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Ni/AntPohs-Catalyzed Stereoselective Asymmetric Intramolecular Reductive Coupling of *N*-1,6-Alkynones

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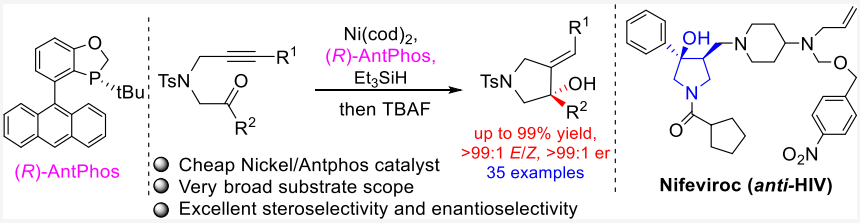

ABSTRACT: An efficient nickel-catalyzed stereoselective asymmetric intramolecular reductive coupling of *N*-1,6-alkynones is reported. A P-chiral monophosphine ligand AntPhos was found to be a privileged catalyst for constructing versatile functionalized chiral pyrrolidine rings using triethylsilane as the reducing reagent. Concise synthesis of pyrrolidines with chiral tertiary allylic alcohols was achieved in high yields (99%), excellent stereoselectivity (>99:1 *E*/*Z*), and enantioselectivity (>99:1 er) with very broad substrate scope. Totally, thirty-five *N*-1,6-alkynones were synthesized and applied in this reaction successfully. This reaction can be scaled up to gram scale without loss of its enantioselectivity. Ligand effects and reaction mechanism are investigated in detail. While the developed asymmetric synthesis of pyrrolidine with chiral tertiary allylic alcohols is anticipated to find wider applications in organic synthesis and chemical biology, the discovered new reactions of *N*-1,6-alkynone with AntPhos using different catalyst systems would further expanded its new research fields and attract more detailed explorations in the future.

INTRODUCTION

Chiral pyrrolidines are privileged substructures of numerous biologically active natural products and drugs (Figure 1). L-Proline is natural cyclic chiral amino acid playing a pivotal role in the protein structure. Its derivatives were used as efficient ligands for asymmetric synthesis.[1] Nicotine is the second most widely used recreational drug after caffeine. Anisomycin is an anticancer antibiotic inhibiting protein synthesis. Cocaine was widely used as a topical anesthetic in dentistry and in ophthalmology. Hygrine has antispasmodic activity. Domic acid has a powerful neuroexcitatory property.[2] Nifeviroc is a novel antagonist for CCR5 in clinical development for HIV infection treatment.[3] Norsecurinamine A showed significant biological activities on the central nervous system and cytotoxicity.[4] Many chiral pyrrolidine-related compounds display a wide variety of biological activity and are prevalent in active pharmaceutical ingredients. Therefore, new methods for the synthesis of chiral pyrrolidines in enantiomerically enriched form are valuable. Although numerous catalytic enantioselective reactions to give the chiral pyrrolidine derivatives have been described,[5] methods for the pyrrolidines with chiral tertiary allylic alcohols are limited due to steric and electronic constraints regarding the substrates and reagents, and hence, it is still a challenge to establish a high level of asymmetric induction as well as a high stereoselectivity.

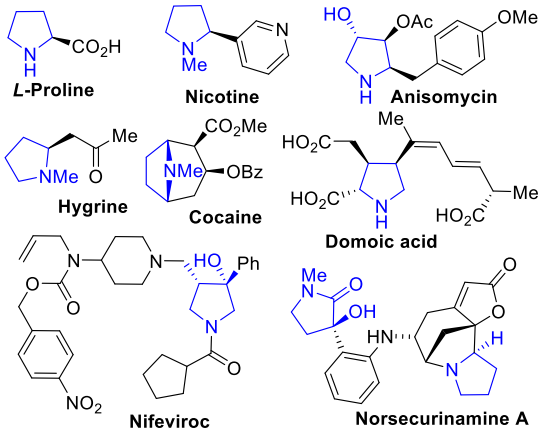

Figure 1. Chiral pyrrolidines in natural products and drugs.

Transition metal-catalyzed coupling of alkynes with carbonyls[6] is a highly powerful and practical method for direct construction of new carbon−carbon bonds with allylic

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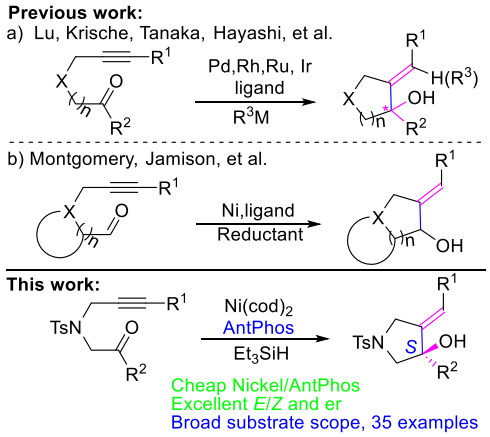
alcohols, valuable building blocks in organic synthesis that commonly occur as key subunits embedded within bioactive natural products as well as versatile precursors for a variety of synthetic transformations.[7] Although catalysts based on Pd,[6b,8] Rh,[9] Ru,[10] and Ir,[11] and so forth have been successfully employed in coupling of alkynes with various carbonyls in the past years, these metals are very expensive as their reserves are declining, limiting their application in the industry. Thus, earth-abundant transition metal Ni-catalyzed reactions have become more attractive as nickel is abundant, inexpensive, and environmentally friendly for its further industrial utilization. Ni-catalyzed reductive couplings of alkynes with aldehydes have been first developed by Montgomery[12] and Jamison,[13] but the enantioselective synthesis has not been achieved until chiral N-heterocyclic carbenes[14] and chiral phosphorus ligands[15] were applied for this kind of reactions. While limited Ni-catalyzed reductive coupling of alkynes with ketones have been reported,[16] a practical stereoselective asymmetric Ni-catalyzed intramolecular reductive coupling of *N*-1,6-alkynones[17] is yet to be explored (Scheme 1).

Scheme 1. Transition-Metal-Catalyzed Asymmetric Intramolecular Reductive Coupling for the Construction of Cyclic Allylic Alcohols

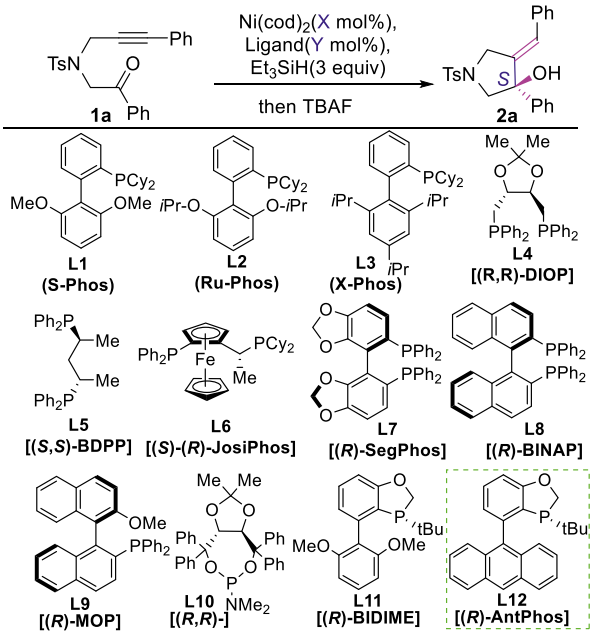


AntPhos was an efficient ligand for catalytic enantioselective synthesis. It was successfully applied in the catalytic enantioselective intramolecular reactions, such as reductive cyclization[16b] and dearomatic cyclization.[18] It is proposed that the pyrrolidines with chiral tertiary allylic alcohols could be prepared by the reductive cyclization of *N*-1,6-alkynones catalyzed by this ligand. Herein, we reported an efficient stereoselective asymmetric nickel-catalyzed intramolecular reductive coupling of *N*-1,6-alkynones to give pyrrolidines bearing chiral tertiary allylic alcohols with >99:1 *E*/*Z* stereoselectivity and >99:1 er using privileged monophosphine ligand AntPhos under mild conditions.

RESULTS AND DISCUSSION

We are interested in the phosphorous ligand effects on this type of reductive coupling reactions. Various ligands including achiral ligands and chiral ligands were investigated for their activity and enantioselectivity. Standard *N*-1,6-alkynone (**1a**) was chosen for the nickel-catalyzed intramolecular reductive coupling of *N*-1,6-alkynones using triethylsilane (Et_3SiH) as the reducing reagent. The reactions were performed under nitrogen in dioxane for 24 h in the presence of a nickel catalyst prepared in situ from 10 mol % $Ni(cod)_2$, 10 mol % monophosphorus ligand/5 mol % bisphosphorus ligand, and 3 equiv Et_3SiH; the produced silyl ether was treated with TBAF (tetra-*n*-butylammonium fluoride) to get the alcohol. As shown in Table 1, achiral mono-phosphorus ligands **PPh_3**, **PCy_3**, **S-Phos** (**L1**), **Ru-Phos** (**L2**), and **X-Phos** (**L3**) gave the cyclized product **2a** in a racemic form with high to excellent yields (**PPh_3**: 98%; **PCy_3**: 82%; **S-Phos**: 98%; **Ru-Phos**: 95%; **X-Phos**: 85%, entries 1−5), showed that a simple monophosphine ligand has good reactivity for this reaction. Chiral bisphosphine ligand **L4** [(*R*,*R*)-**DIOP**], **L5** [(*S*,*S*)-**BDPP**], **L6** [(*R*)-(*S*)-**JosiPhos**], **L7** [(*R*)-**SegPhos**], and **L8** [(*R*)-**BINAP**] were further tested. Although **L4** showed mediate reactivity (48% yield) but no enantioselectivity was achieved (entry 6), **L5**, **L6**, and **L7** has no reactivity while **L8** has a trace product which cannot be detected for its enantioselectivity (entries 7−

Table 1. Ligand Effects and Reaction Optimization[a]



Entry	Ligand	X	Y	T (°C)	Yield (%)[b]	*E*/*Z*[c]	er (%)[d]
1	**PPh3**	10	10	25	98	>99:1	50:50
2	**PCy3**	10	10	25	82	>99:1	50:50
3	**L1**	10	10	25	98	>99:1	50:50
4	**L2**	10	10	25	95	>99:1	50:50
5	**L3**	10	10	25	85	>99:1	50:50
6	**L4**	10	5	25	48	>99:1	50:50
7	**L5**	10	5	25	0	nd	nd
8	**L6**	10	5	25	0	nd	nd
9	**L7**	10	5	25	0	nd	nd
10	**L8**	10	5	25	<5	nd	nd
11	**L9**	10	10	25	87	>99:1	25:75
12	**L10**	10	10	25	53	>99:1	80:20
13	**L11**	10	10	25	99	>99:1	96:4
14	**L12**	10	10	25	99	>99:1	98:2
15	**L12**	5	5	25	99	>99:1	98:2
16[e]	**L12**	5	5	0	99	>99:1	99:1
17[e,f]	**L12**	1	1	0	31	>99:1	99:1

[a]Conditions: **1a** (0.2 mmol), $Ni(cod)_2$ (X mol %), ligand (Y mol %), Et_3SiH (0.6 mmol), N_2 in dioxane (0.5 mL), 24 h. [b]Isolated yields. [c]*E*/*Z* ratio confirmed by ^1H NMR. [d]The enantiomeric ratio (er) was determined by HPLC with CHIRALCEL columns. [e]The solvent was dioxane/THF (1:1). [f]The reaction was run in 2 mmol scale of **1a**.

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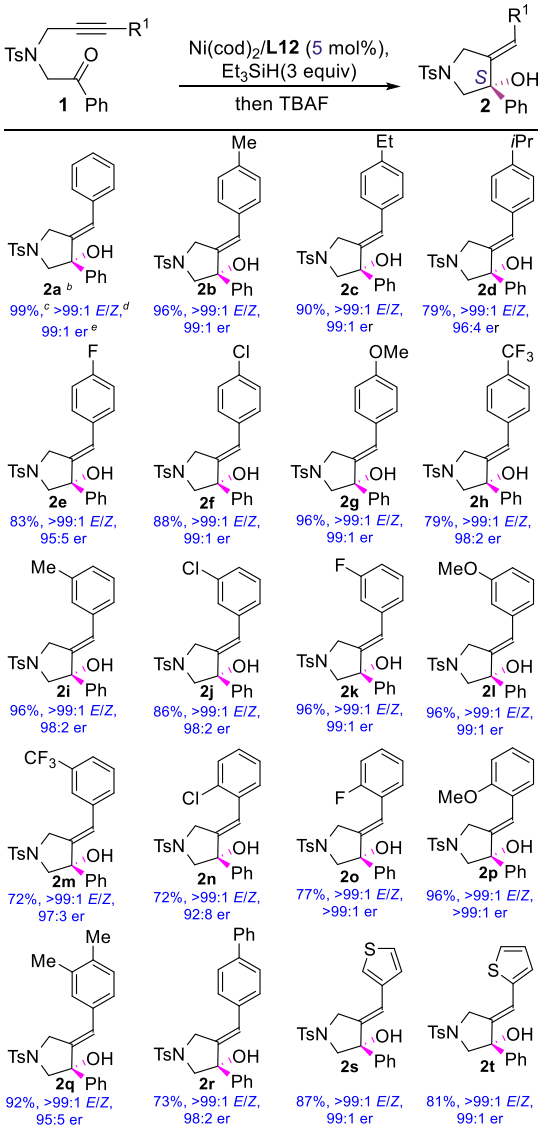
10), which proved that bisphosphine ligands are not applicable to this reaction. As estimated, chiral monophosphine ligand **L9** [(*R*)-**MOP**], **L10** [(*R*,*R*)-], **L11** [(*R*)-**BIDIME**], and **L12** [(*R*)-**AntPhos**] showed mediate to excellent reactivity and enantioselectivity for this coupling (**L9**: 87% yield, 25:75 er; **L10**: 53% yield, 80:20 er; **L11**: 99% yield, 96:4 er; **L12**: 99% yield, 98:2 er; entries 11−14). We are excited to explore the potential of (*R*)-**AntPhos** (**L12**) in consideration of its catalyst loading and enantioselectivity. To our surprise, decreasing the temperature to 0 °C, the enantioselectivity was enhanced to 99:1 er; gradually decreasing the catalyst loading to 1 mol %, 31% yield with 99:1 er was obtained for the desired product (entries 15−17). Interestingly, although different ligands were applied for the transformation of alkyne to alkene, the *E*/*Z* stereoselectivity of the cyclized allylic alcohol was >99:1, no matter how much its enantioselectivity was conducted. Hence, with (*R*)-**AntPhos**, the best result is 99% yield, >99:1 *E*/*Z* stereoselectivity and 99:1 er with highest nickel catalyst TON of 30. On the basis of these results, the conditions of entry 16 were selected for following experiments. The absolute configuration of **2a** was assigned as *S* by referencing the reported physical data in the literature.[16b]

The substrate scope of this process for the enantioselective synthesis of pyrrolidines with chiral tertiary allylic alcohols was then explored in detail with ligand (*R*)-**AntPhos** under the optimized reaction conditions (Table 1, entry 16). First of all, different R^1 groups of aromatic alkynes were found tolerable with very high *E*/*Z* stereoselectivity and enantioselectivity in good yield (Table 2, see details in Supporting Information). All the *N*-1,6-alkynones were coupled to cyclized alkenes with >99:1 *E*/*Z* as only one product was observed afterward. Substrates bearing either an electron-donating or electron-withdrawing group at the p-position of the aromatic ring were converted into their corresponding products in up to 96% yield with excellent enantioselectivities (**2b−2c**, **2f**, **2g**; er: 99:1), however, the bulky *i*Pr-group and electron-withdrawing F- and CF_3-group showed a few decrease of the yields and enantioselectivities (**2d**, **2e**, **2h**; yield: 79, 83, 79%; er: 96:4, 95:5 and 98:2). m-Substituted aromatic alkynes were found to give the desired pyrrolidines with chiral tertiary allylic alcohols in excellent yields (up to 96% yield) and enantioselectivities (**2i−2l**; yield: 96, 86, 96, 96%; er: 96:4, 95:5 and 98:2), except the CF_3-group showed a decrease of the yield and enantioselectivity (**2m**: 72% yield, 97:3 er). When the substituent group was present at the o-positions (**2n−2p**), the corresponding products bearing the electron-withdrawing group (F- and Cl-) were obtained with moderate to good yields and excellent enantioselectivities (**2n**, **2o**; yield: 72, 79%; er: 92:8, >99:1), while the substrates bearing electron-donating groups (MeO-) afforded excellent yield and enantioselectivity (**2p**: 96% yield, 99:1 er). Disubstituted substrates were also examined in the reductive coupling, affording excellent results (**2q**: 92% yield, 95:5 er); *p*-phenyl substituted 1,6-alkynone products **2r** showed less reactivity (73% yield) with excellent er (98:2). When the benzene ring was replaced by thiophenyl groups, good yields and excellent enantioselectivities were obtained (**2s**, **2t**; yield: 87, 81%; er: 99:1, 99:1). Although the reason for the difference of yields and enantioselectivities influenced by electron-withdrawing groups, such as F-, Cl- and CF_3-, at different positions are still not clear, most of their enantioselectivities are >97:3 er.

Further substrate scope was extended by different ketones. Substituted phenyl, alkyl groups were examined for the

Table 2. Substrate Scope of Different Alkynes[a]



[a]Conditions: **1** (0.2 mmol), Ni(cod)$_2$/**L12** (5 mol %), Et_3SiH (0.6 mmol), N_2 in dioxane/THF(1:1, 0.5 mL), 0 °C, 24 h. [b]The reactions were run in 2 mmol scale of **1a**. [c]Isolated yields. [d]Isolated *E*/*Z* ratio confirmed by ^1H NMR analysis. [e]The enantiomeric ratio (er) was determined by HPLC with CHIRALCEL columns. The absolute configuration of **2b−2t** was assigned the same as **2a**.

enantioselective synthesis of pyrrolidines with chiral tertiary allylic alcohols under the same reaction conditions as above mentioned with ligand (*R*)-**AntPhos** (Table 3). Different R^2 groups of ketones can afford the corresponding products with very high *E*/*Z* stereoselectivity and enantioselectivity in good to excellent yield (see details in Supporting Information). All the different ketones were cyclized to give the alkenes with >99:1 *E*/*Z* as only one product was determined by isolation and NMR. Substrates of an electron-donating or electron-withdrawing group at the p-position of the aromatic ring were converted into their corresponding products in up to 95% yield with excellent enantioselectivities (**2u−2y**; er: >99:1); only an electron-withdrawing Cl-group decrease its yield to 82%. m-Substituted aromatic ketones were found to give the desired pyrrolidines with chiral tertiary allylic alcohols in good yields and enantioselectivities (**2z−2ab**; yield: 87, 78, 85%; er: >99:1,

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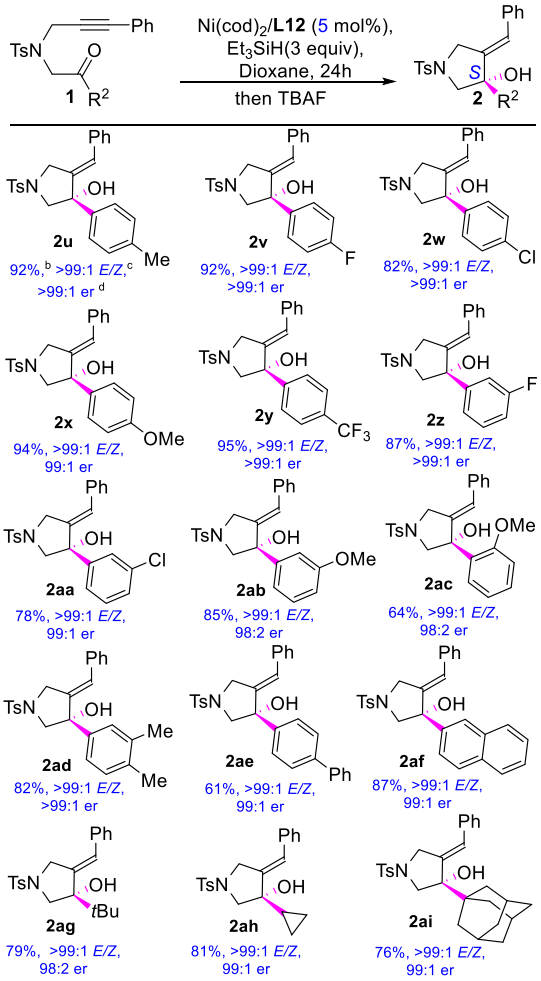
Table 3. Substrate Scope of Different Ketones[a]

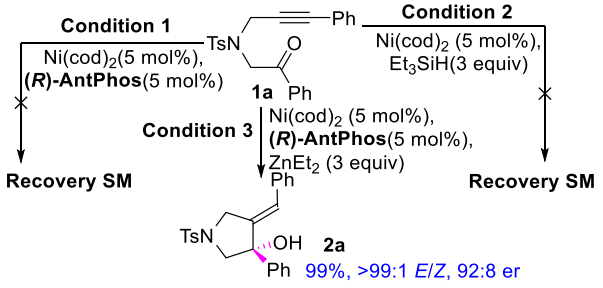


[a]Conditions: **1** (0.2 mmol), Ni(cod)$_2$/**L12** (5 mol %), Et_3SiH (0.6 mmol), N_2 in dioxane/THF(1:1, 0.5 mL), 0 °C, 24 h. [b]Isolated yields. [c]Isolated *E*/*Z* ratio confirmed by ^1H NMR analysis. [d]The enantiomeric ratio (er) was determined by HPLC with CHIRALCEL columns. The absolute configuration of **2u**−**2ai** was assigned the same as **2a**.

99:1 and 98:2). When the electron-donating OMe-group was present at the o-positions, the corresponding product (**2ac**) was obtained with moderate yield (64%) and excellent enantioselectivity (98:2 er). Disubstituted aromatic ketones were also tested, affording excellent results (**2q**: 61% yield, 99:1 er); *p*-phenyl substituted aromatic ketone product **2ae** showed less reactivity (61% yield) with excellent er (99:1). Naphthyl ketone products **2af** showed excellent yield (87%) with excellent er (99:1), when the bulky alkyl *t*Bu-, cyclopropyl- and adamantyl-groups were found to afford the corresponding pyrrolidines in good yields and excellent enantioselectivities (**2ag**−**2ai**; yield: 79, 81, 76%; er: 98:2, 99:1, 99:1). Although several examples showed moderate yields, most of their enantioselectivities are >98:2 er.

Having established the synthetic method efficiently, attention was then turned to understanding how the reactions operate in the presence of (***R***)**-AntPhos**, especially the mechanism for the stereochemical and enantiomeric control of allylic tertiary alcohols. Based on previous experiments, we reasoned that ligand activation of the *N*-1,6-alkynones must play a key role for this process. Several control experiments were carried on to confirm these possibilities. Each experiment was run at the standard conditions as above (Scheme 2). (1)

Scheme 2. Control Experiments of Nickel-Catalyzed Stereoselective Asymmetric Reductive Coupling of *N*-1,6-Alkynones



Without reductant Et_3SiH, the reactions could not be processed, the catalyzed cycle could not be generated, and the starting material **1a** was recovered; (2) without ligand (***R***)**-AntPhos**, the nickel precursor Ni(cod)$_2$ is not enough to generate the active intermediate with *N*-1,6-alkynone; even with the reductant Et_3SiH, the starting material **1a** could not be reduced to simple secondary alcohol and was also recovered; (3) when the reductant was changed to $ZnEt_2$, no influence was found for the yield (99%) and *E*/*Z* stereoselectivity (>99%), but the enantioselectivity was decreased to (92:8 er). Thus, we conclude that the monophosphine ligand (***R***)**-AntPhos** and reductant are necessary for this nickel-catalyzed stereoselective asymmetric reductive coupling of *N*-1,6-alkynones, and different reductants may have different effects on this type of coupling reactions. We also proposed that other transition metal precursors (such as Cu, Co, Pd, Rh, and so forth) accelerated with AntPhos type ligands may start up many new reactions afterward.

On the base of theoretical and computational studies[19] on Ni-catalyzed alkyne-aldehyde reductive coupling by Houk,[19a,c,d] Jamison,[19a] and Montgomery,[19b−d] the mechanism of Ni-catalyzed alkyne−ketone (alkynone) reductive coupling has been depicted.[16b,17] We thus proposed the catalytic cycle of our asymmetric reductive coupling of *N*-1,6-alkynones with (***R***)**-AntPhos** as the monomeric metallacyclic model, which was illustrated in Figure 2. Before adding the substrate **1a**, (***R***)**-AntPhos** was coordinated with Ni(cod)$_2$ to form the Ni(0) species **I**; then, addition of *N*-1,6-alkynone **1a** generated the cyclization process through the stage **II** and provided Ni(II) metallacycle **III**. At this stage, the detailed stereochemical model of Ni(II) metallacycle **III** presented two possible formation with opposite enantiomeric selectivity at the tertiary C−O bond position. The enantioselectivity and stereoselectivity is apparently determined at the cycloaddition stage. Conformational analysis of metallacycle **III** with (***R***)**-AntPhos** indicates that the conformer **IIIB** is unflavored as its big steric hindrance between the phenyl group of the bicycle ring and the anthracenyl moiety of (***R***)**-AntPhos**. Thus, the favored conformer **IIIA** generates Ni(II) hydride species **IV** by coordination and *δ*-bond metathesis of Et_3SiH. Reductive elimination of **IV** regenerates the Ni(0) catalyst **I** and provides **2a** as the cyclization product with *S* configuration, which is in accordance with referenced data,[16b] which was determined by X-ray crystallography.

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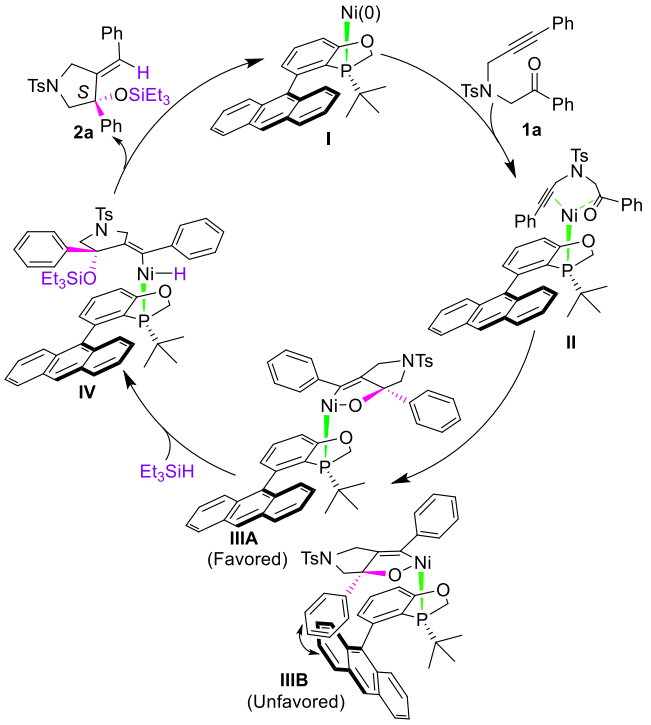


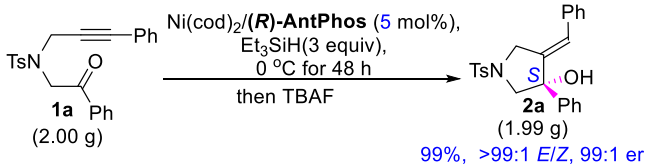
Figure 2. Proposed mechanism and stereochemical model.

To confirm our estimation, a stereochemical model was developed for this enantioselective process based on the proposed mechanism, and a React-IR experiment was set up for monitoring the stoichiometric reaction procedure (Figure 3). A stoichiometric amount of $Ni(cod)_2$ was mixed with ligand (*R*)-**AntPhos** with stirring in dioxane at room temperature; an absorption peak at 1392 cm^{-1} was monitored; possibly, the Ni(0)−P bond asymmetric stretch indicated the formation of Ni(0) species with phosphorus ligand (*R*)-**AntPhos**, which is stage **I**. After the addition of *N*-1,6-alkynone **1a**, the solution was turned dark brown quickly, the peak at 1708 cm^{-1} for ketone functional group appeared dramatically, and then gradually decreased as **1a** was consumed to the Ni(II) metallacycle **III**; thus, a peak at 1350 cm^{-1} was found and gradually increased at the same time and persisted until the curve changed to flat in 1 h. Then, the reductant $HSiEt_3$ was added; the peak 1708 and 1350 cm^{-1} was dropped quickly afterward, while the peak of 2092 cm^{-1} showed the trends of $HSiEt_3$ absorption and was slowly consumed with the cyclized tertiary allylic alcohol **2a** produced.

With the successful development of this efficient nickel catalyst, we are curious for its practicability of the reductive coupling reaction. Under the optimized reaction conditions, a gram-scale reductive coupling of **1a** (2.00 g) was carried out in dioxane/THF(1:1) at 0 °C for 48 h in the presence of 5 mol % $Ni(cod)_2$ and 5 mol % (*R*)-**AntPhos** using Et_3SiH as the reductant and then treated with TBAF to obtain the product **2a** (1.99 g) in 99% yield, >99:1 *E*/*Z* and 99:1 er (Scheme 3). There is no loss of its reactivity, stereoselectivity, and enantioselectivity, which proved that this Ni-catalyzed stereoselectivity asymmetric reductive coupling reaction is practical and efficient.

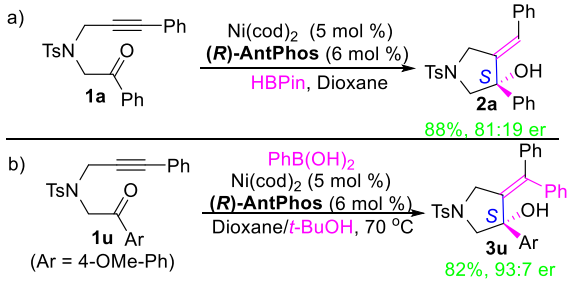
Temporarily clarifying the mechanism of this nickel catalyzed coupling reaction, the highly enantioselective transformation with (*R*)-**AntPhos** promoted us to further explore its other asymmetric coupling reactions. Surprisingly, two new

Scheme 3. Gram-Scale Reductive Coupling with (*R*)-AntPhos



reactions were discovered with good reactivity and enantioselectivity using 1,6-alkynone as the substrate (Scheme 4). (a) by

Scheme 4. New Asymmetric Couplings with (*R*)-AntPhos and *N*-1,6-Alkynone



Ni catalyzed reductive cyclization using HBPin as the reductant, in one step, the tertiary allylic alcohol **2a** was achieved in 88% yield with 81:19 er under similar catalytic conditions. (b) In Ni catalyzed tandem reductive cyclization and cross-coupling, the initial results showed that the new product **3u** was obtained in 82% yield with 93:7 er when **1u** was coupled with $PhB(OH)_2$ using *t*BuOH as the solvent. These initial results are interesting and might expand its other new research fields and need more detailed explorations in the future.

CONCLUSIONS

In summary, we have developed a highly efficient stereoselective asymmetric intramolecular reductive coupling of *N*-1,6-alkynones catalyzed by a $Ni(cod)_2$ with P-chiral monophosphine ligand (*R*)-**AntPhos** with triethylsilane as the reducing agent. Varieties of pyrrolidines bearing a chiral tertiary allylic alcohol were synthesized in high yields (up to 99%), excellent stereoselectivity (>99:1 *E*/*Z*), and enantioselectivity (>99:1 er). Totally, 35 substrates were affordable for this process, and very broad substrate scope was realized. Detailed mechanistic studies were investigated by the proposed stereochemical model of catalytic cycle and React-IR analysis of stoichiometric reaction with $Ni(cod)_2$, (*R*)-**AntPhos**, and other reactants. The results showed that the cycloaddition stage Ni(II) metallacycle **III** is the enantioselective-determined step, while ligand (*R*)-**AntPhos** played an important role for providing a large π-conjugated system or steric interactions, thus processing excellent stereoselectivity and enantioselectivity of the product. Control experiments were set up to confirm our estimation of its mechanism. This method has been proved to be a practical pathway for concise synthesis of pyrrolidines with chiral tertiary alcohol as gram-scale preparation of the pyrrolidine product was conducted to show the capability and scalability of this methodology. Further discovery of new reactions with (*R*)-**AntPhos** and *N*-1,6-alkynone indicated that there are interesting potential for this type of couplings, new

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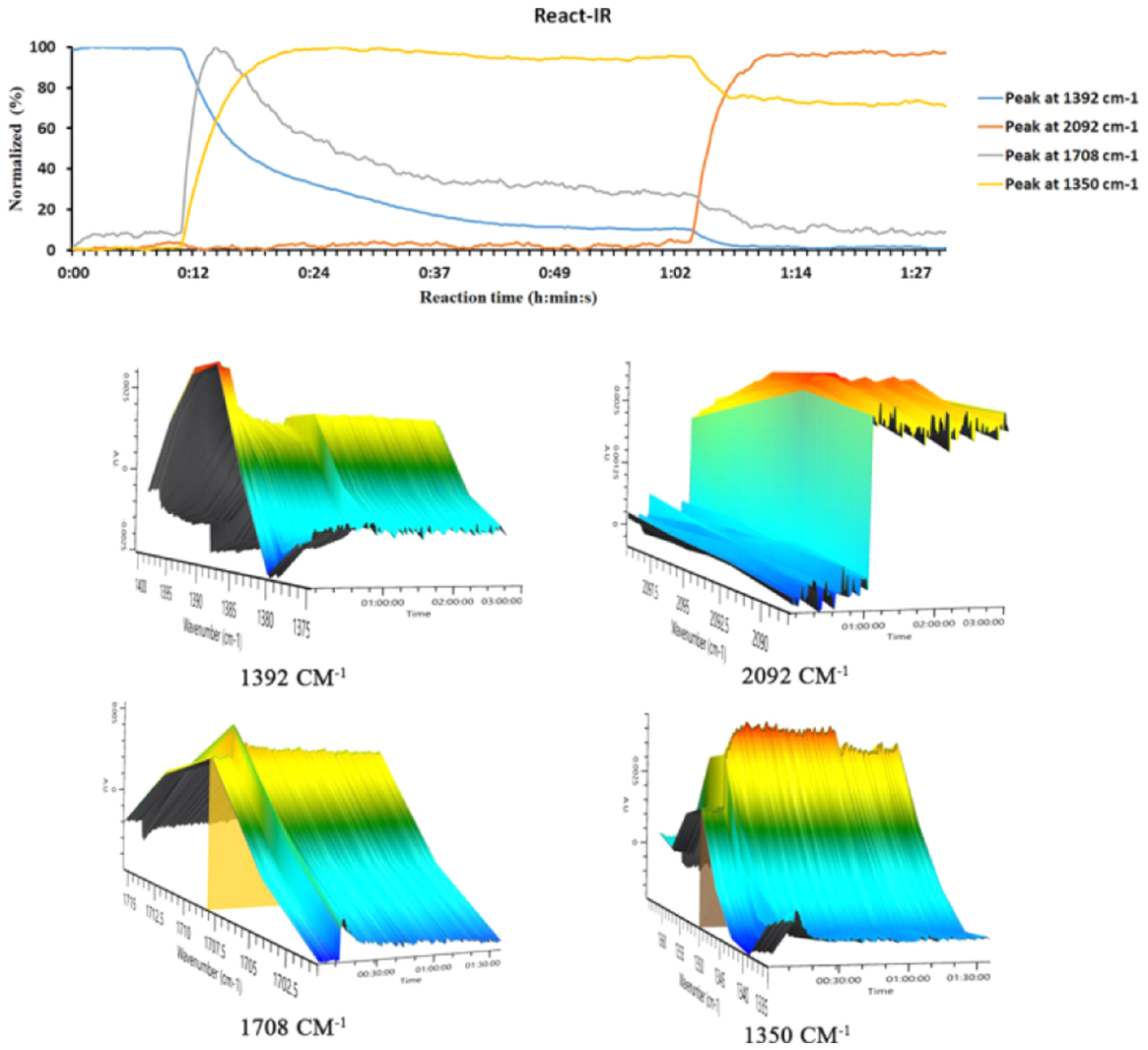


Figure 3. React-IR of stoichiometric reaction.

creative research fields may be explored in the future. P-chiral ligand application to useful organic synthesis has proved to be an effective strategy for developing practical asymmetric transformations. The ligand applied in this study has high potential for application in other coupling reactions. Further exploration on a more practical catalyst system and development of various efficient metal-catalyzed asymmetric reactions are under investigation in our laboratory.

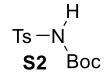
EXPERIMENTAL SECTION

General Information and Materials. All reactions and manipulations were performed in a nitrogen-filled glove box or using standard Schlenk techniques, unless otherwise noted. All anhydrous solvents were purchased from J&K Chemicals or Alfa Chemicals Inc or used after standard purification procedures. $Ni(cod)_2$ was purchased from Strem Chemicals. Commercialized reagents were used without further purifications. All air sensitive ligands were stored in a nitrogen-filled glove box before use. Chiral ligand intermediates were prepared according to our reported procedures cod = 1,5-cyclooctadiene.

^1H, and ^{13}C NMR data were recorded on a Bruker DRX500, DRX400, and NMR spectrometer with $CDCl_3$ or CD_3OD as the solvent. ^1H chemical shifts were referenced to $CDCl_3$ at 7.26 ppm. ^{13}C chemical shifts were referenced to $CDCl_3$ at 77.16 ppm and obtained with ^1H decoupling. ^{31}P shifts were referenced to 85% H_3PO_4 in D_2O at 0.0 ppm as the external standard and obtained with ^1H decoupling. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet−doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br). MS was measured on Agilent 5973N (EI) and Agilent 1100 Series LC/MSD (ESI) mass spectrometers. HRMS was measured on Waters Xevo G2-XS Q-TOF (TOF) mass spectrometers. Column chromatography was performed with silica gel (200−300 mesh). HPLC analyses and purifications were performed on a Thermo Fisher LC system with a UV−vis detector using CHIRALCEL columns.

*Synthesis of N-1,6-Alkynones **1a−1ai**.* The *N*-1,6-alkynones **1a−1ai** were synthesized according to the similar procedure[17] published by Tang et al. with slight adaptations.

*tert-Butyl Tosylcarbamate (**S2**).* 4-Methylbenzenesulfonamide (21.8 g, 127 mmol, 1.0 equiv), triethylamine (20 mL, 140 mmol,



S2

1.1 equiv), and 4-dimethylaminopyridine (1.57 g, 12.7 mmol, 0.1 equiv) were dissolved in 150 mL of dichloromethane (DCM) and stirred to obtain a suspension. Then, di(*tert*-butyl) carbonate was dissolved in 250 mL of DCM and then slowly dropped into the reaction system for 25 min and stirred for 2 h. The reaction was quenched with 1 M HCl 250 mL, extracted with EtOAc, washed with saturated brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was recrystallized with *n*-hexane/EtOAc (80:20) to afford **S2** as a white solid (30.0 g, 87%).

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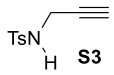
S2: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.19 (s, 1H), 2.45 (s, 3H), 1.38 (s, 9H).

The ^{1}H NMR spectra are in agreement with those reported in the literature.[20]

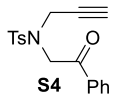
*4-Methyl-N-(prop-2-ynyl)-benzenesulfonamide (**S3**).* *tert*-Butyl tosylcarbamate (35.4 g, 130.6 mmol, 1.0 equiv) and K_2CO_3 (27 g,



195.8 mmol, 1.5 equiv) were dissolved in 100 mL dimethylformamide (DMF) and stirred at rt for 4 h. Then, propargyl bromide (11.3 mL, 143.7 mmol, 1.1 equiv) was added to the above solution and stirred at rt for 10 h. The reaction was quenched with water, extracted with EtOAc, washed with saturated brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was dissolved in 100 mL of DCM and 40 mL of CF_3COOH and stirred at rt overnight. The reaction was quenched with water, extracted with EtOAc, washed with saturated brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was recrystallized with *n*-hexane/EtOAc (90:10) to afford **S3** as a white solid (23.2 g, 85%). ^{1}H NMR (500 MHz, chloroform-*d*): δ 7.77 (d, J = 8.3 Hz, 2H), 7.34−7.30 (m, 2H), 4.50 (s, 1H), 3.84 (dd, J = 6.0, 2.5 Hz, 2H), 2.44 (s, 3H), 2.11 (t, J = 2.5 Hz, 1H).

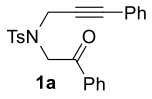
The ^{1}H NMR spectra are in agreement with those reported in the literature.[20]

*4-Methyl-N-(2-oxo-2-phenylethyl)-N-(prop-2-ynyl)-benzenesulfonamide (**S4**).* To a solution of **S3** (6.3 g, 30 mmol, 1.0



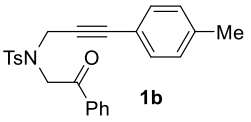
equiv), 2-bromo-1-phenylethan-1-one (6.2 g, 31.5 mmol, 1.05 equiv), and Bu_4NI (1.108 g, 3 mmol, 0.1 equiv) in 60 mL of DMF at 0 °C was added K_2CO_3 (6.2 g, 45 mmol, 1.5 equiv) and stirred at 0 °C for 1 h. Then, the reaction was quenched with water, extracted with EtOAc, washed with saturated brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was recrystallized with *n*-hexane/EtOAc (90:10) to afford **S4** as a white solid (8.55 g, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97−7.92 (m, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 4.81 (s, 2H), 4.29 (d, J = 2.4 Hz, 2H), 2.44 (s, 3H), 2.11 (d, J = 2.5 Hz, 1H). The ^{1}H NMR spectra are in agreement with those reported in the literature.[21]

4-Methyl-N-(2-oxo-2-phenylethyl)-N-(3-phenylprop-2-ynyl)-benzene-sulfonamide. **1a** is synthesized by Sonogashira reaction. **S4**



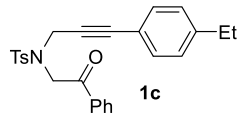
(1.64 g, 5 mmol), $PdCl_2$ (PPh_3)$_2$ (175 mg, 0.25 mmol, 5 mol %), and CuI (48 mg, 0.25 mmol, 5 mol %) in a round-bottomed flask. Seal with rubber triethylamine (20 mL) was added to the septum of the flask, and then, iodobenzene (824 μL, 7.5 mmol) was added. The reaction mixture was stirred under argon until the starting material disappeared (TLC check, 6 h). The reaction mixture was cooled to room temperature, neutralized with 1 M HCl, and the aqueous phase was extracted with ethyl acetate (20 mL). The combined organic phases were washed with water (40 mL), dried over Na_2SO_4, and evaporated in vacuo. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1a** (1.93 g, 96%) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01−7.85 (m, 2H), 7.83 (d, J = 8.3 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 7.32−7.30 (m, 3H), 7.28 (t, J = 7.4 Hz, 2H), 7.23−7.12 (m, 2H), 4.84 (s, 2H), 4.52 (s, 2H), 2.41 (s, 3H). The ^{1}H NMR spectra are in agreement with those reported in the literature.[17]

Preparations of **1b**−**1t** were carried out according to a similar procedure of **1a** from corresponding aryl iodides.



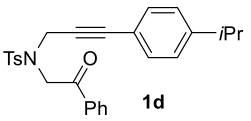
1b. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1b** (1.98 g, 95%) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 7.4 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.08−6.89 (m, 4H), 4.80 (s, 2H), 4.48 (s, 2H), 2.40 (s, 3H), 2.31 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 193.5, 143.8, 138.7, 136.1, 135.0, 133.8, 131.5, 129.7, 128.9, 128.8, 128.2, 127.7, 118.9, 86.4, 80.9, 51.9, 38.4, 21.5, 21.4. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{23}NO_3SNa$, 440.1296; found, 440.1322.

1c. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1c** (1.86 g, 86%) as a white powder.



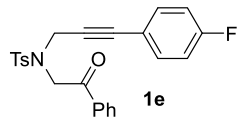
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02−7.98 (m, 2H), 7.84 (d, J = 8.3 Hz, 2H), 7.64−7.60 (m, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.07 (q, J = 8.3 Hz, 4H), 4.83 (s, 2H), 4.51 (s, 2H), 2.63 (q, J = 7.6 Hz, 2H), 2.42 (s, 3H), 1.22 (t, J = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 193.5, 189.8, 145.1, 143.7, 136.1, 135.0, 133.8, 131.6, 129.7, 128.8, 128.2, 127.7, 127.7, 119.2, 86.4, 80.9, 51.9, 38.4, 28.8, 21.5, 15.3. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{26}H_{25}NO_3SNa$, 454.1453; found, 454.1452.

1d. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1d** (1.80 g, 81%) as a white powder.



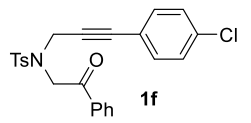
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99−7.95 (m, 2H), 7.81 (d, J = 8.3 Hz, 2H), 7.62−7.57 (m, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.10−7.01 (m, 4H), 4.80 (s, 2H), 4.48 (s, 2H), 2.86 (p, J = 6.9 Hz, 1H), 2.39 (s, 3H), 1.21 (d, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 193.4, 149.7, 143.7, 136.1, 135.0, 133.8, 131.7, 129.7, 128.8, 128.2, 127.7, 126.3, 119.3, 86.5, 80.8, 51.9, 38.4, 34.0, 23.7, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{27}H_{27}NO_3SNa$, 468.1609; found, 468.1609.

1e. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1e** (1.90 g, 90%) as a white powder.



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 7.4 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 7.5 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.13−7.06 (m, 2H), 6.92 (t, J = 8.6 Hz, 2H), 4.81 (s, 2H), 4.46 (s, 2H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 193.4, 163.6, 161.58, 143.8, 136.1, 134.9, 133.9, 133.6, 133.5, 129.7, 128.9, 128.2, 127.8, 118.1, 118.1, 115.6, 115.4, 85.2, 81.4, 51.9, 38.3, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{24}H_{20}FNO_3SNa$, 444.1046; found, 444.1061.

1f. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1f** (1.97 g, 90%) as a white powder.



https://doi.org/10.1021/acs.joc.1c00079
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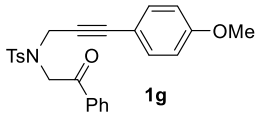
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99−7.96 (m, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.63−7.59 (m, 1H), 7.50−7.47 (m, 2H), 7.32−7.29 (m, 2H), 7.21 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 8.6 Hz, 2H), 4.80 (s, 2H), 4.47 (s, 2H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 193.4, 143.8, 136.1, 134.9, 134.7, 133.9, 132.9, 129.7, 128.9, 128.5, 128.2, 127.8, 120.5, 85.1, 82.8, 52.0, 38.3, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{24}H_{20}ClNO_3SNa$, 460.0750; found, 460.0751.

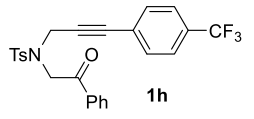
1g. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1g** (1.89 g, 87%) as a white powder.



1g

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, J = 7.6 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.9 Hz, 2H), 7.28 (s, 2H), 7.24 (d, J = 7.7 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.83−6.77 (m, 2H), 4.88 (s, 2H), 4.55 (s, 2H), 3.70 (s, 3H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 193.5, 160.1, 143.6, 136.1, 135.1, 133.7, 133.4, 130.0, 129.6, 128.8, 128.1, 127.7, 120.2, 111.3, 110.4, 85.7, 82.9, 55.5, 51.8, 38.6, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{23}NO_4SNa$, 456.1245; found, 456.1263.

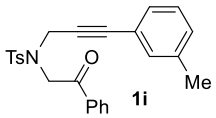
1h. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1h** (1.70 g, 72%) as a white powder.



1h

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 7.4 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.52−7.46 (m, 4H), 7.31 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 4.82 (s, 2H), 4.50 (s, 2H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 193.3, 143.9, 136.0, 134.8, 134.0, 131.9, 129.7, 128.9, 128.2, 127.8, 125.1, 125.1, 84.8, 84.4, 52.0, 38.2, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{20}F_3NO_3SNa$, 494.1014; found, 494.0950.

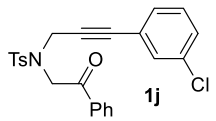
1i. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1i** (1.88 g, 90%) as a white powder.



1i

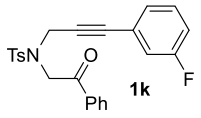
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 7.4 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.13−7.07 (m, 2H), 6.91 (s, 2H), 4.81 (s, 2H), 4.48 (s, 2H), 2.40 (s, 3H), 2.27 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 193.4, 143.7, 137.8, 136.1, 135.0, 133.8, 132.2, 129.7, 129.4, 128.8, 128.7, 128.2, 128.1, 127.8, 121.8, 86.4, 81.2, 51.9, 38.3, 21.5, 21.2. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{23}NO_3SNa$, 440.1296; found, 440.1322.

1j. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1j** (2.01 g, 92%) as a white powder.



1j

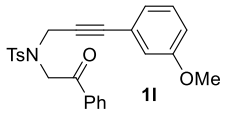
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, J = 7.3 Hz, 2H), 7.81 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 7.2 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.25 (s, 1H), 7.16 (t, J = 7.9 Hz, 1H), 7.03−6.97 (m, 2H), 4.79 (s, 2H), 4.48 (s, 2H), 2.42 (s, 3H). 13C{1H} NMR (126 MHz, $CDCl_3$): δ 193.3, 144.0, 136.0, 134.9, 133.9, 131.5, 129.8, 129.7, 129.5, 128.9, 128.9, 128.2, 127.8, 123.7, 84.8, 82.9, 52.0, 38.2, 21.6. HRMS (ESI) m/z: [M + Na]+ calcd for $C_{24}H_{20}ClNO_3SNa$, 460.0750; found, 460.0751.



1k

1k. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1k** (1.64 g, 78%) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00−7.97 (m, 2H), 7.81 (d, J = 8.3 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.19 (td, J = 8.0, 6.0 Hz, 1H), 6.99 (td, J = 8.4, 2.3 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.75−6.69 (m, 1H), 4.80 (s, 2H), 4.48 (s, 2H), 2.41 (s, 3H). 13C{1H} NMR (126 MHz, $CDCl_3$): δ 193.3, 163.1, 161.1, 144.0, 136.0, 134.9, 133.9, 129.8, 129.8, 128.9, 128.2, 127.8, 127.5, 127.4, 123.8, 123.8, 118.6, 118.4, 116.0, 115.9, 84.9, 82.7, 52.0, 38.2, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{24}H_{20}FNO_3SNa$, 444.1046; found, 444.1061.

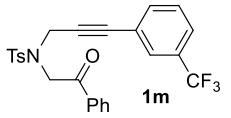
1l. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1l** (1.99 g, 92%) as a white powder.



1l

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 7.4 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 4.81 (s, 2H), 4.47 (s, 2H), 3.79 (s, 3H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 193.5, 159.8, 143.7, 136.1, 135.0, 133.8, 133.1, 129.7, 128.8, 128.2, 127.7, 114.1, 113.8, 86.2, 80.2, 55.3, 51.9, 38.4, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{23}NO_4SNa$, 456.1245; found, 456.1263.

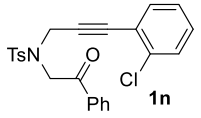
1m. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1m** (1.63 g, 69%) as a white



1m

powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (dd, J = 8.3, 1.1 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.63−7.60 (m, 1H), 7.54−7.47 (m, 3H), 7.36 (d, J = 7.7 Hz, 1H), 7.34−7.30 (m, 4H), 4.80 (s, 2H), 4.50 (s, 2H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 193.3, 144.1, 136.0, 134.8, 134.7, 134.0, 130.9, 130.7, 129.7, 128.9, 128.8, 128.3, 128.2, 127.8, 125.1 (d, J = 3.8 Hz), 124.7, 122.9, 122.5, 84.6, 83.4, 52.0, 38.2, 21.4. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{20}F_3NO_3SNa$, 494.1014; found, 494.0995.

1n. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1n** (1.93 g, 88%) as a white powder.



1n

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, J = 7.2 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.31 (d, J = 7.3 Hz, 1H), 7.28 (s, 2H), 7.17 (ddt, J = 14.8, 13.6, 4.3 Hz, 3H), 4.90 (s, 2H), 4.57 (s, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 193.7, 144.2, 136.3, 136.1, 135.3, 134.2, 133.6, 130.1, 130.0, 129.5, 129.2, 128.5, 128.0, 126.7, 122.4, 87.4, 83.5, 52.2, 38.7, 21.8. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{24}H_{20}ClNO_3SNa$, 460.0750; found, 460.0707.

1o. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1o** (1.83 g, 87%) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 7.2 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 7.4 Hz, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.28 (d, J = 8.3 Hz, 3H), 7.12 (td, J = 7.4, 1.6 Hz, 1H), 7.03−6.97 (m, 2H), 4.84 (s, 2H), 4.54 (s, 2H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (126

https://doi.org/10.1021/acs.joc.1c00079
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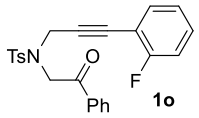
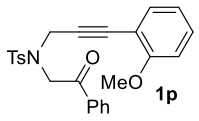


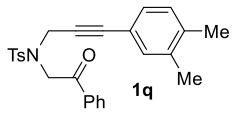
MHz, $CDCl_3$): δ 193.4, 163.7, 161.7, 143.8, 135.9, 135.0, 133.8, 133.4, 130.4, 130.3, 129.7, 128.8, 128.1, 127.7, 123.8, 123.8, 115.5, 115.3, 110.7, 110.6, 87.0, 79.8, 51.8, 38.4, 21.5. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{24}H_{20}FNO_3SNa$, 444.1046; found, 444.1061.

1p. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1p** (1.91 g, 88%) as a white powder.



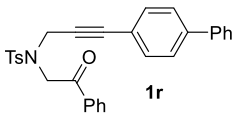
^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.2 Hz, 2H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 1H), 6.83 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.65−6.60 (m, 1H), 4.81 (s, 2H), 4.49 (s, 2H), 3.75 (s, 3H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 193.4, 159.2, 136.1, 134.9, 133.9, 129.7, 129.2, 128.9, 128.2, 127.7, 124.1, 123.0, 116.9, 114.8, 86.1, 55.3, 51.9, 38.3, 21.5. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{25}H_{23}NO_4SNa$, 456.1245; found, 456.1219.

1q. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1q** (1.96 g, 91%) as a white powder.



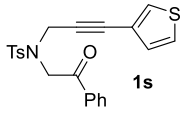
^1H NMR (500 MHz, $CDCl_3$): δ 7.97 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.59 (s, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 6.97 (s, 1H), 6.87 (s, 2H), 4.80 (s, 2H), 4.48 (s, 2H), 2.40 (s, 3H), 2.21 (s, 3H), 2.17 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 193.5, 143.7, 137.5, 136.5, 136.2, 135.0, 133.8, 132.7, 129.7, 129.5, 129.1, 128.8, 128.2, 127.8, 119.2, 86.6, 51.9, 38.4, 21.5, 19.7, 19.5. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{26}H_{25}NO_3SNa$, 454.1453; found, 454.1452.

1r. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1r** (2.11 g, 88%) as a white powder.



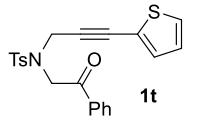
^1H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.54 (s, 2H), 7.47 (dq, *J* = 16.2, 7.8 Hz, 6H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 4.84 (s, 2H), 4.52 (s, 2H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 193.4, 143.8, 141.4, 140.2, 136.1, 135.0, 133.8, 132.1, 129.7, 128.9, 128.9, 128.2, 127.8, 127.0, 126.8, 120.9, 86.1, 82.3, 51.9, 38.4, 21.6. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{30}H_{25}NO_3SNa$, 502.1453; found, 502.1431.

1s. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1s** (1.66 g, 81%) as a yellow



powder. ^1H NMR (500 MHz, $CDCl_3$): δ 7.99−7.96 (m, 2H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.61 (s, 1H), 7.49 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.20 (dd, *J* = 5.1, 1.0 Hz, 1H), 6.98−6.93 (m, 1H), 6.90 (dd, *J* = 5.1, 3.7 Hz, 1H), 4.79 (s, 2H), 4.52 (s, 2H), 2.42 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 193.4, 143.9, 136.0, 134.9, 133.9, 132.5, 129.8, 129.7, 128.8, 128.2, 128.1, 127.7, 127.5, 126.8, 121.9, 85.7, 51.9, 38.5, 21.6. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{19}NO_3S_2Na$, 432.0704; found, 432.0679.

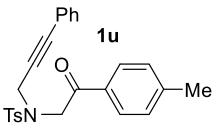
1t. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1t** (1.62 g, 79%)as a yellow powder.



^1H NMR (500 MHz, $CDCl_3$): δ 8.01−7.96 (m, 2H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.21−7.14 (m, 2H), 6.82 (dd, *J* = 4.9, 1.2 Hz, 1H), 4.81 (s, 2H), 4.47 (s, 2H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 193.4, 143.8, 136.1, 135.0, 133.8, 129.7, 129.2, 128.8, 128.2, 127.8, 125.2, 121.1, 81.4, 81.3, 51.9, 38.3, 21.6. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{19}NO_3S_2Na$, 432.0704; found, 432.0679.

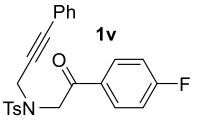
Preparations of **1u−1ai** were carried out according to a similar procedure of **1a** from corresponding 2-bromoaryl ethyl ketones.

1u. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1u** (1.82 g, 87%) as a white powder.



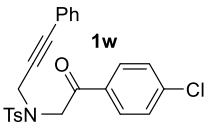
^1H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.31−7.25 (m, 5H), 7.24−7.20 (m, 2H), 7.14−7.05 (m, 2H), 4.78 (s, 2H), 4.48 (s, 2H), 2.41 (s, 3H), 2.38 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 193.0, 144.8, 143.8, 136.1, 132.5, 131.6, 129.7, 129.5, 128.5, 128.3, 128.2, 127.7, 122.1, 86.2, 81.7, 51.8, 38.3, 21.8, 21.5. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{25}H_{23}NO_3SNa$, 440.1296; found, 440.1279.

1v. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1v** (1.73 g, 82%) as a white powder.



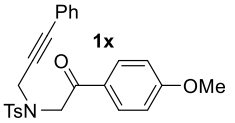
^1H NMR (500 MHz, $CDCl_3$): δ 8.06−8.02 (m, 2H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 3H), 7.23 (dd, *J* = 8.1, 6.6 Hz, 2H), 7.15 (dd, *J* = 11.9, 5.4 Hz, 2H), 7.10 (dd, *J* = 8.3, 1.3 Hz, 2H), 4.74 (s, 2H), 4.45 (s, 2H), 2.39 (s, 3H). The ^1H NMR spectra are in agreement with those reported in the literature.[17]

1w. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1w** (1.47 g, 67%) as a white



powder. ^1H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.09 (d, *J* = 7.2 Hz, 2H), 4.74 (s, 2H), 4.45 (s, 2H), 2.39 (s, 3H). The ^1H NMR spectra are in agreement with those reported in the literature.[17]

1x. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1x** (1.95 g, 90%)as a white powder.



https://doi.org/10.1021/acs.joc.1c00079
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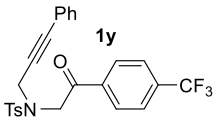
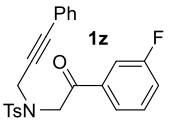
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, J = 8.4 Hz, 3H), 7.52−7.48 (m, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.26−7.21 (m, 3H), 7.14−7.11 (m, 2H), 7.02 (dd, J = 11.0, 4.0 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 4.83 (s, 2H), 4.51 (s, 2H), 3.91 (s, 3H), 2.38 (s, 3H). The ^{1}H NMR spectra are in agreement with those reported in the literature.[17]

1y. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1y** (1.51 g, 64%) as a white powder.



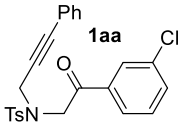
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (dd, J = 8.3, 1.1 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.63−7.59 (m, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.49 (dd, J = 10.7, 4.8 Hz, 2H), 7.37 (t, J = 7.7 Hz, 1H), 7.34−7.29 (m, 4H), 4.80 (s, 2H), 4.50 (s, 2H), 2.38 (s, 3H). The ^{1}H NMR spectra are in agreement with those reported in the literature.[17]

1z. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1z** (1.52 g, 72%) as a white powder.



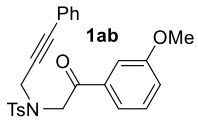
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (t, J = 8.4 Hz, 3H), 7.69−7.63 (m, 1H), 7.51−7.44 (m, 1H), 7.34−7.27 (m, 3H), 7.23 (t, J = 7.4 Hz, 3H), 7.13−7.08 (m, 2H), 4.76 (s, 2H), 4.47 (s, 2H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 192.4, 163.8, 161.9, 144.0, 136.9, 135.8, 131.6, 130.6, 130.6, 129.8, 128.6, 128.2, 127.7, 124.0, 121.9, 121.0, 120.8, 115.1, 114.9, 86.4, 81.4, 52.1, 38.4, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{24}H_{20}FNO_3SNa$, 444.1046; found, 444.1061.

1aa. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1aa** (1.90 g, 87%) as a white



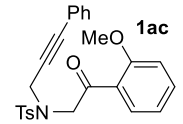
powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (t, J = 1.8 Hz, 1H), 7.89−7.87 (m, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.58−7.56 (m, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.35−7.30 (m, 3H), 7.25−7.21 (m, 2H), 7.13−7.10 (m, 2H), 4.75 (s, 2H), 4.47 (s, 2H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 192.4, 144.0, 136.4, 135.8, 135.2, 133.7, 131.6, 130.2, 129.8, 128.7, 128.2, 128.2, 127.7, 126.3, 121.9, 86.4, 81.4, 52.1, 38.4, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{24}H_{20}ClNO_3SNa$, 460.0750; found, 460.0751.

1ab. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1ab** (1.95 g, 90%) as a white



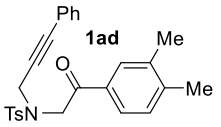
powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 7.7 Hz, 1H), 7.51−7.50 (m, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.25−7.20 (m, 3H), 7.14 (dd, J = 8.2, 2.0 Hz, 1H), 7.12−7.09 (m, 2H), 4.79 (s, 2H), 4.48 (s, 2H), 3.85 (s, 3H), 2.39 (s, 3H). The ^{1}H NMR spectra are in agreement with those reported in the literature.[17]

1ac. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **1ac** (1.88 g, 87%) as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 8.9 Hz, 2H), 7.81 (d, J = 8.3 Hz, 2H), 7.33−7.26 (m, 3H), 7.25−7.19 (m, 2H), 7.13−7.08 (m, 2H), 6.97−6.92 (m, 2H), 4.75 (s, 2H), 4.47 (s, 2H),



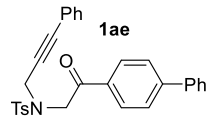
3.88 (s, 3H), 2.38 (s, 3H). The ^{1}H NMR spectra are in agreement with those reported in the literature.[17]

1ad. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1ad** (1.96 g, 91%) as a white



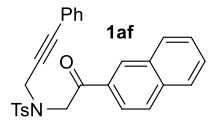
powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 7.7 Hz, 1H), 7.32−7.21 (m, 5H), 7.13−7.08 (m, 2H), 7.06 (d, J = 8.6 Hz, 2H), 4.67 (s, 2H), 4.49 (s, 2H), 2.46 (s, 3H), 2.36 (d, J = 10.1 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 196.3, 143.7, 142.8, 139.3, 136.2, 133.1, 132.5, 131.6, 129.7, 128.8, 128.6, 128.2, 127.7, 126.4, 122.1, 86.2, 81.7, 53.4, 38.3, 21.5, 21.5, 21.3. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{26}H_{25}NO_3SNa$, 454.1453; found, 454.1452.

1ae. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1ae** (2.01 g, 84%) as a white



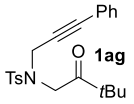
powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.63−7.58 (m, 2H), 7.48 (t, J = 7.5 Hz, 2H), 7.41 (t, J = 7.3 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 2.4 Hz, 1H), 7.22 (t, J = 7.4 Hz, 2H), 7.13−7.08 (m, 2H), 4.83 (s, 2H), 4.50 (s, 2H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 193.0, 146.5, 143.8, 139.7, 136.0, 133.6, 131.6, 129.7, 129.0, 128.8, 128.6, 128.4, 128.2, 127.8, 127.5, 127.3, 122.0, 86.3, 81.6, 52.0, 38.4, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{30}H_{25}NO_3SNa$, 502.1453; found, 502.1476.

1af. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1af** (1.86 g, 82%) as a white



powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.01 (dd, J = 8.6, 1.7 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.89 (dd, J = 13.3, 8.4 Hz, 2H), 7.84 (d, J = 8.3 Hz, 2H), 7.65−7.59 (m, 1H), 7.58−7.54 (m, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.27 (s, 1H), 7.23−7.18 (m, 2H), 7.13−7.09 (m, 2H), 4.94 (s, 2H), 4.52 (s, 2H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 193.4, 143.8, 136.1, 135.9, 132.4, 132.3, 131.7, 130.1, 129.7, 129.7, 128.9, 128.8, 128.6, 128.2, 127.9, 127.7, 127.0, 123.6, 122.0, 86.3, 81.7, 52.0, 38.4, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{28}H_{23}NO_3SNa$, 476.1296; found, 476.1296.

1ag. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1ag** (1.51 g, 79%) as a white



powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.6 Hz, 3H), 7.24 (d, J = 1.6 Hz, 2H), 7.16−7.13 (m, 2H), 4.44 (s, 2H), 4.40 (s, 2H), 2.39 (s, 3H), 1.18 (s, 9H). The ^{1}H NMR spectra are in agreement with those reported in the literature.[17]

1ah. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1ah** (1.41 g, 77%) as a white

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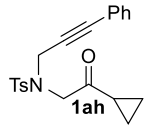
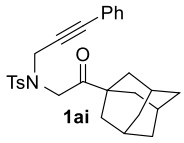


powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, J = 8.3 Hz, 2H), 7.30−7.23 (m, 5H), 7.14−7.10 (m, 2H), 4.41 (s, 2H), 4.23 (s, 2H), 2.36 (s, 3H), 2.21 (ddd, J = 12.4, 7.9, 4.5 Hz, 1H), 1.08 (p, J = 3.7 Hz, 2H), 0.96 (dq, J = 7.4, 3.7 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 205.3, 143.9, 135.7, 131.6, 129.7, 128.6, 128.2, 127.7, 122.0, 86.2, 81.3, 55.6, 38.8, 21.5, 17.9, 11.8. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{21}H_{21}NO_3SNa$, 390.1140; found, 390.1127.

1ai. The resulting residue was purified by column chromatography (90:10, *n*-hexane/EtOAc) to give **1ai** (1.94 g, 84%) as a white



powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 8.3 Hz, 2H), 7.32−7.25 (m, 4H), 7.24 (t, J = 1.7 Hz, 1H), 7.18−7.13 (m, 2H), 4.43 (s, 2H), 4.36 (s, 2H), 2.38 (s, 3H), 2.03 (s, 3H), 1.84 (d, J = 2.5 Hz, 6H), 1.74 (d, J = 12.4 Hz, 3H), 1.67 (d, J = 11.5 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 208.4, 143.6, 136.4, 131.6, 129.6, 128.6, 128.2, 127.6, 122.2, 100.0, 85.9, 81.9, 49.5, 45.9, 38.1, 37.8, 36.4, 27.8, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{28}H_{31}NO_3SNa$, 484.1922; found, 484.1927.

General Procedure of Nickel-Catalyzed Intramolecular Reductive Coupling of *N*-1,6-Alkynones. *General Procedure for Asymmetric Synthesis.* In glove box, Ni(cod)$_2$ (2.8 mg, 0.010 mmol, 5 mol %), **(*R*)-AntPhos** (3.7 mg, 0.010 mmol, 5 mol %), and dioxane/THF (1:1, 0.5 mL) were added to a 5 mL screw-cap vial equipped with a magnetic stirring bar. Then, substrate **1** (0.20 mmol, 1.00 equiv) was added followed by Et_3SiH (93 μL, 0.60 mmol, 3.00 equiv) in one portion. The vial was closed with a screw-cap, and the resulting mixture was stirred at 0 °C for 24 h, and then quenched with saturated $NaHCO_3$ solution, extracted with EtOAc, washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. After desilylation with TBAF in THF, the reaction was quenched with saturated NH_4Cl solution, extracted with EtOAc, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by column chromatography to afford chiral compound **2**.

General Procedure for Preparing the Racemic Product. In the glove box, Ni(cod)$_2$ (2.8 mg, 0.010 mmol, 5 mol %), **PPh$_3$** (2.6 mg, 0.010 mmol, 5 mol %), and dioxane (0.5 mL) were added to a 5 mL screw-cap vial equipped with a magnetic stirring bar. Then, substrate **1** (0.20 mmol, 1.00 equiv) was added followed by Et_3SiH (93 μL, 0.60 mmol, 3.00 equiv) in one portion. The vial was closed with a screw cap, and the resulting mixture was stirred at 25 °C for 24 h and then quenched with saturated $NaHCO_3$ solution, extracted with EtOAc, washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. After desilylation with TBAF in THF, the reaction was quenched with saturated NH_4Cl solution, extracted with EtOAc, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by column chromatography to afford racemic compound **2**.

2a. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2a** (80.3 mg, 99%) as a white solid, 99:1 er. $[\alpha]_D^{25}$ −22.0 (c 1.0, CH_2Cl_2); enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 1 mL/min, hexanes/isopropanol: 15/85, 254 nm, 7.08 min (*S*), 8.11 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 6.6 Hz, 2H), 7.50−7.43 (m, 2H), 7.38−7.26 (m, 8H), 7.15 (d, J = 5.9 Hz, 2H), 6.30 (t, J = 2.0 Hz, 1H), 4.52 (dd, J = 12.0, 2.0 Hz, 1H), 4.27 (dd, J = 12.0, 2.0 Hz, 1H), 3.58 (dd, J = 19.0, 8.3 Hz, 2H), 2.44 (s, 3H), 2.39 (s, 1H). The ^{1}H NMR spectra are in agreement with those reported in the literature.[17]

2b. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2b** (80.6 mg, 96%) as a yellow oil, 99:1 er. $[\alpha]_D^{25}$ −18.1 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 1 mL/min, hexanes/isopropanol: 15/85, 254 nm, 8.23 min (*S*), 15.80 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, J = 6.6 Hz, 2H), 7.51−7.44 (m, 2H), 7.41−7.29 (m, 5H), 7.28 (d, J = 5.6 Hz, 1H), 7.11 (d, J = 6.1 Hz, 1H), 6.97 (d, J = 9.0 Hz, 2H), 6.28 (t, J = 2.0 Hz, 1H), 4.54 (dd, J = 12.0, 2.0 Hz, 1H), 4.29 (dd, J = 12.0, 2.0 Hz, 1H), 3.60 (dd, J = 20.1, 8.3 Hz, 2H), 2.46 (s, 4H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 143.9, 142.3, 141.5, 138.3, 135.5, 133.0, 129.8, 129.5, 128.8, 128.6, 128.3, 127.9, 127.9, 126.7, 126.2, 125.5, 82.0, 61.4, 50.6, 21.6, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{25}NO_3SNa$, 442.1453; found, 442.1470.

2c. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2c** (78.0 mg, 90%) as a white solid, 99:1 er. $[\alpha]_D^{25}$ −29.3 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 20/80, 254 nm, 6.58 min (*R*), 13.86 min (*S*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 8.2 Hz, 2H), 7.47−7.42 (m, 2H), 7.37−7.28 (m, 5H), 7.18 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 6.25 (s, 1H), 4.51 (dd, J = 14.9, 2.4 Hz, 1H), 4.26 (dd, J = 14.9, 2.5 Hz, 1H), 3.60 (d, J = 10.4 Hz, 1H), 3.53 (d, J = 10.4 Hz, 1H), 2.64 (q, J = 7.6 Hz, 2H), 2.43 (s, 3H), 2.37 (s, 1H), 1.23 (t, J = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.3, 143.9, 141.5, 133.0, 129.8, 128.6, 128.3, 128.2, 127.9, 126.5, 126.3, 82.1, 61.5, 50.7, 28.6, 21.6, 15.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{26}H_{27}NO_3SNa$, 456.1609; found, 456.1525.

2d. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2d** (70.7 mg, 79%) as a colorless oil, 96:4 er. $[\alpha]_D^{25}$ −54.9 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 5.03 min (*S*), 9.24 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 8.3 Hz, 2H), 7.48−7.43 (m, 2H), 7.36−7.28 (m, 5H), 7.22 (d, J = 8.3 Hz, 2H), 7.08 (d, J = 8.2 Hz, 2H), 6.26 (t, J = 2.6 Hz, 1H), 4.39 (ddd, J = 128.8, 14.9, 2.6 Hz, 2H), 3.64−3.49 (m, 2H), 2.91 (p, J = 6.9 Hz, 1H), 2.43 (s, 3H), 2.36 (s, 1H), 1.25 (d, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 149.0, 143.9, 141.6, 133.1, 133.0, 129.8, 128.6, 128.3, 127.9, 127.8, 126.8, 126.5, 126.3, 82.1, 61.6, 50.7, 33.9, 23.9, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{27}H_{29}NO_3SNa$, 470.1766; found, 479.1767.

2e. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2e** (70.3 mg, 83%) as a white solid, 95:5 er. $[\alpha]_D^{25}$ −36.6 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 1 mL/min, hexanes/isopropanol: 20/80, 254 nm, 10.41 min (*S*), 13.87 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 5.7 Hz, 2H), 7.50−7.28 (m, 7H), 7.17−6.95 (m, 4H), 6.25 (s, 1H), 4.46 (d, J = 11.7 Hz, 1H), 4.22 (d, J = 11.7 Hz, 1H), 3.57 (q, J = 8.0 Hz, 2H), 2.43 (s, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.0, 142.2, 141.3, 132.9, 130.3, 130.2, 129.9, 128.4, 127.9, 126.2, 125.4, 115.8, 115.6, 81.9, 61.4, 50.5, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{24}H_{22}FNO_3SNa$, 446.1202; found, 446.1214.

2f. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2f** (77.3 mg, 88%) as a colorless oil, 99:1 er, $[\alpha]_D^{25}$ −32.25 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 6.90 min (*S*), 12.03 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 6.6 Hz, 2H), 7.47−7.43 (m, 2H), 7.37−7.30 (m, 7H), 7.07 (d, J = 6.8 Hz, 2H), 6.25 (t, J = 2.5 Hz, 1H), 4.46 (dd, J = 12.0, 2.0 Hz, 1H), 4.22 (dd, J = 12.0, 2.0 Hz, 1H), 3.58 (d, J = 0.9 Hz, 2H), 2.44 (s, 3H), 2.32 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.1, 143.2, 141.2, 134.0, 133.8, 132.9, 129.9, 129.8, 128.9, 128.4, 128.0, 127.9, 126.1, 125.3, 81.9, 61.3, 50.5, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{24}H_{22}ClNO_3SNa$, 462.0907; found, 462.0866.

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2g. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2g** (83.6 mg, 96%) as a white solid, 99:1 er. $[\alpha]_D^{25}$ −36.1 (*c* 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 20/80, 254 nm, 7.93 min (*S*), 20.91 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 6.6 Hz, 2H), 7.45 (dd, *J* = 6.5, 1.0 Hz, 2H), 7.35−7.29 (m, 5H), 7.07 (d, *J* = 7.0 Hz, 2H), 6.88−6.85 (m, 2H), 6.21 (t, *J* = 2.0 Hz, 1H), 4.49 (dd, *J* = 11.8, 2.0 Hz, 1H), 4.24 (dd, *J* = 11.8, 2.0 Hz, 1H), 3.81 (s, 3H), 3.60 (d, *J* = 8.3 Hz, 1H), 3.52 (d, *J* = 8.3 Hz, 1H), 2.47 (s, 1H), 2.42 (s. 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 159.3, 143.9, 141.6, 140.1, 133.0, 130.0, 129.8, 128.3, 127.9, 127.8, 126.3, 126.1, 114.1, 82.1, 61.6, 55.3, 50.7, 21.6. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{25}H_{25}NO_4SNa$, 458.1402; found, 458.1423.

2h. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2h** (74.7 mg, 79%) as a yellow oil, 98:2 er. $[\alpha]_D^{25}$ −6.4 (*c* 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 5.03 min (*S*), 9.24 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.49−7.43 (m, 2H), 7.39−7.31 (m, 5H), 7.24 (d, *J* = 8.2 Hz, 2H), 6.35 (s, 1H), 4.48 (dd, *J* = 15.1, 2.5 Hz, 1H), 4.25 (dd, *J* = 15.2, 2.6 Hz, 1H), 3.60 (d, *J* = 2.1 Hz, 2H), 2.44 (s, 3H), 2.42 (s, H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 145.3, 144.1, 141.1, 139.0, 132.8, 129.9, 128.7, 128.5, 128.1, 127.9, 126.1, 125.6, 125.1 (d, *J* = 3.8 Hz), 81.9, 61.2, 50.4, 21.6. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{25}H_{22}F_3NO_3SNa$, 496.1170; found, 496.1157.

2i. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2i** (80.5 mg, 96%) as a white solid, 98:2 er, $[\alpha]_D^{25}$ −16.2 (*c* 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 1 mL/min, hexanes/isopropanol: 15/85, 254 nm, 5.68 min (*S*), 6.47 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.47−7.42 (m, 2H), 7.39−7.28 (m, 5H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 6.5 Hz, 2H), 6.25 (t, *J* = 1.9 Hz, 1H), 4.50 (dd, *J* = 11.9, 1.9 Hz, 1H), 4.26 (dd, *J* = 11.9, 2.0 Hz, 1H), 3.60 (d, *J* = 8.3 Hz, 1H), 3.54 (d, *J* = 8.3 Hz, 1H), 2.45 (s, 4H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 143.9, 141.6, 141.5, 138.0, 133.0, 132.7, 129.8, 129.4, 128.5, 128.3, 127.9, 127.8, 126.4, 126.3, 82.0, 61.5, 50.7, 21.6, 21.2. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{25}H_{25}NO_3SNa$, 442.1453; found, 442.1427.

2j. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2j** (75.7 mg, 86%) as a white solid, 98:2 er. $[\alpha]_D^{25}$ −16.5 (*c* 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 1 mL/min, hexanes/isopropanol: 15/85, 254 nm, 5.39 min (*S*), 6.25 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 7.4 Hz, 2H), 7.40−7.27 (m, 6H), 7.29−7.20 (m, 2H), 7.15 (d, *J* = 7.4 Hz, 1H), 6.56 (s, 1H), 4.38 (dd, *J* = 14.9, 2.2 Hz, 1H), 4.14 (d, *J* = 2.3 Hz, 1H), 3.72−3.46 (m, 2H), 2.43 (s, 3H), 2.39 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 143.9, 143.1, 140.0, 133.1, 132.9, 132.2, 129.0, 128.9, 128.3, 128.2, 127.5, 127.2, 126.9, 126.0, 125.4, 122.6, 80.8, 60.6, 59.6, 49.1, 20.7. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{24}H_{22}ClNO_3SNa$, 462.0907; found, 462.0910.

2k. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2k** (81.3 mg, 96%) as a yellow oil, 99:1 er. $[\alpha]_D^{25}$ −6.8 (*c* 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 1 mL/min, hexanes/isopropanol: 25/75, 254 nm, 10.77 min (*S*), 11.82 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77−7.65 (m, 2H), 7.50−7.41 (m, 2H), 7.38−7.26 (m, 6H), 6.96 (td, *J* = 6.7, 2.0 Hz, 1H), 6.91 (dd, *J* = 6.2, 1.2 Hz, 1H), 6.82 (dt, *J* = 8.0, 1.7 Hz, 1H), 6.26 (t, *J* = 2.1 Hz, 1H), 4.34 (ddd, *J* = 94.0, 12.1, 2.1 Hz, 2H), 3.58 (d, *J* = 1.7 Hz, 2H), 2.58 (s, 1H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 163.8, 61.8, 144.1, 144.0, 141.3, 137.8, 137.7, 132.8, 130.2, 130.1, 129.9, 128.4, 128.0, 127.9, 126.1, 125.4, 124.3, 115.3, 115.1, 114.9, 114.7, 81.9, 61.3, 50.5, 21.6. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{24}H_{22}FNO_3SNa$, 446.1202; found, 446.1171.

2l. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2l** (83.6 mg, 96%) as a yellow oil, 99:1 er. $[\alpha]_D^{25}$ −22.6 (*c* 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 1 mL/min, hexanes/isopropanol: 15/85, 254 nm, 6.27 min (*S*), 7.60 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.47−7.44 (m, 2H), 7.37−7.26 (m, 6H), 6.82 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.74 (d, *J* = 7.7 Hz, 1H), 6.67−6.62 (m, 1H), 6.26 (t, *J* = 2.5 Hz, 1H), 4.49 (dd, *J* = 15.0, 2.5 Hz, 1H), 4.25 (dd, *J* = 15.0, 2.6 Hz, 1H), 3.79 (s, 3H), 3.61−3.53 (m, 2H), 2.43 (s, 3H), 2.39 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 159.7, 144.0, 142.9, 141.4, 136.9, 132.9, 129.8, 129.7, 128.4, 127.9, 127.8, 126.5, 126.2, 120.8, 114.5, 113.3, 82.0, 61.4, 55.3, 50.6, 21.6. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{25}H_{25}NO_4SNa$, 458.1402; found, 458.1379.

2m. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2m** (68.1 mg, 72%) as a white solid, 97:3 er. $[\alpha]_D^{25}$ −18.6 (*c* 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 4.10 min (*S*), 4.77 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.54−7.44 (m, 4H), 7.40−7.30 (m, 7H), 6.34 (t, *J* = 2.4 Hz, 1H), 4.47 (dd, *J* = 15.1, 2.4 Hz, 1H), 4.24 (dd, *J* = 15.1, 2.5 Hz, 1H), 3.60 (s, 2H), 2.44 (s, 3H), 2.43 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 144.7, 144.1, 141.0, 136.3, 132.8, 131.1, 129.9, 129.2, 128.5, 128.1, 127.9, 126.1, 125.5, 125.1, 124.5, 81.8, 61.2, 50.3, 21.6. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{25}H_{22}F_3NO_3SNa$, 496.1170; found, 496.1157.

2n. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2n** (63.3 mg, 72%) as a yellow oil, 92:8 er. $[\alpha]_D^{25}$ −12.9 (*c* 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 1 mL/min, hexanes/isopropanol: 15/85, 254 nm, 4.74 min (*S*), 6.96 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 6.5 Hz, 2H), 7.48 (d, *J* = 5.9 Hz, 2H), 7.38−7.22 (m, 8H), 7.15 (d, *J* = 5.9 Hz, 1H), 6.56 (t, *J* = 2.1 Hz, 1H), 4.38 (dd, *J* = 12.0, 1.8 Hz, 1H), 4.13 (dd, *J* = 11.1, 1.8 Hz, 1H), 3.66−3.57 (m, 2H), 2.43 (s, 3H), 2.39 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 144.8, 144.0, 140.9, 133.9, 133.8, 133.1, 129.8, 129.7, 129.2, 129.1, 128.4, 128.0, 127.8, 126.9, 126.2, 123.4, 81.6, 61.5, 50.0, 21.6. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{24}H_{22}ClNO_3SNa$, 462.0907; found, 462.0910.

2o. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2o** (65.2 mg, 77%) as a white solid, >99:1 er. $[\alpha]_D^{25}$ −21.1 (*c* 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 1 mL/min, hexanes/isopropanol: 15/85, 254 nm, 5.26 min (*S*), 6.57 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 7.3 Hz, 2H), 7.34−7.27 (m, 5H), 7.16−7.10 (m, 2H), 7.05−6.98 (m, 1H), 6.46 (d, *J* = 2.6 Hz, 1H), 4.37 (dd, *J* = 15.1, 1.9 Hz, 1H), 4.17 (dd, *J* = 15.0, 2.0 Hz, 1H), 3.62−3.56 (m, 2H), 2.62−2.49 (m, 1H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 161.0, 159.1, 144.8, 144.0, 141.3, 132.9, 129.8, 129.7, 129.7, 129.2, 129.1, 128.4, 128.0, 127.8, 126.1, 124.2, 124.1, 123.5, 123.4, 118.8, 115.8, 115.6, 81.7, 61.4, 50.5, 50.4, 21.6. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{24}H_{22}FNO_3SNa$, 446.1202; found, 446.1171.

2p. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2p** (83.6 mg, 96%) as a white solid, >99:1 er. $[\alpha]_D^{25}$ −9.6 (*c* 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 1 mL/min, hexanes/isopropanol: 15/85, 254 nm, 6.78 min (*S*), 8.39 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 6.6 Hz, 2H), 7.51−7.46 (m, 2H), 7.36−7.26 (m, 6H), 7.08 (dd, *J* = 6.1, 1.1 Hz, 1H), 6.96 (t, *J* = 6.0 Hz, 1H), 6.85 (d, *J* = 6.6 Hz, 1H), 6.64 (t, *J* = 2.0 Hz, 1H), 4.37 (dd, *J* = 11.9, 1.9 Hz, 1H), 4.20 (dd, *J* = 11.9, 2.1 Hz, 1H), 3.74 (s, 3H), 3.63−3.53 (m, 2H), 2.43 (s, 3H), 2.36 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 157.0, 143.8, 142.3, 141.8, 133.1, 129.8, 129.4, 128.7, 128.3, 127.8, 127.8, 126.2, 124.6, 121.4, 120.5, 110.7, 81.7, 61.5, 55.4, 50.6, 21.6. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{25}H_{25}NO_4SNa$, 458.1402; found, 458.1379.

2q. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2q** (79.7 mg, 92%) as a white solid, 95:5 er. $[\alpha]_D^{25}$ −24.0 (*c* 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5

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mL/min, hexanes/isopropanol: 15/85, 254 nm, 12.03 min (*S*), 14.69 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 8.2 Hz, 2H), 7.50−7.40 (m, 2H), 7.38−7.27 (m, 5H), 7.12 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 6.6 Hz, 2H), 6.22 (t, J = 2.3 Hz, 1H), 4.52 (dd, J = 14.9, 2.4 Hz, 1H), 4.26 (dd, J = 14.9, 2.4 Hz, 1H), 3.60 (d, J = 10.4 Hz, 1H), 3.53 (d, J = 10.4 Hz, 1H), 2.43 (s, 3H), 2.41 (s, 1H), 2.25 (d, J = 7.3 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 143.9, 141.6, 141.3, 136.9, 136.7, 133.2, 133.0, 130.1, 130.0, 129.8, 128.3, 127.9, 127.8, 126.6, 126.3, 125.8, 82.1, 61.5, 50.6, 21.6, 19.8, 19.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{26}H_{27}NO_3SNa$, 456.1609; found, 456.1525.

2r. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2r** (70.3 mg, 73%) as a white solid, 98:2 er. $[\alpha]_D^{25}$ −38.7 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 9.66 min (*R*), 11.88 min (*S*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, J = 6.6 Hz, 2H), 7.59 (dd, J = 6.5, 1.4 Hz, 4H), 7.51−7.41 (m, 4H), 7.41−7.30 (m, 6H), 7.22 (d, J = 6.6 Hz, 2H), 6.33 (t, J = 2.1 Hz, 1H), 4.56 (dd, J = 12.0, 1.9 Hz, 1H), 4.31 (dd, J = 12.0, 2.0 Hz, 1H), 3.65−3.52 (m, 2H), 2.43 (s, 3H), 2.40 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.0, 142.6, 141.4, 140.7, 140.2, 134.5, 133.0, 129.9, 129.0, 128.9, 128.4, 127.9, 127.8, 127.6, 127.3, 127.0, 126.2, 126.1, 82.0, 61.5, 50.7, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{30}H_{27}NO_3SNa$, 504.1609; found, 504.1618.

2s. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2s** (71.5 mg, 87%) as a white solid, 99:1 er. $[\alpha]_D^{25}$ −18.8 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 5.35 min (*R*), 6.22 min (*S*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 6.5 Hz, 2H), 7.45 (d, J = 5.9 Hz, 2H), 7.38−7.27 (m, 6H), 7.08 (s, 1H), 6.97 (d, J = 4.0 Hz, 1H), 6.29 (t, J = 2.1 Hz, 1H), 4.47 (dd, J = 11.9, 1.7 Hz, 1H), 4.21 (dd, J = 11.9, 1.8 Hz, 1H), 3.62 (d, J = 8.3 Hz, 1H), 3.53 (d, J = 8.3 Hz, 1H), 2.48 (s, 1H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.0, 141.4, 137.2, 132.8, 129.9, 128.3, 127.9, 127.6, 126.2, 126.1, 124.4, 120.4, 81.8, 61.9, 50.9, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{22}H_{21}NO_3S_2Na$, 434.0861; found, 434.0855.

2t. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2t** (66.6 mg, 81%) as a colorless oil, 99:1 er. $[\alpha]_D^{25}$ −18.0 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 4.88 min (*R*), 6.16 min (*S*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, J = 8.2 Hz, 2H), 7.47−7.42 (m, 2H), 7.39−7.29 (m, 6H), 7.06−6.96 (m, 1H), 6.89 (d, J = 3.4 Hz, 1H), 6.45 (t, J = 2.5 Hz, 1H), 4.48 (dd, J = 15.5, 2.4 Hz, 1H), 4.19 (dd, J = 15.5, 2.5 Hz, 1H), 3.63 (d, J = 10.3 Hz, 1H), 3.52 (d, J = 10.3 Hz, 1H), 2.46 (s, 1H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.0, 141.2, 140.5, 139.3, 132.6, 129.9, 128.4, 128.2, 128.0, 127.9, 127.6, 127.1, 126.2, 119.5, 81.8, 62.2, 51.0, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{22}H_{21}NO_3S_2Na$, 434.0861; found, 434.0855.

2u. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2u** (77.2 mg, 92%) as a colorless oil, >99:1 er, $[\alpha]_D^{25}$ −24.3 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 10.80 min (*S*),12.22 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 6.6 Hz, 2H), 7.37−7.24 (m, 7H), 7.18−7.09 (m, 4H), 6.29 (t, J = 1.9 Hz, 1H), 4.48 (dd, J = 12.0, 1.9 Hz, 1H), 4.25 (dd, J = 12.0, 2.0 Hz, 1H), 3.59−3.50 (m, 2H), 2.43 (s, 1H), 2.42 (s, 3H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 143.9, 142.5, 138.5, 137.7, 135.6, 133.0, 129.8, 129.1, 128.7, 128.6, 127.9, 127.8, 126.3, 126.2, 81.9, 61.3, 50.6, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{25}NO_3SNa$, 442.1453; found, 442.1427.

2v. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2v** (78.0 mg, 92%) as a colorless oil, > 99:1 er. $[\alpha]_D^{25}$ −23.7 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 5.25 min (*S*), 5.58 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 6.6 Hz, 2H), 7.46−7.39 (m, 2H), 7.39−7.26 (m, 5H), 7.14 (d, J = 6.0 Hz, 2H), 7.01 (t, J = 6.9 Hz, 2H), 6.28 (t, J = 1.8 Hz, 1H), 4.49 (dd, J = 12.0, 1.9 Hz, 1H), 4.25 (dd, J = 12.0, 2.0 Hz, 1H), 3.58 (d, J = 8.3 Hz, 1H), 3.50 (d, J = 8.3 Hz, 1H), 2.43 (s, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.4, 144.1, 142.3, 137.3, 135.4, 132.9, 129.9, 128.7, 128.6, 128.1, 128.0, 127.8, 126.7, 115.3, 115.1, 81.6, 61.4, 50.6, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{24}H_{22}FNO_3SNa$, 446.1202; found, 446.1171.

2w. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2w** (72.1 mg, 82%) as a colorless oil, >99:1 er, $[\alpha]_D^{25}$ −25.06 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 30/70, 254 nm, 6.07 min (*S*), 6.44 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 8.2 Hz, 2H), 7.42−7.27 (m, 9H), 7.14 (d, J = 7.4 Hz, 2H), 6.27 (t, J = 2.5 Hz, 1H), 4.51 (dd, J = 15.1, 2.5 Hz, 1H), 4.25 (dd, J = 15.1, 2.6 Hz, 1H), 3.59 (d, J = 10.5 Hz, 1H), 3.49 (d, J = 10.5 Hz, 1H), 2.44 (s, 3H), 2.34 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.1, 142.2, 140.0, 135.3, 133.9, 132.9, 129.9, 128.8, 128.6, 128.5, 128.1, 127.9, 127.7, 126.9, 81.7, 61.5, 50.6, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{24}H_{22}ClNO_3SNa$, 462.0907; found, 462.0866.

2x. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2x** (81.8 mg, 94%) as a white solid, 99:1 er, $[\alpha]_D^{25}$ −36.32 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 25/75, 254 nm, 16.85 min (*R*), 21.99 min (*S*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 6.6 Hz, 2H), 7.39−7.32 (m, 3H), 7.31−7.24 (m, 4H), 7.19 (d, J = 5.6 Hz, 2H), 6.97−6.83 (m, 2H), 6.43 (t, J = 2.1 Hz, 1H), 4.41−4.27 (m, 2H), 3.91 (d, J = 7.7 Hz, 1H), 3.83 (s, 1H), 3.70 (s, 3H), 3.37 (d, J = 7.7 Hz, 1H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 156.0, 143.6, 141.3, 136.0, 132.6, 130.8, 129.6, 129.3, 128.6, 128.5, 127.9, 127.8, 127.6, 125.3, 120.9, 111.1, 80.9, 59.6, 55.2, 50.9, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{25}NO_4SNa$, 458.1402; found, 458.1379.

2y. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2y** (89.9 mg, 95%) as a yellow oil, >99:1 er, $[\alpha]_D^{25}$ −18.19 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 30/70, 254 nm, 4.56 min (*S*), 4.99 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 8.1 Hz, 2H), 7.59 (s, 4H), 7.32 (ddt, J = 23.3, 14.6, 7.4 Hz, 5H), 7.14 (d, J = 7.6 Hz, 2H), 6.26 (t, J = 2.1 Hz, 1H), 4.53 (dd, J = 15.1, 2.3 Hz, 1H), 4.27 (dd, J = 15.1, 2.4 Hz, 1H), 3.62 (d, J = 10.5 Hz, 1H), 3.51 (d, J = 10.5 Hz, 1H), 2.59 (s, 1H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.7, 144.2, 142.2, 135.2, 132.7, 129.9, 128.8, 128.6, 128.2, 127.9, 127.2, 126.7, 125.3 (d, J = 3.8 Hz), 125.2, 81.7, 61.6, 50.7, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{22}F_3NO_3SNa$, 496.1170; found, 496.1157.

2z. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2z** (73.7 mg, 87%) as a colorless oil, >99:1 er. $[\alpha]_D^{25}$ −11.1 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 5.23 min (*S*), 6.70 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 6.6 Hz, 2H), 7.38−7.19 (m, 8H), 7.14 (d, J = 6.0 Hz, 2H), 7.05−6.92 (m, 1H), 6.28 (t, J = 1.9 Hz, 1H), 4.51 (dd, J = 12.0, 1.9 Hz, 1H), 4.25 (dd, J = 12.0, 2.0 Hz, 1H), 3.61 (d, J = 8.4 Hz, 1H), 3.50 (d, J = 8.4 Hz, 1H), 2.44 (s, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.1, 142.1, 135.3, 132.8, 130.0, 129.9, 128.7, 128.6, 128.1, 127.9, 127.0, 21.9, 114.9, 114.7, 113.7, 113.5, 100.00, 81.7, 61.5, 50.6, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{24}H_{22}FNO_3SNa$, 446.1202; found, 446.1171.

2aa. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2aa** (68.6 mg, 78%) as a white solid, 99:1 er, $[\alpha]_D^{25}$ −53.0 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 6.60 min (*S*), 7.50

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min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 8.2 Hz, 2H), 7.46 (s, 1H), 7.37−7.25 (m, 8H), 7.14 (d, J = 7.6 Hz, 2H), 6.28 (t, J = 2.6 Hz, 1H), 4.51 (dd, J = 15.0, 2.3 Hz, 1H), 4.25 (dd, J = 15.0, 2.4 Hz, 1H), 3.60 (d, J = 10.5 Hz, 1H), 3.49 (d, J = 10.5 Hz, 1H), 2.53 (s, 1H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.1, 143.8, 142.1, 135.3, 134.4, 132.8, 129.9, 129.7, 128.7, 128.6, 128.1, 128.0, 127.8, 127.0, 126.5, 124.5, 81.6, 61.5, 50.6, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{24}H_{22}ClNO_3SNa$, 462.0907; found, 462.0910.

2ab. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2ab** (74.1 mg, 85%) as a yellow oil, 98:2 er. $[\alpha]_D^{25}$ −32.1 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 25/75, 254 nm, 10.88 min (*R*), 13.37 min (*S*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, J = 8.3 Hz, 2H), 7.41−7.27 (m, 6H), 7.17 (d, J = 7.4 Hz, 2H), 7.11−7.07 (m, 1H), 7.04−6.98 (m, 1H), 6.91−6.84 (m, 1H), 6.34 (t, J = 2.7 Hz, 1H), 4.53 (dd, J = 14.9, 2.4 Hz, 1H), 4.28 (dd, J = 14.9, 2.5 Hz, 1H), 3.83 (s, 3H), 3.63 (d, J = 10.4 Hz, 1H), 3.57 (d, J = 10.4 Hz, 1H), 2.46 (s, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.6, 143.9, 143.2, 142.4, 135.6, 133.0, 129.8, 129.4, 128.7, 128.6, 127.9, 127.8, 126.6, 118.6, 113.1, 112.3, 82.0, 61.5, 55.3, 50.6, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{25}NO_4SNa$, 458.1402; found, 458.1379.

2ac. The resulting residue was purified by column chromatography (80:20, *n*-hexane/EtOAc) to give **2ac** (55.7 mg, 64%) as a white solid, 98:2 er, $[\alpha]_D^{25}$ −19.33 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 25/75, 254 nm, 10.88 min (*R*), 13.37 min (*S*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 6.6 Hz, 2H), 7.41−7.26 (m, 7H), 7.14 (d, J = 5.9 Hz, 2H), 6.89−6.78 (m, 2H), 6.31 (t, J = 2.1 Hz, 1H), 4.48 (dd, J = 12.0, 2.0 Hz, 1H), 4.25 (dd, J = 12.0, 2.0 Hz, 1H), 3.81 (s, 3H), 3.55 (d, J = 1.6 Hz, 2H), 2.42 (s, 3H), 2.36 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.3, 143.9, 142.5, 135.6, 133.4, 129.8, 128.7, 128.6, 127.9, 127.8, 127.5, 126.2, 113.7, 100.0, 81.7, 61.2, 60.4, 55.3, 50.5, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{25}NO_4SNa$, 458.1402; found, 458.1379.

2ad. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2ad** (71.1 mg, 82%) as a colorless oil, >99:1 er. $[\alpha]_D^{25}$ −60.67 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 3.87 min (*R*), 4.87 min (*S*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 7.9 Hz, 1H), 7.36 (t, J = 7.6 Hz, 2H), 7.29 (d, J = 8.3 Hz, 3H), 7.15 (d, J = 7.4 Hz, 2H), 7.06−6.91 (m, 2H), 6.23 (t, J = 2.4 Hz, 1H), 4.57 (d, J = 2.4 Hz, 1H), 4.34 (d, J = 2.5 Hz, 1H), 3.65−3.53 (m, 2H), 2.42 (s, 3H), 2.31 (s, 3H), 2.24 (s, 1H), 2.04 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 143.8, 142.5, 137.9, 136.0, 135.7, 135.1, 133.1, 133.0, 129.7, 128.7, 128.5, 127.9, 127.8, 127.3, 126.4, 125.6, 82.6, 59.7, 50.6, 21.6, 21.3, 20.8. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{26}H_{27}NO_3SNa$, 456.1609; found, 456.1569.

2ae. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2ae** (58.7 mg, 61%) as a white solid, 99:1 er. $[\alpha]_D^{25}$ −0.77 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 9.56 min (*R*), 11.36 min (*S*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 8.2 Hz, 2H), 7.62−7.50 (m, 6H), 7.45 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 7.7 Hz, 3H), 7.30 (dd, J = 13.1, 7.8 Hz, 3H), 7.17 (d, J = 7.5 Hz, 2H), 6.37 (t, J = 2.3 Hz, 1H), 4.53 (dd, J = 15.0, 2.4 Hz, 1H), 4.30 (dd, J = 15.0, 2.5 Hz, 1H), 3.67−3.57 (m, 2H), 2.54 (s, 1H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.0, 142.4, 140.8, 140.5, 140.5, 135.6, 132.9, 129.9, 128.9, 128.7, 128.6, 128.0, 127.9, 127.5, 127.1, 127.0, 126.7, 126.6, 81.9, 61.4, 50.6, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{30}H_{27}NO_3SNa$, 504.1609; found, 504.1618.

2af. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2af** (79.1 mg, 87%) as a white solid, 99:1 er. $[\alpha]_D^{25}$ −43.36 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 8.44 min (*S*), 19.25 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08−7.99 (m, 1H), 7.90−7.76 (m, 3H), 7.74 (d, J = 6.6 Hz, 2H), 7.54−7.45 (m, 2H), 7.43−7.32 (m, 3H), 7.32−7.25 (m, 3H), 7.15 (d, J = 5.9 Hz, 2H), 6.31 (t, J = 1.9 Hz, 1H), 4.59 (dd, J = 12.0, 2.0 Hz, 1H), 4.33 (dd, J = 12.0, 2.0 Hz, 1H), 3.73−3.62 (m, 2H), 2.50 (s, 1H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.0, 142.5, 138.6, 135.5, 133.1, 132.9, 132.8, 129.8, 128.7, 128.6, 128.3, 128.2, 128.0, 127.8, 127.5, 126.9, 126.5, 126.4, 125.4, 124.2, 82.3, 61.3, 50.7, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{28}H_{25}NO_3SNa$, 478.1453; found, 478.1447.

2ag. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2ag** (60.9 mg, 79%) as a white solid, 98:2 er. $[\alpha]_D^{25}$ +7.2 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 5.50 min (*S*), 5.95 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 7.6 Hz, 2H), 7.29 (d, J = 8.0 Hz, 3H), 7.17 (d, J = 7.5 Hz, 2H), 6.55 (t, J = 2.5 Hz, 1H), 4.25 (dd, J = 14.8, 2.4 Hz, 1H), 4.16−4.09 (m, 1H), 3.91 (d, J = 10.4 Hz, 1H), 2.89 (d, J = 10.4 Hz, 1H), 2.40 (s, 3H), 1.67 (s, 1H), 1.02 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 143.8, 140.8, 135.7, 133.0, 129.8, 128.7, 128.6, 127.7, 127.6, 126.7, 84.3, 55.9, 51.5, 38.2, 25.1, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{22}H_{27}NO_3SNa$, 408.1609; found, 408.1611.

2ah. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2ah** (59.8 mg, 81%) as a colorless oil, 99:1 er. $[\alpha]_D^{25}$ −12.0 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 20/80, 254 nm, 9.56 min (*S*), 12.06 min (*R*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82−7.66 (m, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.34−7.26 (m, 3H), 7.18 (dd, J = 7.2, 1.6 Hz, 2H), 6.61 (t, J = 2.6 Hz, 1H), 4.35−4.14 (m, 2H), 3.34 (d, J = 9.9 Hz, 1H), 3.20 (d, J = 9.9 Hz, 1H), 2.41 (s, 3H), 1.70 (s, 1H), 1.06 (tt, J = 8.2, 5.3 Hz, 1H), 0.59−0.39 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 143.8, 140.9, 135.7, 132.9, 129.8, 128.7, 128.6, 127.8, 127.7, 124.2, 78.5, 58.6, 50.6, 21.5, 17.9, 1.2, 0.2. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{21}H_{23}NO_3SNa$, 392.1296; found, 392.1313.

2ai. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2ai** (70.4 mg, 76%) as a white solid, 99:1 er, $[\alpha]_D^{25}$ −11.2 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 20/80, 254 nm, 6.26 min (*R*), 6.85 min (*S*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, J = 7.7 Hz, 2H), 7.38 (d, J = 7.3 Hz, 2H), 7.29 (d, J = 7.1 Hz, 3H), 7.19 (d, J = 7.2 Hz, 2H), 6.47 (s, 1H), 4.24 (d, J = 14.8 Hz, 1H), 4.11 (d, J = 14.6 Hz, 1H), 3.99 (d, J = 10.3 Hz, 1H), 2.80 (d, J = 10.3 Hz, 1H), 2.40 (s, 3H), 1.97 (s, 3H), 1.73−1.54 (m, 13H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 143.7, 139.9, 135.6, 133.0, 129.8, 128.7, 128.6, 127.7, 127.1, 84.2, 54.6, 51.5, 39.6, 36.8, 35.9, 28.3, 21.5. HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{28}H_{33}NO_3SNa$, 486.2079; found, 486.2066.

Discovered New Asymmetric Couplings with (*R*)-AntPhos and *N*-Alkynone. *Synthetic Procedure (Scheme 4a).* In a glove box, $Ni(cod)_2$ (2.8 mg, 0.010 mmol, 5 mol %), **(*R*)-AntPhos** (3.7 mg, 0.010 mmol, 5 mol %), and dioxane (0.5 mL) were added to a 5 mL screw-cap vial equipped with a magnetic stirring bar. Substrate **1a** (83.4 mg, 0.20 mmol, 1.00 equiv) and pinacolborane (HBPin, 73.1, 0.60 mmol, 3.00 equiv) were added to the solution in one portion. The vial was capped with a screw cap, and the resulting mixture was stirred at 70 °C for 24 h, quenched with saturated $NaHCO_3$ solution, extracted with EtOAc, washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by column chromatography to obtain compound **2a**.

2a. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **2a** (71.4 mg, 88%) as a white solid, 81:19 er. $[\alpha]_D^{25}$ −22.0 (c 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 12.58 min (*S*), 15.07 min (*R*). All other physical and spectroscopic data of this compound were identical to those mentioned above for compound **2a**.

Synthetic Procedure (Scheme 4b). In the glove box, $Ni(cod)_2$ (2.8 mg, 0.010 mmol, 5 mol %), **(*R*)-AntPhos** (3.7 mg, 0.010 mmol, 5 mol %) and dioxane (0.5 mL) were added to a 5 mL screw-cap vial

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equipped with a magnetic stirring bar. Substrate **1u** (83.4 mg 0.20 mmol, 1.00 equiv), phenylboronic acid [$PhB(OH)_2$, 73.1 mg, 0.60 mmol, 3.00 equiv], and *tert*-butanol (*t*BuOH, 0.1 mL) were added to the solution in one portion. The vial was capped with a screw cap, and the resulting mixture was stirred at 70 °C for 24 h, quenched with saturated $NaHCO_3$ solution, extracted with EtOAc, washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by column chromatography to obtain compound **3u**.

3u. The resulting residue was purified by column chromatography (85:15, *n*-hexane/EtOAc) to give **3u** (83.2 mg, 82%) as a colorless oil, 93:7 er. $[\alpha]_D^{25}$ −12.12 (*c* 1.0, CH_2Cl_2); the enantiomeric ratio was determined by chiral HPLC. Chiralpark AD-H, 25 °C, flow rate: 0.5 mL/min, hexanes/isopropanol: 15/85, 254 nm, 8.88 min (*S*), 17.36 min (*R*). ^1H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.24 (d, J = 7.4 Hz, 1H), 7.11−6.85 (m, 8H), 6.75−6.70 (m, 2H), 6.64 (d, J = 8.1 Hz, 1H), 6.58 (t, J = 7.3 Hz, 1H), 4.23 (d, J = 13.9 Hz, 1H), 4.03 (d, J = 14.0 Hz, 1H), 3.52 (d, J = 10.0 Hz, 1H), 3.50 (s, 3H), 3.46 (d, J = 10.0 Hz, 1H), 2.93 (s, 1H), 2.48 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 154.9, 143.7, 141.8, 140.5, 139.2, 137.7, 131.9, 130.2, 129.5, 128.5, 128.5, 128.4, 128.2, 127.7, 127.4, 127.3, 126.8, 126.6, 120.4, 110.1, 79.4, 62.2, 54.6, 53.2, 21.6. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{31}H_{29}NO_4SNa$, 534.1715; found, 534.1722.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00079.

Experimental procedures and compound characterization including HPLC chromatograms and ^1H and ^{13}C NMR spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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