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Enantioselective synthesis of 1-vinyltetrahydroisoquinolines via Pd-catalyzed intramolecular asymmetric allylic amination reactions

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Dedicated to Professor Satoshi Omura for his outstanding contribution for the advancement of organic, natural products and medicinal chemistry

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ABSTRACT

1-Vinyltetrahydroisoquinolines serve as versatile intermediates for the synthesis of a variety of naturally occurring isoquinoline alkaloids. 1-Vinyl-6,8-dimethoxytetrahydroisoquinoline **4** and 1-vinyl-5,6,7-trimethoxytetrahydroisoquinoline **6** with >90% ee by means of Pd-catalyzed intramolecular asymmetric allylic amination reactions, using MPN and BOP ligands, developed in our laboratory. The fine-tuning capability of the MPN and BOP ligands has played a significant role in the optimization of enantioselectivity. Interesting substituent effect as well as solvent effect on the product selectivity and enantioselectivity was observed. Plausible mechanisms are proposed, which can accommodate various findings, including the critical importance of the activation of the trifluoroamide moiety through its coordination to the Lewis acidic Pd^{2+} metal center.

1. Introduction

Development of efficient methods for the synthesis of *C*1-substituted tetrahydroisoquinolines has attracted much interest among synthetic organic chemists, mainly due to the interesting pharmacological properties these alkaloids possess.[1] Members of this family (Fig. 1) have shown diverse activities,[2] e.g., anti-inflammatory properties,[3,4] neuromuscular transmission blocking,[5] anti-platelet aggregation activity,[6] enzyme inhibitory activities for acetylcholinesterase (AChE),[7] and α-glucosidase.[8] Thus, in order to study the biological and pharmacological activities of this class of compounds, the efficient synthesis of these alkaloids in enantiomerically pure form is of great importance.

Optically active *C*1-substituted tetrahydroisoquinolines has been prepared through diastereoselective reactions for the introduction of chirality at the C1 position. Other methods utilizing enantioselective reactions to introduce the chirality at the C1 position have been developed in the past decade, e.g., enantioselective Pictet–Spengler reaction,[9] alkylation, vinylation or cyanation of 3,4-dihydroisoquinolines,[10–12] asymmetric hydrogenation of 3,4-dihydroisoquinolines[13,14] as well as 1-alkylidenetetrahydroisoquinolines,[15] and other transformations.[16] In 2003, a Pd-catalyzed intramolecular asymmetric allylic amination (AAA) of catalyzed by a Pd catalyst with a chiral P,N-ligand in the presence of a strong base was reported, which gave 6,7-dimethoxy-1-vinyltetrahydroisoquinoline in a single step, introducing chirality at the C1 position.[17] Although high enantioselectivity (82–88% ee) was realized under optimized conditions, the catalytic activity of this system was insufficient since it required 12–23 days to reach synthetically meaningful conversions.

In order to achieve excellent efficiency and enantioselectivity, the selection of suitable chiral ligands for this process is essential. We have been developing a library of novel enantiopure monodentate phosphite,[18] and phosphoramidite (MPN)[19–22] ligands based on axially chiral biphenols. These ligands can be readily prepared and are fine-tunable for a variety of catalytic asymmetric reactions, e.g., asymmetric hydrogenation,[18] asymmetric hydroformylation,[19] asymmetric conjugate additions to cycloalkenones and nitroalkenes,[19,20] and asymmetric allylic alkylation as well as its application to the total synthesis of (+)-γ-lycorane.[21,22]

Since a couple of these chiral MPN ligands were found to be extremely effective (up to 99.7% ee) in the Pd-catalyzed asymmetric allylic alkylation mentioned above,[21,22] we anticipated that this type of ligands would be effective for this AAA process. Thus, we

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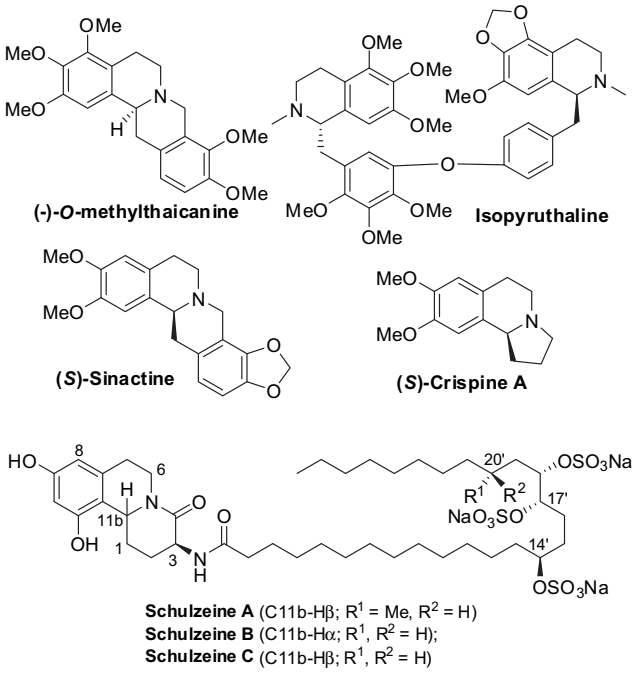
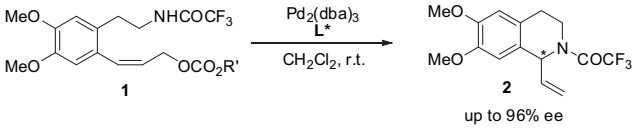


Fig. 1. Selected naturally occurring *C*1-substituted tetrahydroisoquinolines.

employed chiral MPN ligands to this intramolecular AAA reaction of **1**, which indeed gave **2** with excellent enantioselectivity (up to 96% ee) and high catalyst activity under neutral conditions (Scheme 1).[23]



Scheme 1. Highly efficient AAA reaction of **1**.

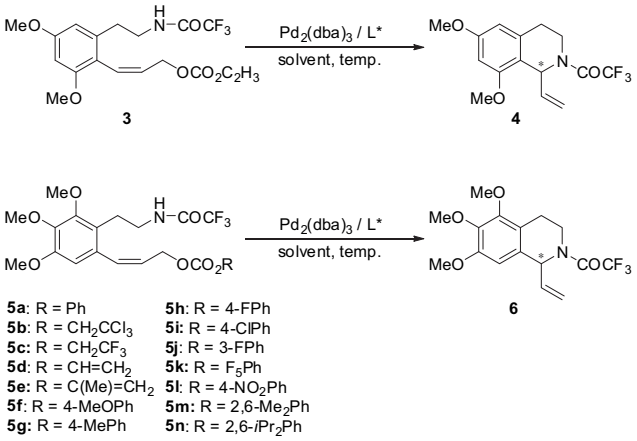
We have also developed a library of novel chiral bidentate bisphosphonite (BOP) ligands based on axially chiral biphenols and successfully applied it to the intermolecular AAA reaction.[24]

Building upon the successful application of our MPN ligands to the enantioselective synthesis of 6,7-dimethoxy-1-vinyltetrahydroisoquinoline **2** through Pd-catalyzed AAA reaction (Scheme 1), we have expanded the scope of the AAA reaction to the enantioselective synthesis of 6,8-dimethoxy-1-vinyltetrahydroisoquinoline **4** and 5,6,7-trimethoxy-1-vinyl>tetrahydroisoquinoline **6** (Scheme 2), using MPN and BOP ligands (Fig. 2), which serve as versatile intermediates for the synthesis of naturally occurring alkaloids exemplified in Fig. 1. We describe here unexpected substituent effects of methoxy groups on the AAA reaction and interesting mechanistic implications, besides the synthetic utility of the process.

2. Results and discussion

2.1. Preparation of allylic carbonate substrates

4,6-Dimethoxy-2-(2-trifluoroacetamidoethyl)phenylallyl carbonate **3** was prepared as illustrated in Scheme 3. 3,5-Dimethoxyphenylethylamide **7** was obtained by the literature procedure.[25,26] The synthetic procedure from **7** to **3** largely followed the protocol reported by us for the preparation of **1**,[23] which was a modification of the Katsuki procedure.[17] In the iodination step, an iodine/silver sulfate combination was found to be more efficient than ICl to give **8**, although the formation of some bis-



Scheme 2. AAA reactions of **3** and **5**.

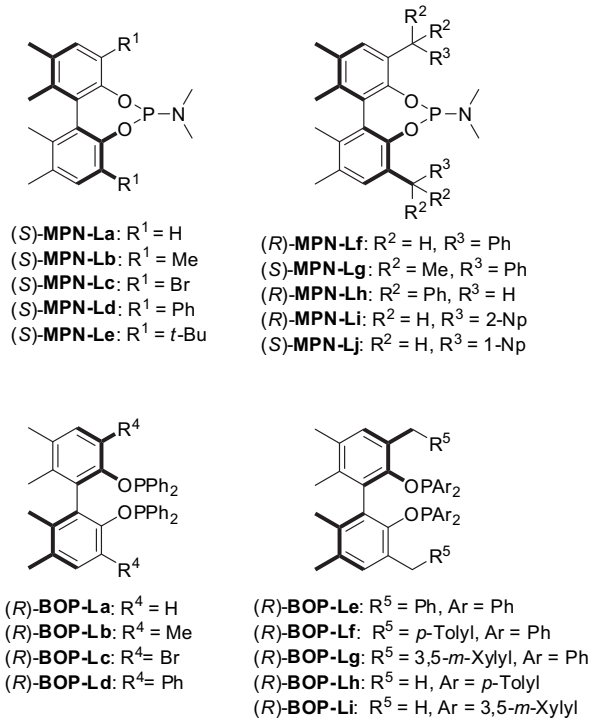
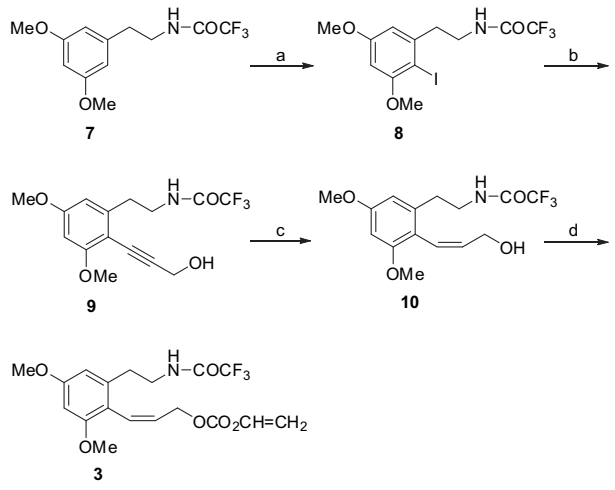


Fig. 2. Phosphoramidite (MPN) and bisphosphonite (BOP) ligands.

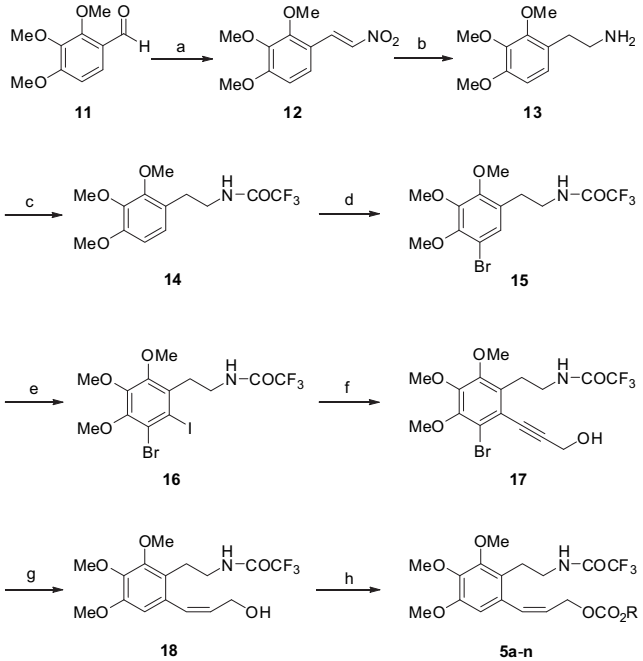
iodinated side product was observed. The Sonogashira coupling of **8** with propargyl alcohol proceeded rather slowly, but gave **9** in high yield. Selective hydrogenation of **9** over P2–Ni catalyst gave *cis*-allylic alcohol **10** exclusively. Acylation of **10** with vinyl chloroformate gave allyl vinyl carbonate **3** in excellent yield.

In a similar manner, 3,4,5-trimethoxy-2-(2-trifluoroacetamidoethyl)phenylallyl carbonates **5a**–**n** were prepared with some modifications, as illustrated in Scheme 4. The nitro-aldol reaction of commercially available 2,3,4-trimethoxybezaldehyde **11** gave (*E*)-nitroalkene **12** exclusively. Nitroalkene **12** was reduced to amine **13** by $LiAlH_4$, followed by reaction with trifluoroacetic anhydride to give trifluoroacetamide **14**. In order to introduce iodine at *ortho* to the trifluoroacetamidoethyl group, bromination of **14** with NBS was used to block the *meta* position, giving **15**. The iodination of **15** by *N*-iodosuccinimide (NIS) afforded **16** in 94% yield. The Sonogashira coupling of **16** with propargyl alcohol took place selectively with



Scheme 3. Preparation of AAA substrate **1** Reagents and conditions: (a) Ag_2SO_4, I_2, EtOH, 0 °C, 6 h, 88%; (b) $Pd(PPh_3)_2Cl_2$, CuI, propargyl alcohol, *i*-Pr_2NH, rt, 48 h, 83%; (c) P2–Ni, EtOH, H_2 (1 atm), rt, 16 h, 97%; (d) $ClCO_2C_2H_3$, pyridine, CH_2Cl_2, 0 °C, 1.5 h, 93%.

the iodide to give **17**. Subsequent hydrogenation of **17** over P2–Ni not only reduced the triple bond, but also removed the bromine to afford the corresponding (*Z*)-allylic alcohol **18**. Finally, the (*Z*)-allylic alcohol **18** was acylated with different chloroformates to give the corresponding allylic carbonates **5a**–**n**.

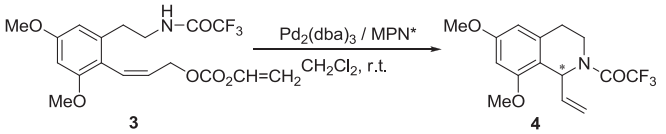


Scheme 4. Preparation of carbonates **5a**–**n**. Reagents and conditions: (a) NH_4OAc, CH_3NO_2, 100 °C, 1 h, 91%; (b) $LiAlH_4$, THF, 65 °C, 3 h; (c) $(CF_3CO)_2O$, NEt_3, CH_2Cl_2, 0 °C, 1.5 h, 65% for two steps; (d) NBS, CCl_4, 60 °C, 16 h, 92%; (e) NIS, CF_3CO_2H, CH_3CN, reflux, 24 h, 94%; (f) $Pd(PPh_3)_2Cl_2$, CuI, propargyl alcohol, *i*-Pr_2NH, reflux, 18 h, 75%; (g) P2–Ni, EtOH, H_2 (1 atm), rt, 40 h, 75%; (h) $ClCO_2R$, pyridine, CH_2Cl_2, 0 °C, 3 h, 71–99%.

2.2. AAA reaction of allylic carbonate 3

The Pd-catalyzed AAA reaction of 4,6-dimethoxyphenylallyl carbonate **3** was first carried out using MPN ligands under the same conditions as those employed in the reaction of 4,5-dimethoxyphenylallyl carbonate **1**,[23] which gave excellent results (Scheme 1). The reaction proceeded smoothly to give (*S*)-(+)-tetrahydroisoquinoline **4** in excellent yield (Table 1). To our surprise, however, the reactions using (*S*)-**MPN-La**–**d** did not give the same high level of enantioselectivity as that observed in the reactions of **1**.[23] As Table 1 shows, the best result was 47% ee (entry 3) when (*S*)-**MPN-Lc** (R^1=Br) was used as the chiral ligand. (*S*)-**MPN-Ld** (R=Ph), which achieved 95–96% ee in the AAA reaction of **1**,[23] gave only 29% ee (entry 4). (*S*)-**MPN-La** (R^1=H) afforded (*R*)-(+)-**4** with 26% ee (entry 1), which has the opposite configuration to that induced by all other MPN ligands examined. The results appear to indicate that the methoxy group at the C3 position of **3**, which is *ortho* to the allyl carbonate moiety, is responsible for the observed marked difference in enantioselectivity for the AAA reaction of **1** and that of **3**.

Table 1
Efficacy of MPN ligands in the Pd-catalyzed AAA reaction of **3**



Entry[a]	Ligand	Time (h)	Conv.[b] (%)	**4** ee[c] (%)
1	(*S*)-**MPN-La**	10	>95	26 (*R*)
2	(*S*)-**MPN-Lb**	16	>95	19 (*S*)
3	(*S*)-**MPN-Lc**	22	>95	47 (*S*)
4	(*S*)-**MPN-Ld**	48	>95	29 (*S*)

[a] Reaction was run with **3** (0.05 mmol), $Pd_2(dba)_3$ (1.25×10^{-4} mmol), and MPN-L (7.50×10^{-4} mmol) in CH_2Cl_2 (1.0 mL) at room temperature.
[b] Determined by ^1H NMR.
[c] Determined by chiral HPLC analysis (OD-H column, isopropanol/hexanes=0.5/99.5), flow rate: 0.5 mL/min.

Since none of simple MPN ligands gave encouraging result, we examined the efficacy of BOP ligands, (*R*)-**BOP-La**–**i**, in this AAA reaction. Results are summarized in Table 2. The reactions proceeded very smoothly in DMF at room temperature and completed in 1.5–8 h. Among the first four BOP ligands employed (**BOP-La**–**d**), which bears H, Me, Br, and Ph groups at the 3,3′ positions, **BOP-Lc** (R^4=Br) gave the best result, i.e., 72% ee (entry 3). However, **BOP-Le** (R^5=Ph and Ar=Ph) achieved even better result, giving (*S*)-(+)-**4** with 79% ee (entry 5). Enantioselectivity was further increased to 84% ee and 88% ee by introducing 4-methylbenzyl (**BOP-Lf**) and 3,5-dimethylbenzyl (**BOP-Lg**) groups, respectively, in place of benzyl group (entries 6 and 9). Introduction of *p*-tolyl (**BOP-Lh**) and 3,5-xylyl (**BOP-Li**) groups as Ar moiety, keeping methyl groups as the 3,3′ substituents, also improved the enantioselectivity to 72% ee and 80% ee, respectively (entries 12 and 13), as compared to 68% ee achieved by the parent ligand, **BOP-Lb** (entry 2).

Table 2
The Pd-catalyzed AAA reaction of **3** with BOP ligands

Entry[a]	Ligand	Temp (°C)	Time (h)	Conv.[b] (%)	**4** (*S*) ee[c] (%)
1	(*R*)-**BOP-La**	rt	1.5	>95	35
2	(*R*)-**BOP-Lb**	rt	4	>95	68
3	(*R*)-**BOP-Lc**	rt	8	>95	72
4	(*R*)-**BOP-Ld**	rt	8	>95	68
5	(*R*)-**BOP-Le**	rt	6	>95	79
6	(*R*)-**BOP-Lf**	rt	8	>95	84
7	(*R*)-**BOP-Lf**	0	24	>95	88
8	(*R*)-**BOP-Lf**	−25	48	<5	nd
9	(*R*)-**BOP-Lg**	rt	8	>95	88
10	(*R*)-**BOP-Lg**	0	24	>95	90
11	(*R*)-**BOP-Lg**	−25	48	<5	nd
12	(*R*)-**BOP-Lh**	rt	8	>95	72
13	(*R*)-**BOP-Li**	rt	12	>95	80

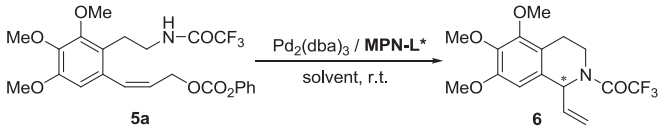
[a] Reaction was run with **3** (0.05 mmol), $Pd_2(dba)_3$ (1.25×10^{-3} mmol) and **BOP-L** (3.75×10^{-3} mmol) in DMF (1.0 mL).
[b] See the captions in Table 1.
[c] See the captions in Table 1.

Lowering the reaction temperature from room temperature to 0 °C improved enantioselectivity to 88% ee (from 84% ee, entry 7) for **BOP-Lf** and to 90% ee (from 88% ee, entry 9) for **BOP-Lg**. However, at −25 °C, the reaction was basically shut down (entries 8 and 11).

2.3. AAA reactions of allylic carbonates 5a–n

The Pd-catalyzed AAA reaction of 3,4,5-trimethoxylphenylallyl carbonate **5d** was first carried out in DMF at room temperature, using (*R*)-**BOP-Lg** ligand since this ligand gave the best result (90% ee), so far, in the reaction of **3**, as described above. However, again to our surprise, the reaction gave (*S*)-(+)-tetrahydroisoquinoline **6** with only 42% ee although the reaction was very fast, clean and completed in 2 h. We also tried one of Trost's representative modular 'DPPBA ligand', (1*R*,2*R*)-*N*,*N*′-bis(2′-diphenylphosphinobenzoyl)-1,2-diaminocyclohexane,[27] under the same conditions, but the conversion was only 18% after 120 h and enantioselectivity was 13% ee. Accordingly, we screened MPN ligands as well as solvents for the reaction of **5a** (R=Ph), which achieved excellent results in the reaction of **1** (Scheme 1). Results are summarized in Table 3. When the AAA reaction was run in DMF, using (*S*)-**MPN-La**–**e**, it proceeded fast and completed in 4–7 h to give **6** in excellent yield (entries 1–3 and 6), except for (*S*)-**MPN-Ld** (entry 4). The best result in DMF (64% ee) was obtained with (*S*)-**MPN-Le** (entry 6). Since the reaction in DMF using (*S*)-**MPN-Ld**, was slow, for some reason, we ran the reaction in CH_2Cl_2 with all other reaction variables intact. Then, the reaction was very fast and gave **6** with 78% ee (entry 5). However, the yield of **6** was reduced to 58% with the unexpected formation of allyl phenyl ether **22a** (R=Ph) as the side product. This side product **22a** should have been formed by the attack of a phenoxide ion, which was generated upon formation of π-allylic Pd intermediate **20a**, on the π-allyl system (Scheme 5). The formation of **22a** is conceptually possible if the intramolecular attack of the trifluoroamide is slow. Nevertheless, we never observed such a side product in the reactions of **1** and **3**.[28] Therefore, this result strongly suggests that there must be some unique reason for the slow nucleophilic cyclization for **20a**, which allows the phenoxide ion to compete.

Table 3
Screening of MPN ligands for the AAA reaction of **5a**



5a **6**

Entry[a]	Ligand	Solvent	Time (h)	Conv.[b] (%)	**6**[b] (%)	**6** (*S*) ee[c] (%)
1	(*S*)-**MPN-La**	DMF	7	>95	98	24 (+)
2	(*S*)-**MPN-Lb**	DMF	7	>95	98	23 (+)
3	(*S*)-**MPN-Lc**	DMF	4	>95	94	46 (+)
4	(*S*)-**MPN-Ld**	DMF	70	>95	97	68 (+)
5	(*S*)-**MPN-Ld**	CH_2Cl_2	3	>95	58	78 (+)
6	(*S*)-**MPN-Le**	DMF	7	>95	93	64 (+)
7	(*S*)-**MPN-Le**	NMP	4	>95	90	64 (+)
8	(*S*)-**MPN-Le**	CH_3CN	70	91	77	17 (−) (*R*)
9	(*S*)-**MPN-Le**	THF	4	>95	55	62 (+)
10	(*S*)-**MPN-Le**	$(CH_2Cl)_2$	4	>95	31	40 (+)
11	(*S*)-**MPN-Le**	CH_2Cl_2	4	>95	29	15 (+)
12	(*S*)-**MPN-Le**	Toluene	4	>95	24	29 (+)

[a] Reaction was run with **5a** (0.05 mmol), $Pd_2(dba)_3$ (1.25×10^{-3} mmol), and **MPN-L** (7.50×10^{-3} mmol) in DMF (1.0 mL).
[b] The conversion and product yield were determined by ^1H NMR.
[c] Determined by chiral HPLC (OD-H column, eluent: isopropanol/hexanes=1.2/98.8), flow rate: 1 mL/min.

Since the choice of solvent showed marked effects on the reaction process and enantioselectivity, several different solvents were employed to assess their effects on the AAA reaction, using (*S*)-**MPN-Le**. As Table 3 shows (entries 6–12), there is a remarkable solvent effect on this reaction. The reaction in acetonitrile gave opposite enantiomer, (*R*)-(−)-**6** with low enantiopurity (entry 8). Also, the formation of side product **22a** is enhanced in less polar or non-polar solvents (entries 9–12). The results may imply a possible involvement of hydrogen bonding somewhere in the mechanism.

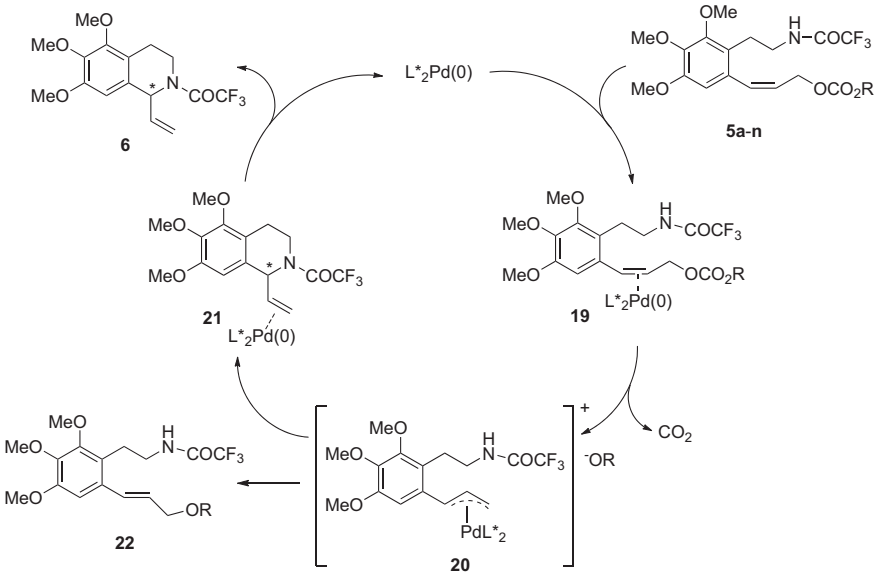
Next, we examined the efficacy of newer MPN ligands, bearing benzyl-type substituents, i.e., $PhCH_2$, $PhCMe_2$, Ph_2CH, 2-$NpCH_2$, and 1-$NpCH_2$, at the 3,3′ positions, **MPN-Lf**–**j** in this reaction. Results are summarized in Table 4. Reaction using (*R*)-**MPN-Lf** in CH_2Cl_2 at room temperature gave **6** with 85% ee in 57% yield (entry 1). Introduction of bulkier substituents, $PhCMe_2$ (**MPN-Lg**), and Ph_2CH (**MPN-Lh**) did not improve the enantioselectivity (entries 2 and 3). However, the use of 2-$NpCH_2$ (**MPN-Lh**) or 1-$NpCH_2$ (**MPN-Lh**) group in place of benzyl group was beneficial to improve the yield of **6** (entries 4 and 5), and the reaction using (*S*)-**MPN-Lj** induced 85% ee, which was the same as that by **MPN-Lf**, but yield of **6** was better (65%) (entry 5). The reaction using (*S*)-**MPN-Lj** at 0 °C improved enantioselectivity to 88% ee, but the side product formation increased as well (entry 6). In a manner similar to the solvent effect observed for the reactions using (*S*)-**MPN-Le** (see Table 3), the use of polar solvent, such as DMF clearly improves the product selectivity to form **6**, but enantioselectivity was lowered (entry 8).

In the hope of minimizing the formation of side product **22**, we prepared various allylic carbonates **5b**–**n** and examined the effects of the substituents on the product selectivity, using (*S*)-**MPN-Lj** as the chiral ligand. Results are summarized in Table 5. When electron-withdrawing substituents, i.e., CH_2CCl_3 (**5b**) and CH_2CF_3 (**5c**), were used, no or minimum amount of **22** was formed (entries 1 and 2). The use of vinyl ethers, CH=CH_2 (**5d**) and C(Me)=CH_2 (**5e**), also eliminated the formation of **22** (entries 3 and 4). In these four substrates, however, enantioselectivity was 66–79% ee. Introduction of strongly electron-withdrawing or very bulky substituents, i.e., C_6F_5 (**5k**), 4-$NO_2C_6H_4$ (**5l**), 2,6-$Me_2C_6H_3$ (**5m**) and 2,6-*i*-$Pr_2C_6H_3$ (**5n**), effectively blocks the formation of **22** as well (entries 10–13). It is noteworthy that allyl carbonates with strongly electron-withdrawing group on the phenyl moiety almost shut down the reaction (entries 10 and 11). The results imply that the basicity of the leaving group, i.e., aryloxide ion, has a significant role in the formation of π-allylic Pd complex **20** (see Scheme 5). Other allyl carbonates, bearing 4-MeO (**5f**), 4-Me (**5g**), 4-F (**5h**), 4-Cl (**5i**) and 3-F (**5j**) on the phenyl moiety, led to 83–89% ee, but with modest to substantial formation of **22** (entries 5–9).

We examined the effects of additives on the product selectivity and enantioselectivity in the AAA reactions of several allylic carbonate substrates in CH_2Cl_2. As mentioned above, there seemed to be a possible involvement of hydrogen bonding when the reaction was run in non-polar solvents. Accordingly, we added *tert*-butanol, trifluoroethanol (TFE), and hexafluoroisopropanol (HFIPA). Results are shown in Table 6.

The reaction of **5a** in CH_2Cl_2 with 1% (v/v) *t*-BuOH did not improve the selectivities (entry 1). In contrast, the addition of 1% (v/v) TFE to the reaction of **5a** increased the enantioselectivity to 91% ee (from 85% ee in pure CH_2Cl_2: see Table 4), giving **6** in 66% yield (entry 2), where in the only side product was **22a**. However, when 5% (v/v) TFE was used, the yield of **6** was dramatically reduced to only 13% (94% ee) and two side products, i.e., **22a** (39%) and **22c** (R=CF_3CH_2, 48%), were formed (entry 3). When 1% (v/v) HFIPA was added, the formation of a mixture of **22a** (33%) and **22o** (R=$(CF_3)_2CH$, 67%) was observed (entry 4).

In the reaction of **5d**, the addition of 1% (v/v) TFE improved the enantiopurity of **6** to 85% ee (from 76% ee in pure CH_2Cl_2: see Table 4) with 88% product selectivity (entry 6). The addition of 0.5% (v/v) TFE, however, did not have appreciable effects (entry 5). With 1% (v/v) HFIPA, the reaction was slowed down and the exclusive



Scheme 5. Proposed mechanism for the intramolecular AAA reaction of **5**.

Table 4
Pd-catalyzed AAA reaction of **5a** with **MPN-Lf–j**

Entry[a]	Ligand	Solvent	Time (h)	Conv.[b] (%)	**6**[b] (%)	**6** ee[c] (%)
1	(*R*)-**MPN-Lf**	CH_2Cl_2	4	>95	57	85 (−)
2	(*S*)-**MPN-Lg**	CH_2Cl_2	2	>95	76	35 (+)
3	(*R*)-**MPN-Lh**	CH_2Cl_2	96	>95	71	35 (−)
4	(*R*)-**MPN-Li**	CH_2Cl_2	2	>95	67	78 (−)
5	(*S*)-**MPN-Lj**	CH_2Cl_2	2	>95	65	85 (+)
6[d]	(*S*)-**MPN-Lj**	CH_2Cl_2	2	>95	59	88 (+)
7	(*S*)-**MPN-Lj**	$CHCl_3$	2	>95	67	83 (+)
8	(*S*)-**MPN-Lj**	DMF	7	>95	98	69 (+)

[a] See the captions in Table 3.
[b] See the captions in Table 3.
[c] See the captions in Table 3.
[d] Reaction was run at 0 °C.

Table 5
Pd-catalyzed AAA reaction of **5b–n** using (*S*)-**MPN-Lj**

Entry[a]	Carbonate	Time (h)	Conv.[b] (%)	**6**[b] (%)	**6** (*S*) ee[c] (%)
1	**5b**	2	>95	100	66 (+)
2	**5c**	2	>95	98	69 (+)
3	**5d**	2	>95	100	76 (+)
4	**5e**	2	>95	100	79 (+)
5	**5f**	2	>95	57	85 (+)
6	**5g**	2	>95	60	83 (+)
7	**5h**	2	>95	46	87 (+)
8	**5i**	2	>95	33	87 (+)
9	**5j**	2	>95	28	89 (+)
10	**5k**	120	<5	100	nd
11	**5l**	120	<5	100	nd
12	**5m**	2	>95	98	70 (+)
13	**5n**	2	>95	100	71 (+)

[a] Reaction was run with **5** (0.05 mmol), $Pd_2(dba)_3$ (1.25×10^{-3} mmol), and (*S*)-**MPN-Lj** (7.50×10^{-3} mmol) in CH_2Cl_2 (1.0 mL) at room temperature.
[b] See the captions in Table 3.
[c] See the captions in Table 3.

formation of side product **22o** was observed (entry 7). The addition of *tert*-butanol slightly improved the enantioselectivity to 79% ee without affecting reaction rate and product selectivity (entry 8). The addition of 1% (v/v) TFE to the reactions of **5e** and **5m** was beneficial, giving **6** with 87% ee (entry 10) and 86% ee (entry 12), respectively, with only a little decrease in the product selectivity

Table 6
Effects of additives on the AAA reaction of **5** using (*S*)-**MPN-Lj** in CH_2Cl_2

Entry[a]	Carbonate	Additive	Time (h)	Conv.[b] (%)	**6**[b] (%)	**6** (*S*) ee[c] (%)
1	**5a**	% *t*-BuOH	2	>95	66[d]	82 (+)
2	**5a**	1% TFE	2	>95	66[d]	91 (+)
3	**5a**	5% TFE	24	>95	13[e]	94 (+)
4	**5a**	1% HFIPA	2	>95	0[f]	nd
5	**5d**	0.5% TFE	2	>95	97[d]	76 (+)
6	**5d**	1% TFE	2	>95	88[d]	85 (+)
7	**5d**	1% HFIPA	48	>95	0[g]	nd
8	**5d**	1% *t*-BuOH	2	>95	100	79 (+)
9	**5e**	1% *t*-BuOH	2	>95	100	74 (+)
10	**5e**	1% TFE	2	>95	91[d]	87 (+)
11	**5e**	1.5% TFE	2	>95	81[d]	91 (+)
12	**5m**	1% TFE	2	>95	88[d]	86 (+)

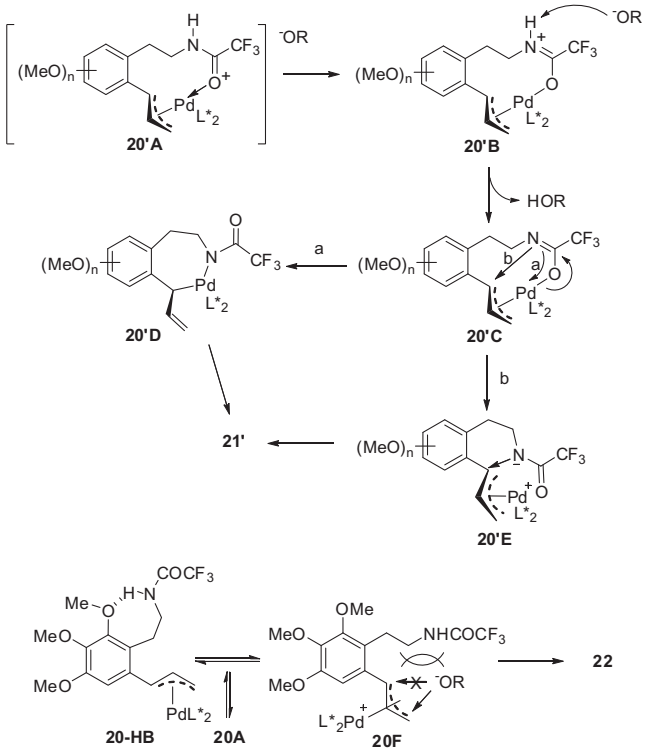
[a] Reaction was run with **5** (0.05 mmol), $Pd_2(dba)_3$ (1.25×10^{-3} mmol), and (*S*)-**MPN-Lj** (7.50×10^{-3} mmol) in CH_2Cl_2 (1.0 mL) at room temperature. The amount of an additive (%) is by volume.
[b] See the captions in Table 3.
[c] See the captions in Table 3.
[d] Compound **22c** was formed as the side product.
[e] A mixure of **22a** and **22c** was formed as side products.
[f] A mixture of **22a** (33%) and **22o** (R=$(CF_3)_2$CH, 67%) was formed.
[g] Compound **22o** was formed exclusively.

(see Table 5, entries 4 and 12 for comparison). The reaction of **5e** with 1.5% (v/v) TFE gave **6** in 81% yield and 91% ee (entry 11), which is practically the best result so far.

2.4. Mechanism of intramolecular AAA reaction

The findings obtained from the solvent effects, allylic carbonate structures, and effects of protic additives, provide the following mechanistic implications (Scheme 6): (i) The $CF_3CONHCH_2$ moiety in π-allylic intermediate **20** (**20′** for substrates **1**, **3**, and **5** in general) needs to be ionized without an extra base to undergo nucleophilic allylic substitution reaction; (ii) The RO^- counter anion in **20′** acts as the base to deprotonate the $CF_3CONHCH_2$ moiety, but the basicity of RO^- anion is not sufficient to do the task without the activation of the amide moiety; (iii) The Pd^{2+} acts as a Lewis acid to activate the $CF_3CONHCH_2$ moiety so that RO^- anion can abstract a proton from this moiety, and produce a neutral ROH (or its tautomer), which is an inert nucleophile under the reaction

conditions; (iv) The C–N bond formation can take place through either reductive elimination (path a) or nucleophilic attack of the amide anion (path b); (v) In a non-polar solvent, there is a plausible hydrogen bonding between the oxygen of the MeO group at C5 and amide hydrogen (see **20-HB**), which is counterproductive for the activation of the amide group through coordination to Pd^{2+} metal center; (vi) While the ionization of the amide group is slowed down, RO^- counter anion exclusively attacks the less hindered terminal carbon of the π-allylic Pd complex (**20F**) to form **22**.

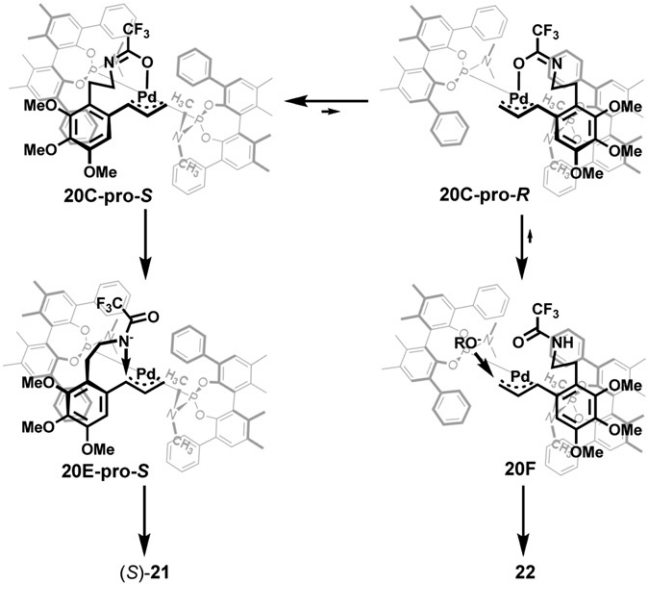


Scheme 6. Proposed mechanism for the formation of **21′** and **22**.

These mechanistic implications nicely explain the unique feature of the AAA reaction of **5** as compared to those of **1** and **3**, wherein the formation of side product **22** was observed only in the reaction of **5** that bears a MeO group at the C5 position.

There is another intriguing mechanistic implication from the observed inverse correlation between enantioselectivity and product selectivity, including the effect of 1% (v/v) TFE as an additive. The results strongly imply that there is a kinetic resolution in the transformation of **20** to **21** and/or **22** (Scheme 5), and the minor diastereomer of **20** reacts preferentially with RO^- anion to enrich the major diastereomer of **20**, which leads to higher enantioselectivity in the formation of desirable product **6**.

To obtain insights into the kinetic resolution implied, we carried out molecular modeling of the two diastereomeric key intermediates, **20C-pro-*S*** and **20C-pro-*R***, bearing (*S*)-**MNP-Ld** as the chiral ligand, using the Spartan Program. For simplicity, we used π-allylic Pd complexes bearing a covalent O–Pd^{2+} bond with an imidate structure (**20C**) for this modeling study (Scheme 7). The semi-empirical energy calculation (PM3) using the Spartan program indicated that **20C-pro-*S*** is more favorable than **20C-pro-*R*** by 31 kJ/mol, which is consistent with the observed formation of (*S*)-(+)-**6**, and also explains the selective elimination of **20F** arising from **20C-pro-*R*** through reaction with RO^- anion to form **22**. However, it should be noted that this molecular mechanics calculation has revealed that (*S*)-**21** (i.e., (*S*)-**6** as well) is formed through either reductive elimination of **20D** (n=3) or the nucleophilic attack of the amide nitrogen anion from the Pd metal side in accordance with the principle of least motion, i.e., not through normal antiperiplanar trajectory. This makes a lot of sense since this is an intramolecular process and the activation of the amide moiety through its coordination to the Lewis acidic Pd^{2+} metal center to generate amide nitrogen anion as the nucleophile (see Scheme 6).



Scheme 7. Proposed mechanism for the kinetic resolution.

3. Conclusions

As described above, we have successfully synthesized 1-vinyl-6,8-dimethoxytetrahydroisoquinoline **4** and 1-vinyl-5,6,7-trimethoxytetrahydroisoquinoline **6** with >90% ee by means of Pd-catalyzed intramolecular AAA reactions, using MPN and BOP ligands, developed in our laboratory. The 1-vinyltetrahydroisoquinolines thus obtained serve as versatile intermediates for the synthesis of a variety of naturally occurring isoquinoline alkaloids. For the optimization of enantioselectivity, the fine-tuning capability of the MPN and BOP ligands has played a significant role. Plausible mechanisms of the reactions that can accommodate the results obtained have been proposed. The solvent effects have revealed the critical importance of the activation of the trifluoroamide moiety through its coordination to the Lewis acidic Pd^{2+} metal center. In the AAA reaction of **5**, a kinetic resolution appears to have taken place to enrich enantioselectivity. The facts that BOP ligands gave the best results in the AAA reaction of **3**, while MPN ligands served best in the reaction of **5**, may indicate the need for more flexibility to accommodate the coordination of trifluoroamide moiety of **5** bearing a sterically demanding methoxy group at the C3 position, which can easily be achieved by non-chelating MPN ligands.

4. Experimental section

4.1. General methods and materials

^1H 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: Shimadzu LC-2010A HPLC system using a Chiralcel OD-H column (hexanes/*i*-PrOH=98.8/1.2, 1.0 mL/min). Melting points were measured on a Thomas Hoover Capillary melting point apparatus

and are uncorrected. Specific 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 reactions were carried out under nitrogen atmosphere.

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. Chiral biphenols, chiral phosphoramidite ligands, **MPN-La–e**, and chiral diphosphonite ligands **BOP-La–i** were prepared according to the procedure previously reported by our laboratory.[23,24] (1*R*,2*R*)-(+)-*N*,*N*′-Bis(2′-diphenylphosphinobenzoyl)-1,2-diaminocyclohexane was purchased from Acros Organics.

4.2. Synthesis of substrates 3 and 5a–n

*4.2.1. 1-Iodo-4,6-dimethoxy-2-[2-(trifluoroacetylamino)ethyl]-benzene (**8**).* To a suspension of 3,5-dimethoxyphenylethylamide **7**[25,26] (277 mg, 1.00 mmol) and Ag_2SO_4 (936 mg, 3.00 mmol) in 10 mL EtOH at 0 °C, was added a solution of I_2 (280 mg, 1.10 mmol) in 30 mL EtOH dropwise over 30 min. The mixture was stirred at the same temperature for another 6 h. TLC analysis indicated full conversion of the starting material and formation of mono-iodinated product **8** as well as bis-iodinated product. The mixture was then filtrated through a pad of Celite and the filtrate was concentrated to afford a crude product. Flash chromatography of the crude produce on silica gel (hexanes/EtOAc=10/1→5/1) gave pure mono-iodinated product **8** (355 mg, 88% yield) as a white solid: mp 126–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (t, *J*=6.9 Hz, 2H), 3.62 (q, *J*=6.9 Hz, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 6.33 (d, *J*=2.7 Hz, 1H), 6.41 (d, *J*=2.7 Hz, 1H), 6.47 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.6, 39.7, 55.4, 56.5, 81.5, 97.6, 106.8, 115.8 (q, *J*=286 Hz), 142.3, 157.0 (q, *J*=36 Hz), 161.1; HRMS (EI) calcd for $C_{12}H_{13}O_3NIF_3$ $[M]^+$ 402.9893, found 402.9892 (Δ=−0.1 ppm).

*4.2.2. 3-{4,6-Dimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl} prop-2-ynol (**9**).* A mixture of **8** (403 mg, 1.00 mmol), $Pd(Ph_3)_2Cl_2$ (21 mg, 0.025 mmol), and CuI (9.5 mg, 0.05 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 analysis indicated the completion of the reaction (48 h). Then, saturated ammonium chloride solution (5 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (15 mL×3). The combined organic layer was dried over anhydrous $MgSO_4$. Crude product was obtained after filtration and evaporation of the solvent. Further purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc=5/1→1/1) afforded **9** as a white solid (275 mg, 83% yield): mp 121.5–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.99 (t, *J*=6.9 Hz, 2H), 3.15 (br s, 1H), 3.59 (q, *J*=6.9 Hz, 2H), 3.79 (s, 3H), 3.83 (s, 3H), 4.54 (s, 2H), 6.33 (br s, 2H), 7.09 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.3, 40.4, 51.7, 55.4, 79.8, 94.7, 96.9, 104.3, 106.1, 115.9 (q, *J*=286 Hz), 142.9, 157.5 (q, *J*=36 Hz), 160.9, 161.6; HRMS (EI) calcd for $C_{15}H_{16}NO_4F_3$ $[M]^+$ 331.1031, found 331.1034 (Δ=+0.3 ppm).

*4.2.3. (Z)-3-{4,6-Dimethoxyl-2-[2-(trifluoroacetylamino)ethyl]-phenyl}prop-2-enol (**10**).* P2–Ni catalyst was generated in situ following the standard procedure[29] 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 nitrogen 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, **9** (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 analysis indicated the completion of the reaction. The reaction was quenched by addition of water. The aqueous layer was extracted with EtOAc (10 mL×3). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. 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 **10** (161 mg, 97% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (br s, 1H), 2.83 (t, *J*=6.9 Hz, 2H), 3.52 (q, *J*=6.6 Hz, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 3.95 (d, *J*=6.6 Hz, 2H), 6.03 (dt, *J*=6.9, 11.1 Hz, 1H), 6.31 (d, *J*=11.1 Hz, 1H), 6.33 (d, *J*=2.4 Hz, 1H), 6.39 (d, *J*=2.4 Hz, 1H), 6.80 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.8, 39.7, 55.3, 55.7, 60.1, 97.3, 105.9, 115.8 (q, *J*=286 Hz), 117.2, 124.5, 133.1, 137.9, 157.3 (q, *J*=37 Hz), 157.7, 160.0; HRMS (ESI) calcd for $C_{15}H_{17}NO_3F_3$ $[M-OH]^+$ 316.1161, found 316.1172 (Δ=+3.5 ppm).

*4.2.4. Ethenyl (Z)-3-{4,6-dimethoxy-2-[2-(trifluoroacetylamino)-ethyl]phenyl}prop-2-enyl carbonate (**3**).* To a solution of **10** (166 mg, 0.5 mmol) and pyridine (1.0 mL) in CH_2Cl_2 (10 mL) was added slowly vinyl 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 (10 mL×4). Combined organic layer was washed with water, brine and dried over anhydrous $MgSO_4$. 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 **3** (187 mg, 93% yield) as a white solid: mp 65–67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 (t, *J*=6.9 Hz, 2H), 3.53 (q, *J*=6.9 Hz, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 4.56 (m, 3H), 4.88 (dd, *J*=2.1, 13.8 Hz, 1H), 5.91 (dt, *J*=6.3, 11.1 Hz, 1H), 6.30 (d, *J*=2.1 Hz, 1H), 6.39 (d, *J*=2.7 Hz, 1H), 6.45 (d, *J*=11.4 Hz, 1H), 6.71 (br s, 1H), 6.95 (dd, *J*=6.3, 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.6, 39.3, 55.3, 55.5, 66.4, 97.3, 98.0, 106.2, 115.8 (q, *J*=286 Hz), 116.0, 126.7, 127.2, 138.2, 142.3, 152.9, 157.3 (q, *J*=37 Hz), 157.8, 160.3; HRMS (ESI) calcd for $C_{15}H_{17}NO_3F_3$ $[M-OCO_2C_2H_3]^+$ 316.1161, found 316.1157 (Δ=−1.3 ppm).

*4.2.5. N-[2-(2,3,4-Trimethoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (**14**).* A mixture of 2,3,4-trimethoxybenzaldehyde (**11**) (2.55 g, 13.0 mmol), ammonium acetate (1.10 g, 14.3 mmol) in nitromethane (65 mL) was stirred for 1 h at 100 °C. The reaction mixture was cooled to room temperature, treated with water (50 mL) to quench the reaction, and extracted with ether (60 mL×3). The combined organic layer was washed with brine (50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue recrystallized from EtOH to give **12** (2.82 g, 91% yield) as a pale yellow solid: mp 77.0–77.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.92 (s, 3H), 3.99 (s, 3H), 6.72 (d, *J*=8.8 Hz, 1H), 7.20 (d, *J*=8.8 Hz, 1H), 7.77 (d, *J*=13.6 Hz, 1H), 8.08 (d, *J*=13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 60.9, 61.2, 107.7, 117.1, 126.5, 135.2, 142.5, 154.3, 157.3.

To a solution of $LiAlH_4$ (3.23 g, 85.1 mmol) in THF (25 mL) was added a solution of **12** (5.09 g, 21.3 mmol) in THF (175 mL) slowly at 0 °C. The reaction mixture was heated to 65 °C and stirred for 3 h. The reaction was then quenched by 20% KOH. The resulting slurry was filtered through Celite pad and the filtrate was concentrated in vacuo. The residue was extracted with ether (30 mL×3) and the combined organic layer was washed with brine (20 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give 2-(2,3,4-trimethoxyphenyl)ethylamine (**13**) (3.44 g, 16.3 mmol) as a yellow liquid, which was directly used in the next amidation step without further purification.

To a stirred solution of **13** (3.44 g, 16.3 mmol) and NEt_3 (4.12 g, 40.7 mmol) in CH_2Cl_2 (96 mL) was added dropwise trifluoroacetic anhydride (3.45 mL, 24.4 mmol) at 0 °C with stirring. The mixture was stirred at 0 °C for 1 h. Reaction was quenched by the addition of water at the same temperature, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (30 mL×3), and combined organic layer was washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After concentrated in vacuo, crude product was purified by column chromatography on silica gel (hexanes/EtOAc=4/1) to give **14** (4.24 g, 65% in two steps) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (t, J=6.8 Hz, 2H), 3.45 (q, J=6.4 Hz, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 6.58 (d, J=8.4 Hz, 1H), 6.78 (d, J=8.4 Hz, 1H), 7.49 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.8, 41.2, 55.7, 60.4, 60.7, 107.6, 115.7 (q, J=286 Hz), 123.7, 124.3, 142.0, 151.4, 152.7, 157.1 (q, J=36 Hz); HRMS (ESI) calcd for $C_{13}H_{17}F_3NO_4$ $[M+H]^+$ 308.1110, found 308.1103 (Δ=−2.3 ppm).

*4.2.6. N-[2-(5-Bromo-2,3,4-trimethoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (**15**).* *N*-Bromosuccinimide (NBS) (5.15 g, 28.93 mmol) was added to a solution of **14** (5.93 g, 19.29 mmol) in CCl_4 (50 mL). The mixture was stirred at 60 °C for 16 h and then cooled to room temperature. Water (50 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (3×60 mL). The combined organic layer was washed with saturated Na_2SO_3 (50 mL) and brine (50 mL) and dried over anhydrous $MgSO_4$. After concentrated in vacuo, crude product was purified by column chromatography on silica gel (hexanes/EtOAc=4/1) to give **15** (6.86 g, 92%) as a white solid: mp 62.5–64.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (t, J=6.8 Hz, 2H), 3.49 (q, J=6.4 Hz, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 7.07 (s, 1H), 7.19 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.9, 41.1, 60.8, 60.9, 61.0, 111.7, 115.8 (q, J=287 Hz), 127.9, 128.3, 147.4, 150.4, 151.2, 157.2 (q, J=37 Hz); HRMS (ESI) $C_{13}H_{16}BrF_3NO_4$ $[M+H]^+$ 386.0215, found 386.0215 (Δ=0.0 ppm).

*4.2.7. N-[2-(5-Bromo-6-iodo-2,3,4-trimethoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (**16**).* *N*-Iodosuccinimide (NIS) (6.41 g, 28.50 mmol) was added to a solution of **15** (7.34 g, 19.00 mmol) in CH_3CN (75 mL). To this mixture was added trifluoroacetic acid (2.12 mL, 28.50 mmol) dropwise. The mixture was refluxed for 24 h and then cooled to room temperature. Water (50 mL) was added to the reaction mixture, and CH_3CN was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3×60 mL) and the combined organic layer was washed with saturated Na_2SO_3 (50 mL) and water (50 mL), and dried over anhydrous $MgSO_4$. After concentrated in vacuo, crude product was purified by column chromatography on silica gel (hexanes/EtOAc=4/1) to give **16** (9.11 g, 94%) as a off-white solid: mp 75.0–77.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.23 (t, J=6.4 Hz, 2H), 3.54 (q, J=6.8 Hz, 2H), 3.88 (m, 6H), 3.92 (s, 3H), 6.96 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.8, 38.7, 60.8, 61.0, 61.2, 101.7, 115.8 (q, J=286 Hz), 121.9, 132.4, 147.3, 150.9, 151.0, 157.3 (q, J=37 Hz); HRMS (ESI) calcd for $C_{13}H_{15}BrF_3INO_4$ $[M+H]^+$ 511.9181, found 511.9185 (Δ=+0.8 ppm).

*4.2.8. 3-{2-Bromo-3,4,5-trimethoxy-6-[2-(trifluoroacetylamino)-ethyl]phenyl}prop-2-ynol (**17**).* Arylpropynol **17** was synthesized in the same manner as that described for **9**: 75% yield; brown solid; mp 88.5–90.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (t, J=7.2 Hz, 2H), 3.53 (q, J=6.4 Hz, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 4.55 (s, 2H), 7.12 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 40.1, 51.5 60.9, 61.0, 61.2, 81.8, 96.0, 115.8 (q, J=286 Hz), 116.0, 120.7, 130.6, 147.8, 150.6, 151.2, 157.6 (q, J=36 Hz); HRMS (ESI) calcd for $C_{16}H_{18}BrF_3NO_5$ $[M+H]^+$ 440.0320, found 440.0316 (Δ=−0.9 ppm).

*4.2.9. (Z)-3-{3,4,5-Trimethoxy-2-[2-(trifluoroacetylamino)ethyl]-phenyl}prop-2-enol (**18**).* Arylpropenol **18** was synthesized in the same manner as that described for **8**: 75% yield; yellow solid; mp 83.0–85.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (br s, 1H), 2.83 (t, J=6.4 Hz, 2H), 3.43 (q, J=6.0 Hz, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 4.18 (d, J=6.8 Hz, 2H), 5.94 (dt, J=6.8, 11.6 Hz, 1H), 6.46 (s, 1H), 6.56 (d, J=11.6 Hz, 1H), 7.24 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.3, 56.0 59.0, 60.6, 60.9, 109.5, 115.8 (q, J=286 Hz), 121.7, 129.1, 131.5, 132.4, 141.3, 151.6, 151.9, 157.4 (q, J=36 Hz); HRMS (ESI) calcd for $C_{16}H_{20}F_3NO_5Na$ $[M+Na]^+$ 386.1191, found 386.1192 (Δ=+0.3 ppm).

Carbonates **5a** to **5n** were synthesized in the same manner as that described for **3**.

*4.2.10. Phenyl (Z)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino) ethyl]phenyl}prop-2-enyl carbonate (**5a**).* Yield 90%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (t, J=6.4 Hz, 2H), 3.43 (q, J=6.0 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 4.84 (d, J=7.2 Hz, 2H), 6.00 (dt, J=7.2, 11.6 Hz, 1H), 6.54 (s, 1H), 6.79 (d, J=11.6 Hz, 1H), 7.14–7.55 (m, 4H), 7.35–7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.4, 56.0, 60.6, 61.0, 65.0, 109.2, 115.8 (q, J=286 Hz), 120.9, 122.2, 125.9, 126.0, 129.4, 129.5, 130.5, 133.0, 141.8, 151.0, 151.8, 152.1, 153.6, 157.3 (q, J=37 Hz); HRMS (ESI) calcd for $C_{23}H_{24}F_3NO_7Na$ $[M+Na]^+$ 506.1403, found 506.1402 (Δ=−0.2 ppm).

*4.2.11. 2,2,2-Trichloroethyl (Z)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (**5b**).* Yield 71%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (t, J=6.0 Hz, 2H), 3.43 (q, J=6.4 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H), 4.76 (s, 2H), 4.81 (d, J=7.2 Hz, 2H), 5.96 (dt, J=7.2, 11.6 Hz, 1H), 6.54 (s, 1H), 6.78 (d, J=11.6 Hz, 1H), 7.12 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.4, 56.0, 60.6, 60.9, 65.3, 76.7, 94.3, 109.1, 115.8 (q, J=286 Hz), 122.1, 125.6, 130.4, 133.2, 141.7, 151.7, 152.1, 153.8, 157.2 (q, J=36 Hz); HRMS (ESI) calcd for $C_{19}H_{21}Cl_3F_3NO_7Na$ $[M+Na]^+$ 560.0233, found 560.0237 (Δ=+0.7 ppm).

*4.2.12. 2,2,2-Trifluoroethyl (Z)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (**5c**).* Yield 74%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84 (t, J=6.0 Hz, 2H), 3.42 (q, J=6.8 Hz, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H), 4.50 (q, J=8.4 Hz, 2H), 4.79 (dd, J=1.2, 6.8 Hz, 2H), 5.94 (dt, J=6.8 Hz, 11.6 Hz, 1H), 6.51 (s, 1H), 6.78 (d, J=11.6 Hz, 1H), 7.11 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.6, 56.1, 60.7, 61.0, 63.5 (q, J=37 Hz), 65.5, 109.2, 115.8 (q, J=286 Hz), 122.2, 122.5 (q, J=276 Hz), 125.6, 130.4, 133.4, 141.9, 151.8, 152.2, 153.9, 157.3 (q, J=36 Hz); HRMS (ESI) calcd for $C_{19}H_{21}F_6NO_7Na$ $[M+Na]^+$ 512.1120, found 512.1122 (Δ=+0.4 ppm).

*4.2.13. Ethenyl (Z)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino) ethyl]phenyl}prop-2-enyl carbonate (**5d**).* Yield 90%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84 (t, J=6.4 Hz, 2H), 3.43 (q, J=6.4 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H), 4.59 (dd, J=2.0, 6.4 Hz, 1H), 4.78 (dd, J=1.6, 7.2 Hz, 2H), 4.92 (dd, J=2.4, 14.0 Hz, 1H), 5.94 (dt, J=7.2, 11.2 Hz, 1H), 6.53 (s, 1H), 6.76 (dd, J=0.4, 7.2 Hz, 1H), 7.04 (dd, J=6.0, 13.6 Hz, 1H), 7.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.5, 56.1, 60.7, 61.0, 64.9, 98.0, 109.2, 115.8 (q, J=286 Hz), 122.2, 125.8, 130.5, 133.0, 141.8, 142.6, 151.8, 152.2, 152.6, 157.3 (q, J=37 Hz); HRMS (ESI) calcd for $C_{19}H_{22}F_3NO_7Na$ $[M+Na]^+$ 456.1246, found 456.1249 (Δ=+0.7 ppm).

*4.2.14. 1-Methylethenyl (Z)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (**5e**).* Yield 91%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (s, 3H), 2.85 (t, J=6.0 Hz, 2H), 3.43 (q, J=6.8 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.69–4.79 (m, 4H), 5.95 (dt, J=6.8, 11.6 Hz, 1H), 6.52 (s, 1H), 6.75 (d, J=11.6 Hz, 1H), 7.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 25.3, 40.5, 56.1, 60.7, 61.0, 64.6, 101.9, 109.2, 115.9 (q, J=287 Hz), 122.2, 126.2, 130.6, 132.7, 141.8, 151.8, 152.1, 152.8, 152.9, 157.3 (q, J=37 Hz);

HRMS (ESI) calcd for $C_{20}H_{24}F_3NO_7Na$ $[M+Na]^+$ 470.1403, found 470.1398 (Δ=−1.1 ppm).

*4.2.15. 4-Methoxyphenyl (Z)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (**5f**).* Yield 95%; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.86 (t, *J*=6.4 Hz, 2H), 3.43 (q, *J*=6.8 Hz, 2H), 3.79 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.83 (dd, *J*=1.2, 7.2 Hz, 2H), 6.00 (dt, *J*=7.2, 11.6 Hz, 1H), 6.54 (s, 1H), 6.78 (d, *J*=11.6 Hz, 1H), 6.87 (d, *J*=9.2 Hz, 2H), 7.06 (d, *J*=9.2 Hz, 2H) 7.11 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.5, 55.6, 56.1, 60.7, 61.0, 64.9, 109.3, 114.5, 115.9 (q, *J*=281 Hz), 121.8, 122.2, 126.1, 130.6, 132.9, 141.8, 144.7, 151.8, 152.2, 154.0, 157.3 (q, *J*=34 Hz), 157.5; HRMS (ESI) calcd for $C_{24}H_{26}F_3NO_8Na$ $[M+Na]^+$ 536.1508, found 536.1509 (Δ=+0.2 ppm).

*4.2.16. 4-Methylphenyl (Z)-3-{3,4,5-trimethoxy-2-[2-(trifluoro-acetylamino)ethyl]phenyl}prop-2-enyl carbonate (**5g**).* Yield 92%; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.85 (t, *J*=6.4 Hz, 2H), 3.43 (q, *J*=6.0 Hz, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.83 (d, *J*=6.8 Hz, 2H), 6.00 (dt, *J*=6.8, 11.6 Hz, 1H), 6.54 (s, 1H), 6.78 (d, *J*=11.6 Hz, 1H), 7.02 (d, *J*=8.4 Hz, 2H), 7.15–7.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 25.3, 40.5, 56.0, 60.6, 61.0, 64.9, 109.2, 115.8 (q, *J*=287 Hz), 120.6, 122.2, 126.0, 129.9, 130.6, 132.9, 135.8, 141.8, 148.9, 151.8, 152.1, 153.8, 157.3 (q, *J*=36 Hz); HRMS (ESI) calcd for $C_{24}H_{26}F_3NO_7Na$ $[M+Na]^+$ 520.1559, found 520.1564 (Δ=+1.0 ppm).

*4.2.17. 4-Fluorophenyl (Z)-3-{3,4,5-trimethoxy-2-[2-(trifluoro-acetylamino)ethyl]phenyl}prop-2-enyl carbonate (**5h**).* Yield 91%; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.85 (t, *J*=6.4 Hz, 2H), 3.42 (q, *J*=6.4 Hz, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 4.83 (dd, *J*=1.2, 6.8 Hz, 2H), 5.98 (dt, *J*=6.8, 11.6 Hz, 1H), 6.53 (s, 1H), 6.79 (d, *J*=11.6 Hz, 1H), 7.02–7.06 (m, 2H), 7.09–7.13 (m, 2H), 7.17 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.4, 56.0, 60.6, 61.0, 65.1, 109.2, 115.8 (q, *J*=286 Hz), 116.1 (d, *J*=24 Hz), 122.2, 122.4 (d, *J*=8 Hz), 125.8, 130.5, 133.0, 141.8, 146.9 (d, *J*=3 Hz), 151.8, 152.1, 153.6, 157.3 (q, *J*=37 Hz), 160.3 (d, *J*=244 Hz); HRMS (ESI) calcd for $C_{23}H_{23}F_4NO_7Na$ $[M+Na]^+$ 524.1308, found 524.1311 (Δ=+0.6 ppm).

*4.2.18. 4-Chlorophenyl (Z)-3-{3,4,5-trimethoxy-2-[2-(trifluoro-acetylamino)ethyl]phenyl}prop-2-enyl carbonate (**5i**).* Yield 94%; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.85 (t, *J*=6.0 Hz, 2H), 3.42 (q, *J*=6.4 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 3.92 (s, 3H), 4.83 (dd, *J*=1.2, 7.2 Hz, 2H), 5.98 (dt, *J*=7.2, 11.6 Hz, 1H), 6.53 (s, 1H), 6.79 (d, *J*=11.6 Hz, 1H), 7.10 (d, *J*=8.8 Hz, 2H), 7.16 (br s, 1H), 7.33 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.5, 56.1, 60.6, 61.0, 65.2, 109.2, 115.8 (q, *J*=286 Hz), 122.2, 122.3, 125.7, 129.5, 130.5, 131.5, 133.1, 141.8, 149.5, 151.8, 152.1, 153.3, 157.3 (q, *J*=36 Hz); HRMS (ESI) calcd for $C_{23}H_{23}ClF_3NO_7Na$ $[M+Na]^+$ 540.1013, found 540.1012 (Δ=−0.2 ppm).

*4.2.19. 3-Fluorophenyl (Z)-3-{3,4,5-trimethoxy-2-[2-(trifluoro-acetylamino)ethyl]phenyl}prop-2-enyl carbonate (**5j**).* Yield 82%; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.84 (t, *J*=6.4 Hz, 2H), 3.41 (q, *J*=6.0 Hz, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 4.83 (dd, *J*=0.8, 7.2 Hz, 2H), 5.97 (dt, *J*=7.2, 11.6 Hz, 1H), 6.53 (s, 1H), 6.79 (d, *J*=11.6 Hz, 1H), 6.91–6.96 (m, 3H), 7.21 (br s, 1H), 7.28–7.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.4, 56.0, 60.6, 60.9, 65.2, 109.0 (d, *J*=23 Hz), 109.1, 113.0 (d, *J*=21 Hz), 115.8 (q, *J*=287 Hz), 116.6 (q, *J*=3 Hz), 122.2, 125.6, 130.2 (d, *J*=9 Hz), 130.4, 133.1, 141.8, 151.7 (d, *J*=11 Hz), 151.8, 152.1, 153.0, 157.2 (q, *J*=36 Hz), 162.7 (d, *J*=247 Hz); HRMS (ESI) calcd for $C_{23}H_{23}F_4NO_7Na$ $[M+Na]^+$ 524.1308, found 524.1305 (Δ=−0.6 ppm).

*4.2.20. Pentafluorophenyl (Z)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (**5k**).* Yield 89%; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.85 (t, *J*=6.4 Hz, 2H), 3.42 (q, *J*=6.4 Hz, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.90 (dd, *J*=1.2, 7.2 Hz, 2H), 5.99 (dt, *J*=7.2, 11.6 Hz, 1H), 6.52 (s, 1H), 6.85 (d, *J*=11.6 Hz, 1H), 7.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 40.4, 56.0, 60.7, 61.0, 66.8, 109.0, 115.8 (q, *J*=286 Hz), 122.3, 124.7, 125.6 (m), 130.2, 134.2, 136.6 (m), 138.5 (m), 139.1 (m), 140.0 (m), 141.1 (m), 141.9, 142.5 (m), 151.2, 151.9, 152.2, 157.3 (q, *J*=36 Hz); LC–MS (ESI) calcd for $C_{23}H_{19}F_8NO_7$ $[M]^+$ 573.1, found 591.0 $[M+NH_4]^+$.

*4.2.21. 4-Nitrophenyl (Z)-3-{3,4,5-trimethoxy-2-[2-(trifluoro-acetylamino)ethyl]phenyl}prop-2-enyl carbonate (**5l**).* Yield 80%; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.85 (t, *J*=6.4 Hz, 2H), 3.43 (q, *J*=6.4 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 3.92 (s, 3H), 4.87 (dd, *J*=1.2, 6.8 Hz, 2H), 5.99 (dt, *J*=6.8, 11.2 Hz, 1H), 6.52 (s, 1H), 6.82 (d, *J*=11.2 Hz, 1H), 7.15 (br s, 1H), 7.36 (d, *J*=9.2 Hz, 2H), 8.25 (d, *J*=9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.5, 56.1, 60.7, 61.0, 65.6, 109.4, 115.8 (q, *J*=287 Hz), 121.7, 122.2, 125.3, 125.4, 130.4, 133.4, 141.8, 145.4, 151.8, 152.2, 152.4, 155.4, 157.3 (q, *J*=36 Hz); HRMS (ESI) calcd for $C_{23}H_{23}F_3N_2O_9Na$ $[M+Na]^+$ 551.1253, found 551.1248 (Δ=−0.9 ppm).

*4.2.22. 2,6-Dimethylphenyl (Z)-3-{3,4,5-trimethoxy-2-[2-(trifluoro-acetylamino)ethyl]phenyl}prop-2-enyl carbonate (**5m**).* Yield 99%; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 6H), 2.86 (t, *J*=6.4 Hz, 2H), 3.43 (q, *J*=6.4 Hz, 2H), 3.83 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.85 (dd, *J*=1.2, 6.8 Hz, 2H), 6.00 (dt, *J*=6.8, 11.2 Hz, 1H), 6.53 (s, 1H), 6.79 (d, *J*=11.2 Hz, 1H), 7.05–7.07 (m, 3H), 7.10 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 25.2, 40.3, 55.9, 60.5, 60.8, 65.0, 109.1, 115.7 (q, *J*=286 Hz), 122.2, 125.9, 126.0, 128.6, 129.9, 130.4, 132.9, 141.7, 148.2, 151.7, 152.0, 152.8, 157.2 (q, *J*=36 Hz); HRMS (ESI) calcd for $C_{25}H_{28}F_3NO_7Na$ $[M+Na]^+$ 534.1716, found 534.1718 (Δ=+0.4 ppm).

*4.2.23. 2,6-Diisopropylphenyl (Z)-3-{3,4,5-trimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (**5n**).* Yield 72%; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, *J*=6.8 Hz, 12H), 2.86 (t, *J*=6.4 Hz, 2H), 3.01 (, *J*=6.8 Hz, 2H) 3.43 (q, *J*=6.0 Hz, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.86 (dd, *J*=1.2, 7.2 Hz, 2H), 6.00 (dt, *J*=7.2, 11.2 Hz, 1H), 6.57 (s, 1H), 6.80 (d, *J*=11.2 Hz, 1H), 7.14–7.24 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 25.3, 27.3, 40.4, 56.0, 60.6, 60.9, 65.1, 109.1, 115.8 (q, *J*=287 Hz), 122.2, 124.0, 126.1, 126.8, 130.5, 132.8, 140.3, 141.7, 145.7, 151.8, 152.1, 153.7, 157.3 (q, *J*=36 Hz); HRMS (ESI) calcd for $C_{29}H_{36}F_3NO_7Na$ $[M+Na]^+$ 590.2342, found 590.2346 (Δ=+0.7 ppm).

4.3. Intramolecular asymmetric allylic amination

*4.3.1. (S)-(+)-1-Ethenyl-3,5-dihydro-6,8-dimethoxy-2-trifluro-acetyl-1,2,3,4-tetrahydroisoquinoline (**4**).* A solution of (*R*)-**BOP-Lg** (2.8 mg, 0.0033 mmol) and $Pd_2(dba)_3$ (1.0 mg, 0.0011 mmol) in DMF (0.5 mL) was added to a 5 mL round-bottomed flask with a stirring bar under N_2. The mixture was stirred at room temperature until the color of the solution turned to light yellow from purple, and cooled down to 0 °C. Then, **3** (20 mg, 0.05 mmol) in DMF (0.5 mL) was added to the catalyst solution via a syringe. The mixture was stirred at 0 °C until TLC analysis indicated the completion of the reaction (24 h). The reaction mixture was passed through a short pad of silica gel using hexanes/EtOAc (12/1→8/1) as the eluent. The filtrate was then concentrated and subject to HPLC analysis, using a Chiralcel OD-H column (hexanes/*i*-PrOH=99.5/0.5, 0.5 mL/min). Product **4** was isolated in quantitative yield as colorless oil: 90% ee; $[\alpha]_D^{23}$ +159.7 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) (a mixture of two rotamers in 2:1 ratio) δ 2.75–2.83 (m, 1H), 2.92–3.02 (m, 1H), [3.30 (td, *J*=4.8, 12.0 Hz, 0.33H)], 3.63 (td, *J*=4.8, 12.0, 0.67H)], 3.80 (s, 3H), 3.81 (s, 3H), [3.92–3.97 (m, 0.67H), 4.37–4.43 (m, 0.33H)], 4.88–4.94 (m, 1H), 5.18–5.23 (m, 1H), [5.74–5.75 (m, 0.33H), 6.16–6.17 (m, 0.67H)], 5.90–5.99 (m, 1H), [6.26–6.27 (m, 0.67H), 6.28–6.29 (m, 0.33H)], 6.35 (d, *J*=2.0 Hz, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$) (a mixture of two rotamers) (major) δ 29.5, 39.9, 51.5, 55.5, 55.6, 97.1, 104.3, 115.1, 116.8 (q, *J*=287 Hz), 135.2, 135.4, 135.9, 156.0 (q, *J*=36 Hz), 157.6, 160.1 (minor) δ 28.0, 38.0, 53.4, 55.5, 55.6, 97.0, 104.6, 115.0, 116.8 (q, *J*=287 Hz), 135.1, 135.9, 136.1, 156.0 (q, *J*=36 Hz), 157.0, 160.3; HRMS (ESI^+) calcd for $C_{15}H_{17}NO_3F_3$ $[M+H]^+$ 316.1161, found 316.1153 (Δ=−2.5 ppm).

*4.3.2. (S)-(+)-1-Ethenyl-2-trifluoroacetyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**6**).* Reactions were run in the same manner as that for **3**, but using MPN ligands and several different solvents with and without additives, as well as running the reaction at room temperature. The result using **5a**, (*S*)-**MPN-Lj** in CH_2Cl_2 with 1% (v/v) TFE is shown as a typical example:

Compound **6**: 99% yield; yellow oil; 91% ee; $[\alpha]_D^{23}$ +134.6 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) (a 79:21 mixture of two rotamers) δ 2.69–2.87 (m, 2H), [3.16 (td, *J*=4.8, 14.0 Hz, 0.21H), 3.45 (td, *J*=4.8, 14.0 Hz, 0.79H)], 3.80 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), [3.99–4.04 (m, 0.79H), 4.45–4.50 (m, 0.21H)], 5.02–5.15 (m, 1H), 5.26–5.29 (m, 1H), [5.40–5.41 (m, 0.21H), 5.88–6.02 (m, 1.79H)], [6.38 (s, 0.21H), 6.41 (s, 0.79H)]; ^{13}C NMR (100 MHz, $CDCl_3$) (a 79:21 mixture of two rotamers) (major) δ 23.3, 39.6, 55.5, 55.9, 60.4, 60.7, 106.5, 116.4 (q, *J*=286 Hz), 118.4, 119.6, 128.2, 135.3, 141.0, 150.8, 152.3, 155.5 (q, *J*=36 Hz) (minor) δ 21.7, 37.3, 55.5, 55.9, 57.8, 60.3, 106.2, 116.5 (q, *J*=286 Hz), 118.3, 120.3, 128.0, 136.3, 141.3, 151.1, 152.1, 155.5 (q, *J*=36 Hz); HRMS (ESI^+) calcd for $C_{16}H_{18}F_3NO_4$ $[M]^+$ 345.1188, found 346.1264 (Δ=−0.6 ppm).

This reaction was accompanied by the formation of side product **22**. The characterization data of **22a** and **22c** are shown below.

*4.3.3. 1-[(Z)-3-Phenoxyprop-1-enyl]-2-[2-(trifluoroacetylamino)-ethyl]-2,3,4-trimethoxybenzene (**22a**).* White solid; mp 100.0–102.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.89 (t, *J*=6.0 Hz, 2H), 3.40 (q, *J*=6.0 Hz, 2H), 3.85 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 4.73 (dd, *J*=1.2, 5.6 Hz, 2H), 6.24 (dt, *J*=5.6, 15.6 Hz, 1H), 6.83 (s, 1H), 6.87 (d, *J*=15.6 Hz, 1H), 6.96–6.99 (m, 3H), 7.06 (br s, 1H), 7.29–7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 41.0, 56.0, 60.7, 61.0, 68.2, 105.9, 106.0, 114.8, 115.8 (q, *J*=286 Hz), 121.0, 121.7, 127.2, 129.5, 131.7, 141.9, 151.5, 152.5, 157.3 (q, *J*=36 Hz), 158.4; HRMS (ESI) calcd for $C_{22}H_{24}F_3NO_5$ $[M]^+$ 439.1607, found 462.1498 (Δ=−1.3 ppm).

*4.3.4. 1-[(Z)-3-(2,2,2-Trifluoroethoxy)prop-1-enyl]-2-[2-(trifluoroacetylamino)ethyl]-2,3,4-trimethoxybenzene (**22c**).* Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.93 (t, *J*=6.4 Hz, 2H), 3.45 (q, *J*=6.0 Hz, 2H), 3.85–3.92 (m, 11H), 4.31 (dd, *J*=0.8, 6.4 Hz, 2H), 6.10 (dt, *J*=6.4, 15.6 Hz, 1H), 6.81 (s, 1H), 6.81 (d, *J*=15.6 Hz, 1H), 7.08 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 41.0, 56.0, 60.7, 61.0, 67.4 (q, *J*=34 Hz), 72.7, 105.9, 115.8 (q, *J*=286 Hz), 121.8, 124.0 (q, *J*=278 Hz), 126.9, 130.2, 131.4, 142.1, 151.5, 152.6, 157.3 (q, *J*=36 Hz); HRMS (ESI) calcd for $C_{18}H_{21}F_6NO_5Na$ $[M+Na]^+$ 468.1222, found 468.1226 (Δ=+0.9 ppm).

*4.3.5. 1-[(Z)-3-(1,1,1,3,3,3-Hexafluoroprop-2-yloxy)prop-1-enyl]-2-[2-(trifluoroacetylamino)ethyl]-2,3,4-trimethoxybenzene (**22o**).* Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.93 (t, *J*=6.4 Hz, 2H), 3.44 (q, *J*=6.4 Hz, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 4.22 (septet, *J*=6.0 Hz, 1H), 4.51 (d, *J*=6.6 Hz, 2H), 6.10 (dt, *J*=6.6, 15.6 Hz, 1H), 6.80 (s, 1H), 6.87 (d, *J*=15.6 Hz, 1H), 7.04 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 40.9, 56.0, 60.7, 61.0, 70.7, 74.9–75.9 (m), 106.0, 115.8 (q, *J*=287 Hz), 121.6 (q, *J*=282 Hz), 122.0, 125.4, 130.9, 132.4, 142.4, 151.6, 152.6, 157.4 (q, *J*=36 Hz); HRMS (ESI) calcd for $C_{19}H_{20}F_9NO_5Na$ $[M+Na]^+$ 536.1095, found 536.1098 (Δ=+0.6 ppm).

4.4. Phosphoramidite ligands

*4.4.1. O,O′-(R)-(3,3′-Dibenzyl-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl)-N,N-dimethylphosphoramidite [(R)-**MPN-Lf**].* To a mixture of (*S*)-3,3′-Dibenzyl-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diol[24] (0.42 g, 1.00 mmol) in toluene (5 mL) was added hexamethylphosphorous triamide (248 mg, 1.50 mmol) under nitrogen. The resulting mixture was stirred at 80 °C for 17 h. The solvent was evaporated under reduced pressure to afford a gel-like product, which was further purified by column chromatography on silica gel (pretreated with 1% NEt_3 in hexanes) using hexanes/EtOAc (19/1) as the eluent to give (*R*)-**MPN-Lf** (0.32 g, 65%) as a white solid: mp 110.0–112.0 °C; $[\alpha]_D^{22}$ −176.2 (*c* 0.5, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.94 (s, 3H), 2.01 (s, 3H), 2.22 (s, 3H), 2.23 (s, 3H), 2.52 (s, 3H), 2.55 (s, 3H), 3.70 (d, *J*=15.2 Hz, 1H), 4.17 (m, 1H), 6.86 (s, 1H), 6.91 (s, 1H), 7.28 (m, 10H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 140.8; HRMS (EI) calcd for $C_{24}H_{26}NO_2P$ $[M]^+$ 391.1701, found 391.1703 (Δ=+0.5 ppm).

Other new MPN ligands were synthesized in the same manner as that for (*R*)-**MPN-Lf**, using the corresponding arylmagnesium bromides.

*4.4.2. O,O′-(S)-[3,3′-Bis(dimethylphenylmethyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl]-N,N-dimethylphosphoramidite [(S)-**MPN-Lg**].* Yield 69%; white solid; mp 157–159 °C; $[\alpha]_D^{20}$ +225.4 (*c* 0.6, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (s, 3H), 1.62 (s, 3H), 1.65 (s, 3H), 1.66 (s, 3H), 1.72 (s, 3H), 1.80 (s, 3H), 1.85 (s, 3H), 2.12 (br s, 3H), 2.16 (s, 3H), 2.29 (s, 3H), 6.83 (s, 1H), 7.08–7.26 (m, 10H), 7.29 (s, 1H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 142.7; HRMS (EI) calcd for $C_{36}H_{42}NO_2P$ $[M]^+$ 551.2953, found 551.2934 (Δ=−1.9 ppm).

*4.4.3. O,O′-(R)-[3,3′-Bis(diphenylmethyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl]-N,N-dimethylphosphoramidite [(R)-**MPN-Lh**].* Yield 65%; colorless oil; $[\alpha]_D^{20}$ −177.8 (*c* 0.5, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (s, 3H), 2.00 (s, 3H), 2.16 (s, 3H), 2.19 (s, 3H), 2.33 (s, 3H), 2.36 (s, 3H), 5.75 (s, 1H), 5.95 (s, 1H), 6.74 (d, *J*=6.6 Hz, 2H), 6.98 (d, *J*=6.9 Hz, 2H), 7.13–7.33 (m, 18H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 142.1; HRMS (EI) calcd for $C_{44}H_{42}NO_2P$ $[M]^+$ 647.2953, found 647.2969 (Δ=+1.7 ppm).

*4.4.4. O,O′-(R)-[3,3′-Bis(naphthalen-2-ylmethyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl]-N,N-dimethylphosphoramidite [(R)-**MPN-Li**].* Yield 63%; colorless oil; $[\alpha]_D^{20}$ −490.9 (*c* 0.5, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.93 (s, 3H), 2.00 (s, 3H), 2.18 (s, 3H), 2.19 (s, 3H), 2.53 (s, 3H), 2.56 (s, 3H), 3.83 (d, *J*=15.6 Hz, 1H), 4.22 (d, *J*=15.6 Hz, 1H), 4.29 (d, *J*=15.6 Hz, 1H), 4.36 (d, *J*=15.6 Hz, 1H), 6.86 (s, 1H), 6.90 (s, 1H), 7.39–7.46 (m, 6H), 7.69–7.83 (m, 8H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 140.5; HRMS (EI) calcd for $C_{40}H_{38}NO_2P$ $[M]^+$ 595.2640, found 595.2659 (Δ=+1.9 ppm).

*4.4.5. O,O′-(S)-[3,3′-Bis(naphthalen-1-ylmethyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diyl]-N,N-dimethylphosphoramidite [(S)-**MPN-Lj**].* Yield 92%; colorless oil; $[\alpha]_D^{20}$ +389.5 (*c* 0.5, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.95 (s, 3H), 2.02 (s, 3H), 2.13 (s, 3H), 2.14 (s, 3H), 2.60 (s, 3H), 2.62 (s, 3H), 4.06 (d, *J*=15.9 Hz, 1H), 4.56 (d, *J*=15.9 Hz, 1H), 4.62 (d, *J*=15.9 Hz, 1H), 4.79 (d, *J*=15.9 Hz, 1H), 6.74 (d, *J*=8.1 Hz, 2H), 7.38–7.52 (m, 8H), 7.77–7.92 (m, 4H), 8.07–8.15 (m, 2H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 140.4; HRMS (EI) calcd for $C_{40}H_{38}NO_2P$ $[M]^+$ 595.2640, found 595.2623 (Δ=−1.7 ppm).

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28. In the reactions of 4,6-*O*,*O*′-disubstituted dihydroxyphenylallyl carbonate, only vinyl carbonate **3** (4,6-dimethoxy) was employed in this study. However, we also examined phenyl derivatives of 4,6-dibenzyloxy- and 4,6-bis(4-methoxybenzyl-oxy)phenylallyl carbonates in our approach to the enantioselective total synthesis of schulzelines A–C. In these substrates bearing a nucleophilic leaving group (i.e., phenoxy group), no side product (i.e., **22a**-type) formation was observed at all. The results will be published elsewhere.
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