subsequently reduced by DIBAL-H to afford *E*-allylic alcohol **4a-t**. Then, **4a-t** was reacted with methyl chloroformate to give *E*-allylic carbonate substrate **5a-1-t** in high overall yield.

2.3. Pd-catalyzed intramolecular asymmetric allylic amination of substrates 5

The screening of the best chiral ligand among the small library of monodentate phosphoramidite ligands, **L1**–**L7**, shown in Figure 2 was conducted in two steps. First, we examined the effect of the amine moiety on the catalyst activity and enantioselectivity, using **5a-1** as the substrate (Scheme 3). For this comparison, we used ligands **L1a** and **L2**–**L7**, which do not have any susbtituents at the 3 and 3′ positions of the biphenyl moiety. The reactions were carried out in CH_2Cl_2 using $Pd_2(dba)_3$ (2.5 mol %) and 3 equiv of a chiral ligand/Pd at 0.05 M concentration of **5a-1** at room temperature (25 °C). Results are summarized in Table 1.

As Table 1 shows, all reactions completed within 5–12 h to give the desired cyclization product **7a**(*R*) in quantitative

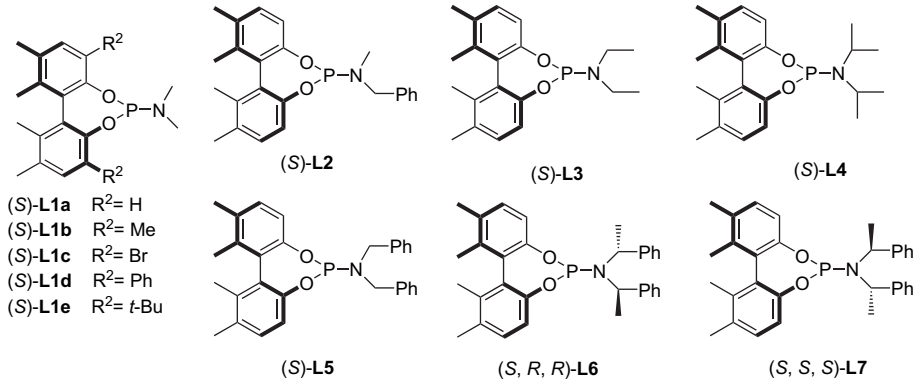
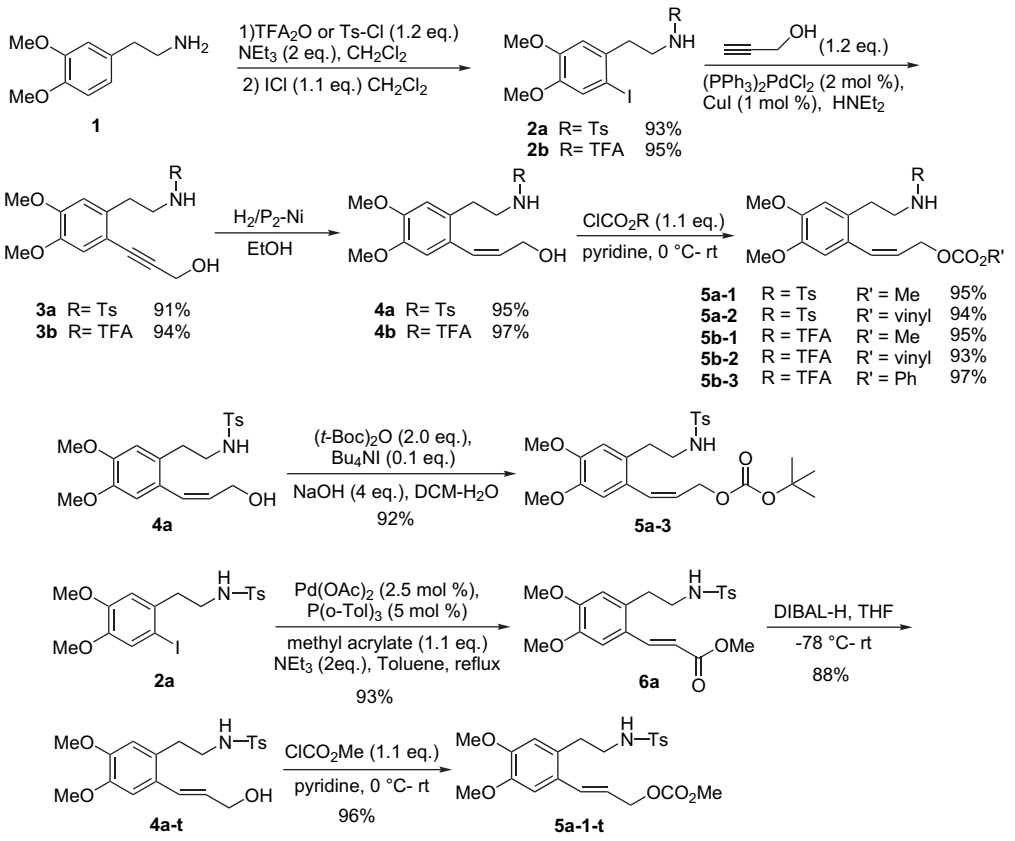
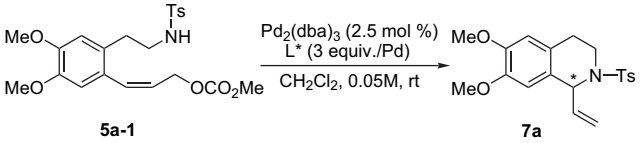


Figure 2. Library of enantiopure monodentate phosphoramidite ligands used in this study.



Scheme 2. Preparation of substrates **5**.



Scheme 3. Intramolecular asymmetric allylic amination of **5a-1** for ligand screening.

Table 1. Ligand screening: effect of the amine moiety

Entry	Ligand	Time (h)	Conv.[a,b] (%)	% ee[b]
1	**L1a**	5	100	45 (*R*)
2	**L2**	5	100	25 (*R*)
3	**L3**	7	100	42 (*R*)
4	**L4**	7	100	0.5 (*R*)
5	**L5**	7	100	13 (*R*)
6	**L6**	12	100	45 (*R*)
7	**L7**	12	100	0.1 (*R*)

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC using Chiralpak AD-RH, CH_3CN/H_2O.

yield based on the ^{1}H NMR and HPLC analyses. It is worthy of note that this catalyst/reaction system does not require any additional base, e.g., Cs_2CO_3, K_2CO_3, and Na_2CO_3, which is essential for Katsuki's catalyst/reaction system in CH_2Cl_2.[22] It is clear from the results shown in Table 1 that bulkier the amine moiety becomes, slower the reaction. Also, bulkier amine moieties give lower enantioselectivity as exemplified by the use of **L4** bearing a diisopropylamine moiety (entry 4). Only exception for this general observation is ligand **L6**(*S*,*R*,*R*), which bears a bulky bis(1-phenylethyl)amine moiety (entry 6). However, ligand **L7**(*S*,*S*,*S*), which is a diastereomer of **L6**(*S*,*R*,*R*), induces virtually no asymmetric induction (entry 7). These results clearly indicate that **L6** is a matching pair and **L7** mismatching pair. It is of interest to note that ligand **L7** was one of the better ligands in the asymmetric allylic alkylation reaction for (+)-lycorane synthesis, achieving 92.6% ee.[26] The observed sharp contrast indicates how different these two reaction systems are even though both are asymmetric allylic substitution reactions. After the first screening, we selected **L1a** bearing a small dimethylamine moiety as our lead ligand in terms of the catalyst activity and enantioselectivity.

Next, the effect of the substituent R^2 at the 3 and 3′ positions of the biphenyl moiety on the catalytic activity and enantioselectivity was examined under the same reaction conditions as those for the first ligand screening mentioned above. Thus, ligands **L1a**–**L1e** were examined for their efficacy in the formation of tetrahydroisoquinoline **7a**. Results are shown in Table 2. Apparently, the enantioselectivity increases (45% ee±74% ee) as the bulkiness of the substituent at the 3 and 3′ positions increases, i.e., H<Me<Br<Ph (entries 1–4), but *t*-Bu is so bulky that it causes negative effect (entry 5). However, the most dramatic effect of the 3,3′-substituents is the direction of asymmetric induction, i.e., **L1a** (R^2=H) induces *R* configuration in the product **7a**, while **L1b** (R^2=Me), **L1c** (R^2=Br), **L1d** (R^2=Ph), and **L1e** (R^2=*t*-Bu) give **7a** with *S* configuration. Thus, the substituent R^2 at the 3 and 3′ positions exert a significant influence on the extent and direction of asymmetric induction, as anticipated from our experience in the previous catalytic

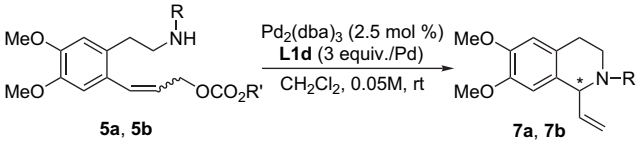
Table 2. Ligand screening: effect of the substituent R^2

Entry	Ligand	Time (h)	Conv.[a,b] (%)	% ee[b]
1	**L1a** (R^2=H)	5	100	45 (*R*)
2	**L1b** (R^2=Me)	7	100	48 (*S*)
3	**L1c** (R^2=Br)	10	100	59 (*S*)
4	**L1d** (R^2=Ph)	10	100	74 (*S*)
5	**L1e** (R^2=*t*-Bu)	16	100	23 (*S*)

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC using Chiralpak AD-RH, CH_3CN/H_2O.

asymmetric transformations using this type of ligands.[23–27] After two-step ligand screenings, we selected **L1d** (R^2=Ph) as the ligand of choice for the intramolecular asymmetric allylic amination of the substrates of this type.

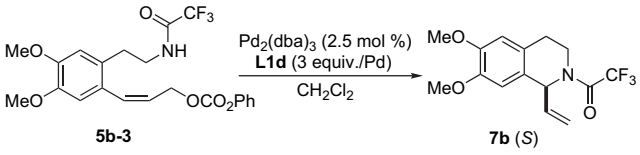
Although the enantioselectivity attained by **L1d** was only 74% ee in the reaction of **5a-1**, we hypothesized that much higher enantioselectivity could be achieved through modification of the substrate structure. In fact, as described below, excellent enantioselectivity (95% ee) has been, indeed, achieved through substrate structure modifications. As described above, we have prepared six substrates bearing an *N*-tosyl moiety (**5a**) and an *N*-trifluoroacetyl moiety (**5b**) as well as methyl, vinyl, *tert*-butyl, and phenyl in the carbonate moiety. In addition to the six substrates bearing a *Z* olefin moiety, a substrate with *E* olefin geometry, **5a-1-t**, was also prepared and examined. The reactions were run under the same conditions as those used for the screening of the ligands described above, using **L1d** as the chiral ligand (Scheme 4). Results are summarized in Table 3.



Scheme 4. Reactions of **5a** and **5b** using **L1d** as the chiral ligand.

As Table 3 shows, the bulkiness of the carbonate substituent R′ does not have much influence on the reaction in the **5a** series of substrates (R=Ts) although *t*-Bu-carbonate **5a-3** gives a slightly better enantioselectivity (77% ee) and slower reaction rate (entry 3) than Me-carbonate **5a-1** (entry 1). The introduction of a vinyl group to the carbonate moiety accelerates the reaction, but lowers enantioselectivity (entry 2). The geometry of the olefin moiety is critical for the direction of asymmetric induction, i.e., the substrate bearing an *E* olefin geometry, **5a-1-t**, gives **7a** with opposite configuration (*R*) (entry 4), but the enantiopurity of the product (71% ee) is only slightly lower than **7a**(*S*) obtained in the reaction of **5a-1** with *Z* olefin geometry (entry 1). The results indicate that the sense of enantioface selection by the chiral catalyst is the same in these two cases, leading to the formation of the two enantiomers of **7a**. In contrast to the **5a** series, the reactions of the **5b** series (R=CF_3CO) are highly sensitive to the carbonate substituent R′ (entries 5–7). The introduction of a vinyl- or a phenyl-carbonate to the **5b** series substantially increases the enantioselectivity of the reaction, and tetrahydroisoquinoline **7b** with 95% ee (*S*) is obtained with the phenyl-carbonate substrate **5b-3** (entry 7). It is also noteworthy that a marked difference is observed between **5a-2** (46% ee) and **5b-2** (89% ee), which have the same vinyl-carbonate moiety but differs in the amide moiety, i.e., *N*-Ts versus *N*-CF_3CO (entries 2 and 6).

Finally, the effects of the reaction variables, i.e., reaction temperature and concentration, on the reaction rate and enantioselectivity were examined with the optimized ligand and substrate combination using **L1d** as the chiral ligand and **5b-3** as the substrate (Scheme 5). As Table 4 shows, the substrate concentration only affects reaction rate, as anticipated. The enantioselectivity increases slightly when the reaction is run at a lower temperature (−25 °C) (entry 5, 96% ee). However, the enantioselectivity clearly drops when the reaction is carried out at 50 °C (entry 6, 84% ee). Thus, the reaction at room temperature (25 °C) and 0.5 M concentration appears to be near optimal, which is synthetically very convenient.



Scheme 5. Highly efficient catalytic asymmetric synthesis of tetrahydroisoquinoline **7b**.

3. Experimental

3.1. General method and material

^{1}H and ^{13}C NMR spectra were measured on a Varian Inova-300 NMR or a Varian Inova-400 NMR spectrometer in a deuterated solvent. The enantiomeric excess was determined by HPLC: Waters M45 system with Waters 484 detector using

Table 3. Reactions of **5a** and **5b** using **L1d** as the chiral ligand

Entry	Substrate	R	R′	Olefin geometry	Time (h)	Conv.[a,b] (%)	% ee[b]
1	**5a-1**	Ts	Me	*Z*	10	100	74 (*S*)
2	**5a-2**	Ts	Vinyl	*Z*	5	100	46 (*S*)
3	**5a-3**	Ts	*t*-Bu	*Z*	18	100	77 (*S*)
4	**5a-1-t**	Ts	Me	*E*	10	100	71 (*R*)
5	**5b-1**	CF_3CO	Me	*Z*	10	100	79 (*S*)
6	**5b-2**	CF_3CO	Vinyl	*Z*	7	100	89 (*S*)
7	**5b-3**	CF_3CO	Ph	*Z*	7	100	95 (*S*)

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC; for *N*-Ts products **7a**: Chiralpak AD-RH, CH_3CN/H_2O; for *N*-TFA products **7b**: Chiralcel OD-H, hexanes/*i*-PrOH.

Table 4. Effects of reaction temperature and concentration

Entry	Concn (M)	Temp (°C)	Time (h)	Conv.[a,b] (%)	% ee[b]
1	0.01	25	14	100	95 (*S*)
2	0.05	25	7	100	95 (*S*)
3	0.5	25	6	100[c]	94 (*S*)
4	0.05	0	10	100	95 (*S*)
5	0.05	−25	14	100	96 (*S*)
6[d]	0.05	50	5	100	84 (*S*)

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC using Chiralcel OD-H, hexanes/*i*-PrOH.
[c] Isolated yield of 87% (100% product selectivity) in 1.0 mmol scale reaction.
[d] Reaction was performed in a sealed tube.

Chiralcel OD-H column (hexanes/*i*-PrOH=98:2, 0.5 mL/min) or a Shimadzu LC-2010A HPLC system using a Chiralpak AD-RH column (CH_3CN/H_2O=50:50, 0.5 mL/min). Melting points were measured on a Thomas Hoover Capillary melting point apparatus. Optical rotations were measured on a Perkin–Elmer Model 241 polarimeter. TLC was performed on Merck DC-alufolien with Kieselgel $60F_{254}$ and flash chromatography was carried out on silica gel 60 (Silicyle; 40–63 μm particle size). High-resolution mass spectrometric analyses were carried out at the Mass Spectrometry Laboratory, University of Illinois Urbana-Champaign, Urbana, IL. All solvents were purified using the Solvent Purification System 400-4 from Innovative Technology, Inc. All chemicals were purchased from Aldrich and Acros Chemical Co. unless otherwise noted. Tris(dibenzylideneacetone)dipalladium(0) was purchased from Strem Chemicals Inc. All reactions were carried out under nitrogen or argon atmosphere.

3.2. Monodentate phosphoramidite ligands

Chiral ligands **L1a–e**, **L4–L7** were prepared according to the procedures previously reported by our laboratory.[23,27] Two new phosphoramidite ligands, **L2** and **L3**, were obtained using the same method as that reported for the preparation of **L4** and **L5**.[27]

3.2.1. *O*,*O*′-(*S*)-(5,5′,6,6′-Tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N*-benzyl-*N*-methylphosphoramidite (L2). White solid; 75% yield; mp 106.5–108 °C; $[\alpha]_D^{22}$ 242.9 (*c* 0.40, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (s, 3H), 1.96 (s, 3H), 2.17 (d, *J*=6.0 Hz, 3H), 2.20 (s, 3H), 2.23 (s, 3H), 3.80 (dd, *J*=12.6 Hz, 15 Hz, 1H), 4.21 (dd, *J*=8.7 Hz, 15.7 Hz, 1H), 6.70 (d, *J*=7.8 Hz, 1H), 6.95–7.28 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4 (d, *J*=3.8 Hz), 20.2 (d, *J*=2.9 Hz), 32.1 (d, *J*=10.3 Hz), 53.1 (d, *J*=31.6 Hz), 118.5 (d, *J*=20.0 Hz), 127.1, 128.3 (d, *J*=13.7 Hz), 129.7, 132.3, 133.4, 136.7 (d, *J*=54.1 Hz), 138.6 (d, *J*=3.7 Hz), 148.4 (d, *J*=4.3 Hz), 149.1; ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 141.9; HRMS (EI) calcd for $C_{24}H_{26}NO_2P$ $[M]^+$ 391.1701, found 391.1703 (Δ=0.5 ppm).

3.2.2. *O*,*O*′-(*S*)-(5,5′,6,6′-Tetramethyl-1,1′-biphenyl-2,2′-diyl)-*N*,*N*-diethylphosphoramidite (L3). White solid; 85% yield; mp 123–124 °C; $[\alpha]_D^{22}$ 213.9 (*c* 0.38, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, *J*=6.9 Hz, 6H), 1.98 (s, 3H), 2.04 (s, 3H), 2.29 (s, 6H), 2.76–2.84 (m, 2H), 2.93–3.02 (m, 2H), 6.83 (d, *J*=8.1 Hz, 1H), 6.99 (d, *J*=8.1 Hz, 1H), 7.06 (d, *J*=8.1 Hz, 1H), 7.13 (d, *J*=8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (d, *J*=2.3 Hz), 17.3 (d, *J*=6.3 Hz), 20.1, 38.0 (d, *J*=21.6 Hz), 118.0, 118.5 (d. *J*=2.3 Hz), 129.2, 129.4 (d, *J*=13.4 Hz), 148.8 (d, *J*=4.0 Hz), 149.3; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 144.1; HRMS (EI) calcd for $C_{20}H_{26}NO_2P$ $[M]^+$ 343.1701, found 343.1701 (Δ=0 ppm).

3.3. Synthesis of substrates 5a-1–5a-3 and 5b-1–5b-3

3.3.1. 1-Iodo-4,5-dimethoxy-2-[2-(trifluoroacetylamino)ethyl]benzene (2b). To a stirred solution of homoveratrylamine (**1**) (1 g, 5.5 mmol) and NEt_3 (1.2 g, 11 mmol) in CH_2Cl_2 (8 mL) was added slowly trifluoroacetic anhydride (1.4 g, 6.6 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. Reaction was quenched by addition of water at the same temperature and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 three times, and combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford *N*-trifluoroacetyl-**1** as a pale yellow solid. Mp 82.0–83.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (t, *J*=6.7 Hz, 2H), 3.60 (q, *J*=6.7 Hz, 2H), 3.87 (s, 6H), 6.27 (br, 1H), 6.69 (d, *J*=1.7 Hz, 1H), 6.73 (dd, *J*=1.7 Hz, 8.1 Hz, 1H), 6.83 (d, *J*=8.1 Hz, 1H). The product was used in the next step without further purification.

To a well-stirred solution of *N*-trifluoroacetyl-**1** in CH_2Cl_2 (10 mL), 1 M ICl in CH_2Cl_2 (6.1 mL) was added dropwise at room temperature. The reaction mixture was stirred at room temperature until TLC had indicated the complete conversion of the starting material. The reaction was quenched by addition of saturated Na_2SO_3 solution. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. The crude product was obtained after filtration and evaporation of the solvent. Recrystallization of the crude product from MeOH afforded **2b** as a white solid (2.1 g, 95% yield). Mp 124.5–125.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97 (t, *J*=7.2 Hz, 2H), 3.61 (q, *J*=6.6 Hz, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 6.37 (br s, 1H), 6.69 (s, 1H), 7.24 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.9, 40.0, 55.8, 56.1, 87.9, 112.6, 115.7 (q, *J*=286 Hz), 121.8, 132.6, 148.5, 149.6, 157.3 (q, *J*=36 Hz); HRMS (ESI) calcd for $C_{12}H_{14}NO_3F_3I$ $[M+H]^+$ 403.9971, found 403.9981 (Δ=2.5 ppm).

3.3.2. 1-Iodo-4,5-dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl]benzene (2a). This compound was synthesized in the same manner as that described for **2b**. White solid; 93% isolated yield; mp 125–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.84 (t, *J*=6.9 Hz, 2H), 3.18 (q, *J*=4.8 Hz, 2H), 3.80 (s, 3H), 3.81 (s, 3H), 4.70 (br s, 1H), 6.67 (s, 1H), 7.13 (s, 1H), 7.27 (d, *J*=8.1 Hz, 2H), 7.70 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 40.2, 43.0, 55.9, 56.1, 87.9, 112.9, 121.7, 127.0, 129.6, 132.8, 136.9, 143.4, 148.3, 149.4; HRMS (ESI) calcd for $C_{17}H_{21}INO_4S$ $[M+H]^+$ 462.0236, found 462.0245 (Δ=1.9 ppm).

3.3.3. 3-{4,5-Dimethoxy-2-[2-(trifluoroacetylamino)-ethyl]phenyl}prop-2-ynol (3b). A mixture of **2b** (403 mg, 1 mmol), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol), and CuI (1.9 mg, 0.01 mmol) was placed in a 50 mL round-bottomed flask. After purging the flask with nitrogen, diethylamine (5 mL) was added to the mixture, and the solution was stirred for 20 min. Propargyl alcohol (68 mg, 1.2 mmol) was added to the reaction mixture via a syringe. The reaction mixture was stirred at room temperature until TLC indicated the completion of the reaction. Then, saturated ammonium chloride solution was added to quench the reaction. The aqueous layer was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$. Crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (hexanes/EtOAc=5:1–1:1) afforded **3b** as a white solid (311 mg, 94% yield). Mp 117.5–119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.99 (t, *J*=7.2 Hz, 2H), 3.02 (br s, 1H), 3.59 (q, *J*=7.2 Hz, 2H), 3.83 (s, 3H), 3.85 (s,

3H), 4.49 (s, 2H), 6.56 (br s, 1H), 6.89 (s, 1H), 6.98 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.5, 40.7, 51.4, 55.9, 55.9, 83.6, 90.3, 112.1, 114.4, 114.6, 115.9 (q, J=280 Hz), 133.0, 147.6, 149.6, 157.5 (q, J=36 Hz); HRMS (ESI) calcd for $C_{15}H_{17}NO_4F_3$ $[M+H]^+$ 332.1110, found 332.1116 (Δ=1.8 ppm).

3.3.4. 3-{4,5-Dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl]phenyl}prop-2-ynol (3a). This compound was synthesized in the same manner as that described for **3b**. White solid; 91% isolated yield; mp 126–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.95 (t, J=6.9 Hz, 2H), 3.23 (q, J=6.1 Hz, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 4.50 (s, 2H), 4.63 (t, J=6.1 Hz, 1H), 6.56 (s, 1H), 6.89 (s, 1H), 7.25 (d, J=8.4 Hz, 2H), 7.68 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 34.8, 43.9, 51.4, 55.8, 55.9, 83.7, 90.5, 112.1, 114.2, 114.6, 126.9, 129.6, 133.5, 136.9, 143.3, 147.4, 149.5; MS (ES) cacld for $C_{20}H_{22}NO_4S$ $[M-OH]^+$ 372.1, found 372.1; HRMS (ESI) calcd for $C_{20}H_{22}NO_4S$ $[M-OH]^+$ 372.1270, found 372.1268 (Δ=−0.5 ppm).

3.3.5. (*Z*)-3-{4,5-Dimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enol (4b). P2–Ni catalyst was generated in situ following the standard procedure by adding $NaBH_4$ (1.0 mg, 0.02 mmol) to a suspension of $Ni(OAc)_2$ (3.0 mg, 0.01 mmol) in EtOH (2 mL) at room temperature under an nitrogen atmosphere with stirring. After 30 min, neat ethylenediamine (1.64 μL, 0.024 mmol) was introduced to the reaction mixture. After stirring the catalyst solution for 10 min, **3b** (165 mg, 0.5 mmol) in ethanol (5 mL) was added. The nitrogen atmosphere was then replaced by hydrogen. The reaction mixture was stirred until TLC indicated the completion of the reaction. The reaction was quenched by addition of water. The aqueous layer was extracted with EtOAc three times. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine. After dried over $MgSO_4$, crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (hexanes/EtOAc=3:1–1:1) afforded **4b** as a colorless oil (161 mg, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (br s, 1H), 2.83 (t, J=6.9 Hz, 2H), 3.52 (q, J=6.6 Hz, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 4.23 (dd, J=1.5 Hz, 6.9 Hz, 2H), 5.90 (dt, J=6.9 Hz, 11.4 Hz, 1H), 6.62 (d, J=11.4 Hz, 1H), 6.64 (s, 1H), 6.66 (s, 1H), 6.81 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.2, 40.2, 55.9, 56.0, 59.2, 112.8, 113.1, 115.8 (q, J=286 Hz), 127.8, 128.1, 129.6, 131.3, 147.4, 148.4, 157.3 (q, J=37 Hz); HRMS (ESI) calcd for $C_{15}H_{18}NO_4F_3Na$ $[M+Na]^+$ 356.1086, found 356.1088 (Δ=0.6 ppm).

3.3.6. 3-{4,5-Dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl]phenyl}prop-2-enol (4a). This compound was synthesized in the same manner as that described for **4b**. White solid; 95% isolated yield; mp 104–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (s, 1H), 2.41 (s, 3H), 2.73 (t, J=6.2 Hz, 2H), 3.14 (q, J=6.0 Hz, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 4.23 (dd, J=1.2 Hz, 6.9 Hz, 2H), 4.64 (t, J=6.0 Hz, 1H), 5.90 (dt, J=6.9 Hz, 8.9 Hz, 1H), 6.53 (d, J=8.9 Hz, 1H), 6.57 (s, 1H), 6.60 (s, 1H), 7.25 (d, J=8.1 Hz, 2H), 7.64 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 33.1, 44.1, 56.2, 56.3, 59.6, 112.9, 113.4, 127.3, 128.3, 128.7, 129.9, 130.1, 132.1, 137.1, 143.7, 147.6, 148.8; HRMS (ESI) calcd for $C_{20}H_{24}NO_4S$ $[M-OH]^+$ 374.1426, found 374.1425 (Δ=−0.3 ppm).

3.3.7. (*E*)-3-{4,5-Dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl]phenyl}prop-2-enol (4a-t). Compound **2a** (461 mg, 1.0 mmol) was added to a solution of $Pd(OAc)_2$ (5.6 mg, 0.0025 mmol) and P(*o*-tol)$_3$ (15.2 mg, 0.0050 mmol), and NEt_3 (202 mg, 2.0 mmol) in toluene (10 mL). Then, methyl acrylate (95 mg, 1.1 mmol) was added to this mixture via a syringe. The reaction mixture was heated to reflux until TLC indicated the disappearance of the starting material, and was cooled to room temperature. After filtration through a pad of Celite, the filtrate was concentrated in vacuo and redissolved in CH_2Cl_2, washed with 2 N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$. Crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (hexane/EtOAc=8:1–3:1) afforded methyl (*E*)-3-{4,5-dimethoxy-2-[2-(4-methylbenzenesulfonyl)ethyl]phenyl}propenoate (**6a**) as a white solid (388 mg, 93% isolated yield). Mp 149–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.92 (t, J=6.9 Hz, 2H), 3.14 (q, J=6.6 Hz, 2H), 3.80 (s, 3H), 3.88 (s, 6H), 4.41 (t, J=6.0 Hz, 1H), 6.23 (d, J=15.9 Hz, 1H), 6.64 (s, 1H), 7.00 (s, 1H), 7.27 (d, J=5.1 Hz, 2H), 7.68 (d, J=5.1 Hz, 2H), 7.79 (d, J=15.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 33.0, 44.2, 51.7, 55.9, 56.0, 108.9, 113.1, 117.1, 125.2, 127.0, 129.6, 131.3, 136.9, 140.9, 143.4, 148.1, 150.9, 167.4; HRMS (ESI) calcd for $C_{21}H_{26}NO_6S$ $[M+H]^+$ 420.1481, found 420.1477 (Δ=−1.0 ppm).

To a solution of **6a** (210 mg, 0.5 mmol) in toluene at −78 °C, was added dropwise 1 M DIBAL-H (2.0 mL) in hexanes. The mixture was kept at −78 °C for 1 h, warmed up to room temperature and kept for 3 h. The reaction was quenched by MeOH (0.5 mL), followed by the addition of saturated Rochelle′s salt solution. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$. Crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (CH_2Cl_2/MeOH=95:5) afforded **4a-t** as a colorless oil (172 mg, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.83 (t, J=7.2 Hz, 2H), 3.11 (q, J=6.9 Hz, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 4.30 (dd, J=1.2 Hz, 5.6 Hz, 2H), 4.81 (t, J=6.3 Hz, 1H), 6.13 (dt, J=5.6 Hz, 15.6 Hz, 1H), 6.53 (s, 1H), 6.76 (dt, J=1.2 Hz, 15.6 Hz, 1H), 6.93 (s, 1H), 7.24 (d, J=6.6 Hz, 2H), 7.67 (d, J=6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 33.2, 44.1, 55.9, 63.6, 109.2, 112.8, 126.9, 127.9, 128.0, 128.4, 129.5, 129.6, 137.0, 143.4, 148.0, 148.7; HRMS (ESI) calcd for $C_{20}H_{25}NO_5SNa$ $[M+Na]^+$ 414.1351, found 414.1342 (Δ=−2.2 ppm).

3.3.8. Methyl (*Z*)-3-{4,5-dimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (5b-1). To a solution of **4b** (166 mg, 0.5 mmol) and pyridine (1.0 mL) in CH_2Cl_2 (10 mL) was added slowly methyl chloroformate (52 mg, 0.55 mmol) in 3 mL CH_2Cl_2 (3 mL) at 0 °C. After stirring the mixture at 0 °C for 3 h, the reaction was quenched by saturated $CuSO_4$, and aqueous phase was extracted with diethyl ether four times. Combined organic layer was washed with water and brine, and dried over $MgSO_4$. Crude product

was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (hexanes/EtOAc=3:1) afforded **5b-1** as a white solid (185 mg, 95% yield). Mp 76.5–77.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (t, J=6.6 Hz, 2H), 3.58 (q, J=6.6 Hz, 2H), 3.78 (s, 3H), 3.92 (s, 6H), 4.83 (dd, J=1.2 Hz, 6.6 Hz, 2H), 5.91 (dt, J=6.6 Hz, 11.4 Hz, 1H), 6.69 (s, 1H), 6.71 (s, 1H), 6.84 (d, J=11.4 Hz, 1H), 6.85 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.0, 39.8, 54.8, 55.8, 56.0, 64.4, 113.1, 115.8 (q, J=286 Hz), 125.7, 126.9, 128.4, 132.7, 147.3, 148.7, 155.8, 157.3 (q, J=37 Hz); HRMS (ESI) calcd for $C_{17}H_{20}NO_6F_3Na$ $[M+Na]^+$ 414.1140, found 414.1156 (Δ=3.9 ppm).

Other carbonates, **5a-1**, **5a-2**, **5b-2**, **5b-3**, and **5a-1-t**, were synthesized in the same manner as that described for **5b-1**.

3.3.9. Methyl (*Z*)-3-{4,5-dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl]phenyl}prop-2-enyl carbonate (5a-1). White solid; 95% isolated yield; mp 49–50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.75 (t, J=6.2 Hz, 2H), 3.17 (q, J=6.0 Hz, 2H), 3.76 (s, 3H), 3.84 (s, 6H), 4.26 (dd, J=1.2 Hz, 6.9 Hz, 2H), 4.61 (t, J=6.0 Hz, 1H), 5.93 (dt, J=6.9 Hz, 8.9 Hz, 1H), 6.55 (d, J=8.9 Hz, 1H), 6.57 (s, 1H), 6.64 (s, 1H), 7.27 (d, J=8.1 Hz, 2H), 7.64 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 33.6, 43.8, 55.2, 56.2, 56.3, 64.8, 113.1, 113.2, 125.8, 127.3, 127.4, 128.9, 129.9, 132.9, 137.4, 143.6, 147.6, 149.0, 156.0; HRMS (ESI) calcd for $C_{22}H_{27}NO_7SNa$ $[M+Na]^+$ 472.1406, found 472.1395 (Δ=−2.3 ppm).

3.3.10. Ethenyl (*Z*)-3-{4,5-dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl]phenyl}prop-2-enyl carbonate (5a-2). White solid; 94% isolated yield; mp 68–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.72 (t, J=7.2 Hz, 2H), 3.10 (q, J=7.2 Hz, 2H), 3.83 (s, 6H), 4.57 (dd, J=1.2 Hz, 6.0 Hz, 1H), 4.64 (t, J=5.7 Hz, 1H), 4.71 (dd, J=1.2 Hz, 6.6 Hz, 2H), 4.91 (dd, J=1.2 Hz, 11.1 Hz, 1H), 5.81 (dt, J=6.9 Hz, 14.4 Hz, 1H), 6.62 (s, 2H), 6.69 (d, J=14.4 Hz, 1H), 7.04 (dd, J=6.0 Hz, 11.1 Hz, 1H), 7.27 (d, J=6.3 Hz, 2H), 7.68 (d, J=6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 33.3, 43.4, 55.9, 64.9, 97.9, 112.7, 112.9, 124.9, 126.9, 127.0, 128.6, 129.6, 133.2, 137.0, 142.6, 143.3, 147.4, 148.7, 152.6; HRMS (ESI) calcd for $C_{23}H_{28}NO_7S$ $[M+H]^+$ 462.1586, found 462.1583 (Δ=−0.6 ppm).

3.3.11. Methyl (*E*)-3-{4,5-dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl]phenyl}prop-2-enyl carbonate (5a-1-t). Colorless oil; 96% isolated yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.82 (t, J=6.9 Hz, 2H), 3.12 (q, J=6.9 Hz, 2H), 3.80 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 4.58 (t, J=6.3 Hz, 1H), 4.75 (dd, J=1.2 Hz, 6.6 Hz, 2H), 6.03 (dt, J=6.6 Hz, 15.3 Hz, 1H), 6.55 (s, 1H), 6.78 (d, J=15.3 Hz, 1H), 6.90 (s, 1H), 7.26 (d, J=8.1 Hz, 2H), 7.67 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 33.1, 43.9, 54.8, 55.9, 68.6, 109.1, 112.8, 122.8, 127.0, 127.4, 128.3, 129.6, 132.0, 137.0, 143.3, 148.0, 149.2, 155.6; HRMS (ESI) calcd for $C_{22}H_{27}NO_7SNa$ $[M+Na]^+$ 472.1406, found 472.1397 (Δ=−1.9 ppm).

3.3.12. Ethenyl (*Z*)-3-{4,5-dimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (5b-2). White solid; 93% isolated yield; mp 59–60.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (t, J=6.9 Hz, 2H), 3.51 (q, J=6.3 Hz, 2H), 3.85 (s, 6H), 4.57 (dd, J=2.1 Hz, 6.0 Hz, 1H), 4.84 (dd, J=1.2 Hz, 6.9 Hz, 2H), 4.90 (dd, J=2.1 Hz, 13.8 Hz, 1H), 5.87 (dt, J=6.9 Hz, 11.4 Hz, 1H), 6.64 (s, 1H), 6.65 (s, 1H), 6.65 (br s, 1H), 6.81 (d, J=11.4 Hz, 1H), 6.98 (dd, J=6.0 Hz, 13.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.0, 39.9, 55.9, 56.0, 64.9, 98.2, 113.1, 115.9 (q, J=286 Hz), 125.1, 126.8, 128.4, 133.2, 142.4, 147.4, 148.8, 152.8, 157.3 (q, J=37 Hz); HRMS (ESI) calcd for $C_{18}H_{20}NO_6F_3Na$ $[M+Na]^+$ 426.1140, found 426.1148 (Δ=1.9 ppm).

3.3.13. Phenyl (*Z*)-3-{4,5-dimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (5b-3). Colorless oil; 97% isolated yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (t, J=6.6 Hz, 2H), 3.54 (q, J=6.6 Hz, 2H), 3.90 (s, 3H), 3.92 (s, 3H), 4.94 (dd, J=1.2 Hz, 6.9 Hz, 2H), 5.99 (dt, J=6.9 Hz, 11.4 Hz, 1H), 6.70 (s, 1H), 6.72 (s, 1H), 6.80 (br s, 1H), 6.90 (d, J=11.4 Hz, 1H), 7.14 (m, 2H), 7.30 (m, 1H), 7.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.9, 39.8, 55.8, 55.9, 65.0, 113.0, 115.6 (q, J=286 Hz), 120.8, 125.0, 126.1, 126.7, 128.5, 129.4, 133.3, 147.2, 148.6, 150.8, 153.8, 157.2 (q, J=37 Hz); HRMS (ESI) calcd for $C_{22}H_{22}NO_6F_3Na$ $[M+Na]^+$ 476.1297, found 476.1313 (Δ=3.4 ppm).

3.3.14. *tert*-Butyl (*Z*)-3-{4,5-dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl]phenyl}-prop-2-enyl carbonate (5a-3). To a solution of **4a** (195 mg, 0.5 mmol), (t-Boc)$_2$O (133 mg, 1 mmol), and Bu_4NI (18 mg, 0.05 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise 1 mL 2 M NaOH aqueous solution (1.0 mL) at 0 °C. After addition, the mixture was stirred overnight. The reaction was quenched by addition of water. The aqueous layer was separated and extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine and dried over $MgSO_4$. Crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (hexanes/EtOAc=2:1) afforded **5a-3** as a colorless oil (225 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.41 (s, 3H), 2.72 (t, J=7.2 Hz, 2H), 3.15 (q, J=7.2 Hz, 2H), 3.83 (s, 6H), 4.53 (t, J=6.0 Hz, 1H), 4.59 (dd, J=1.5 Hz, 6.9 Hz, 2H), 5.79 (dt, J=6.9 Hz, 11.4 Hz, 1H), 6.60 (s, 1H), 6.62 (d, J=11.4 Hz, 1H), 6.64 (s, 1H), 7.27 (d, J=6.3 Hz, 2H), 7.68 (d, J=6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 27.7, 33.3, 43.4, 55.9, 63.5, 83.3, 112.7, 112.9, 125.9, 127.0, 127.2, 128.5, 129.6, 132.0, 137.1, 143.3, 147.3, 148.5, 153.3; HRMS (ESI) calcd for $C_{25}H_{33}NO_7SNa$ $[M+H]^+$ 514.1875, found 514.1878 (Δ=0.6 ppm).

3.4. Intramolecular asymmetric allylic amination

3.4.1. 1-Ethenyl-2-trifluoroacetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7b). A solution of ligand **L1d** (3.5 mg, 0.0075 mmol) and $Pd_2(dba)_3$ (1.2 mg, 0.00125 mmol) in CH_2Cl_2 (0.5 mL) was added to a 5 mL round-bottomed flask with a stirring bar under N_2. The solution was stirred at room temperature until the color of the solution turned to light yellow from purple. Then, **5b-3** (23 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was added to the catalyst solution via a syringe. The mixture was stirred at room temperature until TLC indicated completion of the

reaction. The reaction mixture was passed through a short pad of silica gel using hexanes/EtOAc (10:1–6:1) as the eluent. The filtrate was then concentrated and subject to HPLC analysis, using a Chiralcel OD-H column (hexanes/*i*-PrOH=98:2, 0.5 mL/min), which indicated that the enantiopurity of the product **7b** was 95% ee with 100% conversion and product selectivity. The product **7b** was isolated as colorless oil as a mixture of two rotamers in 75:25 ratio (determined by ^{1}H NMR at 25 °C). $[\alpha]_D^{23}$ 169.7 (*c* 0.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68–2.78 (m, 1H), 2.91–3.01 (m, 1H), 3.01–3.28 (m, 0.25H), 3.50–3.58 (m, 0.75H), 3.83 (s, 2.25H), 2.854 (s, 2.25H), 3.85 (s, 0.75H), 3.86 (s, 0.75H), 3.99–4.04 (m, 0.75H), 4.47–4.52 (m, 0.25H), 5.01–5.17 (m, 1H), 5.29–5.33 (m, 1H), 5.43–5.45 (m, 0.25H), 5.91–6.07 (m, 1.75H), 6.59 (s, 0.75H), 6.61 (s, 0.75H), 6.55 (s, 0.25H), 6.63 (s, 0.25H); ^{13}C NMR (100 MHz, $CDCl_3$) Major: δ 28.9, 40.2, 55.8, 56.1, 56.2, 110.9, 111.3, 116.8 (q, *J*=287 Hz), 118.9, 125.0, 125.5, 135.9, 148.1, 148.6, 155.9 (q, *J*=26 Hz); Minor: δ 27.5, 38.0, 56.2, 56.3, 58.1, 110.5, 111.7, 116.8 (q, *J*=287 Hz), 118.7, 124.7, 126.3, 136.8, 148.0, 148.9, 156.0 (q, *J*=26 Hz); HRMS (ESI) calcd for $C_{15}H_{17}NO_3F_3$ $[M+H]^+$ 316.1161, found 316.1164 (Δ=0.9 ppm).

3.4.2. 1-Ethenyl-2-(4-methylbenzenesulfonyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7a). This compound was obtained in the same manner as that described for **7b**. White solid; 87% isolated yield; 74% ee (Chiralpak AD-RH; CH_3CN/H_2O=50:50, 0.5 mL/min); mp 137–138 °C; $[\alpha]_D^{23}$ 67 (*c* 0.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.47–2.52 (m, 1H), 2.63–2.75 (m, 1H), 3.25–3.35 (m, 1H), 3.81 (s, 3H), 3.83 (s, 3H), 3.87–3.88 (m, 1H), 5.05 (dt, *J*=1.5 Hz, 17.1 Hz, 1H), 5.17 (dt, *J*=1.5 Hz, 10.2 Hz, 1H), 5.46 (d, *J*=5.4 Hz, 1H), 5.90 (ddd, *J*=5.4 Hz, 10.2 Hz, 17.1 Hz, 1H), 6.64 (s, 1H), 6.52 (s, 1H), 7.19 (d, *J*=6.3 Hz, 2H), 7.66 (d, *J*=6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 27.2, 39.1, 55.8, 55.9, 57.7, 110.4, 111.3, 117.6, 125.4, 125.6, 127.1, 129.4, 137.3, 137.9, 143.0, 147.4, 148.0; HRMS (ESI) calcd for $C_{20}H_{24}NO_4S$ $[M+H]^+$ 374.1426, found 374.1436 (Δ=2.7 ppm).

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