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Palladium-catalyzed asymmetric umpolung allylation of imines with allylic alcohols

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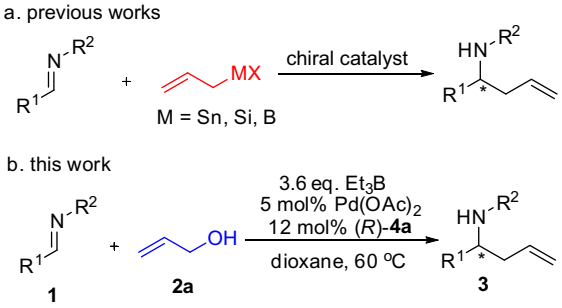
Dedicated to Professor Henri Kagan, a pioneer of asymmetric synthesis, on the occasion of his 80th birthday

ABSTRACT

A palladium-catalyzed asymmetric umpolung allylation reaction of imines with allylic alcohols has been developed. In the presence of chiral spiro phosphoramidite ligand **4**, the allylation was accomplished with high yields and good enantioselectivities. The use of highly stable and easily available allylic alcohols instead of allylic metal reagents facilitated the preparation of chiral homoallylic amines.

1. Introduction

Chiral homoallylic amines are amongst the most versatile intermediates in organic synthesis and are ubiquitous motifs in bioactive nature products and pharmaceuticals.[1] The transition metal-catalyzed nucleophilic allylation of imines represents one of the most powerful protocols for the preparation of chiral homoallylic amines. Although a large number of efficient chiral transition metal catalysts have been developed for the highly enantioselective allylation of carbonyl compounds,[2] only a few catalytic asymmetric allylations of imines have been developed. Moreover, all transition metal-catalyzed enantioselective allylations of imines use allylic metal reagents such as stannanes,[3] silanes,[4] and boranes[5] (Scheme 1, part a). All allylic metals require a multi-step preparation and generally are either air or moisture sensitive, limiting their wide application in organic synthesis. Thus, the search for more stable and available allylating reagents instead of commonly used allylic metals has become one of the major challenges in catalytic asymmetric nucleophilic allylation reactions and will advance the usefulness of this important transformation. Over the past decade, people have developed several efficient catalytic systems by using allylic halides[6] or allylic acetates[7] as allylating reagents in the asymmetric allylation reactions of aldehydes or even ketones, however, there is still no efficient transition metal catalysts for the enantioselective allylation of imines in the absence of allylic metal reagents. In view of availability and stability, the allylic alcohol is an ideal allylating reagent. The direct use of allylic alcohols can avoid the transformation of allylic alcohols to their derivatives bearing a wasteful leaving group, and enhances the synthetic application of the allylation reaction of imines.



Scheme 1. Transition metal-catalyzed asymmetric allylation of imines.

Quite recently, several research groups developed the transition metal-mediated allylation of imines with allylic alcohols, which demonstrated that the direct use of allylic alcohols as allylating reagents in asymmetric allylation of imines is possible.[8] Our recent research revealed that the palladium complexes of chiral spiro monodentated phosphorous ligands are efficient chiral catalysts for the allylations of aldehydes and activated ketones with allylic alcohols via umpolung of π-allylpalladium species.[9] As a continuous effort on the development of allylic alcohols as allylic reagents in the palladium-catalyzed asymmetric umpolung allylation reactions, we herein report our preliminary studies of the palladium-catalyzed asymmetric allylation of imines with allylic alcohols (Scheme 1, part b). By using chiral spiro phosphoramidite ligands, a variety of homoallylic amines were obtained in high yields with moderate to good enantioselectivities (up to 81% ee).

2. Results and discussion

The palladium-catalyzed allylation of *N*-tosyl imine **1a** with allylic alcohol **2a** was first studied in THF at 60 °C with 3.6 equiv

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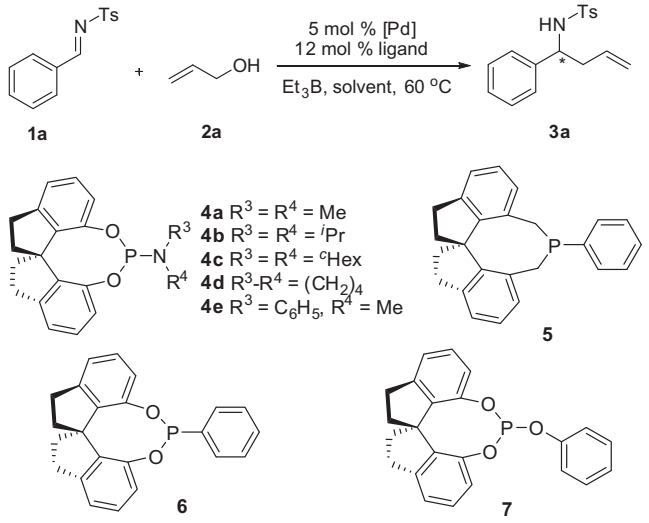
of triethylborane as umpolung agent (Table 1). When the catalyst prepared in situ from palladium acetate and the chiral spiro monodentated phosphoramidite (*R*)-**4a** was used, the allylation reaction ran smoothly to afford homoallylic amine **3a** with excellent yield (91%) and moderate enantioselectivity (66% ee) (entry 1). We then tested various chiral spiro ligands developed in this laboratory in the allylation reaction. The phosphoramidite ligands with different amine moieties **4a**–**4e** (R^3-*N*-R^4) were firstly evaluated in the allylation reaction. All the spiro phosphoramidite ligands with *N*-alkyl moieties **4a**–**4d** were efficient for the allylation reaction, while *N*-phenyl-substituted **4e** was less efficient in view of the yield and enantioselectivity (entries 1–5). In all the tested phosphoramidite, **4a** with a dimethylamino group afforded the best result. The other three types of chiral monodentate phosphorus ligands, including phospholane **5**, phosphonite **6**, and phosphite **7**, were also evaluated in the allylation reaction, however, reactivities and enantioselectivities were significantly lower than those obtained with ligand **4a** (entries 6–8). To increase the enantioselectivity further, the reaction conditions were optimized carefully. Besides palladium acetate, the Pd(0) complexes $Pd(dba)_2$ gave essentially the same level of enantioselectivity albeit with lower yield (entry 9). Conversely, the $[Pd(C_3H_5)Cl]_2$ containing an inner chloride ligand was ineffective for the allylation of imines (entry 10). The ether solvents THF, dimethoxyethane (DME), and dioxane and toluene were suitable for the allylation reaction. The reaction performed in toluene gave the highest level of enantioselectivity (72% ee), unfortunately, the yield was lower (73%). Considering both the yield and the ee value, dioxane was the best solvent of choice.

Under the optimal reaction conditions, the palladium-catalyzed allylation of various *N*-tosyl-protected imines with allylic alcohol was carried out. The *para*-substituted benzaldehyde-derived imines **1b**–**1f**, regardless of the electronic properties of the substitute groups, were favorable for higher enantioselectivity (Table 2, entries 2–6). When **1c** derived from 4-chlorobenzaldehyde was used, the highest enantioselectivity (80% ee) was obtained with excellent yield (95%) (entry 3). The *ortho*-substitution groups of imines had almost no impact on the reactivities and enantioselectivities of the allylation reaction (entries 9 and 10). The *meta*-substitution groups of imines decreased the enantioselectivities significantly (entries 7 and 8). Besides the substituted benzaldehyde imines, the allylation of furan-2-carbaldehyde imine **1k** with prop-2-en-1-ol **2a** proceeded smoothly under the standard conditions and produced the corresponding homoallylic amines with good level of enantioselectivities (75% ee) (entry 11). The α,β-unsaturated aldehyde imine **1l** was also a suitable substrate for the allylation reaction, with 76% ee and 60% yield (entry 12).

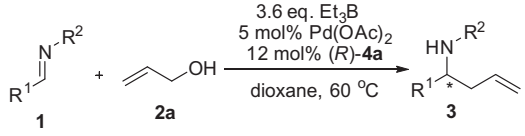
Table 1
Palladium-catalyzed asymmetric allylation of an amine with an allylic alcohol: Optimizing the reaction conditions[a]



Entry	[Pd]	Ligand	Solvent	Yield[b] (%)	ee[c] (%)
1	$Pd(OAc)_2$	(*R*)-**4a**	THF	91	66
2	$Pd(OAc)_2$	(*R*)-**4b**	THF	81	58
3	$Pd(OAc)_2$	(*R*)-**4c**	THF	86	60
4	$Pd(OAc)_2$	(*R*)-**4d**	THF	86	60
5	$Pd(OAc)_2$	(*R*)-**4e**	THF	36	33
6	$Pd(OAc)_2$	(*R*)-**5**	THF	50	19
7	$Pd(OAc)_2$	(*R*)-**6**	THF	NR[d]	—
8	$Pd(OAc)_2$	(*R*)-**7**	THF	28	34
9	$Pd(dba)_2$	(*R*)-**4a**	THF	46	65
10	$[Pd(C_3H_5)Cl]_2$	(*R*)-**4a**	THF	NR	—
11	$Pd(OAc)_2$	(*R*)-**4a**	DME	56	67
12	$Pd(OAc)_2$	(*R*)-**4a**	Dioxane	86	68
13	$Pd(OAc)_2$	(*R*)-**4a**	Toluene	73	72

[a] Reaction conditions: [Pd]/ligand/**1a**/**2a**/Et_3B = 0.0125/0.03/0.25/0.50/0.9 mmol, 2.0 mL solvent at 60 °C, 48–72 h. TS = *p*-toluenesulfonyl, dba = (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one.
[b] Isolated yield.
[c] Determined by HPLC using a Chiralcel OD-H column.
[d] No reaction.

Table 2
Palladium-catalyzed asymmetric allylation of imines with allylic alcohols[a]

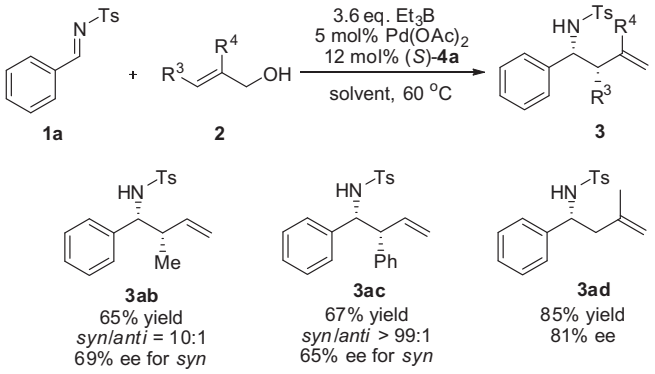


Entry	R^1	R^2	Product	Yield (%)	ee (%)
1	C_6H_5 **1a**	Ts	**3aa**	86	68 (−)
2[b]	4-FC_6H_4 **1b**	Ts	**3ba**	88	77 (+)
3	4-ClC_6H_4 **1c**	Ts	**3ca**	95	80 (−)
4	4-$CF_3C_6H_4$ **1d**	Ts	**3da**	82	79 (−)
5[b]	4-MeC_6H_4 **1e**	Ts	**3ea**	89	69 (+)
6	4-$MeOC_6H_4$ **1f**	Ts	**3fa**	94	74 (−)
7	3-ClC_6H_4 **1g**	Ts	**3ga**	88	58 (−)
8	3-MeC_6H_4 **1h**	Ts	**3ha**	88	46 (−)
9	2-ClC_6H_4 **1i**	Ts	**3ia**	93	65 (−)
10	2-$MeOC_6H_4$ **1j**	Ts	**3ja**	86	64 (−)
11	2-furyl **1k**	Ts	**3ka**	71	75 (*S*)
12	(*E*)-PhCH=CH **1l**	Ts	**3la**	60	76 (−)
13[b]	cHexyl **1m**	Ts	**3ma**	75	77 (+)
14[b,c]	C_6H_5 **1n**	4-$CF_3C_6H_4SO_2$	**3na**	62	60 (+)
15[b,c]	C_6H_5 **1o**	4-$MeOC_6H_4SO_2$	**3oa**	92	67 (+)
16[c]	C_6H_5 **1p**	$C_6H_5SO_2$	**3pa**	92	63 (*S*)

[a] The reaction conditions were the same as those in Table 1, entry 5.
[b] (*S*)-**4a** was used.
[c] The reaction performed in THF.

The protecting group of the imine strongly affected the reactivity of the allylation reaction. All the sulfonyl-protected imines underwent the allylation reaction smoothly (entries 14–16). The *para*-trifluoromethyl-substituted sulfonyl-protected imine **1n** exhibited lower reactivity as well as enantioselectivity, while the *para*-methoxy counterpart **1o** gave slightly higher enantioselectivity.

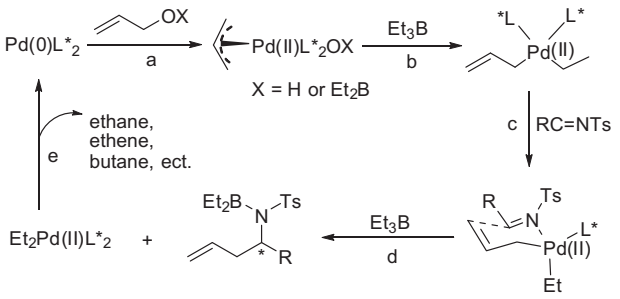
Further studies revealed that allylic alcohols with different substituent patterns were suitable substrates for the allylation reaction (Scheme 2). 1-Substituted *E*-crotyl alcohol **2b** (R^3 = Me, R^4 = H) and *E*-cinnamyl alcohol **2c** (R^3 = Ph, R^4 = H) reacted with *N*-tosyl imine **1a** under the standard reaction conditions to produce the corresponding homoallylic amines with excellent diastereoselectivities (*syn*/*anti* = 10:1 and >99:1) and moderate



Scheme 2.

enantioselectivities (69% and 65% ee). Moreover, 2-methylprop-3-en-1-ol **2d** (R^3 = H, R^4 = Me) achieved the highest level of enantioselectivity (81% ee) in the allylation reaction.

A full view of the mechanism is still under study in this laboratory. A mechanism was proposed as shown in Scheme 3 to rationalize the 'umpolung' of the π-allylpalladium, which was similar to the mechanism of allylation of aldehyde.[9g] In the proposed mechanism, the transfer of the electron-rich ethyl group from boron to palladium (step b) was thought to be essential to change the electronic property of the palladium center and enhance the nucleophilicity of allyl ligand to imine. However, a detailed mechanism is still unclear and further studies are highly desired.



Scheme 3. Proposed mechanism.

3. Conclusion

In conclusion, a palladium-catalyzed asymmetric umpolung allylation of imines, using allylic alcohols as allylic reagents, was developed. The palladium complexes of spiro monodentated phosphoramidites were efficient catalysts for this transformation, producing homoallylic amines with good to excellent yields and moderate to good enantioselectivities. The present allylation reaction is one of the few asymmetric allylations via the umpolung of π-allylpalladium. The direct use of stable and readily available allylic alcohols instead of allylic metal reagents expanded upon in the application of asymmetric allylation of imines.

4. Experimental

4.1. General methods

All reactions and manipulations were performed using standard Schlenk techniques. THF, DME, dioxane, and toluene were distilled from sodium benzophenone ketyl. $Pd(OAc)_2$, $[Pd(C_3H_5)Cl]_2$, and Et_3B, were purchased from Acros or Aldrich Co. Ltd and used as received. $Pd_2(dba)_4$[10] and imines[11] were prepared according to the literature procedures. Chiral spiro phosphorous ligands **4**, **5**, and **6** were prepared according to the previously reported procedures.[12] Ligand **4a** and **7** can be purchased from STREM Co. Ltd. Melting points were measured on a RY-I apparatus and uncorrected. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on Varian Mercury 400 MHz or Bruker 300 MHz spectrometers. Chemical shifts (δ values) are reported in ppm downfield from internal Me_4Si. Optical rotations were determined using a Perkin Elmer 341 MC polarimeter. Mass spectra were recorded on a VG-7070E or VG ZAB-HS spectrometer. HPLC analyses were performed on a Hewlett Packard Model HP 1100 Series or Waters 2996 instruments.

4.2. Representative procedure for the palladium-catalyzed asymmetric allylation of imines with allylic alcohols

To a mixture of $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol) and (*R*)-**4a** (9.8 mg, 0.03 mmol) in an argon-filled Schlenk tube, dioxane (2.0 mL) was added. After the mixture was stirred at 25 °C for 10 min, *N*-benzylidene-4-methylbenzenesulfonamide **1a** (65 mg, 0.25 mmol), prop-2-en-1-ol **2a** (30 mg, 0.5 mmol), and Et_3B (0.9 mL, 1.0 M in hexane, 0.9 mmol) were added sequentially. The mixture was stirred at 60 °C for 48 h. The reaction mixture was diluted with ethyl acetate (20 mL) and the reaction was quenched by adding 3 g of silica gel. After concentrating under reduced pressure, the residue was transferred to a silica gel pad and washed with ethyl acetate/petroleum ether (1:10 to 1:5, v/v) to afford the allylation product.

4.2.1. (−)-*N*-(1-Phenylbut-3-enyl)-4-methylbenzenesulfonamide 3aa[13]

White solid, 86% yield, 68% ee. Mp: 79–81 °C. $[\alpha]_D^{15} = -60.6$ (*c* 0.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.20–7.02 (m, 7H), 5.57–5.42 (m, 1H), 5.08–4.92 (m, 3H), 4.36 (dd, *J* = 6.4 and 13.2 Hz, 1H), 2.50–2.39 (m, 2H), 2.36 (s, 3H). HPLC conditions: Chiralcel OD-H column, *n*-hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 15.0 min (minor), and t_R = 20.6 min (major).

4.2.2. *N*-(1-(4-Fluorophenyl)but-3-enyl)-4-methylbenzenesulfonamide 3ba[14]

White solid, 88% yield, 77% ee. Mp: 66–77 °C. $[\alpha]_D^{19} = +55.2$ (*c* 0.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.06–7.03 (m, 2H), 6.89–6.82 (m, 2H), 5.54–5.44 (m, 1H), 5.13 (d, *J* = 6.4 Hz, 1H), 5.07–5.03 (m, 2H), 4.35 (q, *J* = 6.8 Hz, 1H), 2.47–2.41 (m, 2H), 2.38 (s, 3H). HPLC conditions: Chiralcel OD-H column, *n*-hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 18.1 min (major), and t_R = 22.9 min (minor).

4.2.3. *N*-(1-(4-Chlorophenyl)but-3-enyl)-4-methylbenzenesulfonamide 3ca[15]

White solid, 95% yield, 80% ee. Mp: 118–120 °C. $[\alpha]_D^{18} = -80.4$ (*c* 0.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.20–7.06 (br, 4H), 7.04–6.90 (m, 2H), 5.52–5.40 (m, 1H), 5.32 (m, 1H), 5.10–5.00 (m, 2H), 4.32 (dd, *J* = 6.4 and 12.8 Hz, 1H), 2.54–2.30 (m, 5H). HPLC conditions: Chiralcel OD-H column, *n*-hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 10.4 min (minor), and t_R = 12.6 min (major).

4.2.4. *N*-(1-(4-Trifluoromethylphenyl)but-3-enyl)-4-methylbenzenesulfonamide 3da

White solid, 82% yield, 79% ee. Mp: 118–120 °C. $[\alpha]_D^{18} = -58.6$ (*c* 0.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 2H),

7.36 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 5.56–5.47 (m, 2H), 5.07–5.03 (m, 2H), 4.44 (dd, J = 6.8 and 13.6 Hz, 1H), 2.49–2.39 (m, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 143.4, 137.1, 132.4, 129.3, 127.1, 125.1, 119.7, 56.9, 41.5, 21.3. ESI-HRMS Calcd for [$C_{18}H_{18}F_3NO_2SNa$, M+Na]$^+$: 392.0903. Found: 392.0898. HPLC conditions: Chiralcel OD-H column, n-hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 9.6 min (minor), and t_R = 11.8 min (major).

4.2.5. *N*-(1-(4-Methylphenyl)but-3-enyl)-4-methylbenzenesulfonamide 3ea[13]

White solid, 89% yield, 69% ee. Mp: 120–121 °C. $[\alpha]_D^{19} = +66.4$ (c 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 6.97 (dd, J = 8.0 and 12.8 Hz, 4H), 5.55–5.45 (m, 1H), 5.06–5.02 (m, 2H), 4.96–4.92 (m, 1H), 4.31 (q, J = 6.8 Hz, 1H), 2.50–2.40 (m, 2H), 2.37 (s, 3H), 2.27 (s, 3H). HPLC conditions: Chiralcel OD-H column, n-hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 14.1 min (major), and t_R = 18.2 min (minor).

4.2.6. *N*-(1-(4-Methoxyphenyl)but-3-enyl)-4-methylbenzenesulfonamide 3fa[15]

White solid, 94% yield, 74% ee. Mp: 88–90 °C. $[\alpha]_D^{18} = -69.6$ (c 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.6 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 5.55–5.43 (m, 1H), 5.08–5.00 (m, 2H), 4.87 (d, J = 6.0 Hz, 1H), 4.30 (dd, J = 6.4 and 13.2 Hz, 1H), 3.75 (s, 3H), 2.46–2.34 (m, 5H). HPLC conditions: Chiralcel OD-H column, n-hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 225 nm, t_R = 14.2 min (minor), and t_R = 16.0 min (major).

4.2.7. *N*-(1-(3-Chlorophenyl)but-3-enyl)-4-methylbenzenesulfonamide 3ga

Viscous oil, 88% yield, 58% ee. $[\alpha]_D^{18} = -45.4$ (c 1.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 2H), 7.14–7.09 (m, 4H), 7.01–6.94 (m, 2H), 5.55–5.44 (m, 1H), 5.41 (d, J = 6.8 Hz, 1H), 5.07–5.03 (m, 2H), 4.34 (dd, J = 6.8 and 13.6 Hz, 1H), 2.46–2.38 (m, 2H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 142.3, 137.1, 134.1, 132.6, 129.6, 129.3, 127.3, 127.0, 126.8, 124.8, 119.5, 56.7, 41.6, 21.4. ESI-HRMS Calcd for [$C_{17}H_{18}ClNO_2SNa$, M+Na]$^+$: 358.0639. Found: 358.0645. HPLC conditions: Chiralcel OD-H column, n-hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 9.2 min (minor), and t_R = 12.7 min (major).

4.2.8. *N*-(1-(3-Methylphenyl)but-3-enyl)-4-methylbenzenesulfonamide 3ha

Viscous oil, 88% yield, 46% ee. $[\alpha]_D^{18} = -36.5$ (c 1.75, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.06 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.78 (s, 1H), 5.58–5.47 (m, 1H), 5.21 (br, 1H), 5.07–5.02 (m, 2H), 4.33 (dd, J = 6.8 and 13.6 Hz, 1H), 2.50–2.40 (m, 2H), 2.36 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 140.1, 137.8, 137.5, 133.2, 129.1, 128.2, 128.0, 127.2, 127.1, 123.6, 119.0, 57.2, 41.8, 21.4, 21.2. ESI-HRMS Calcd for [$C_{18}H_{21}NO_2SNa$, M+Na]$^+$: 338.1185. Found: 338.1191. HPLC conditions: Chiralcel OD-H column, n-hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 8.3 min (minor), and t_R = 10.6 min (major).

4.2.9. *N*-(1-(2-Chlorophenyl)but-3-enyl)-4-methylbenzenesulfonamide 3ia[15]

White solid, 93% yield, 65% ee. Mp: 98–100 °C. $[\alpha]_D^{18} = -44.2$ (c 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.0 Hz, 2H), 7.21–7.05 (m, 6H), 5.54–5.43 (m, 1H), 5.36–5.30 (m, 1H), 5.07–5.01 (m, 2H), 4.80 (dd, J = 7.2 and 13.2 Hz, 1H), 2.50–2.37 (m, 2H), 2.35 (s, 3H). HPLC conditions: Chiralcel OD-H column, n-hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 10.3 min (minor), and t_R = 12.9 min (major).

4.2.10. *N*-(1-(2-Methoxyphenyl)but-3-enyl)-4-methylbenzenesulfonamide 3ja

Viscous oil, 86% yield, 64% ee. $[\alpha]_D^{18} = -26.0$ (c 1.6, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.0 Hz, 2H), 7.07 (t, J = 7.2 Hz, 1H), 7.01 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 7.2 Hz, 1H), 6.70 (t, J = 7.2 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 5.60–5.54 (m, 2H), 5.00–4.96 (m, 2H), 4.45 (dd, J = 7.2 and 16.4 Hz, 1H), 3.71 (s, 3H), 2.60–2.43 (m, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 142.6, 137.5, 134.2, 128.9, 128.8, 128.3, 127.4, 126.8, 120.3, 117.8, 110.4, 56.3, 55.0, 40.0, 21.3. ESI-HRMS Calcd for [$C_{18}H_{21}NO_3SNa$, M+Na]$^+$: 354.1134. Found: 354.1127. HPLC conditions: Chiralcel OD-H column, n-hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 10.1 min (minor), and t_R = 12.7 min (major).

4.2.11. *N*-(1-(Furan-2-yl)but-3-enyl)-4-methylbenzenesulfonamide 3ka[16]

White solid, 71% yield, 75% ee. Mp: 63–65 °C. $[\alpha]_D^{18} = -44.2$ (c 0.5, CH_2Cl_2) and $[\alpha]_D^{15} = -43.6$ (c 0.5, $CHCl_3$) [lit.[16] $[\alpha]_D^{23} = -74.8$ (c 0.78, $CHCl_3$) for (S)-enantiomer]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.12 (s, 1H), 6.09 (s, 1H), 5.94 (d, J = 2.8 Hz, 1H), 5.59–5.48 (m, 1H), 5.40 (d, J = 8.4 Hz, 1H), 5.03–4.90 (m, 2H), 4.70 (dd, J = 6.8 and 14.8 Hz, 1H), 2.57–2.42 (m, 2H), 2.36 (s, 3H). HPLC conditions: Chiralcel OD-H column, n-hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 225 nm, t_R = 8.6 min for (R)-enantiomer, and t_R = 10.3 min for (S)-enantiomer.

4.2.12. (*E*)-*N*-(1-Phenylhexa-1,5-diene-3-yl)-4-methylbenzenesulfonamide 3la[13]

Viscous oil, 60% yield, 76% ee. $[\alpha]_D^{18} = -91.2$ (c 1.2, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 2H), 7.26–7.10 (m, 7H), 6.26 (d, J = 16.0 Hz, 1H), 5.80 (q, J = 7.6 Hz, 1H), 5.71–5.60 (m, 1H), 5.26 (d, J = 7.6 Hz, 1H), 5.13–5.00 (m, 2H), 4.06–3.97 (m, 1H), 2.38–2.23 (m, 5H). HPLC conditions: Chiralcel OD-H column, n-hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 23.6 min (major), and t_R = 26.9 min (minor).

4.2.13. *N*-(1-Cyclohexylbut-3-enyl)-4-methylbenzenesulfonamide 3ma

White solid, 75% yield, 77% ee. Mp = 89–90 °C. $[\alpha]_D^{19} = +8.8$ (c 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 5.46–5.35 (m, 1H), 4.88–4.81 (m, 2H), 4.66 (d, J = 8.8 Hz, 1H), 3.06–2.99 (m, 1H), 2.35 (s, 3H), 1.99 (t, J = 6.4 Hz, 2H), 1.63–1.48 (m, 5H), 1.33–1.26 (m, 1H), 1.10–0.77 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 137.4, 132.7, 128.5, 126.1, 117.3, 57.1, 39.7, 34.9, 28.1, 27.4, 25.3, 25.1, 20.5. ESI-HRMS Calcd for [$C_{17}H_{25}NO_2SNa$, M+Na]$^+$: 330.1498. Found: 330.1500. HPLC conditions: Chiralcel OD-H column, n-hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 17.0 min (minor), and t_R = 20.0 min (major).

4.2.14. *N*-(1-Phenylbut-3-enyl)-4-trifluoromethylbenzenesulfonamide 3na

White solid, 62% yield, 60% ee. Mp: 82–84 °C. $[\alpha]_D^{15} = +24.6$ (c 0.98, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.14–7.07 (m, 3H), 6.99–6.97 (m, 2H), 5.63–5.53 (m, 1H), 5.41 (d, J = 6.8 Hz, 1H), 5.11–5.07 (m, 2H), 4.46 (dd, J = 6.8 and 13.6 Hz, 1H), 2.48 (t, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 139.4, 133.9 (q), 132.8, 128.4, 127.6, 127.5, 126.6, 125.6 (q), 119.4, 57.6, 41.8. ESI-HRMS Calcd for [$C_{17}H_{16}F_3NO_2SNa$, M+Na]$^+$: 378.0746. Found: 378.0750. HPLC conditions: Chiralcel OD-H column, n-hexane/2-propanol = 90:10,

flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 9.0 min (major), and t_R = 13.4 min (minor).

4.2.15. *N*-(1-Phenylbut-3-enyl)-4-methoxybenzenesulfonamide 3oa

White solid, 92% yield, 67% ee. Mp: 81–83 °C. $[\alpha]_D^{15} = +44.5$ (*c* 1.58, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.19–7.12 (m, 3H), 7.09–7.07 (m, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 5.59–5.45 (m, 2H), 5.07–5.02 (m, 2H), 4.36 (dd, *J* = 7.2 and 14.0 Hz, 1H), 3.81 (s, 3H), 2.52–2.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 140.4, 133.3, 132.1, 129.2, 128.3, 127.3, 126.6, 119.0, 113.8, 57.4, 55.6, 41.9. ESI-HRMS Calcd for [$C_{17}H_{19}NO_3SNa$, M+Na]$^+$: 340.0978. Found: 340.0977. HPLC conditions: Chiralcel OD-H column, *n*-hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 14.6 min (major), and t_R = 19.8 min (minor).

4.2.16. *N*-(1-Phenylbut-3-enyl)benzenesulfonamide 3pa[3d]

White solid, 92% yield, 63% ee. Mp: 88–90 °C. $[\alpha]_D^{15} = -45.2$ (*c* 1.55, CH_2Cl_2) and $[\alpha]_D^{15} = -43.4$ (*c* 0.5, $CHCl_3$) [lit.[3d] $[\alpha]_D$ = +47 (*c* 0.27, $CHCl_3$) for (*R*)-enantiomer with 73% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (m, 2H), 7.47–7.41 (m, 1H), 7.35–7.29 (m, 2H), 7.17–7.11 (m, 3H), 7.10–7.06 (m, 2H), 5.61–5.49 (m, 2H), 5.09–5.00 (m, 2H), 4.42 (dd, *J* = 6.8 and 12.0 Hz, 1H), 2.54–2.41 (m, 2H). HPLC conditions: Chiralcel OD-H column, *n*-hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 14.3 min for (*R*)-enantiomer, and t_R = 20.9 min for (*S*)-enantiomer.

4.2.17. *N*-(2-Methyl-1-phenylbut-3-enyl)-4-methylbenzenesulfonamide 3ab[13]

White solid, 64% yield, *syn*/*anti* = 10:1, 69% ee for *syn*-isomer. Mp: 98–101 °C. $[\alpha]_D^{19} = +55.4$ (*c* 0.5, CH_2Cl_2). ^{1}H NMR for *syn*-isomer (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.12–7.09 (m, 3H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.94–6.92 (m, 2H), 5.50–5.41 (m, 1H), 5.13 (br, 1H), 5.04–5.00 (m, 2H), 4.26 (dd, *J* = 8.4 and 6.0 Hz, 1H), 2.57–2.49 (m, 1H), 2.32 (s, 3H), 0.93 (d, *J* = 6.8 Hz, 3H). HPLC conditions: Chiralcel OJ-H column, *n*-hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 12.4 min (minor), and t_R = 29.2 min (major).

4.2.18. *N*-(1,2-Diphenylbut-3-enyl)-4-methylbenzenesulfonamide 3ac[17]

White solid, 67% yield, *syn*/*anti* >99:1, 65% ee for *syn*-isomer. Mp: 136–138 °C. $[\alpha]_D^{19} = +15.6$ (*c* 0.5, CH_2Cl_2). ^{1}H NMR for *syn*-isomer (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.25–7.23 (m, 3H), 7.16–7.08 (m, 3H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.96–6.94 (m, 2H), 6.90–6.88 (m, 2H), 5.84–5.75 (m, 1H), 5.01 (d, *J* = 10.0 Hz, 1H), 4.88 (d, *J* = 17.2 Hz, 1H), 4.76 (d, *J* = 6.0 Hz, 1H), 4.53 (t, *J* = 7.0 Hz, 1H), 3.53 (t, *J* = 8.0 Hz, 1H), 2.34 (s, 3H). HPLC conditions: Chiralcel OD-H column, *n*-hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 17.8 min (minor), and t_R = 24.9 min (major).

4.2.19. *N*-(3-Methyl-1-phenylbut-3-enyl)-4-methylbenzenesulfonamide 3ad[18]

White solid, 85% yield, 81% ee. Mp: 77–79 °C. $[\alpha]_D^{19} = +95$ (*c* 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.17–7.12 (m, 7H), 4.83 (s, 2H), 4.73 (s, 1H), 4.39–4.34 (m, 1H), 2.36–2.35 (m, 5H), 1.52 (s, 3H). HPLC conditions: Chiralcel OD-H column, *n*-hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 210 nm, t_R = 13.8 min (major), and t_R = 17.5 min (minor).

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