

# A Unified Strategy for the Asymmetric Synthesis of Highly Substituted 1,2-Amino Alcohols Leading to Highly Substituted Bisoxazoline Ligands

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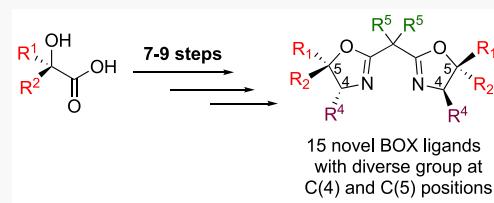


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**ABSTRACT:** A general procedure for the asymmetric synthesis of highly substituted 1,2-amino alcohols in high yield and diastereoselectivity is described that uses organometallic additions of a wide range of nucleophiles to *tert*-butylsulfinimines as the key step. The addition of organolithium reagents to these imines follows a modified Davis model. The diastereoselectivity for this reaction depends significantly on both the nucleophile and electrophile. These highly substituted 1,2-amino alcohols are used to synthesize stereochemically diverse and structurally novel, polysubstituted 2,2'-methylene(bisoxazoline) ligands in high yields.



## INTRODUCTION

1,2-Amino alcohols are found in a wide range of natural and synthetic compounds. Naturally occurring bioactive molecules like bestatin, hapalosin, and vancomycin contain 1,2-amino alcohols (Chart 1).<sup>1–6</sup> Cyclic amino alcohols are found in biologically active alkaloids such as vinblastine,<sup>7</sup> (+)-castanospermine,<sup>8</sup> and anisomycin.<sup>9</sup> Bioactive lipids such as sphingosine<sup>10</sup> and myriocin<sup>11</sup> also contain a 1,2-amino alcohol moiety. 1,2-Amino alcohols are found as aminoglycosides in various natural products such as daunomycin,<sup>12</sup> elsamycin A,<sup>13</sup> and neomycin B.<sup>14</sup> In addition to these natural products, synthetic, pharmacologically active molecules like saquinavir possess these moieties.<sup>15</sup> 1,2-Amino alcohols and their derivatives are also popular as chiral auxiliaries for various asymmetric reactions (Figure 1).<sup>16</sup> Asymmetric alkylation of acyclic chiral auxiliaries such as pseudoephedrine and ephedrine are well known.<sup>17,18</sup> Proline-derived ligands such as oxazaborolidinones are widely used in reduction of carbonyl compounds.<sup>19–21</sup> Oxazolidinones accomplish various asymmetric reactions such as alkylation,<sup>22</sup>  $\alpha$ -halogenation,<sup>23</sup>  $\alpha$ -amination,<sup>24</sup> oxygenation,<sup>25</sup> sulfenylation,<sup>26</sup> aldol,<sup>27</sup> and conjugate additions.<sup>28</sup>

1,2-Amino alcohols are employed in the synthesis of  $C_2$ -symmetric, chiral bisoxazoline (BOX) ligands, which are frequently used in metal-catalyzed asymmetric reactions.<sup>29,30</sup> These ligands possess a conformationally rigid geometry as well as Lewis basic nitrogen atoms, which can ligate metal ions to produce chiral catalysts for myriad enantioselective carbon–carbon and carbon–heteroatom bond-forming reactions (Scheme 1). BOX ligands are widely used with copper salts for catalytic intermolecular and intramolecular enantioselective cyclopropanation reactions.<sup>31,32</sup> The copper–BOX

ligand catalyst system can also affect the enantioselective aziridination of alkenes.<sup>33</sup> Mukaiyama aldol reactions are effectively catalyzed by chiral tin–BOX complexes as illustrated in the synthesis of the marine natural product phorboxazole B.<sup>34</sup> A palladium catalyst and a chiral bisoxazoline ligand afford five- and six-membered ring heterocycles and carbocycles in good yields in the allylic reaction of allenes with aryl and vinyl iodides.<sup>35</sup> Porter et al. reported the use of a zinc–BOX complex to promote radical reactions of alkyl iodides, acryloyloxazolidinones, and allyltributylstannanes, resulting in substituted acrylamides products.<sup>36</sup> An Evans copper–BOX hexafluoroantimonate complex is used to catalyze a Diels–Alder reaction of an  $\alpha$ -methylene lactam and an (*E*)-diene to construct a highly functionalized spiro lactam as a single diastereomer in high enantioselectivity. This spiro lactam is a key intermediate in the total synthesis of the marine toxin gymnodimine.<sup>37</sup>

## BACKGROUND

**1,2-Amino Alcohols.** Given the importance and utility of 1,2-amino alcohols, many methods are reported for the enantioselective and diastereoselective synthesis of this motif (Scheme 2).<sup>1,38</sup> Generally, 1,2-amino alcohols are synthesized through the functional group manipulation of molecules

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Chart 1. Selected Examples of Natural Products and Pharmaceutically Active Compounds with 1,2-Amino Alcohol Motifs

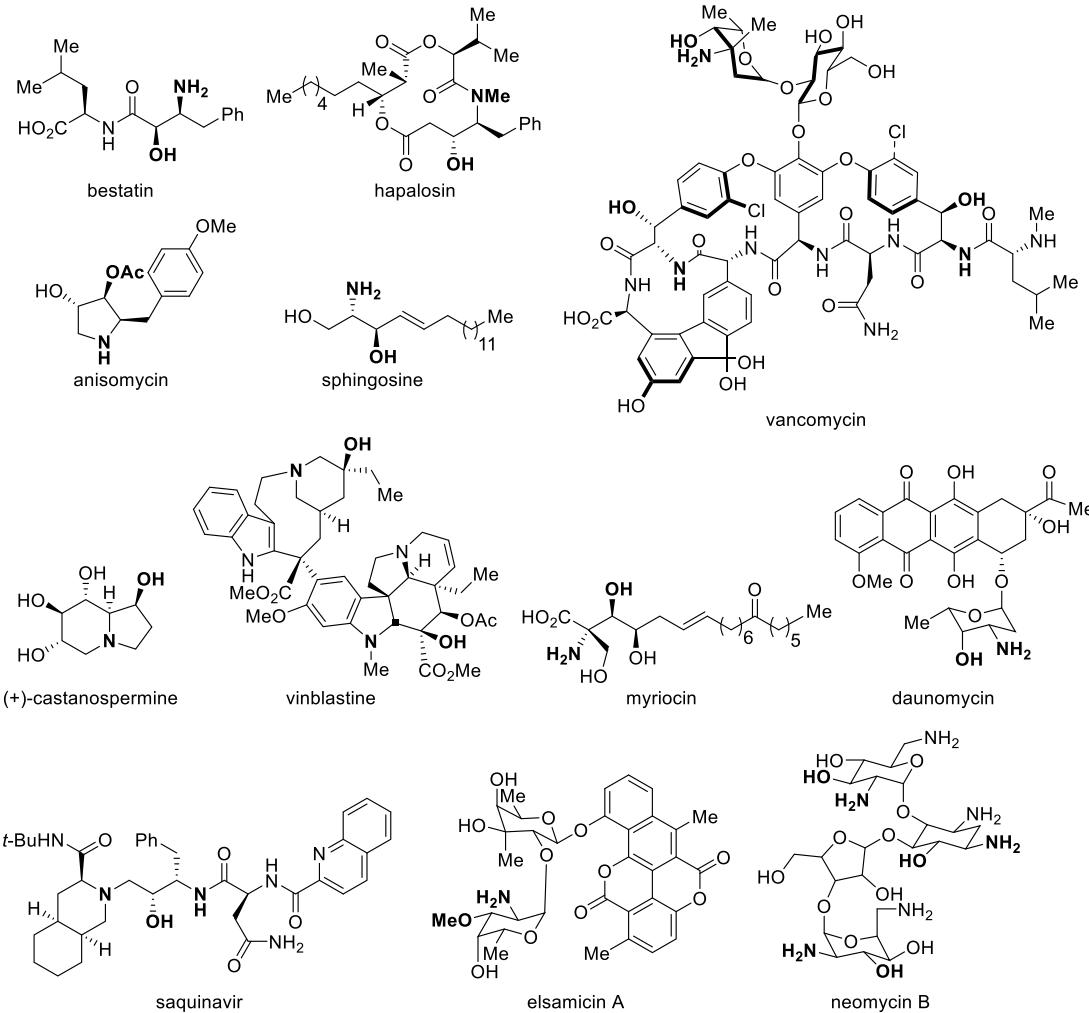


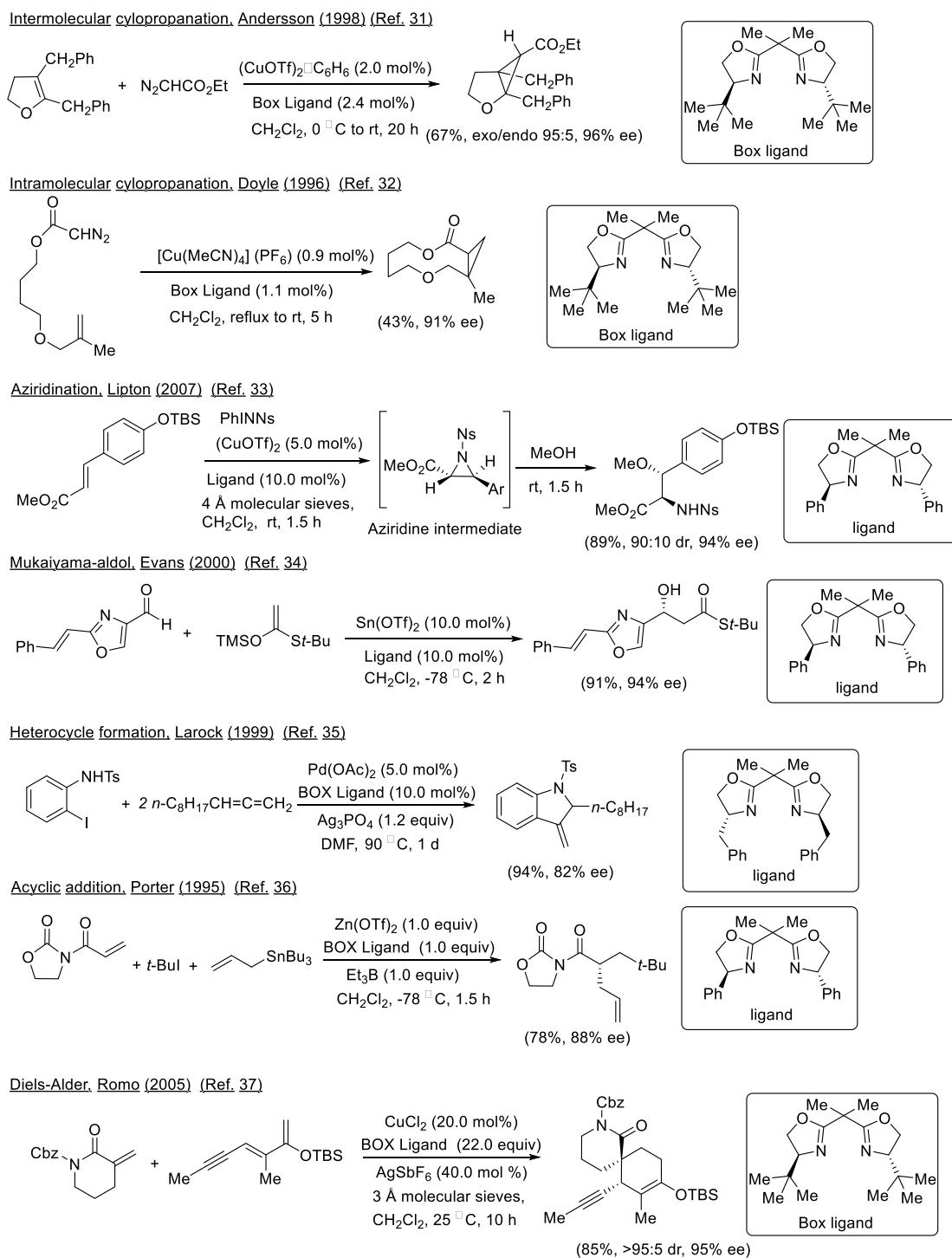
Figure 1. Examples of 1,2-amino alcohol-containing chiral auxiliaries.

containing two heteroatoms on vicinal carbons, for example, by reduction or nucleophilic addition to carbonyl or imine groups. The ring-opening reactions of an epoxide or aziridine with a nitrogen or oxygen nucleophile also provide the 1,2-amino alcohol.<sup>1</sup> The addition of one heteroatom to a molecule already containing a heteroatom also gives 1,2-amino alcohols. Here, the configuration of the resident heteroatom controls or directs the stereochemical approach of the incoming nucleophile. Another commonly used method for the synthesis of 1,2-amino alcohols is amino-hydroxylation of an alkene, in which both nitrogen and oxygen are added in a single reaction. Nucleophilic addition of an  $\alpha$ -heteroalkylmetal reagent and an aldehyde or imine or pinacol-type coupling between an aldehyde and imine also produces 1,2-amino alcohols.<sup>39</sup> Chemoenzymatic strategies such as the use of transaminases, kinetic resolutions, dynamic resolutions, or biocatalytic C–C bond formations are also

used for the synthesis of 1,2-amino alcohols.<sup>40</sup> Illustrations of these disconnections are summarized in Scheme 3.

For the functional group manipulation approach, *syn*- or *anti*-1,2-amino alcohols are prepared by the addition of chiral allylboronates to Garner's aldehyde.<sup>41</sup> For the epoxide ring opening reaction approach, treatment of benzhydryl amine with an epoxide prepared from the corresponding allylic alcohol via a Katsuki–Sharpless asymmetric epoxidation provides the vicinal amino alcohol in good yield.<sup>42</sup> Opening of an aziridine ring employs aza-Payne rearrangements of hydroxy aziridines to provide an epoxy amine intermediate, which is then treated with an organocuprate to give diastereomerically pure *N*-protected 1,2-amino alcohols.<sup>43</sup> 1,2-Amino alcohols generated by the addition of one heteroatom are exemplified in the Schenck ene reaction of an allylamine with singlet oxygen in the presence of tetraphenylporphyrin.<sup>44,45</sup> Sharpless<sup>46</sup> and co-workers have developed the aminohydroxylation method for the preparation of  $\alpha$ -hydroxy- $\beta$ -amino esters from the corresponding  $\alpha,\beta$ -unsaturated esters. Nitro aldol or Henry reactions have been employed to obtain *syn*-1,2-amino alcohols in high yield and enantioselectivity.<sup>47</sup> Similarly, pinacol-type coupling reactions with chemoenzymatic methods are available for the synthesis of a wide range of enantiopure 1,2-amino alcohols.<sup>48</sup> During the synthesis of protected imino-digitoxose, a key 1,2-amino alcohol intermediate was prepared via an L-threonine

## Scheme 1. Examples of Enantioselective Reactions of BOX Ligands



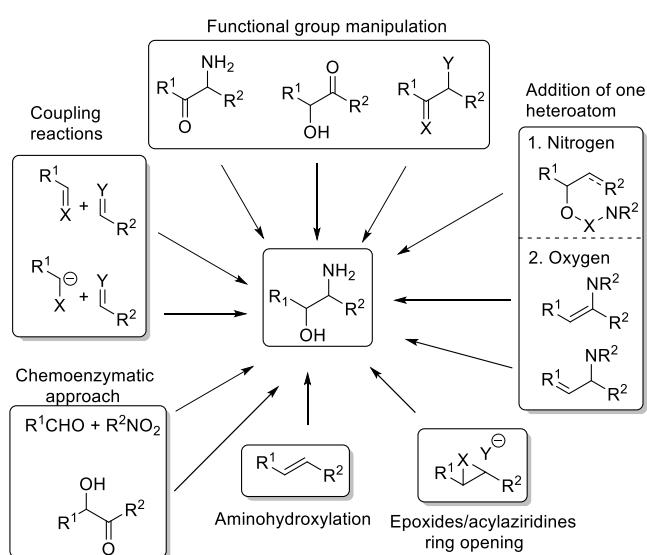
aldolase-catalyzed aldol condensation of (2*S*,3*S*)-2,3-O-isopropyliden-4-penten-1-al and glycine.<sup>49,50</sup>

**Bisoxazolines.** The classic approach for the synthesis of bisoxazoline ligands combines a malonyl dichloride with a 1,2-amino alcohol to give a key bisamide intermediate (Scheme 4).<sup>29,51–53</sup> The resulting bisamide can undergo cyclization with either inversion or retention of configuration at a substituted C(5) carbon. Dehydrating agents such as titanium(IV) isopropoxide,<sup>54</sup> methanesulfonic acid,<sup>55</sup> ammonium molybdate,<sup>56</sup> lanthanide chloride salts,<sup>57</sup> or a zeolite<sup>58</sup> affect retentive cyclization of the bisamide. Retentive ring

closure of the bisamide can also be accomplished by using the Masamune protocol using dibutyltin dichloride.<sup>59</sup> You and co-workers successfully cyclized the bisamide using triphenylphosphine under basic conditions with overall retention of configuration.<sup>60</sup> Owing to low catalytic activities, these reactions need an excess of reagent or a high reaction temperature. Furthermore, these catalytic methods are limited to simple acid- or base-tolerant substrates, resulting in poor functional group tolerance.

In addition to formation of bisamides from 1,2-amino alcohols, other condensation reactions have been employed

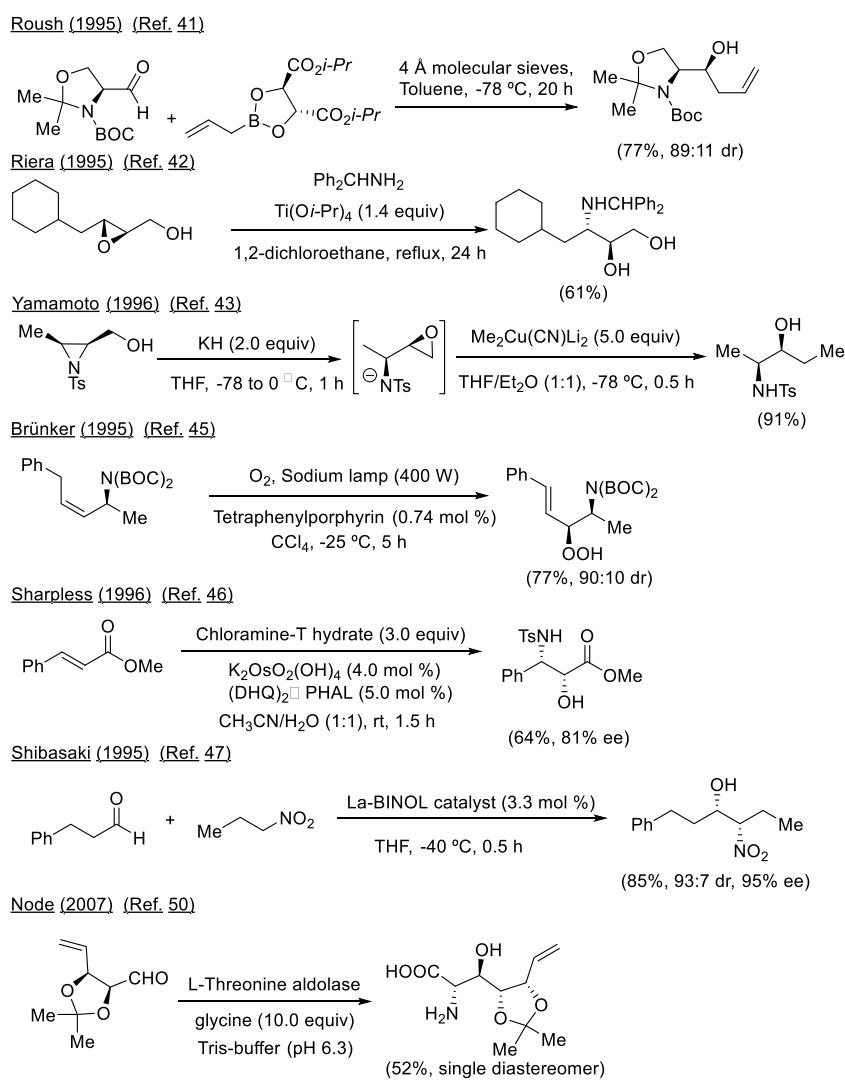
**Scheme 2. Various Approaches for the Synthesis of 1,2-Amino Alcohols**



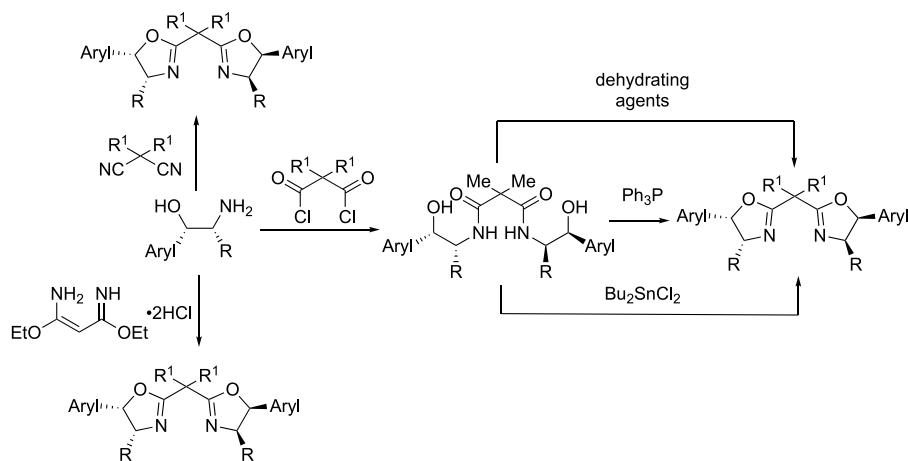
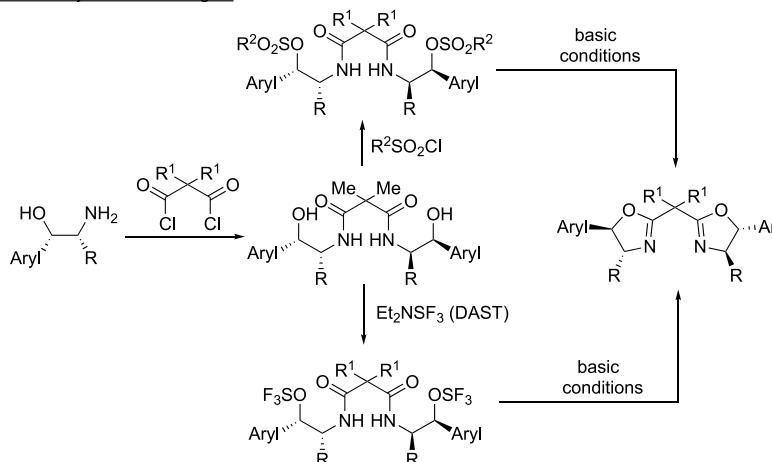
to construct BOX ligands retentively. For example, a Ritter reaction between a malononitrile and indanediol gives the BOX ligand in high regio- and diastereoselectivity.<sup>61</sup> Cadmium diacetate catalyzed synthesis of a BOX ligand from (*R,R*)-threoninol and dimethylmalononitrile has also been reported.<sup>62</sup> Condensation of (+)-(1*S,2S*)-2-amino-1-phenylpropane-1,3-diol with the bisimide prepared from treatment of malononitrile with ethanol in the presence of HCl gas in a Pinner reaction also produces BOX ligands.<sup>63</sup> The reaction between a bisimide and L- or D-serine amide hydrochloride produces BOX ligands as well.<sup>64</sup> Zinc(II) chloride has also been used to prepare BOX ligands from bisamides.<sup>65</sup>

To affect invertive cyclization, the hydroxyl groups of the bisamides are converted to mesyl or tosyl groups. Invertive cyclization then occurs under basic conditions.<sup>66</sup> Similarly, diethylaminosulfur trifluoride (DAST) also affects invertive cyclization of bisamides.<sup>67</sup> One of the major challenges of the invertive cyclization method is the formation of the monocyclized product owing to partial formation of the activated hydroxyl group. Since, the cyclization occurs by an invertive displacement of the carbon bearing the leaving

**Scheme 3. Examples of Asymmetric Synthesis of 1,2-Amino Alcohols**



Scheme 4. Various Strategies for the Retentive and Invertive Construction of BOX Ligands

Retentive cyclization strategiesInvertive cyclization strategies

group, the efficacy of this displacement is strongly dependent upon substitution at the C(5) position.

## RESEARCH PLAN

In general, the challenge in constructing highly substituted BOX ligands is not in the ring-closure step, but rather in the synthesis of the requisite 1,2-amino alcohols in stereodefined form. Key to the success of the BOX ligand architecture as a privileged class is the ability to extensively vary the substituents at the C(4)- and C(5)-positions of the oxazolines. In most of the commonly employed BOX ligands, the substituents at the C(4)- and C(5)-positions are rather simple, generally derived from chiral pool sources such as natural amino acids. Many of them lack substituents at the S-position altogether.<sup>51,52,65,68,69</sup> The lack of structural diversity ultimately relates back to the 1,2-amino alcohols or 1,2-diols from which the ligands are prepared.<sup>61,70,71</sup>

In the context of our chemoinformatic workflow for the discovery and optimization of enantioselective catalysts,<sup>72–74</sup> we targeted the 2,2'-(methylene)bisoxazoline architecture as a highly diversifiable scaffold via modular construction. This workflow requires the generation of an *in silico* library of 10<sup>4</sup>–10<sup>5</sup> synthetically accessible, hypothetical ligands, with significant structural diversity at the C(4)-center. Ultimately, a training set of 20–30 representatives will have to be prepared in quantity to generate data for machine-learning

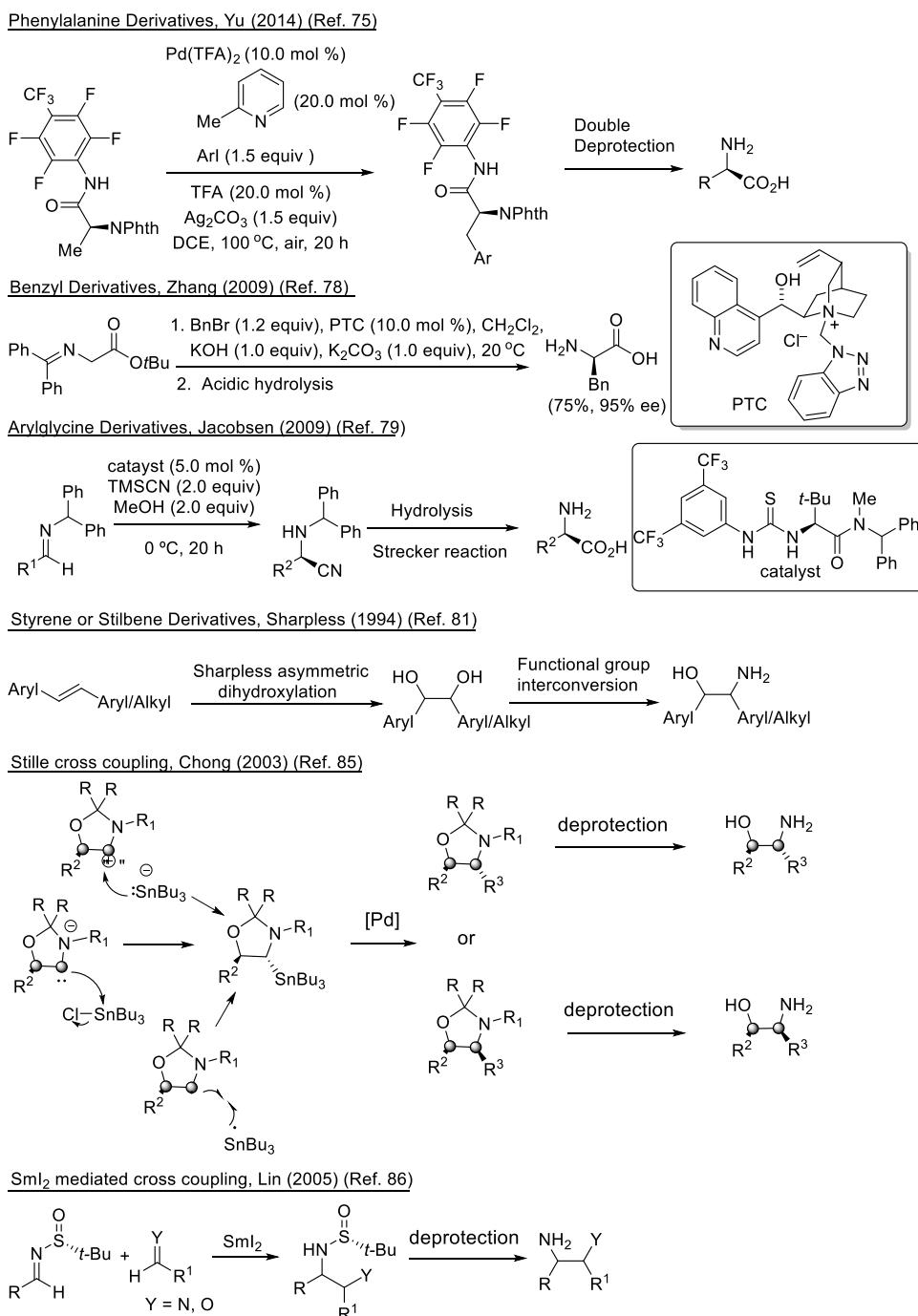
modeling. This training set will comprise highly substituted ligands bearing substituents at the C(4)-position that have never been prepared before, as well as both *cis*- and *trans*-diastereomers at the C(4)- and C(5)-positions. In early synthesis campaigns, existing methods to prepare the requisite 1,2-amino alcohols failed to provide a general solution. This paper reports a general, asymmetric synthesis of highly substituted 1,2-amino alcohols from sulfinyl imines as the common intermediate. Diverse 1,2-amino alcohols are then used to synthesize novel 4,5-polysubstituted BOX ligands.

## RESULTS

**Failures of Classical and Modern Methods to Provide a General Synthesis of Stereodefined 1,2-Amino Alcohols.** Although it is generally ill advised to document failures in publications, given the widespread belief that BOX ligand synthesis is a solved problem, it is appropriate to briefly summarize why that belief is misguided.

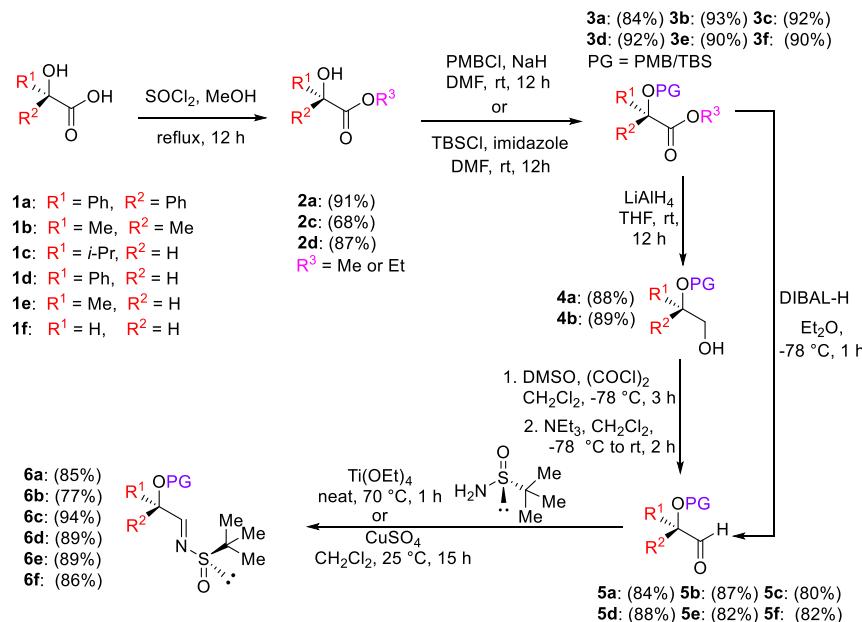
Depending upon the substituent pattern on the target final BOX ligands, different synthetic routes were explored. First, those ligands bearing benzyl substituents at the C(4)-position (e.g., phenylalanine derivatives) would be synthesized using the method described by Yu (Scheme 5).<sup>75</sup> Here, phenylalanine derivatives prepared by insertion into the methyl C–H bond of the parent alanine would provide a convenient route to unnatural amino acids. After testing this route,

**Scheme 5.** Various Routes Examined for the Synthesis of 1,2-Amino Alcohols



several limitations were encountered. First, this method gave lower yields on a large scale. Second, excessive amounts of palladium(II) trifluoroacetate and silver carbonate were needed. Alternatively, for targets with stereocenters also at the C(5)-position of the oxazoline ring, the Reetz route<sup>76</sup> was evaluated but abandoned over concerns regarding the configurational stability of the intermediate  $\alpha$ -amino aldehyde. Ultimately, the C(4)-benzyl-substituted BOX ligands were to be accessed through the enantioselective O'Donnell phase-transfer-catalyzed alkylation reaction.<sup>77,78</sup> Although this reaction gave high yield and high enantioselectivity, the substrate scope was limited.

Next, those ligands bearing aryl substituents at the C(4)-position (e.g., aryl glycine derivatives) were to be prepared by an enantioselective Strecker reaction.<sup>79</sup> The transformation worked well, but the hydrolysis of the Strecker products required much optimization on a case-by-case basis. An alternative approach employed the Sharpless enantioselective dihydroxylations of stilbenes or styrenes and subsequent functional group interconversions.<sup>80,81</sup> Despite being a good method for the introduction of stereocenters, the number of diverse BOX ligands which could be prepared in this manner was limited, owing to the substrate requirements for enantioselective dihydroxylation. Furthermore, many bulky substituents lead to sluggish reactions, and increasing the

Scheme 6. General Routes for the Synthesis of  $\alpha$ -Siloxy Sulfinimines from Hydroxy Acids and Esters

catalyst loading failed to produce a substantial increase in yield owing to slow turnover. Similarly, Shi epoxidation<sup>82</sup> failed to provide any conversion for these substrates with nearly quantitative recovery of the starting material.

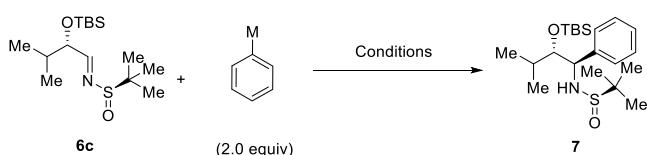
Another approach envisioned the diastereoselective construction of a stable, secondary tin reagent which could then undergo enantiospecific cross coupling to furnish a library of amino alcohol precursors.<sup>83,84</sup> Installation of the organotin unit by directed lithiation was first attempted on an *N*-Boc-oxazolidinone, which was unsuccessful. Addition of the organotin nucleophile to ((*R*)-5-methyl-5*H*-1,2,3-oxathiazole 2,2-dioxide) was also unsuccessful.<sup>85</sup> Samarium iodide mediated cross couplings of *N*-*tert*-butanesulfinyl imines with  $\alpha$ -branched aliphatic aldehydes to access the corresponding amino alcohols with high enantio- and diastereoselectivity have been reported.<sup>86</sup> These couplings worked as reported for the electron-rich or -neutral sulfinimines, but the yield suffered for electron-deficient sulfinimines as well as polyaromatic systems.

**The Robustness and Generalizability of the Ellman Imine Approach. Synthesis of the Sulfinimine Substrates.** Inspired by two concurrent reports by Ellman and Barrow regarding the diastereoselective addition of Grignard reagents to  $\alpha$ -siloxy sulfinimines followed by global deprotection to give the corresponding 1,2-amino alcohols,<sup>87–90</sup> the synthesis of  $\alpha$ -siloxy sulfinimines was initiated. These building blocks are easily prepared from commercially available hydroxy acids and esters, including benzilic acid, methyl 2-hydroxyisobutyrate, L-(+)-mandelic acid, L-(−)-ethyl lactate, and methyl glycolate (Scheme 6). Hydroxy acid 1c bearing an isopropyl group was prepared from L-valine.<sup>91</sup> The esterification of hydroxy acids 1a,<sup>92</sup> 1c,<sup>91</sup> and 1d<sup>93</sup> using thionyl chloride and methanol gave the corresponding methyl esters. The hydroxyl group of esters 2a,b was protected using 4-methoxybenzyl chloride (PMBCl).<sup>94</sup> The 4-methoxybenzyl protection of the hydroxyl group of chiral esters 2c–e was unsuccessful because sodium hydride (NaH) caused epimerization of the stereogenic center. Though PMB protection of these chiral esters was successful using 4-methoxybenzyl trichloroacetimidate as

a benzylating agent,<sup>95</sup> the diisobutylaluminum hydride reduction gave low yield. Consequently, esters 2c–f were protected with *tert*-butyldimethylsilyl chloride (TBSCl).<sup>96</sup> The PMB-protected esters 3a–b were reduced with lithium aluminum hydride to provide the corresponding alcohols 4a,b, which were further subjected to Swern oxidation to afford the corresponding aldehydes. TBS protected esters 3c–f were directly converted to the corresponding aldehydes using diisobutylaluminum hydride reduction at  $-78^\circ\text{C}$  with no loss of stereochemical purity. Aldehydes 5a–e were condensed with (*R*)-*tert*-butylsulfinamine using titanium(IV) ethoxide to generate the requisite  $\alpha$ -siloxy sulfinimines. Aldehyde 5f required copper(II) sulfate to affect condensation.<sup>87,97</sup>

**Addition of Organometallic Nucleophiles to the Sulfinimines.** The initial optimization of the organometallic additions began with  $\alpha$ -siloxy (*R*)-sulfinimine 6c as a model system. Treatment of 6c with phenylmagnesium bromide in  $\text{CH}_2\text{Cl}_2$  resulted in no conversion at  $-40^\circ\text{C}$  (Table 1, entry 1). Increasing the temperature to  $-20^\circ\text{C}$  led to 25% conversion to the desired product with 88:12 dr (entry 2). Full consumption of the starting material was achieved at  $0^\circ\text{C}$ , but the dr of the product was unacceptably low at 57:43 (entry 3). Changing the solvent to toluene allowed for 80% conversion at cryogenic temperatures, but again with a low dr (entry 4). Using THF as solvent provided 71% conversion with a modest increase in diastereoselectivity compared to toluene (entry 5) and addition of TMEDA<sup>90</sup> had no effect on the results (entry 6). Changing the absolute configuration of the sulfinimine to (*S*) provided the corresponding product in a low 77:33 dr apparently corresponding to the mismatched case (entry 7). Organolithium reagents are also competent nucleophiles for 1,2-addition to chiral sulfinimines to afford  $\beta$ -amino alcohols.<sup>90</sup> Accordingly, using phenyllithium resulted in complete consumption of the starting material and provided the corresponding 1,2-addition product in a 91:9 dr (entry 8). Once again, no change was observed by the addition of TMEDA (entry 9). All these reactions were run on a 0.2 mmol scale for 24 h.

**Table 1. Optimization of Diastereoselective Addition to Imine **6c**<sup>a</sup>**



entry	M	solvent (0.05 M)	temp (°C)	conv <sup>b</sup> (%)	dr <sup>c</sup>
1	MgBr	CH <sub>2</sub> Cl <sub>2</sub>	-40	0	
2	MgBr	CH <sub>2</sub> Cl <sub>2</sub>	-20	25	88:12
3	MgBr	CH <sub>2</sub> Cl <sub>2</sub>	0	100	57:43
4	MgBr	toluene	-60	80	82:18
5	MgBr	THF	-70	71	88:12
6	MgBr/TMEDA	THF	-70	68	87:13
7	MgBr	THF	-70	73	77:33 <sup>d</sup>
8	Li	THF	-78	>99	91:9
9	Li/TMEDA	THF	-78	>99	91:9

<sup>a</sup>Reactions were run on a 0.2 mmol scale for 24 h. <sup>b</sup>Conversion was determined by <sup>1</sup>H NMR spectroscopy of the crude mixture.

<sup>c</sup>Diastereomeric ratio was determined by <sup>1</sup>H NMR spectroscopy of the crude mixture. <sup>d</sup>(S)-N-((S,E)-2-((tert-Butyldimethylsilyl)oxy)-3-methylbutyldene)-2-methylpropane-2-sulfonamide was used for the reaction.

The scope of electronically and sterically diverse aryllithium species was examined in the addition to various  $\alpha$ -oxy (R)-sulfonimines. Both [1,1'-biphenyl]-4-yllithium and (3,5-di-*tert*-butylphenyl)lithium were cleanly incorporated in sulfonimine **6a** to afford the corresponding products **8** and **9** with excellent dr of 99:1 for both (Table 2, entries 1 and 2). Addition of 1-(lithiomethyl)naphthalene to sulfonimine **6b** provided the corresponding product **10** in full conversion and 85:15 dr (entry 3). Addition of 2,6-dimethylphenyllithium to **6b** provided the corresponding product **11** in full conversion but significantly reduced 60:40 dr (entry 4). Next, addition of 4-(trifluoromethyl)phenyllithium and 1,3,5-trimethoxyphenyllithium to sulfonimine **6c** provided the corresponding products **12** and **13** in full conversion and 99:1 dr for both (entries 5 and 6). Addition of (4-methoxyphenyl)lithium and (2,4,6-triisopropylphenyl)lithium to the sulfonimine **6d** afforded the corresponding products **14** and **15** with 98:2 and 99:1 dr, respectively (entries 7 and 8). Heterocyclic 2-pyridyllithium produced **16** with 95:5 dr (entry 9) with sulfonimine **6e**, while polyaromatic 1-pyrenyllithium afforded **17** with 99:1 dr (entry 10). Addition of more challenging nucleophiles such as (3,3",5,5"-tetrakis(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-yl)lithium and 9-anthracyllithium to sulfonimine **6f** afforded the corresponding products **18** and **19** with poorer dr of 67:33 and 69:31 respectively (entries 11 and 12). The configurations of the major diastereomers for the addition products **11**, **13**, **18**, and **19** were established by X-ray crystallography at various stages on the way to the final bisoxazoline ligands (see *Establishment of Absolute Configuration of the Products by X-ray Crystallography*).

Simple aliphatic organometallic nucleophiles were neither problematic nor of interest for our chemoinformatic training set. Nevertheless, in preliminary experiments, *n*-BuLi added to **6a** and **6b** in 71% yield (99:1 dr) and 88% yield (86:14 dr), respectively. Finally, *t*-BuLi added to **6d** in 30% yield (99:1 dr); the major product arose from reduction.

**Deprotection to Form 1,2-Amino Alcohols.** Global deprotection under the action of 6 N HCl in methanol provided the 1,2-amino alcohols after basic workup in excellent yields. HCl in dioxane has been reported to affect global deprotection,<sup>98</sup> but HCl in methanol was used to simplify workup. Under these conditions, sulfonamides **8–14**, **16**, and **17** were cleanly deprotected to give corresponding 1,2-amino alcohols **22–28**, **30**, and **31** after basic workup in good to excellent yields (Table 3).

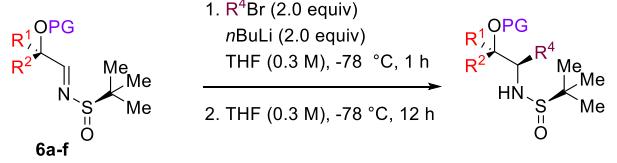
The global deprotection of compound **15** was difficult using the standard conditions. Instead, sulfonamide **15** was treated with 12 N HCl in methanol which removed *tert*-butylsulfinyl group. Then, the crude product obtained after basic workup was further heated at 60 °C with tetra-*N*-butylammonium fluoride (TBAF) to remove the TBS group, resulting in the isolation of the desired 1,2-amino alcohol **29** in excellent yield.

**Construction of the BOX Ligands.** The condensation of 1,2-amino alcohols **22–31** with dimethylmalonyl dichloride was carried out in the presence of triethylamine to afford the corresponding bisamides **34–43** in good to excellent yield (Table 4). Synthesis of another series of bisamides **44** and **45**, which contained different substituents on the methylene bridge, were also investigated. Bisamide **44** was prepared by condensation of the amino alcohol **32** and 2,2-bis(4-methoxybenzyl)malonyl dichloride **III** while the bisamide **45** was prepared by condensation of the amino alcohol **33** and 2,2-Bis(naphthalen-2-ylmethyl)malonyl dichloride **VI**, which in turn was synthesized from 2,2-dimethyl-1,3-dioxane-4,6-dione following the three-step sequence shown in Scheme 7.

The cyclization of the bisamides **34–37** in the presence of catalytic amounts of titanium(IV) isopropoxide afforded the corresponding bisoxazoline ligands **46–49** in good to excellent yields (Table 5). The cyclization afforded novel BOX ligands with *gem*-diphenyl groups at pro-C(5), with the biphenyl group (**46**) and 3,5-di-*tert*-butylphenyl group (**47**) at the pro-C(4) position. The same cyclization condition was effective with *gem*-dimethyl substitution at pro-C(5) with a benzyl derivative (**48**) and a sterically hindered aryl group (**49**) at the pro-C(4) position. For those bisamides with an oxygen-bearing stereogenic center, the cyclizations proceeded with retention of configuration. Thus, this method was effective with an isopropyl group at pro-C(5) and an electron-deficient aryl group (**50**) or a sterically hindered aryl group (**51**) at pro-C(4). Similarly, the BOX ligand with a phenyl group at pro-C(5) and an electron-rich aryl group (**52**) at pro-C(4) was prepared. The BOX ligands containing a heterocyclic group (**53**) and a polyaromatic group (**54**) at pro-C(4) with a methyl group at pro-C(5) were also synthesized in a similar fashion.

The invertive cyclization of bisamides **38**, **40**, and **41** was achieved by treating with methanesulfonyl chloride (5.0 equiv) and triethylamine (6.0 equiv) in dichloromethane at 0 °C (Table 6). This afforded the corresponding bismesylates, which were then heated at reflux in an aqueous ethanolic solution of sodium hydroxide (NaOH) (5.0 equiv) for 12 h to afford the corresponding bisoxazolines **55–57** in high yield. Bisamides **43–45** were also closed by cyclization using diethylaminosulfur trifluoride (DAST, 3.0 equiv) and potassium carbonate to afford the corresponding bisoxazolines **58–60** in high yield. Invertive cyclization for bisamide **39** by treatment with thionyl chloride was successful but was

Table 2. Substrate Scope for Diastereoselective 1,2-Additions



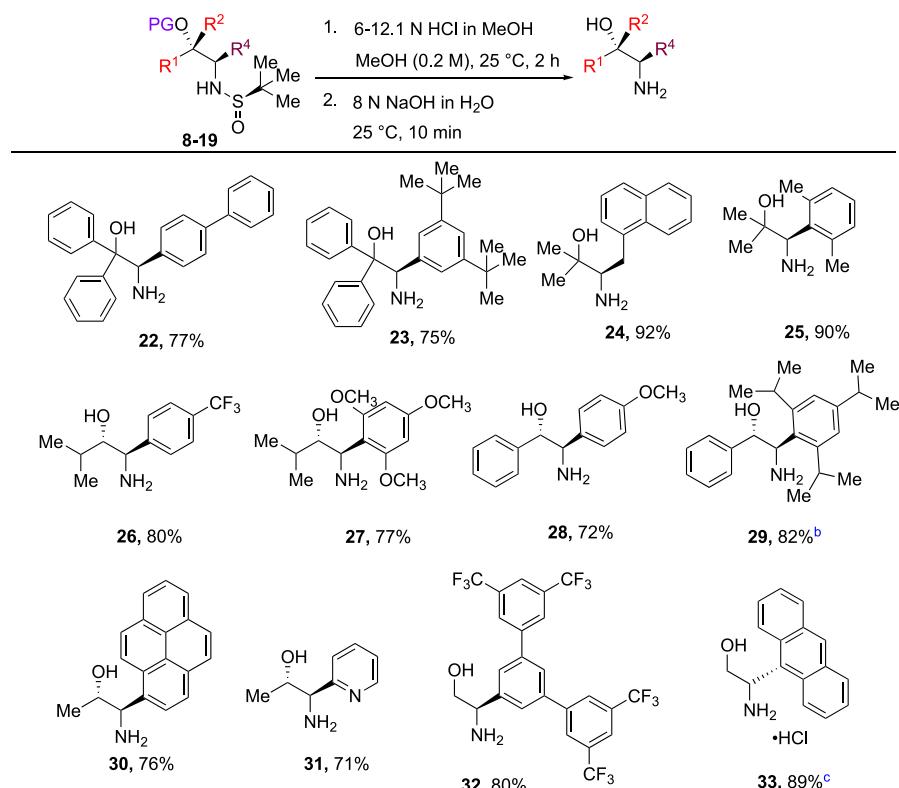
entry	sulfonimine	R <sup>1</sup>	R <sup>2</sup>	PG	nucleophile (R <sup>4</sup> )	product	yield (%) <sup>a</sup>	dr <sup>b</sup>
1	<b>6a</b>	Ph	Ph	PMB		<b>8</b>	88	99:1
2	<b>6a</b>	Ph	Ph	PMB		<b>9</b>	86	99:1
3	<b>6b</b>	Me	Me	PMB		<b>10</b>	80	85:15
4	<b>6b</b>	Me	Me	PMB		<b>11</b>	86	60:40
5	<b>6c</b>	i-Pr	H	TBS		<b>12</b>	80	99:1
6	<b>6c</b>	i-Pr	H	TBS		<b>13</b>	78	>99:1
7	<b>6d</b>	Ph	H	TBS		<b>14</b>	76	98:2
8	<b>6d</b>	Ph	H	TBS		<b>15</b>	75	99:1
9	<b>6e</b>	Me	H	TBS		<b>16</b>	89	95:5
10	<b>6e</b>	Me	H	TBS		<b>17</b>	80	99:1
11	<b>6f</b>	H	H	TBS		<b>18</b>	90	67:33
12	<b>6f</b>	H	H	TBS		<b>19</b>	90	69:31 <sup>c</sup>

<sup>a</sup>Isolated yield of analytically pure material. The absolute configuration at sulfur is (R). <sup>b</sup>Diastereomeric ratio was determined by <sup>1</sup>H NMR spectroscopy of the crude mixture. <sup>c</sup>Switch in configuration of the major isomer, *vide infra*.

nonreproducible on scale up. Other invertive cyclization methods for bisamide **39** did not produce the desired BOX ligand.

**Establishment of Absolute Configuration of the Products by X-ray Crystallography.** To establish the absolute configuration of **20**, **21**, **27**, and **37**, single crystals were grown for X-ray structure determination. The major (*R,R*) isomer always had the higher *R<sub>f</sub>* value on silica gel chromatography. However, the diastereomers of products **18** and **19** could not be separated by silica gel column

chromatography and thus were subjected to TBS deprotection using tetrabutylammonium fluoride. The deprotected products **20** and **21** were separable by silica gel chromatography. Owing to the low diastereoselectivity for the addition of terphenyllithium and anthracenyllithium, these hydroxy sulfonimines were analyzed by X-ray crystallography. The major diastereomer (**20**) formed from the addition of the terphenyl-derived organolithium reagent had the expected (*R,R*) configuration, whereas the major diastereomer (**21**) formed from addition of 9-anthracenyllithium had the (*R,S*)

Table 3. Substrate Scope for 1,2-Amino Alcohols<sup>a</sup>

<sup>a</sup>Isolated yield of analytically pure material. <sup>b</sup>Reaction run with 12.1 N HCl in MeOH for 12 h. After neutralization with 8 N NaOH, the crude was refluxed at 60 °C in the presence of TBAF for further 12 h. <sup>c</sup>Reaction run with 1 N HCl in Et<sub>2</sub>O (0.02 M) at 25 °C for 20 min.

configuration (Figure 2). In keeping with the established trend, **21** had the lower  $R_f$  value on silica gel chromatography. Similarly, the major diastereomers of adducts **11** and **13** were established be (*R,R*) by X-ray crystallographic analysis of amino alcohol **27** and bisamide **37**, respectively.<sup>99</sup> The configuration of the rest of the compounds were assumed by analogy.

## ■ DISCUSSION

**Diastereoselectivity of Addition to Sulfinimines.** Early on, Ellman developed a working model for the diastereoselectivity of the addition of nucleophiles to chiral *tert*-butylsulfinylimines.<sup>100</sup> The model posits that coordination of the organometallic reagent to the sulfinyl oxygen leads to a chairlike transition state with equatorial substituents, rationalizing the observed sense of diastereoselectivity (*ul* selectivity, *R*-sulfinimine leads to *Si*-face attack) (Figure 3, eq 1). In 2001, both Barrow<sup>88</sup> and Ellman<sup>87</sup> reported that the addition to  $\alpha$ -alkoxy aldimines led to a different diastereomer. To explain this reversal, Barrow and co-workers postulated the formation of a chairlike transition state wherein the  $\alpha$ -alkoxy group coordinates to the organometallic nucleophile, thus presenting the *Re* face for attack (*lk* selectivity) (Figure 3, eq 2). Alternatively, Barrow and co-workers also proposed an open transition state analogous to that suggested by Davis<sup>101,102</sup> for addition to  $\alpha$ -imino esters in which coordination of the sulfinyl oxygen by a Lewis acid (e.g., a magnesium cation) interrupts binding of the nucleophile and shields the *Si* face of the imine from nucleophile attack, resulting in the observed selectivity (Figure 3, eq 3).

In subsequent investigations, Ellman reported the addition of Grignard reagents to *N*-*tert*-butylsulfinylimines derived from O-protected *S*-lactaldehydes.<sup>103</sup> Addition of aryl- and alkyl-Grignard reagents afforded the corresponding 1,2-disubstituted amino alcohols in good yields and diastereoselectivities, though the *dr* was weakly dependent upon the O-protecting group (Figure 4). The major isomer was obtained in good yield and high diastereoselectivity with either the *tert*-butyldimethylsilyl or benzyl ether. The bulkier *tert*-butyldiphenylsilyl protecting group also provided the major isomer in good yield but with slightly lower diastereoselectivity.

Given the dependence of diastereoselectivity on various factors, including solvent and substrate structure, extrapolating these trends to reactions with organolithium reagents in pure THF is tenuous. Nevertheless, several studies on record do report the use of a wide variety of organolithium nucleophiles (aryl- or alkylolithium) for addition into *N*-sulfinyl aldimines.<sup>87,88,100</sup> Some reports suggest that aryl-lithium reagents are superior to their Grignard counterparts and afford a broader scope, improved yields, and higher diastereoselectivities.<sup>104,105</sup> Despite having limited substrate scope with respect to the aryllithium nucleophile addition to ketimines bearing coordinating  $\alpha$ -substituents,<sup>87,106</sup>  $\alpha$ -stereocenters<sup>106</sup> have also been reported. Although direct comparisons are not possible, the general sense of diastereoselectivity persists, namely that (*R*)-sulfinimines with (*S*)- $\alpha$ -oxy aldimines represent the matched auxiliary case, leading to selective addition to the *Re* face of the imine to afford the (*R*)-nitrogen-bearing center. Ellman rationalizes this behavior as follows:<sup>103</sup> “The anti-selectivity observed for

Table 4. Preparation of Bisamides

1,2-amino alcohol	bisamide	yield (%) <sup>a</sup>	1,2-amino alcohol	bisamide	yield (%) <sup>a</sup>
22	34	81	28	40	70
23	35	85	29	41	80
24	36	80	30	42	65 <sup>b</sup>
25	37	80	31	43	87 <sup>b</sup>
26	38	83	32	44	78
27	39	81	33	45	82

<sup>a</sup>Isolated yield of analytically pure bisamide. <sup>b</sup>Bisamide prepared using 2.2 equiv of 1,2-amino alcohols.

the addition of nucleophiles is consistent with both Felkin–Anh<sup>107–109</sup> and Cornforth<sup>110,111</sup> models, as well as the inherent selectivity previously observed for nucleophilic additions to *N*-sulfinyl *R*-silyloxyacetaldimines.<sup>87</sup> Our results support that analysis and, as illustrated in Figure 5, constitute modifications of the Davis open transition-state model.

This trend was observed in the majority of the cases reported herein. The structures of both the nucleophile and the electrophile are influential in determining the diastereoselectivity for the addition reaction. Two limiting cases can be identified. In the first case, composed of the electrophiles derived from lactic acid, mandelic acid, and valine-containing  $\alpha$  stereocenters, the matched diastereocontrol leads to

Scheme 7. Preparation of Malonyl Dichlorides with Various Bridging Substituents

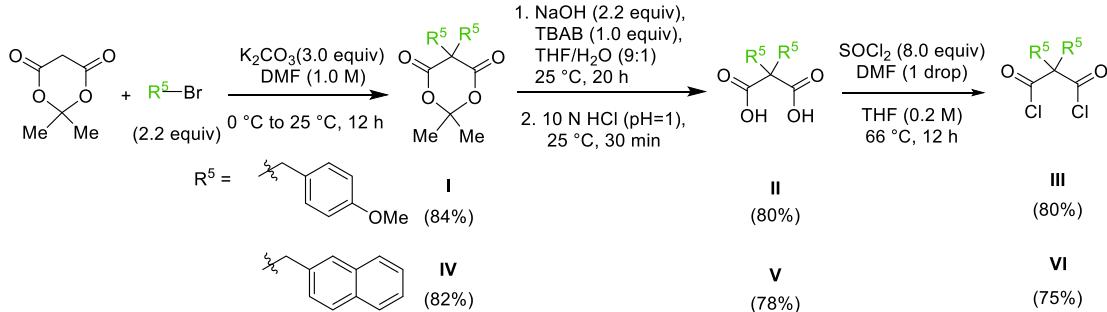


Table 5. Preparation of Bisoxazolines by Retentive Ring Closure

The table details the conversion of bisamides (34, 35, 36, 37) to bisoxazolines (46, 47, 48, 49) and the synthesis of various bisoxazoline ligands (38–54) using  $\text{Ti}(\text{O}i\text{-Pr})_4$  (20 mol %) in xylene (0.04 M) at  $160^\circ\text{C}$  for 12 h.

bisamide	bisoxazoline	yield (%) <sup>a</sup>	bisamide	bisoxazoline	yield (%) <sup>a</sup>
34	46	85	38	50	77
35	47	70	39	51	80
36	48	77	41	52	82
37	49	78	42	53	43
			43	54	58

<sup>a</sup>Isolated yield of analytically pure bisoxazoline ligand.

excellent selectivity in all cases independent of the bulk of the nucleophile (Table 2, entries 5–10). In the second case, composed of the geminally disubstituted electrophiles **6a**, **6b**, and **6f**, the steric bulk of the nucleophile is an important factor in the diastereoselectivity of addition. Considering reactions with diphenyl-substituted substrate **6a**, nonhindered aryl nucleophiles furnished the products in excellent selectivity. For the less sterically demanding dimethyl-substituted substrate **6b**, addition of the less hindered 1-(lithiomethyl)naphthalene afforded diminished selectivity

(85:15) whereas addition of the hindered 2,6-dimethylphenyllithium was much poorer (60:40). Without the additional  $\alpha$ -stereocenters, the stereochemical course of the reaction was entirely dependent on the control exerted by the auxiliary.

The most dramatic illustrations of that dependence were observed with the unsubstituted substrate **6f** for which the additions of bulky nucleophiles derived from anthracene and a terphenyl led to poor selectivities and in fact an inversion of the major diastereomer in the 9-anthrancenyllithium addition (Table 2, entries 11 and 12). It is very difficult to speculate

Table 6. Preparation of Bisoxazolines by Invertive Ring Closure

bisamide	bisoxazoline	yield (%) <sup>a</sup>	bisamide	bisoxazoline	yield (%) <sup>a</sup>
38	55	76 <sup>b</sup>	43	58	67 <sup>c</sup>
40	56	85 <sup>b</sup>	44	Arly: 3,5-CF <sub>3</sub> Ph	87 <sup>c</sup>
41	57	75 <sup>b</sup>	45	60	90 <sup>c</sup>

<sup>a</sup>Isolated yield of analytically pure bisoxazoline ligand. <sup>b</sup>Conditions: triethylamine and MsCl in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C for 1.5 h followed by heating with NaOH in ethanol. <sup>c</sup>Conditions: DAST in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C for 1.5 h followed by treatment with K<sub>2</sub>CO<sub>3</sub>.

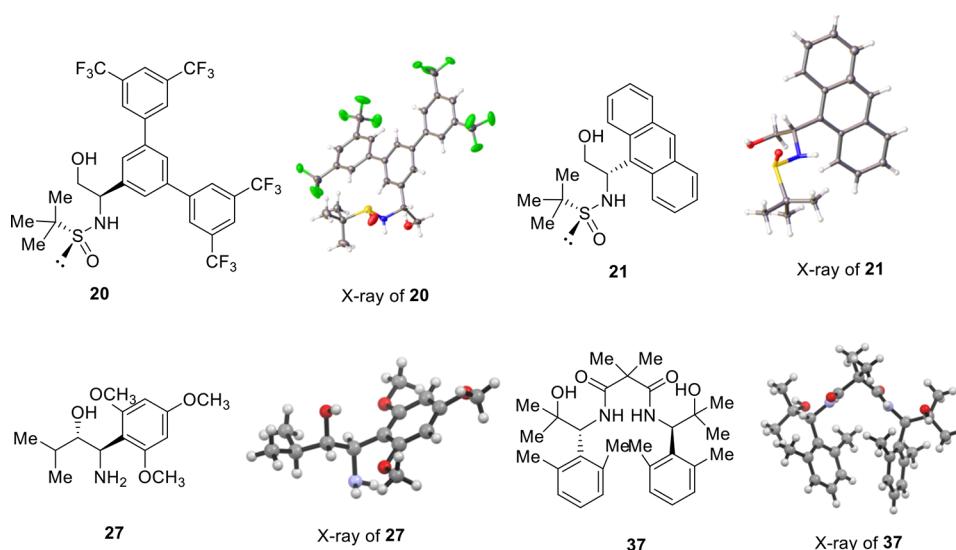


Figure 2. X-ray crystal structures of compounds 20, 21, 27, and 37.

about the origin of the low selectivities given uncertainty around the relevant transition state models, but in the Davis model (Figure 3, eq 3) it is possible that a sufficiently bulky nucleophile may begin to experience repulsive interactions with the *tert*-butyl group in the *Re* face addition (Figure 6).

## CONCLUSION

In summary, a general procedure for the asymmetric synthesis of highly substituted 1,2-amino alcohols has been described that affords high yields and diastereoselectivities from *tert*-butylsulfurfinimines as the common intermediates. Syntheses of

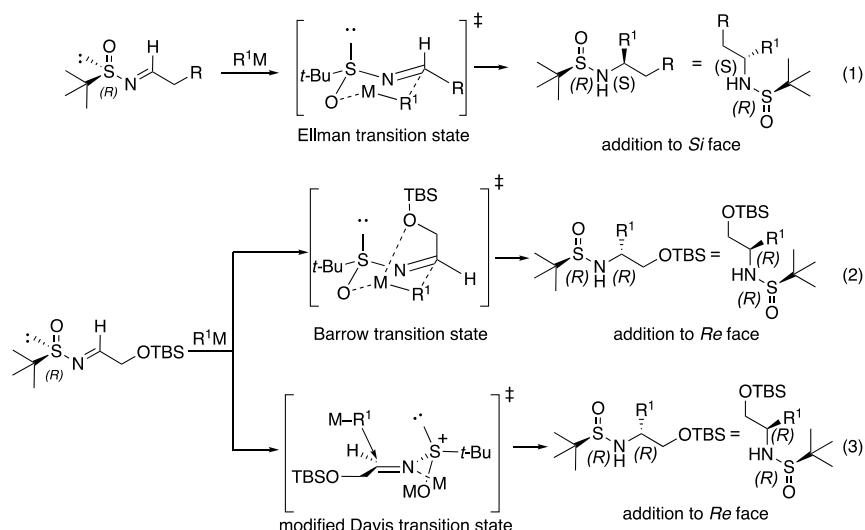


Figure 3. Transition-state hypothesis rationalizing the reversal of diastereoselectivity in the addition to  $\alpha$ -alkoxy imines.

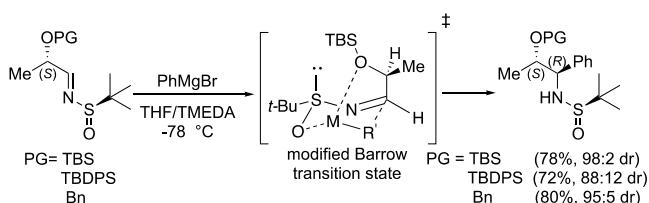


Figure 4. Influence of protecting group on diastereoselectivity and yield.

novel polysubstituted BOX ligands were achieved in high yields using these 1,2-amino alcohols. The addition of structurally diverse organolithium reagents to imines follows a modified Davis model. The steric properties of both nucleophile and electrophile play vital roles for the determination of diastereoselectivity of the addition. This method enables the expansion of diversity for other chiral auxiliaries and ligand classes such as oxazaborolidines, oxazolidinones, Py-BOX and spiro-BOX ligands. The utility of these interesting novel chiral BOX ligands in asymmetric, metal-catalyzed reactions will be the subject of future reports.

## EXPERIMENTAL SECTION

**General Experimental Procedures.** All reactions were performed in oven- ( $150\text{ }^{\circ}\text{C}$ ) and/or flame-dried glassware under an atmosphere of dry nitrogen, unless otherwise indicated. Room temperature (rt) was approximately  $23\text{ }^{\circ}\text{C}$ . “Brine” refers to a saturated solution of sodium chloride in  $\text{H}_2\text{O}$ .

**NMR Spectroscopy.**  $^1\text{H}$  and  $^{13}\text{C}[^1\text{H}]$  NMR spectra were recorded Bruker 500 (500 MHz,  $^1\text{H}$ ; 126 MHz,  $^{13}\text{C}$ ) MHz spectrometers. Acquisition times were 4.096 s for  $^1\text{H}$  NMR and 1.024 s for  $^{13}\text{C}$  NMR. Spectra are referenced to residual chloroform ( $\delta = 7.26\text{ ppm}$ ,  $^1\text{H}$ ; 77.16 ppm,  $^{13}\text{C}$ ). Chemical shifts are reported in parts per million (ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet) and m (multiplet). Coupling constants,  $J$ , are reported in hertz. Integration is provided, and assignments are indicated.  $^1\text{H}$  and  $^{13}\text{C}$  assignments are corroborated through 2-D NMR experiments (COSY, HSQC, HMBC).

**Infrared Spectroscopy.** Infrared (IR) spectra were recorded on a PerkinElmer FT-IRATR system as thin films. Peaks are reported in  $\text{cm}^{-1}$  with indicated relative intensities: s (strong, 0–33% T); m (medium, 34–66% T), w (weak, 67–100% T), and br (broad).

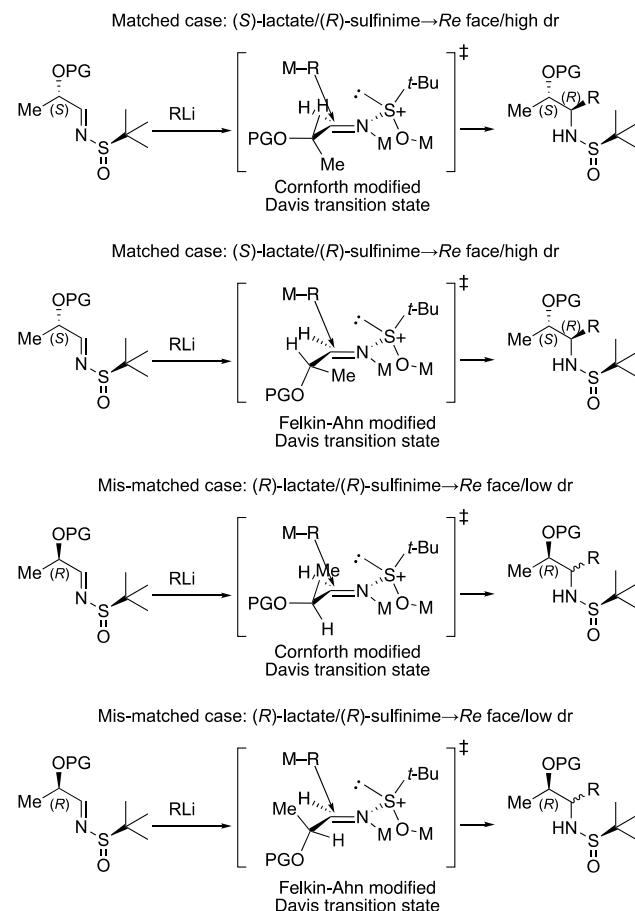
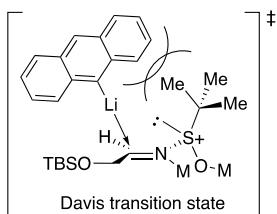


Figure 5. Modified Davis models for matched and mismatched additions.

**Mass Spectrometry.** Mass spectrometry (MS) was performed by the University of Illinois Mass Spectrometry Laboratory. Electron Impact ( $\text{EI}^+$ ) spectra were performed at 70 eV using methane as the carrier gas, with either a double-focusing sector field (DFSF) or time-of flight (TOF) mass analyzer. Chemical ionization ( $\text{CI}^+$ ) spectra were performed with methane reagent gas, with either a double-focusing sector field (DFSF) or time-of-flight (TOF) mass analyzer. Electrospray ionization ( $\text{ESI}^+$ ) spectra were performed



**Figure 6.** Origin of decreased selectivity in addition to **6f** with bulky nucleophiles.

using a time-of-flight (TOF) mass analyzer. Data are reported in the form of *m/z* (intensity relative to the base peak = 100).

**Melting Points.** Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and Büchi melting point B-540 apparatus in vacuum-sealed capillary tubes and are corrected.

**Elemental Analysis.** Elemental analysis was performed by the University of Illinois Microanalysis Laboratory. Reported data is the average of at least two runs.

**Distillation.** Bulk-to-bulk distillation was performed on a Büchi Kugelrohr, with boiling points (bp) corresponding to uncorrected air-bath temperatures (ABT). A vacuum of  $10^{-5}$  mm Hg was achieved using a BOC Edwards SI100 diffusion pump.

**Chromatography.** Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 plates. Visualization was accomplished with UV light and/or potassium permanganate ( $\text{KMnO}_4$ ) solution. Retention factor ( $R_f$ ) values reported were measured using a  $10 \times 2$  cm TLC plate in a developing chamber containing the solvent system (10 mL) described. Flash column chromatography was performed using Silicycle SiliaFlashP60 (40–63  $\mu\text{m}$  particle size, 230–400 mesh) ( $\text{SiO}_2$ ). Unless otherwise specified, “silica” refers to P60 grade silica gel. Automatic flash chromatography was performed by ISCO (50  $\mu\text{m}$  particle size).

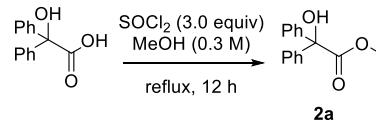
**Solvents.** Reaction solvents tetrahydrofuran (THF) (Fisher, HPLC grade), ether ( $\text{Et}_2\text{O}$ ) (Fisher, BHT stabilized ACS grade), and  $\text{CH}_2\text{Cl}_2$  ( $\text{CH}_2\text{Cl}_2$ ) (Fisher, unstabilized HPLC grade) were dried by percolation through two columns packed with neutral alumina under a positive pressure of argon. Reaction solvent toluene (ACS grade) was dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant (supported copper catalyst for scavenging oxygen) under a positive pressure of argon. Reaction solvent dimethylformamide (DMF) (Fischer, ACS grade) was dried by percolation through two columns of activated molecular sieves. Reaction solvent ethanol (absolute, Decon Laboratories) was used as received. Solvents for filtration, transfers, chromatography, and recrystallization  $\text{CH}_2\text{Cl}_2$  ( $\text{CH}_2\text{Cl}_2$ ) (amylene stabilized, ACS grade), ether ( $\text{Et}_2\text{O}$ ) (BHT stabilized, ACS grade), ethyl acetate ( $\text{EtOAc}$ ) (ACS grade), hexane (HPLC grade), ethanol ( $\text{EtOH}$ ) (ACS grade), isopropyl alcohol (IPA) (ACS grade), methanol ( $\text{MeOH}$ ) (ACS grade), pentane (ACS grade), xylenes (ACS grade), *n*-hexane (95%) (EMD Millipore), and petroleum ether (35–60 °C, ACS grade).

**Chemicals.** Sodium hydride (Alfa Aesar, 57–63% oil dispersion) was washed with hexane and dried and used. Benzilic acid (Aldrich, 99%), methyl 2-hydroxyisobutyrate (Chem Impex, 99.26%), *n*-butyllithium (1.6 M in hexanes, Aldrich), L-valine (Oakwood, 99%), L-(+)-mandelic acid (Oakwood, 99%), (−)-ethyl L-lactate (Oakwood, 99%), methyl 2-hydroxy acetate (Oakwood, 99%), (R)-(+)-*tert*-butylsulfonamide (Chem Impex, 99.6%), thionyl chloride (TCI, 98%), 4-methoxybenzyl chloride (AK Scientific, 95%), lithium aluminum hydride (Alfa Aesar, 95%), dimethyl sulfoxide (Macro fine chemical, ACS grade), oxalyl chloride (Aldrich, 99%), triethylamine (Acros, 99%), titanium ethoxide (Oakwood, 95%), titanium isopropoxide (Aldrich, 97%), sodium nitrite (Aldrich, 97%), diisobutylaluminum hydride (1.0 M in hexane, Acros), sulfuric acid (Macron Fine Chemical, concentrated), hydrochloric acid (Macron Fine Chemical, concentrated), sodium hydroxide (Fisher Chemical, pellets), tetra-*n*-butylammonium fluoride (1.0 M in THF,

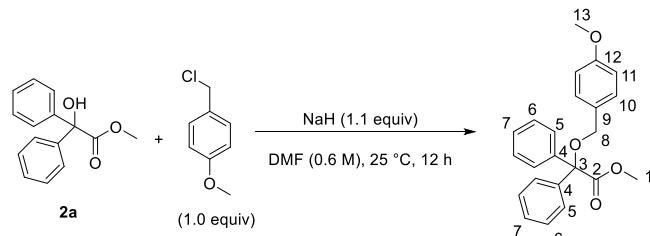
Aldrich), 4-bromobiphenyl (Aldrich, 98%), 1-Bromo-3,5-ditert-butylbenzene (Oakwood, 99%), 2,6-dimethylbromobenzene (Oakwood, 98%), 1-(bromomethyl)naphthalene (Chem Impex, 99.4%), 4-bromobenzotrifluoride (Oakwood, 99%), 1,3,5-trimethoxybenzene (Aldrich, 99%), 4-bromoanisole (Oakwood, 99%), 1-bromo-2,4,6-triisopropylbenzene (Oakwood, 97%), 1-bromopyridine (Aldrich, 99%), 1-bromopyrene (AK Scientific, 98%), 2-(bromomethyl)-naphthalene (Oakwood, 96%), Meldrum’s acid (Chem Impex, 99.5%), potassium carbonate (96%), *tert*-butyldimethylchlorosilane (Oakwood, 99%), diethylaminosulfur trifluoride (Oakwood, 95%), methanesulfonyl chloride (Aldrich, 99.7%), imidazole (Aldrich, 99.5%), dimethylmalonic acid (Oakwood, 99%), and tetra-*n*-butylammonium bromide (Aldrich, 99%) were used as received.

**Literature Preparations.** 2,2-Dimethylmalonyl dichloride was prepared from 2,2-dimethylmalonic acid and the characterization data matched those previously reported.<sup>112</sup> 3,5-Bis(3,5-bis-CF<sub>3</sub>-phenyl)iodobenzene was prepared by literature method, and the characterization data matched those previously reported.<sup>113</sup>

**Experimental Procedures.** *Synthesis of Bisoxazoline Ligands with a Geminal Diphenyl Substituent at the C(5)-Position.*

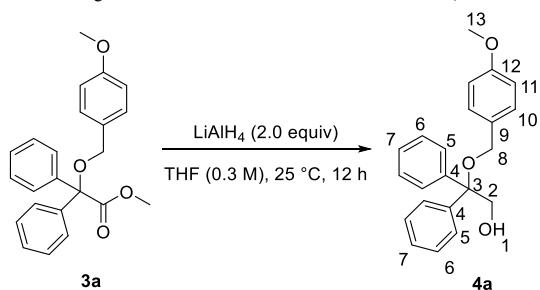


**Preparation of Methyl 2-Hydroxy-2,2-diphenylacetate (2a).** A 250 mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with benzilic acid (11.41 g, 50.0 mmol) and MeOH (distilled, 120 mL) under nitrogen. The solution was cooled in an ice bath for 10 min, and  $\text{SOCl}_2$  (17.84 g, 10.94 mL, 150.0 mmol, 3.0 equiv) was added dropwise by syringe over 5 min at 0 °C. The mixture was heated to reflux using a condenser in 75 °C oil bath for 12 h. After the solution was cooled to 25 °C, the volatile components are removed by rotary evaporation (30 °C, 50 mbar). The resulting residue was diluted with ethyl acetate (200 mL), and satd aq  $\text{NaHCO}_3$  (200 mL) was added slowly because of the evolution of gas. The mixture was transferred to a 500 mL separatory funnel, and the organic layer was removed. The aqueous layer was extracted with ethyl acetate (3 × 100 mL), and the organic layers were combined, washed with brine (1 × 100 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by recrystallization with hot hexane (300 mL) to afford (11.00 g, 91%) **2a** as a white solid. The spectroscopic data for **2a** matched the literature values.<sup>114</sup> Data for **2a**: <sup>1</sup>H NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48–7.46 (m, 4H), 7.40–7.34 (m, 6H), 4.29 (s, 1H), 3.87 (s, 3H).

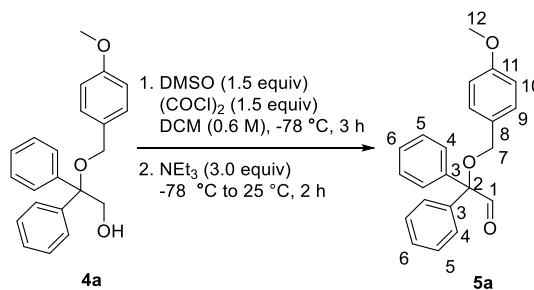


**Preparation of Methyl 2-((4-Methoxybenzyl)oxy)-2,2-diphenylacetate (3a).** A 250 mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **2a** (11.00 g, 45.5 mmol), NaH (1.20 g, 50.0 mmol, 1.1 equiv), and DMF (75 mL) under nitrogen. The solution was stirred at 25 °C for 10 min, and  $\text{PMBCl}$  (7.12 g, 6.17 mL, 45.5 mmol, 1.0 equiv) was added dropwise by syringe over 5 min. The mixture was stirred at 25 °C for 12 h. The resulting mixture was diluted in ethyl acetate (200 mL), transferred to 500 mL separatory funnel, washed with water (3 × 100 mL) and brine (1 × 100 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The resulting residue was recrystallized from hot hexane (200 mL) to afford **3a** as a white solid (14.00 g, 84% yield).

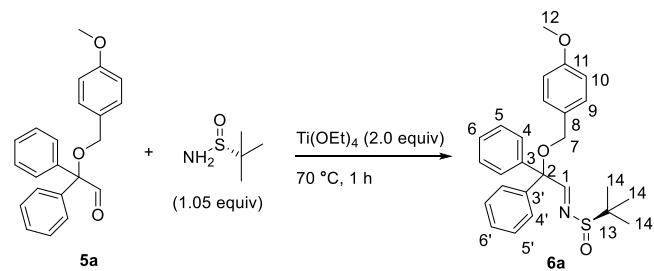
Data for **3a**: mp 106–108 °C (hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 (d,  $J$  = 6.5 Hz, 4H, HC(5)), 7.34 (m, 6H, HC(6,7)), 7.30 (d,  $J$  = 8.1 Hz, 2H, HC(10)), 6.88 (d,  $J$  = 8.5 Hz, 2H, HC(11)), 4.29 (s, 2H, HC(8)), 3.81 (s, 6H, HC(1,13));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  172.5 (C(2)), 159.1 (C(12)), 141.1 (C(4)), 130.9 (C(9)), 129.3 (C(10)), 128.7 (C(5)), 128.2 (C(7)), 128.1 (C(6)), 113.8 (C(11)), 87.0 (C(3)), 67.7 (C(8)), 55.4 (C(13)), 52.7 (C(1)); IR (neat) 2949 (w), 1733 (s), 1586 (w), 1513 (m), 1490 (w), 1462 (w), 1445 (m), 1384 (w), 1304 (w), 1238 (s), 1197 (m), 1179 (s), 1111 (w), 1094 (m), 1069 (m), 1030 (m), 1021 (m), 1011 (s), 943 (w), 902 (w), 854 (w), 823 (m), 808 (m), 767 (m), 752 (m), 724 (m), 696 (s), 675 (m), 641 (w), 630 (m), 612 (m), 549 (m), 517 (m), 503 (w), 483 (w); HRMS (ESI)  $m/z$  (M + Na) $^+$  calcd for  $\text{C}_{23}\text{H}_{22}\text{O}_4\text{Na}$  385.1416, found 385.1416; TLC  $R_f$  0.48 (silica gel, hexanes/EtOAc, 8:2, UV,  $\text{KMnO}_4$ ).



**Preparation of 2-((4-Methoxybenzyl)oxy)-2,2-diphenylethan-1-ol (4a).** A 250 mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **3a** (12.30 g, 34.0 mmol) and THF (120 mL, SDS) under nitrogen. The solution was cooled to 0 °C in an ice bath, and  $\text{LiAlH}_4$  (2.58 g, 68.0 mmol, 2.0 equiv) was added portionwise under nitrogen flow over 5 min. The slurry was slowly warmed to 25 °C and was stirred for 12 h. Then the reaction mixture was cooled in an ice bath and was quenched by the addition of 2.7 mL of water, 2.7 mL of 15% aq NaOH solution, and 8.2 mL of water with vigorous stirring. The mixture was stirred for 10 min and then was filtered through Buchner funnel (90 mm diameter) to a filter flask (250 mL) to remove the precipitates, and the filter cake was washed with diethyl ether (2 × 75 mL). The filtrate was transferred to a 500 mL separatory funnel, diluted with ethyl acetate (300 mL), washed with satd aq  $\text{Na}_2\text{CO}_3$  (1 × 100 mL), and brine (1 × 100 mL), dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by recrystallization from hot hexane (250 mL) to afford (10.00 g, 88%) **4a** as a white solid. Data for **4a**: mp 103–105 °C (hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 (d,  $J$  = 7.2 Hz, 4H, HC(5)), 7.34 (m, 8H, HC(6,7,10)), 6.94 (d,  $J$  = 8.2 Hz, 2H, HC(11)), 4.43 (d,  $J$  = 6.4 Hz, 2H, HC(2)), 4.32 (s, 2H, HC(8)), 3.84 (s, 3H, HC(13)), 1.90 (t,  $J$  = 6.3 Hz, 1H, HC(1));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1 (C(12)), 142.6 (C(4)), 130.8 (C(9)), 129.0 (C(10)), 128.3 (C(6)), 127.5 (C(7)), 127.3 (C(5)), 113.9 (C(11)), 83.1 (C(3)), 65.9 (C(2)), 64.9 (C(8)), 55.3 (C(13)); IR (neat) 3479 (w), 3023 (w), 2995 (w), 2933 (w), 2876 (w), 2835 (w), 1611 (m), 1586 (w), 1513 (m), 1490 (w), 1463 (w), 1447 (m), 1421 (w), 1384 (w), 1324 (w), 1305 (w), 1249 (s), 1231 (m), 1206 (m), 1175 (m), 1101 (m), 1069 (m), 1035 (m), 1004 (s), 987 (m), 947 (m), 935 (m), 907 (m), 869 (m), 855 (w), 826 (m), 811 (m), 784 (w), 752 (s), 729 (s), 720 (s), 713 (m), 697 (s), 649 (s), 623 (m), 572 (m), 531 (m), 509 (m), 465 (w); HRMS (ESI)  $m/z$  (M + Na) $^+$  calcd for  $\text{C}_{22}\text{H}_{22}\text{O}_3\text{Na}$  357.1475, found 357.1467; TLC  $R_f$  0.27 (silica gel, hexanes/EtOAc, 8:2, UV,  $\text{KMnO}_4$ ).

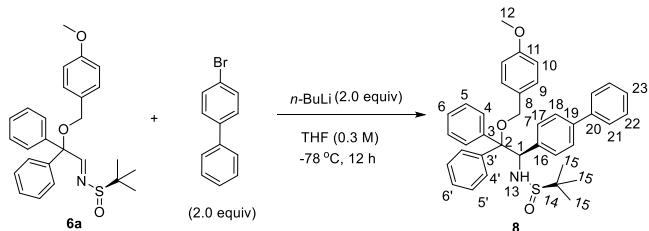


**Preparation of 2-((4-Methoxybenzyl)oxy)-2,2-diphenylacetalddehyde (5a).** A 200 mL, three-necked round-bottomed flask equipped with nitrogen inlet, an egg-shaped stir bar (50.8 × 19.1 mm), an internal temperature probe, and two rubber septa was charged with oxalyl chloride (5.70 g, 3.86 mL 45.0 mmol, 1.5 equiv) and  $\text{CH}_2\text{Cl}_2$  (40 mL, SDS) under nitrogen. The solution was cooled to  $-78$  °C using a cryocooler in an *i*-PrOH bath, and DMSO (3.50 g, 3.19 mL, 45.0 mmol, 1.5 equiv) was added dropwise to maintain internal temperature below  $-70$  °C. The solution was stirred at  $-78$  °C for 10 min, and the solution of **4a** (10.00 g, 30.0 mmol, solution in 10 mL of  $\text{CH}_2\text{Cl}_2$ ) was added dropwise to maintain the internal temperature below  $-70$  °C. The resulting mixture was stirred at  $-78$  °C for 3 h, and triethylamine (freshly distilled, 9.10 g, 12.50 mL, 90.0 mmol, 3.0 equiv) was added dropwise to maintain the internal temperature below  $-70$  °C and was stirred for 2 h. The mixture was slowly warmed to 0 °C, and 30 mL of water was added. The two phases were transferred to a 250 mL separatory funnel, and the organic layer was separated. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 × 100 mL), and the organic layers were combined, washed with water (1 × 100 mL) and brine (1 × 100 mL), dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by recrystallization with hot hexane (250 mL) to afford (8.40 g, 84%) **5a** as a white solid. Data for **5a**: mp 71–73 °C (hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.96 (s, 1H, HC(1)), 7.53 (m, 4H, HC(4)), 7.44–7.35 (m, 8H, HC(5,6,9)), 6.94 (d,  $J$  = 8.5 Hz, 2H, HC(10)), 4.36 (s, 2H, HC(7)), 3.83 (s, 3H, HC(12));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  198.4 (C(1)), 159.2 (C(11)), 138.0 (C(3)), 130.3 (C(8)), 129.2 (C(9)), 128.7 (C(6)), 128.6 (C(4)), 128.4 (C(5)), 113.8 (C(10)), 88.9 (C(2)), 67.1 (C(7)), 55.3 (C(12)); IR (neat) 2909 (w), 2800 (w), 1728 (m), 1587 (w), 1515 (m), 1492 (w), 1461 (w), 1445 (m), 1380 (w), 1304 (w), 1238 (s), 1175 (m), 1115 (w), 1091 (m), 1066 (s), 1032 (m), 1017 (m), 998 (m), 917 (w), 834 (m), 819 (m), 773 (m), 761 (m), 752 (m), 711 (m), 696 (s), 671 (m), 635 (w), 628 (w), 575 (s), 546 (m), 516 (m), 488 (m), 752 (s), 729 (s), 720 (s), 713 (m), 697 (s), 649 (s), 623 (m), 572 (m), 531 (m), 509 (m), 465 (w); HRMS (ESI)  $m/z$  (M + Na) $^+$  calcd for  $\text{C}_{22}\text{H}_{20}\text{O}_3$  355.1300, found 355.1310; TLC  $R_f$  0.50 (silica gel, hexanes/EtOAc, 8:2, UV,  $\text{KMnO}_4$ ).



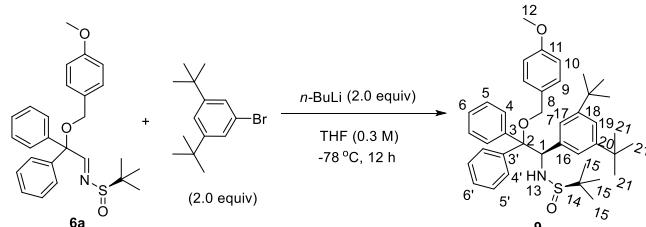
**Preparation of (R,E)-N-(2-((4-Methoxybenzyl)oxy)-2,2-diphenylacetamido)-2-methylpropane-2-sulfonamide (6a).** A 100 mL, one-necked Schlenk flask with an egg-shaped stir bar (38.1 × 15.9 mm) was charged with **5a** (8.40 g, 25.3 mmol), (R)-2-methylpropane-2-sulfonamide (3.21 g, 26.5 mmol, 1.05 equiv), and titanium(IV) ethoxide (11.54 g, 10.6 mL, 50.6 mmol, 2.0 equiv) under nitrogen. The mixture was stirred in 70 °C oil bath for 60 min and then was diluted with ethyl acetate (50 mL). The resulting solution was poured into a 200 mL Erlenmeyer flask with an egg-shaped stir bar

( $50.8 \times 19.1$  mm) and brine (5 mL), and the flask was rinsed with ethyl acetate ( $2 \times 25$  mL) to help the transfer. The suspension was stirred at  $25^\circ\text{C}$  for 10 min and then was filtered through fritted funnel (7.5 mm diameter) containing Celite. The Celite cake was washed with ethyl acetate ( $2 \times 100$  mL). The combined filtrates were transferred to a 250 mL separatory funnel, washed with water ( $1 \times 100$  mL) and brine ( $1 \times 100$  mL), dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation ( $30^\circ\text{C}$ , 50 mbar). The crude product was purified by column chromatography (silica, 4 cm  $\varnothing \times 12$  cm column) eluting with hexanes/diethyl ether, 7:3 to afford **6a** (9.40 g, 85%) as a white solid. Data for **6a**: mp 91–93  $^\circ\text{C}$  (hexanes/Et<sub>2</sub>O); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.58 (s, 1H, HC(1)), 7.46 (m, 4H, HC(4, 4')), 7.38–7.29 (m, 8H, HC-(S,5',6',9)), 6.88 (d,  $J = 8.6$  Hz, 2H, HC(10)), 4.36 (q,  $J = 10.6$  Hz, 2H, HC(7)), 3.81 (s, 3H, HC(12)), 1.16 (s, 9H, HC(14)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  169.0 (C(1)), 159.1 (C(11)), 141.3 (C(3)), 141.0 (C(3')), 130.8 (C(9)), 129.1 (C(8)), 128.4 (C(5)), 128.4 (C(5')), 128.4 (C(6)), 128.3 (C(6')), 128.2 (C(4)), 128.1 (C(4')), 113.7 (C(10)), 86.4 (C(2)), 66.7 (C(7)), 57.7 (C(13)), 55.3 (C(12)), 22.6 (C(14)); IR (neat) 2955 (w), 1615 (m), 1514 (m), 1489 (w), 1447 (m), 1379 (w), 1365 (w), 1304 (w), 1241 (m), 1172 (m), 1127 (m), 1084 (s), 1072 (s), 1030 (m), 924 (w), 831 (m), 817 (s), 760 (m), 749 (m), 697 (s), 636 (w), 583 (w), 542 (w), 514 (s), 455 (m); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>26</sub>H<sub>30</sub>NO<sub>3</sub>S 436.1945, found 436.1946; TLC  $R_f$  0.27 (silica gel, hexanes/EtOAc, 8:2, UV, KMnO<sub>4</sub>).

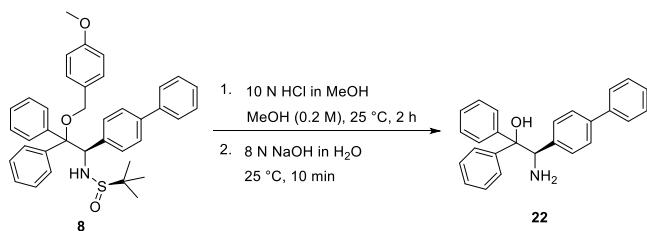


**Preparation of (R)-N-((R)-1-[(1,1'-Biphenyl)-4-yl]-2-((4-methoxybenzyl)oxy)-2,2-diphenylethyl)-2-methylpropane-2-sulfonamide (8).** A 100 mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1  $\times$  15.9 mm) was charged with 4-bromo-1,1'-biphenyl (4.66 g, 20.0 mmol, 2.0 equiv) and THF (25 mL) under nitrogen. The solution was cooled to  $-78^\circ\text{C}$  using a cryocooler in an *i*-PrOH bath, and *n*-butyllithium (1.28 g, 13.0 mL, 1.6 M in hexane, 20.0 mmol, 2.0 equiv) was added dropwise by syringe. The resulting solution was stirred at  $-78^\circ\text{C}$  using a cryocooler in an *i*-PrOH bath for 1 h. Then another 50 mL Schlenk flask containing an egg-shaped stir bar (19.1  $\times$  9.5 mm) was charged with **6a** (4.35 g, 10.0 mmol) and THF (25 mL) under nitrogen and was cooled to  $-78^\circ\text{C}$  using a cryocooler in an *i*-PrOH bath. The *N*-sulfinyl imine solution was transferred to the organolithium solution using a syringe dropwise over 5 min. The resulting mixture was stirred at  $-78^\circ\text{C}$  using a cryocooler in an *i*-PrOH bath for 12 h. The reaction was quenched by the addition of satd aq NH<sub>4</sub>Cl solution (50 mL) at  $-78^\circ\text{C}$  and slowly warmed to  $25^\circ\text{C}$ . The mixture was transferred to a 250 mL separatory funnel. The organic layer was removed, the aqueous layer was extracted with ethyl acetate (3  $\times$  50 mL), and the organic layers were combined, washed with brine (1  $\times$  100 mL), dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation ( $30^\circ\text{C}$ , 50 mbar). The dr of the crude product was 99:1 by <sup>1</sup>H NMR analysis. The crude product was purified by column chromatography (silica, 4 cm  $\varnothing \times 12$  cm column) eluting with hexanes/EtOAc, 1:1 to afford **8** (5.20 g, 88%) as a white solid. Data for **8**: mp 87–89  $^\circ\text{C}$  (hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.66–7.61 (m, 2H, HC(21)), 7.50–7.35 (m, 15H, HC(4,4',5,5',6,18,22,23)), 7.29 (d,  $J = 8.6$  Hz, 2H, HC(9)), 6.97 (d,  $J = 7.9$  Hz, 2H, HC(17)), 6.94 (d,  $J = 8.6$  Hz, 2H, HC(10)), 5.79 (s, 1H, HC(1)), 4.53 (s, 1H, HN(13)), 4.35 (d,  $J = 11.1$  Hz, 1H, HC(7)), 4.16 (d,  $J = 11.1$  Hz, 1H, HC(7)), 3.85 (s, 3H, HC(12)), 1.22 (s, 9H, HC(15)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  158.8 (C(11)), 140.7 (C(19)), 140.2 (C(20)), 138.5 (C(3)), 138.5 (C(3')), 135.5 (C(16)), 131.2 (C(17)), 130.6 (C(22)), 130.1

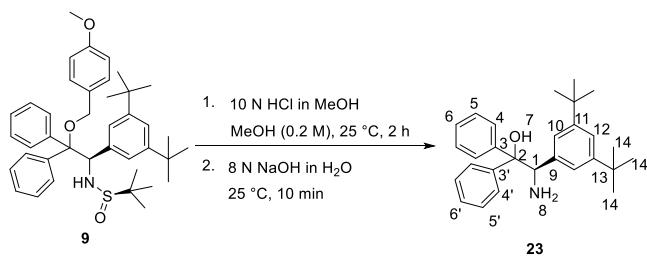
(C(6')), 129.7 (C(6)), 128.6 (C(5)), 128.3 (C(5')), 128.1 (C(8)), 127.9 (C(9)), 127.7 (C(23)), 127.5 (C(4')), 127.2 (C(4)), 126.9 (C(21)), 125.4 (C(18)), 113.6 (C(10)), 86.8 (C(2)), 65.5 (C(7)), 62.3 (C(1)), 55.5 (C(14)), 55.2 (C(12)), 22.6 (C(15)); IR (neat) 3290 (w), 3032 (w), 2956 (w), 2235 (w), 1613 (w), 1585 (w), 1513 (m), 1488 (w), 1447 (w), 1365 (w), 1301 (w), 1247 (m), 1173 (m), 1065 (s), 1035 (m), 1008 (m), 908 (m), 839 (m), 822 (m), 762 (m), 730 (s), 698 (s), 646 (m), 624 (m), 586 (m), 561 (w), 524 (m), 478 (m); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>38</sub>H<sub>40</sub>NO<sub>3</sub>S 590.2735, found 590.2729; TLC  $R_f$  0.18 (silica gel, hexanes/EtOAc, 7:3, UV, KMnO<sub>4</sub>).



**Preparation of (R)-N-((R)-1-(3,5-Di-tert-butylphenyl)-2-((4-methoxybenzyl)oxy)-2,2-diphenylethyl)-2-methylpropane-2-sulfonamide (9).** A 100 mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1  $\times$  15.9 mm) was charged with 1-bromo-3,5-di-tert-butylbenzene (5.38 g, 20.0 mmol, 2.0 equiv) and THF (25 mL) under nitrogen. The solution was cooled to  $-78^\circ\text{C}$  using a cryocooler in an *i*-PrOH bath, and *n*-butyllithium (1.28 g, 13.0 mL, 1.6 M in hexane, 20.0 mmol, 2.0 equiv) was added dropwise by syringe. The resulting solution was stirred at  $-78^\circ\text{C}$  using a cryocooler in an *i*-PrOH bath for 1 h. Then another 50 mL Schlenk flask containing a stir bar was charged with **6a** (4.35 g, 10.0 mmol) and THF (25 mL) under nitrogen and was cooled to  $-78^\circ\text{C}$  using a cryocooler in an *i*-PrOH bath. The *N*-sulfinyl imine solution was transferred to an organolithium solution using a syringe dropwise over 5 min. The resulting mixture was stirred at  $-78^\circ\text{C}$  using a cryocooler in *i*-PrOH bath for 12 h. The reaction was quenched by the addition of satd aq NH<sub>4</sub>Cl solution (50 mL) at  $-78^\circ\text{C}$  and slowly warmed to  $25^\circ\text{C}$ . The mixture was transferred to a 250 mL separatory funnel. The aqueous layer was extracted with ethyl acetate (3  $\times$  50 mL), and the organic layers were combined, washed with brine (1  $\times$  100 mL), dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation ( $30^\circ\text{C}$ , 50 mbar). The dr of the crude product was 99:1 by <sup>1</sup>H NMR analysis. The crude product was purified by column chromatography (silica, 4 cm  $\varnothing \times 12$  cm column) eluting with hexanes/EtOAc, 1:1 to afford **9** (5.4 g, 86%) as a white solid. Data for **9**: mp 61–63  $^\circ\text{C}$  (hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.42–7.29 (m, 10H, HC(4,5,6)), 7.24–7.19 (m, 3H, HC(9,19)), 6.86 (d,  $J = 8.5$  Hz, 2H, HC(10)), 6.67 (s, 2H, HC(17)), 5.67 (s, 1H, HC(1)), 4.43 (s, 1H, HN(13)), 4.20 (d,  $J = 11.1$  Hz, 1H, HC(7)), 4.02 (d,  $J = 11.1$  Hz, 1H, HC(7)), 3.79 (s, 3H, HC(12)), 1.15 (s, 9H, HC(15)), 1.13 (s, 18H, HC(21)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  158.8 (C(11)), 148.6 (C(18)), 138.4 (C(3)), 138.2 (C(3')), 134.8 (C(16)), 130.7 (C(8)), 130.2 (C(5)), 129.8 (C(5')), 128.3 (C(9)), 127.9 (C(6)), 127.7 (C(6')), 127.6 (C(4)), 127.4 (C(4')), 125.1 (C(17)), 121.4 (C(19)), 113.6 (C(10)), 87.0 (C(2)), 65.6 (C(7)), 63.4 (C(1)), 55.4 (C(14)), 55.2 (C(12)), 34.5 (C(20)), 31.3 (C(21)), 22.6 (C(15)); IR (neat) 2954 (m), 2866 (w), 1614 (w), 1600 (w), 1514 (m), 1494 (w), 1447 (m), 1362 (m), 1302 (m), 1247 (s), 1173 (m), 1067 (s), 1036 (s), 908 (m), 876 (m), 822 (m), 757 (m), 725 (s), 702 (s), 654 (m), 625 (m), 591 (m), 507 (m); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>40</sub>H<sub>52</sub>NO<sub>3</sub>S 626.3696, found 626.3668; TLC  $R_f$  0.33 (silica gel, hexanes/EtOAc, 7:3, UV, KMnO<sub>4</sub>).

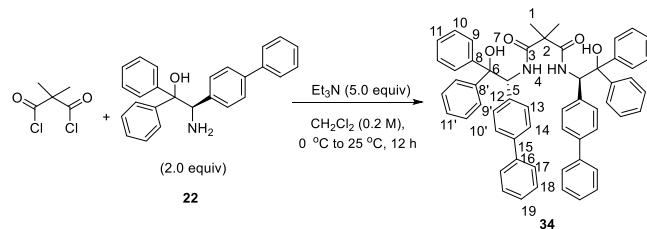


**Preparation of (R)-2-[(1,1'-Biphenyl)-4-yl]-2-amino-1,1-diphenylethan-1-ol (22).** A 250 mL, one-necked Schlenk flask with an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **8** (5.13 g, 8.7 mmol) and methanol (10 mL) under nitrogen. HCl (10 N) in MeOH (87 mL) was added dropwise by syringe. The reaction was stirred for 2 h at 25 °C, and then the solvent was removed by rotary evaporation (30 °C, 50 mbar). The crude solid was suspended in ethyl acetate (50 mL), and 8 N NaOH in H<sub>2</sub>O (130 mL) was added while the solution was stirred vigorously. The solution was stirred for 10 min and then was transferred to a 500 mL separatory funnel. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). pH paper was used to check the neutralization of the solution (pH = 7). The organic layers were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm Ø × 12 cm column) eluting with hexanes/EtOAc, 7:3 to afford **22** (2.40 g, 77%) as a white solid. The spectroscopic data for **22** matched the literature values.<sup>115</sup> Data for **22**: <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 7.74 (d, *J* = 7.6 Hz, 2H), 7.56–7.00 (m, 16H), 5.16 (s, 1H), 4.76 (s, 1H), 1.66 (s, 2H).

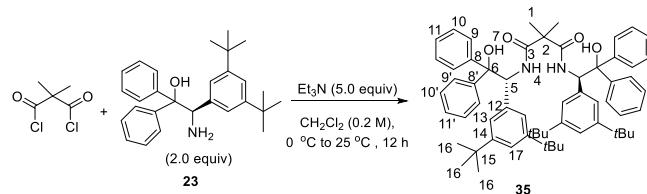


**Preparation of (R)-2-Amino-2-(3,5-di-tert-butylphenyl)-1,1-diphenylethan-1-ol (23).** A 250 mL, one-necked Schlenk flask with an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **9** (5.32 g, 8.5 mmol) and methanol (10 mL) under nitrogen. HCl (10 N) in MeOH (85 mL) was added dropwise by syringe. The reaction was stirred for 2 h at 25 °C, and then the solvent was removed by rotary evaporation (30 °C, 50 mbar). The crude solid was suspended in ethyl acetate (50 mL), and 8 N NaOH in H<sub>2</sub>O (127 mL) was added while the solution was stirred vigorously. The solution was stirred for 10 min and then was transferred to a 500 mL separatory funnel. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). pH paper was used to check the neutralization of the solution (pH = 7). The organic layers were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm Ø × 12 cm column) eluting with hexanes/EtOAc, 7:3 to afford **23** (2.60 g, 75%) as a white solid. Data for **23**: mp 156–158 °C (hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.77 (d, *J* = 8.5 Hz, 2H, HC(4)), 7.42 (t, *J* = 7.4 Hz, 2H, HC(5)), 7.30 (t, *J* = 7.3 Hz, 1H, HC(6)), 7.18 (s, 1H, HC(12)), 7.11–6.94 (m, 5H, HC(4',5',6')), 6.89 (s, 2H, HC(10)), 4.99 (s, 1H, HC(1)), 4.66 (s, 1H, HO(7)), 1.65 (s, 2H, HN(8)), 1.19 (s, 18H, HC(14)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 149.5 (C(11)), 146.5 (C(3)), 144.2 (C(3')), 138.8 (C(9)), 128.5 (C(5)), 127.3 (C(5')), 127.0 (C(6)), 126.9 (C(4)), 126.3 (C(4')), 126.2 (C(6')), 123.0 (C(10)), 121.0 (C(12)), 79.7 (C(2)), 62.2 (C(1)), 34.7 (C(13)), 31.5 (C(14)); IR (neat) 2955 (m), 1601 (w), 1449 (m), 1362 (m), 1249 (w), 1178 (w), 1051 (w), 969 (w), 887 (m), 872 (m), 748 (s), 705 (s), 692 (s), 645 (s), 582 (m), 486 (m); HRMS (ESI) *m/z*

(M + H)<sup>+</sup> calcd for C<sub>28</sub>H<sub>36</sub>NO 402.2810, found 402.2797; TLC *R*<sub>f</sub> 0.41 (silica gel, hexanes/EtOAc, 8:2, UV, KMnO<sub>4</sub>).

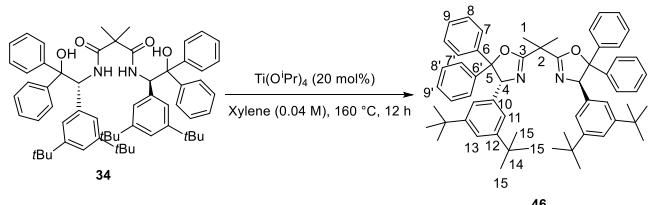


**Preparation of N<sup>1</sup>,N<sup>3</sup>-Bis((R)-1-[(1,1'-Biphenyl)-4-yl]-2-hydroxy-2,2-diphenylethyl)-2,2-dimethylmalonamide (34).** A 50 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **22** (1.50 g, 4.1 mmol, 2.0 equiv), Et<sub>3</sub>N (1.04 g, 1.43 mL, 10.2 mmol, 5.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (10 mL) under nitrogen. The solution was cooled to 0 °C using an ice bath, and 2,2-dimethylmalonyl dichloride (0.34 g, 0.27 mL, 2.05 mmol) was added dropwise by syringe over 2 min. The resulting mixture was slowly warmed to 25 °C and was stirred at 25 °C for 12 h. The mixture was transferred to a 125 mL separatory funnel. The reaction mixture was washed with water (1 × 50 mL) and then brine (1 × 50 mL). The organic layer was removed, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 mL), and the organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm Ø × 15 cm column) eluting with hexanes/EtOAc, 7:3 gradient to 0:1 to afford **34** (1.40 g, 81%) as a white solid. Data for **34**: mp 214–216 °C (hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.78 (d, *J* = 8.6 Hz, 2H, HN(4)), 7.61 (d, *J* = 7.7 Hz, 4H, HC(9)), 7.39–7.33 (m, 8H, HC(10,17)), 7.32–7.25 (m, 12H, HC(9',10',18)), 7.25–7.17 (m, 8H, HC(14,11',19)), 7.17–7.12 (m, 2H, HC(11)), 6.94 (d, *J* = 8.2 Hz, 4H, HC(13)), 6.10 (d, *J* = 8.6 Hz, 2H, HC(5)), 2.67 (s, 2H, HO(7)), 0.97 (s, 6H, HC(1)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 172.5 (C(3)), 144.1 (C(8')), 144.1 (C(8)), 140.3 (C(16)), 140.1 (C(15)), 136.2 (C(12)), 128.9 (C(13)), 128.8 (C(18)), 128.4 (C(10')), 128.2 (C(9')), 127.3 (C(14)), 127.2 (C(19)), 127.2 (C(17)), 126.8 (C(10)), 126.5 (C(9)), 125.8 (C(11')), 125.6 (C(11)), 81.0 (C(6)), 59.1 (C(5)), 49.0 (C(2)), 23.4 (C(1)); IR (neat) 3407 (w), 1639 (m), 1511 (m), 1493 (m), 1449 (w), 1332 (w), 1189 (w), 1157 (m), 1058 (m), 1008 (w), 977 (w), 898 (m), 796 (w), 753 (s), 741 (s), 694 (s), 668 (w), 635 (m), 614 (m), 546 (m), 479 (m); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>57</sub>H<sub>51</sub>N<sub>2</sub>O<sub>4</sub> 827.3884, found 827.3849; TLC *R*<sub>f</sub> 0.18 (silica gel, hexanes/EtOAc, 7:3, UV, KMnO<sub>4</sub>).

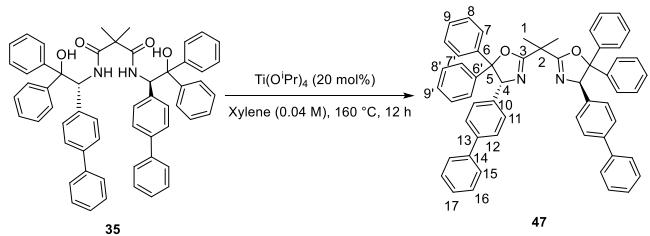


**Preparation of N<sup>1</sup>,N<sup>3</sup>-Bis((R)-1-(3,5-Di-tert-butylphenyl)-2-hydroxy-2,2-diphenylethyl)-2,2-dimethylmalonamide (35).** A 50 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **23** (1.76 g, 4.4 mmol, 2.0 equiv), Et<sub>3</sub>N (1.11 g, 1.53 mL, 11.0 mmol, 5.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (10 mL) under nitrogen. The solution was cooled to 0 °C using an ice bath, and 2,2-dimethylmalonyl dichloride (0.37 g, 0.29 mL, 2.2 mmol) was added dropwise by syringe over 2 min. The resulting mixture was slowly warmed to 25 °C and was stirred at 25 °C for 12 h. The mixture was transferred to a 125 mL separatory funnel. The reaction mixture was washed with water (1 × 50 mL) and then brine (1 × 50 mL). The organic layer was removed, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 mL), and the organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm Ø ×

15 cm column) eluting with hexanes/EtOAc, 7:3 gradient to 0:1 to afford **35** (1.70 g, 85%) as a white solid. Data for **35**: mp 123–125 °C (hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.92 (d, *J* = 9.2 Hz, 2H, HC(4)), 7.68–7.61 (m, 4H, HC(9)), 7.33–7.26 (m, 8H, HC(10,9')), 7.23–7.16 (m, 6H, HC(10',11)), 7.10 (t, *J* = 1.6 Hz, 4H, HC(11',17)), 6.69 (d, *J* = 1.7 Hz, 4H, HC(13)), 6.12 (d, *J* = 9.2 Hz, 2H, HC(5)), 2.52 (s, 2H, HO(17)), 1.01 (s, 36H, HC(16)), 0.90 (s, 6H, HC(1)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 172.4 (C(3)), 150.1 (C(14)), 144.6 (C(8')), 144.0 (C(8)), 135.3 (C(12)), 128.3 (C(10)), 128.105 (C(9')), 127.055 (C(11')), 126.975 (C(11)), 125.895 (C(9)), 125.5 (C(12)), 122.4 (C(13)), 121.6 (C(17)), 81.0 (C(6)), 59.4 (C(5)), 48.6 (C(2)), 34.6 (C(15)), 31.3 (C(16)), 23.8 (C(1)); IR (neat) 2962 (m), 1665 (m), 1495 (m), 1448 (m), 1362 (m), 1249 (m), 1199 (m), 1056 (w), 898 (w), 747 (m), 697 (s), 658 (m), 588 (m); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>61</sub>H<sub>74</sub>N<sub>2</sub>O<sub>4</sub> 899.5755, found 899.5727; TLC *R<sub>f</sub>* 0.30 (silica gel, hexanes/EtOAc, 8:2, UV, KMnO<sub>4</sub>).



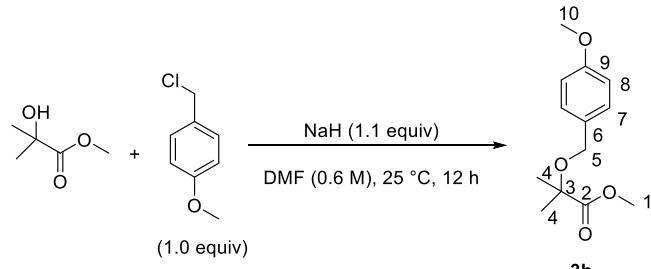
**Preparation of (4*R*,4*R*)-2,2'-(Propane-2,2-diyl)bis(4-(3,5-di-*tert*-butylphenyl)-5,5-diphenyl-4,5-dihydrooxazole) (46).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **34** (0.45 g, 0.50 mmol) and xylenes (12 mL) under nitrogen. The mixture was heated to reflux in a 160 °C oil bath using a condenser connected to a Dean–Stark apparatus which was itself connected to a Schlenk flask. Once the bisamide alcohol dissolved completely, Ti(Oi-Pr)<sub>4</sub> (0.028 g, 0.030 mL, 20 mol %) was added to the solution in one portion. The reaction mixture was refluxed for 12 h with removal of the water byproduct. After the reaction mixture was cooled to room temperature, the solution was concentrated by rotary evaporation (60 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm ø × 15 cm column) eluting with *n*-hexane (95%)/EtOAc, 7:3 to afford **46** (0.37 g, 85%) as a white solid. Data for **46**: mp 85–87 °C (*n*-hexane (95%)/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.65 (d, *J* = 7.8 Hz, 4H, HC(7)), 7.35–7.27 (m, 6H, HC(7',9)), 7.03–6.98 (m, 6H, HC(8,13)), 6.93–6.89 (m, 6H, HC(8',9')), 6.86 (d, *J* = 1.6 Hz, 4H, HC(11)), 5.97 (s, 2H, HC(4)), 1.89 (s, 6H, HC(1)), 1.11 (s, 36H, HC(15)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 168.4 (C(3)), 149.7 (C(12)), 145.1 (C(6)), 140.5 (C(6')), 137.5 (C(10)), 128.3 (C(7')), 127.9 (C(9)), 127.0 (C(8')), 127.0 (C(8)), 126.6 (C(7)), 126.2 (C(9')), 123.0 (C(11)), 120.7 (C(13)), 95.0 (C(5)), 80.4 (C(4)), 39.7 (C(2)), 34.6 (C(14)), 31.3 (C(15)), 25.3 (C(1)); IR (neat) 2961 (s), 1660 (s), 1600 (s), 1447 (s), 1361 (s), 1248 (s), 1146 (s), 1123 (s), 964 (s), 871 (s), 821 (s), 753 (s), 601 (s); LRMS [ESI<sup>+</sup>, TOF] 843.6(2), 863.5(100), 864.5(70), 865.5(25), 866.5(8), 881.5(2); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>61</sub>H<sub>71</sub>N<sub>2</sub>O<sub>2</sub> 863.5526, found 863.5516; TLC *R<sub>f</sub>* 0.40 (silica gel, hexanes/EtOAc, 9:1, UV, KMnO<sub>4</sub>); [α]<sub>D</sub><sup>24</sup> +319.6 (*c* = 1.0, CHCl<sub>3</sub>). Anal. Calcd for C<sub>61</sub>H<sub>70</sub>N<sub>2</sub>O<sub>2</sub>: C, 84.87; H, 8.17; N, 3.25. Found: C, 84.85; H, 8.08; N, 3.23.



**Preparation of (4*R*,4*R*)-2,2'-(propane-2,2-diyl)bis(4-([1,1'-bi-phenyl]-4-yl)-5,5-diphenyl-4,5-dihydrooxazole) (47).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9

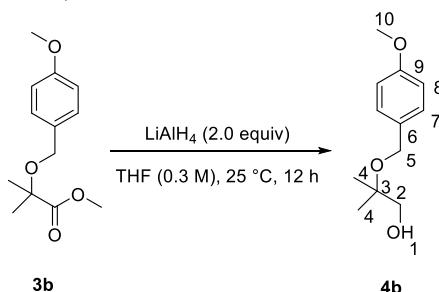
× 6.35 mm) was charged with **35** (0.41 g, 0.50 mmol) and xylenes (12 mL) under nitrogen. The mixture was heated to reflux in a 160 °C oil bath using a condenser connected to a Dean–Stark apparatus which was itself connected to a Schlenk flask. Once the bisamide alcohol dissolved completely then Ti(Oi-Pr)<sub>4</sub> (0.028 g, 0.030 mL, 20 mol %) was added to the solution in one portion. The reaction mixture was refluxed for 12 h with removal of the water byproduct. After the reaction mixture was cooled to room temperature, the solution was concentrated by rotary evaporation (60 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm ø × 15 cm column) eluting with *n*-hexane (95%)/EtOAc, 7:3 to afford **47** (0.30 g, 75%) as a white solid. Recrystallization from *n*-hexane (95%) afforded 0.27 g (70%) of **47** as a white solid. Data for **47**: mp 106–108 °C (*n*-hexane (95%)); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.85–7.77 (m, 4H, HC(7)), 7.55–7.46 (m, 8H, HC(8,12)), 7.44–7.37 (m, 6H, HC(15,17)), 7.37–7.29 (m, 10H, HC(9',11,16)), 7.24–7.20 (m, 4H, HC(7')), 7.04–6.94 (m, 6H, HC(8',9)), 6.18–5.15 (m, 2H, HC(4)), 1.86 (s, 6H, HC(1)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 168.7 (C(3)), 144.6 (C(6)), 140.8 (C(14)), 140.1 (C(13)), 139.8 (C(6')), 137.6 (C(10)), 128.9 (C(11)), 128.7 (C(12)), 128.5 (C(16)), 128.2 (C(8)), 127.3 (C(15)), 127.1 (C(8')), 127.0 (C(9)), 126.9 (C(7')), 126.8 (C(9')), 126.5 (C(7)), 126.4 (C(16)), 95.4 (C(5)), 78.7 (C(4)), 39.5 (C(2)), 24.6 (C(1)); IR (neat) 1655 (s), 1487 (s), 1446 (s), 1306 (s), 1240 (s), 1147 (s), 1122 (s), 1084 (s), 962 (s), 815 (s), 749 (m), 694 (m), 502 (s); LRMS [ESI<sup>+</sup>, TOF] 246.1(1), 791.3(100), 792.3(75), 793.3(27), 794.3(7), 813.3(4); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>57</sub>H<sub>47</sub>N<sub>2</sub>O<sub>2</sub> 791.3647, found 791.3638; TLC *R<sub>f</sub>* 0.49 (silica gel, hexanes/EtOAc, 8:2, UV, KMnO<sub>4</sub>); [α]<sub>D</sub><sup>24</sup> +507.0 (*c* = 1.0, CHCl<sub>3</sub>). Anal. Calcd for C<sub>57</sub>H<sub>46</sub>N<sub>2</sub>O<sub>2</sub>·0.35H<sub>2</sub>O: C, 86.55; H, 5.86; N, 3.54. Found: C, 85.87; H, 5.90; N, 3.51.

**Synthesis of Bisoxazoline Ligands with a Geminal Dimethyl Substituent at the C(5)-position.**

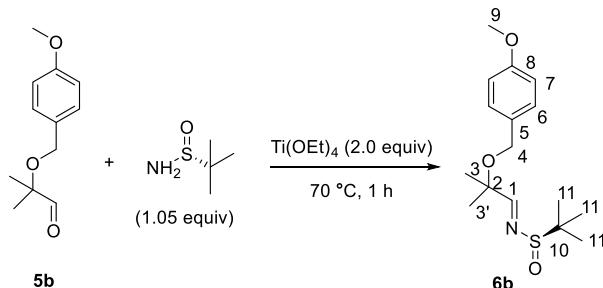


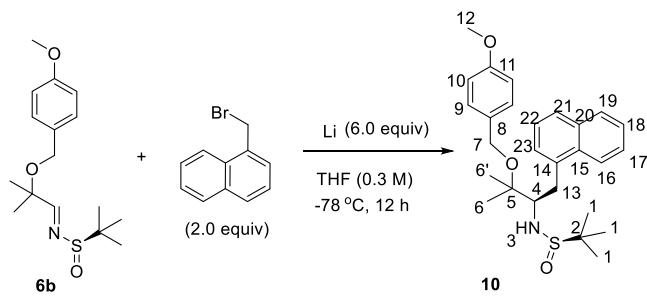
**Preparation of Methyl 2-((4-Methoxybenzyl)oxy)-2-methylpropanoate (3b).** A 250 mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with methyl 2-hydroxy-2-methylpropanoate (5.90 g, 5.76 mL, 50.0 mmol), NaH (1.32 g, 55.0 mmol, 1.1 equiv), and DMF (SDS, 80 mL) under nitrogen. The solution was stirred at 25 °C for 10 min, and PMBCl (7.83 g, 6.77 mL, 50.0 mmol, 1.0 equiv) was added dropwise over 5 min. The mixture was stirred at 25 °C for 12 h. The resulting mixture was diluted in ethyl acetate (200 mL), transferred to 500 mL separatory funnel, washed with water (3 × 100 mL) and brine (1 × 100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/EtOAc, 9:1 to afford **3b** (11.07 g, 93%) as a colorless oil. Data for **3b**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.31 (d, *J* = 8.5 Hz, 2H, HC(7)), 6.87 (d, *J* = 8.7 Hz, 2H, HC(8)), 4.39 (s, 2H, HC(5)), 3.77 (s, 3H, HC(1)), 3.75 (s, 3H, HC(10)), 1.51 (s, 6H, HC(4)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 175.1 (C(2)), 159.1 (C(9)), 130.6 (C(6)), 129.2 (C(7)), 113.7 (C(8)), 77.8 (C(3)), 66.7 (C(5)), 55.1 (C(10)), 51.9 (C(1)), 24.9 (C(4)); IR (neat) 2991 (w), 2952 (w), 1733 (s), 1614 (m), 1587 (w), 1514 (s), 1465 (m), 1383 (m), 1362 (w), 1301 (m), 1279 (m), 1247 (s), 1172 (s), 1139 (s), 1034 (s), 1003 (m), 913 (w), 822 (m), 755 (w), 731 (m), 648 (w), 612 (w), 575 (w), 519 (w); HRMS (ESI) *m/z* (M + Na)<sup>+</sup> calcd for C<sub>13</sub>H<sub>18</sub>O<sub>4</sub>Na

261.1103, found 261.1103; TLC  $R_f$  0.46 (silica gel, hexanes/EtOAc, 8:2, UV, KMnO<sub>4</sub>).

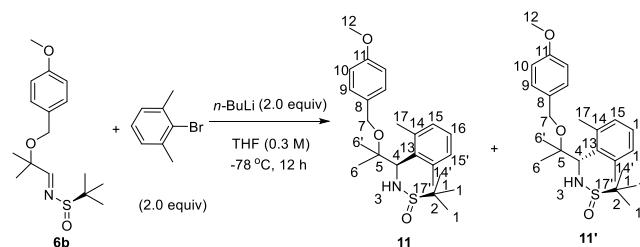


–78 °C for 3 h and triethylamine (freshly distilled, 13.00 g, 18.0 mL, 130.0 mmol, 3.0 equiv) was added dropwise to maintain the internal temperature below –70 °C and was stirred for 2 h. The mixture was slowly warmed to 0 °C, and 30 mL of water was added. The two phases were transferred to a 250 mL separatory funnel, and the organic layer was separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 100 mL), and the organic layers were combined, washed with water (1 × 100 mL) and brine (1 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/Et<sub>2</sub>O, 7:3 to afford **5b** (7.60 g, 87%) as a colorless oil. Data for **5b**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.63 (s, 1H, HC(1)), 7.29 (d, *J* = 9.0 Hz, 2H, HC(6)), 6.89 (d, *J* = 8.8 Hz, 2H, HC(7)), 4.40 (s, 2H, HC(4)), 3.79 (s, 3H, HC(9)), 1.35 (s, 6H, HC(3)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 204.3 (C(1)), 159.3 (C(8)), 130.3 (C(5)), 129.2 (C(6)), 113.9 (C(7)), 80.3 (C(2)), 66.3 (C(4)), 55.2 (C(9)), 21.0 (C(3)); IR (neat) 2981 (w), 2837 (w), 1732 (m), 1613 (m), 1587 (w), 1514 (s), 1465 (m), 1385 (m), 1361 (w), 1302 (m), 1246 (s), 1168 (s), 1110 (w), 1034 (s), 821 (m), 774 (w), 749 (w), 638 (w), 611 (w), 520 (w); HRMS (ESI) *m/z* (M + Na)<sup>+</sup> calcd for C<sub>12</sub>H<sub>16</sub>O<sub>3</sub>Na 231.1001, found 233.0997; TLC  $R_f$  0.50 (silica gel, hexanes/EtOAc, 8:2, UV, KMnO<sub>4</sub>).

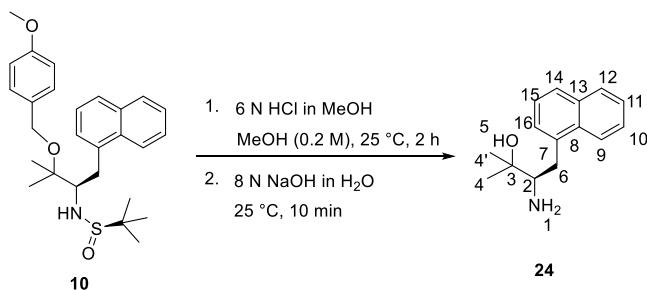




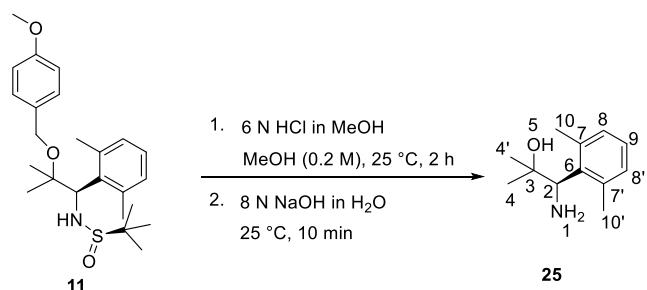
**Preparation of (R)-N-((R)-3-((4-Methoxybenzyl)oxy)-2-methylpropyl)-2-methylpropane-2-sulfonamide (10).** A 100 mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1 × 15.9 mm) was charged with hexane-washed small pieces of lithium (0.62 g, 6.0 mmol, 6.0 equiv) and was stirred with pure hexane (SDS, 25 mL) for 25 min at 25 °C, so as to remove lithium oxide (white solid). After 25 min, hexane was removed using a syringe, and lithium pieces were dried in vacuum. Then THF (30 mL) was added under nitrogen. The solution of 1-(bromomethyl)-naphthalene (6.63 g, 30.0 mmol, 2.0 equiv) in THF (20 mL) was added dropwise by syringe. The resulting solution was stirred at 25 °C for 1 h, and the color of the mixture turned into rust (dark brown). The formation of the organolithium was confirmed by quenching an aliquot by NH<sub>4</sub>Cl solution and confirming through proton NMR analysis. Then, the organolithium solution was cooled to -78 °C using a cryocooler in an *i*-PrOH bath and the temperature was monitored using an internal temperature probe. Another 25 mL, one-necked Schlenk flask containing **6b** (4.66 g, 15.0 mmol) and THF (10 mL) under nitrogen was cooled to -78 °C using a cryocooler in an *i*-PrOH bath. This cooled imine was added dropwise into Schlenk flask containing cooled organolithium using a syringe maintaining the internal temperature below -70 °C. The reaction was quenched by the addition of satd aq NH<sub>4</sub>Cl solution (50 mL) at -78 °C, and was slowly warmed to 25 °C. The mixture was transferred to a 250 mL separatory funnel. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the organic layers were combined, washed with brine (1 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The dr of the crude product was 85:15 by <sup>1</sup>H NMR analysis. The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/EtOAc, 1:1 to afford **10** (3.60 g, 80%) as a yellow oil. Data for **10**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.07 (d, *J* = 8.8 Hz, 1H, HC(16)), 7.85–7.83 (m, 1H, HC(19)), 7.73 (d, *J* = 7.7 Hz, 1H, HC(21)), 7.51–7.45 (m, 2H, HC(18,22)), 7.43–7.34 (m, 4H, HC(9,17,23)), 6.92 (d, *J* = 8.7 Hz, 2H, HC(10)), 4.49 (dd, *J* = 20.0, 10.0 Hz, 2H, HC(7)), 3.90 (d, *J* = 6.2 Hz, 1H, HN(3)), 3.87–3.78 (m, 4H, HC(4,12)), 3.54 (dd, *J* = 14.2, 4.2 Hz, 1H, HC(13)), 3.24 (dd, *J* = 14.2, 9.8 Hz, 1H, HC(13)), 1.53 (s, 3H, HC(6')), 1.44 (s, 3H, HC(6)), 0.81 (s, 9H, HC(1)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 158.9 (C(11)), 135.4 (C(14)), 133.9 (C(15)), 132.5 (C(20)), 131.3 (C(8)), 129.1 (C(9)), 128.8 (C(19)), 128.3 (C(22)), 127.2 (C(21)), 126.0 (C(18)), 125.4 (C(17)), 125.2 (C(23)), 123.8 (C(16)), 113.8 (C(10)), 77.6 (C(5)), 63.5 (C(4)), 63.3 (C(7)), 55.8 (C(2)), 55.3 (C(12)), 34.9 (C(13)), 23.2 (C(6')), 23.0 (C(6)), 22.3 (C(1)); IR (neat) 2955 (s), 1612 (s), 1512 (m), 1463 (s), 1388 (s), 1365 (s), 1301 (s), 1246 (m), 1173 (s), 1143 (s), 1035 (m), 908 (s), 821 (s), 790 (m), 729 (m), 644 (s), 581 (s), 515 (s); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>27</sub>H<sub>36</sub>NO<sub>3</sub>S 454.2410, found 454.2416; TLC *R*<sub>f</sub> 0.6 (silica gel, hexanes/EtOAc, 1:1; UV, KMnO<sub>4</sub>).



**Preparation of (R)-N-((R)-1-(2,6-Dimethylphenyl)-2-((4-methoxybenzyl)oxy)-2-methylpropyl)-2-methylpropane-2-sulfonamide (11).** A 100 mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1 × 15.9 mm) was charged with 2-bromo-1,3-dimethylbenzene (5.55 g, 3.99 mL, 30.0 mmol, 2.0 equiv) and THF (25 mL) under nitrogen. The solution was cooled to -78 °C using a cryocooler in an *i*-PrOH bath, and *n*-butyllithium (1.92 g, 18.75 mL, 1.6 M in hexane, 30.0 mmol, 2.0 equiv) was added dropwise by syringe. The resulting solution was stirred at -78 °C using a cryocooler in an *i*-PrOH bath for 1 h. Then another 25 mL Schlenk flask containing a stir bar was charged with **6b** (4.67 g, 15.0 mmol, 1.0 equiv) and THF (10 mL) under nitrogen and was cooled to -78 °C using a cryocooler in an *i*-PrOH bath. The *N*-sulfinyl imine solution was transferred to organolithium solution using a syringe dropwise over 5 min. The resulting mixture was stirred at -78 °C using a cryocooler in an *i*-PrOH bath for 12 h. The reaction was quenched by the addition of satd aq NH<sub>4</sub>Cl solution (50 mL) at -78 °C and slowly warmed to 25 °C. The mixture was transferred to a 250 mL separatory funnel. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the organic layers were combined, washed with brine (1 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The dr of the crude product was 60:40 by <sup>1</sup>H NMR analysis. The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/EtOAc, 1:1 to afford **11** (3.24 g, 52%) and **11'** (2.16 g, 34%) as a colorless oil. Data for **11** (Major isomer): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.27 (d, *J* = 8.6 Hz, 2H, HC(9)), 7.04 (t, *J* = 7.4 Hz, 1H, HC(16)), 7.02–6.95 (m, 2H, HC(15,15')), 6.87 (d, *J* = 8.6 Hz, 2H, HC(10)), 5.00 (d, *J* = 4.4 Hz, 1H, HC(4)), 4.65 (d, *J* = 4.3 Hz, 1H, HC(3)), 4.47 (d, *J* = 10.3 Hz, 1H, HC(7)), 4.40 (d, *J* = 10.3 Hz, 1H, HC(7)), 3.81 (s, 3H, HC(12)), 2.45 (d, *J* = 4.2 Hz, 6H, HC(17,17')), 1.48 (s, 3H, HC(6')), 1.14 (s, 3H, HC(6)), 1.13 (s, 9H, HC(1)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 159.0 (C(11)), 138.3 (C(13)), 137.6 (C(14')), 136.0 (C(14)), 131.0 (C(8)), 130.8 (C(15')), 129.3 (C(9)), 128.4 (C(15)), 127.0 (C(16)), 113.8 (C(10)), 78.7 (C(5)), 63.5 (C(7)), 62.4 (C(4)), 55.5 (C(2)), 55.3 (C(12)), 24.2 (C(6')), 23.5 (C(6)), 22.7 (C(1)), 22.5 (C(17')), 22.5 (C(17)); IR (neat) 2955 (s), 1613 (s), 1513 (m), 1464 (s), 1364 (s), 1301 (s), 1247 (m), 1173 (s), 1145 (s), 1066 (m), 1032 (m), 958 (s), 923 (s), 873 (s), 821 (s), 792 (s), 770 (m), 728 (m), 587 (s), 519 (s), 493 (s); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>24</sub>H<sub>36</sub>NO<sub>3</sub>S 418.2406, found 418.2416; TLC *R*<sub>f</sub> 0.50 (silica gel, hexanes/EtOAc, 6:4, UV, KMnO<sub>4</sub>). Data for **11'** (Minor isomer): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.25 (d, *J* = 8.5 Hz, 2H, HC(9)), 7.04 (d, *J* = 7.0 Hz, 1H, HC(16)), 6.99 (d, *J* = 7.4 Hz, 2H, HC(15,15')), 6.90 (d, *J* = 8.5 Hz, 2H, HC(10)), 4.82 (q, *J* = 8.6 Hz, 2H, HC(4,3)), 4.40 (s, 2H, HC(7)), 3.83 (s, 3H, HC(12)), 2.53 (s, 3H, HC(17)), 2.44 (s, 3H, HC(17')), 1.53 (s, 3H, HC(6')), 1.14 (s, 9H, HC(1)), 1.10 (s, 3H, HC(6)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 158.9 (C(11)), 138.0 (C(13)), 137.1 (C(14')), 136.7 (C(14)), 131.1 (C(8)), 130.8 (C(15')), 129.0 (C(9)), 128.3 (C(15)), 126.9 (C(16)), 113.6 (C(10)), 78.6 (C(5)), 63.5 (C(7)), 61.2 (C(4)), 56.5 (C(2)), 55.2 (C(12)), 24.9 (C(6')), 22.8 (C(17)), 22.7 (C(6)), 22.5 (C(1)), 22.3 (C(17)); IR (neat) 2973 (s), 1612 (s), 1513 (m), 1463 (s), 1387 (s), 1301 (s), 1247 (m), 1172 (s), 1148 (m), 1109 (m), 1033 (m), 958 (s), 955 (s), 910 (s), 822 (s), 791 (s), 769 (m), 729 (m), 644 (s), 572 (s), 528 (s); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>24</sub>H<sub>36</sub>NO<sub>3</sub>S 418.2416, found 418.2416; TLC *R*<sub>f</sub> 0.0.53 (silica gel, hexanes/EtOAc, 6:4, UV, KMnO<sub>4</sub>).

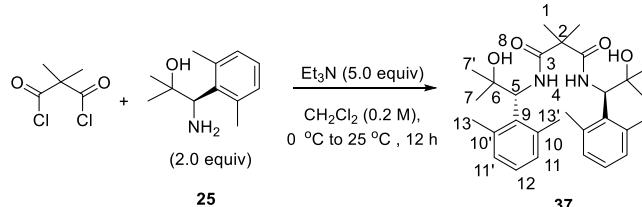


**Preparation of (R)-3-Amino-2-methyl-4-(naphthalen-1-yl)butan-2-ol (24).** A 300 mL, one-necked Schlenk flask with an egg-shaped stir bar ( $50.8 \times 19.1$  mm) was charged with **10** (2.85 g, 6.3 mmol) and methanol (10 mL) under nitrogen. HCl (6 N) in MeOH (63 mL) was added dropwise by syringe. The mixture was stirred for 2 h at 25 °C, and then the solvent was removed rotary evaporation (30 °C, 50 mbar). The crude solid was suspended in ethyl acetate (50 mL), and 8 N NaOH in H<sub>2</sub>O (94.5 mL) was added while the solution was stirred vigorously. The solution was stirred for 10 min and then was transferred to a 500 mL separatory funnel. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2  $\times$  50 mL). pH paper was used to check the neutralization of the solution (pH = 7). The organic layers were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm  $\phi$   $\times$  12 cm column) eluting with MeOH/EtOAc, 1:9 to afford **24** (1.36 g, 92%) as a white solid. Data for **24**: mp 124–126 °C (MeOH/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.05 (d, *J* = 8.2 Hz, 1H, HC(9)), 7.88 (d, *J* = 7.9 Hz, 1H, HC(12)), 7.77 (d, *J* = 8.3 Hz, 1H, HC(14)), 7.52 (p, *J* = 7.1 Hz, 2H, HC(11,15)), 7.42 (t, *J* = 7.7 Hz, 1H, HC(10)), 7.33 (d, *J* = 6.9 Hz, 1H, HC(16)), 3.61 (d, *J* = 13.9 Hz, 1H, HC(6')), 3.02 (d, *J* = 11.2 Hz, 1H, HC(2)), 2.64 (t, *J* = 12.6 Hz, 1H, HC(6)), 1.38 (d, *J* = 42.5 Hz, 6H, HC(4,4')); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  135.7 (C(7)), 134.1 (C(13)), 132.0 (C(8)), 128.9 (C(12)), 127.5 (C(16)), 127.3 (C(14)), 126.0 (C(15)), 125.7 (C(10)), 125.4 (C(11)), 123.6 (C(9)), 71.7 (C(3)), 60.1 (C(2)), 36.2 (C(6)), 27.1 (C(4')), 24.1 (C(4)); IR (neat) 2963 (s), 1568 (s), 1449 (s), 1384 (s), 1153 (s), 1092 (s), 1023 (s), 969 (w), 960 (s), 904 (s), 781 (s), 597 (s), 572 (s), 499 (s); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>15</sub>H<sub>20</sub>NO 230.1540, found 230.1545; TLC *R*<sub>f</sub> 0.45 (silica gel, MeOH/EtOAc, 2:8, UV, KMnO<sub>4</sub>).

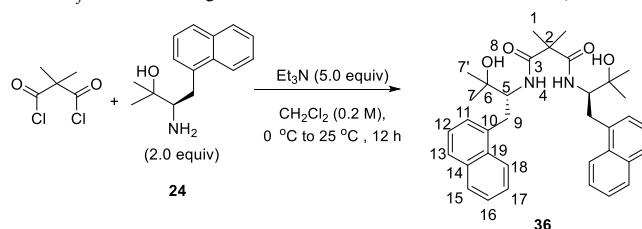


**Preparation of (R)-1-Amino-1-(2,6-Dimethylphenyl)-2-methylpropan-2-ol (25).** A 300 mL, one-necked Schlenk flask with an egg-shaped stir bar ( $50.8 \times 19.1$  mm) was charged with **11** (2.25 g, 5.4 mmol) and methanol (10 mL) under nitrogen. HCl (6 N) in MeOH (54 mL) was added dropwise by syringe. The mixture was stirred for 2 h at 25 °C, and then the solvent was removed rotary evaporation (30 °C, 50 mbar). The crude solid was suspended in ethyl acetate (50 mL), and 8 N NaOH in H<sub>2</sub>O (81 mL) was added while the solution was stirred vigorously. The solution was stirred for 10 min and then was transferred to a 500 mL separatory funnel. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2  $\times$  50 mL). pH paper was used to check the neutralization of the solution (pH = 7). The organic layers were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar).

The crude product was purified by column chromatography (silica, 4 cm  $\phi$   $\times$  12 cm column) eluting with MeOH/EtOAc, 1:9 to afford **25** (0.94 g, 90%) as a colorless oil. Data for **25**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.11–6.93 (m, 3H, HC(8,8',9)), 4.43 (s, 1H, HC(2)), 3.05 (s, 3H, HN, HO(1,5)), 2.61 (s, 3H, HC(10')), 2.36 (s, 3H, HC(10)), 1.37 (s, 3H, HC(4')), 1.01 (s, 3H, HC(4)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  138.63 (C(6)), 136.93 (C(7')), 136.83 (C(7)), 130.93 (C(8')), 128.33 (C(8)), 126.63 (C(9)), 72.63 (C(3)), 59.13 (C(2)), 30.43 (C(4')), 26.63 (C(4)), 22.53 (C(10')), 22.3 (C(10)); IR (neat) 2969 (s), 1581 (s), 1449 (s), 1465 (s), 1375 (s), 1162 (s), 954 (s), 908 (w), 960 (m), 769 (m), 728 (w), 645 (s), 601 (s), 567 (s), 474 (s); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>12</sub>H<sub>20</sub>N 194.1538, found 194.1545; TLC *R*<sub>f</sub> 0.32 (silica gel, MeOH/EtOAc, 0.5:9.5, UV, KMnO<sub>4</sub>).

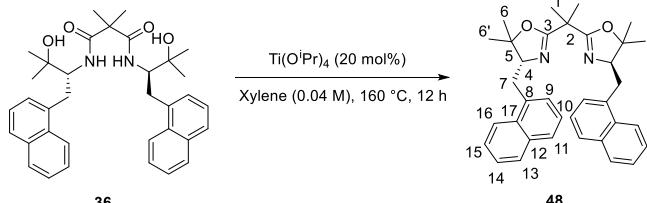


**Preparation of N<sup>1</sup>,N<sup>3</sup>-Bis((R)-1-(2,6-Dimethylphenyl)-2-hydroxy-2-methylpropyl)-2,2-dimethylmalonamide (37).** A 50 mL, one-necked Schlenk flask containing an egg-shaped stir bar ( $15.9 \times 6.35$  mm) was charged with **25** (0.81 g, 4.2 mmol, 2.0 equiv), Et<sub>3</sub>N (1.06 g, 1.46 mL, 10.5 mmol, 5.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (7 mL) under nitrogen. The solution was cooled to 0 °C using an ice bath, and 2,2-dimethylmalonyl dichloride (0.35 g, 0.27 mL, 2.1 mmol) was added dropwise over 2 min by syringe. The resulting mixture was slowly warmed to 25 °C and was stirred at 25 °C for 12 h. The mixture was transferred to a 125 mL separatory funnel. The reaction mixture was washed with water (1  $\times$  50 mL) and then brine (1  $\times$  50 mL). The organic layer was removed, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  20 mL), and the organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm  $\phi$   $\times$  15 cm column) eluting with hexanes/EtOAc, 1:1 to afford **37** (0.81 g, 80%) as a white solid. The compound **37** was crystallized from 1:1 mixture of hexanes/EtOAc at –35 °C. Data for **37**: mp 213–215 °C (hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.70 (d, *J* = 8.5 Hz, 2H, HC(4)), 7.01–6.94 (m, 4H, HC(11,11')), 6.78 (dd, *J* = 6.9, 2.2 Hz, 2H, HC(12)), 5.34 (d, *J* = 8.5 Hz, 2H, HC(5)), 2.46 (s, 6H, HC(11)), 2.41 (s, 2H, HC(8)), 2.15 (s, 6H, HC(13)), 1.52 (s, 6H, HC(1)), 1.33 (s, 6H, HC(7')), 1.00 (s, 6H, HC(7)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  172.5 (C(3)), 137.6 (C(9)), 136.8 (C(10')), 135.4 (C(10)), 130.7 (C(12)), 128.4 (C(11')), 126.8 (C(11)), 73.6 (C(6)), 57.4 (C(5)), 49.6 (C(2)), 29.7 (C(7')), 27.4 (C(7)), 23.9 (C(1)), 22.0 (C(13')), 21.7 (C(13)); IR (neat) 3423 (s), 1665 (s), 2975 (s), 1652 (s), 1504 (s), 1470 (s), 1371 (s), 1303 (s), 1159 (s), 1133 (s), 1081 (s), 964 (s), 932 (s), 895 (s), 827 (s), 765 (s), 732 (s), 711 (s), 578 (s); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>61</sub>H<sub>74</sub>N<sub>2</sub>O<sub>4</sub> 899.5755, found 899.5727; TLC *R*<sub>f</sub> 0.33 (silica gel, hexanes/EtOAc, 6:4, UV, KMnO<sub>4</sub>).



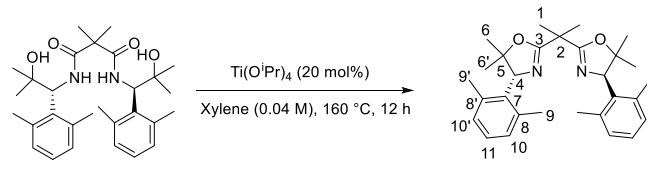
**Preparation of N<sup>1</sup>,N<sup>3</sup>-Bis((R)-3-Hydroxy-3-methyl-1-(naphthalen-1-yl)butan-2-yl)-2,2-dimethylmalonamide (36).** A 50 mL, one-necked Schlenk flask containing an egg-shaped stir bar ( $15.9 \times 6.35$  mm) was charged with **24** (1.05 g, 4.6 mmol, 2.0 equiv), Et<sub>3</sub>N (1.16 g, 1.60 mL, 11.5 mmol, 5.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (8 mL)

under nitrogen. The solution was cooled to 0 °C using an ice bath, and 2,2-dimethylmalonyl dichloride (0.38 g, 0.30 mL, 2.3 mmol) was added dropwise over 2 min by syringe. The resulting mixture was slowly warmed to 25 °C and was stirred at 25 °C for 12 h. The mixture was transferred to a 125 mL separatory funnel. The reaction mixture was washed with water (1 × 50 mL) and then brine (1 × 50 mL). The organic layer was removed, the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 × 20 mL), and the organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm  $\varnothing$  × 15 cm column) eluting with hexanes/EtOAc, 1:9 to afford **36** (1.00 g, 80%) as a white solid. Data for **36**: mp 156–158 °C (hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99 (d,  $J$  = 8.4 Hz, 2H, HC(18)), 7.80 (d,  $J$  = 8.0 Hz, 2H, HC(15)), 7.66 (d,  $J$  = 8.2 Hz, 2H, HC(13)), 7.46 (dt,  $J$  = 24.2, 7.1 Hz, 4H, HC(12,16)), 7.30 (t,  $J$  = 7.6 Hz, 2H, HC(17)), 7.23 (d,  $J$  = 6.9 Hz, 2H, HC(11)), 6.42 (d,  $J$  = 9.2 Hz, 2H, HC(4)), 4.19 (ddd,  $J$  = 12.5, 9.4, 3.8 Hz, 2H, HC(5)), 3.49 (dd,  $J$  = 14.4, 3.7 Hz, 2H, HC(9')), 3.39 (s, 2H, HC(8)), 3.03 (dd,  $J$  = 14.3, 11.6 Hz, 2H, HC(9)), 1.30 (s, 6H, HC(7')), 1.25 (s, 6H, HC(7)), 0.55 (s, 6H, HC(1));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.8 (C(3)), 134.5 (C(10)), 133.8 (C(14)), 132.2 (C(19)), 128.9 (C(15)), 127.3 (C(11)), 127.3 (C(13)), 126.3 (C(12)), 125.6 (C(16)), 125.2 (C(17)), 123.3 (C(18)), 73.5 (C(6)), 58.5 (C(5)), 49.1 (C(2)), 32.3 (C(9,9')), 27.9 (C(7)), 25.8 (C(7')), 22.9 (C(1)); IR (neat) 3381 (s), 2974 (s), 2975 (s), 1659 (s), 1639 (s), 1512 (s), 1456 (s), 1365 (s), 1165 (s), 1077 (s), 952 (s), 789 (s), 771 (m), 727 (s), 569 (s), 518 (s), 484 (m); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_{35}\text{H}_{43}\text{N}_2\text{O}_4$  555.3218, found 555.3223; TLC  $R_f$  0.39 (silica gel, hexanes/EtOAc, 3:7, UV,  $\text{KMnO}_4$ ).



**Preparation of (4*R*,4'*R*)-2,2'-(Propane-2,2-diyl)bis(5,5-dimethyl-4-(naphthalen-1-ylmethyl)-4,5-dihydrooxazole) (**48**).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **36** (0.27 g, 0.50 mmol) and xylenes (12 mL) under nitrogen. The mixture was heated to reflux in a 160 °C oil bath using a condenser connected to a Dean–Stark apparatus which was itself connected to Schlenk flask. Once the bisamide alcohol dissolved completely then  $\text{Ti}(\text{O}i\text{-Pr})_4$  (0.028 g, 0.030 mL, 20 mol %) was added to the solution in one portion. The reaction mixture was refluxed for 12 h with removal of the water byproduct. After the reaction mixture was cooled to room temperature, the solution was concentrated by rotary evaporation (60 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm  $\varnothing$  × 15 cm column) eluting with *n*-hexane (95%)/EtOAc, 7:3 to afford **48** (0.210 g, 80%) as a white solid. Recrystallization from anhydrous diethyl ether afforded 0.20 g (77%) of **48** as a white solid. Data for **48**: mp 155–157 °C ( $\text{Et}_2\text{O}$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.15 (d,  $J$  = 8.4 Hz, 2H, HC(16)), 7.88 (d,  $J$  = 8.1 Hz, 2H, HC(13)), 7.77 (d,  $J$  = 8.0 Hz, 2H, HC(11)), 7.58–7.41 (m, 8H, HC(9,10,14,15)), 4.19 (dd,  $J$  = 8.3, 6.5 Hz, 2H, HC(4)), 3.31 (qd,  $J$  = 14.2, 7.3 Hz, 4H, HC(7)), 1.54 (s, 6H, HC(1)), 1.45 (s, 6H, HC(6)), 1.35 (s, 6H, HC(6'));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  167.8 (C(3)), 135.3 (C(8)), 134.0 (C(12)), 132.2 (C(17)), 128.8 (C(13)), 127.1 (C(11)), 127.0 (C(15)), 125.7 (C(14)), 125.4 (C(10)), 125.4 (C(9)), 124.1 (C(16)), 86.4 (C(5)), 74.0 (C(4)), 38.6 (C(2)), 34.4 (C(7)), 28.2 (C(6')), 23.7 (C(1)), 21.7 (C(6)); IR (neat) 2972 (s), 1651 (s), 1460 (s), 1386 (s), 1372 (s), 1275 (s), 1133 (s), 1114 (s), 1075 (s), 971 (s), 935 (s), 818 (s), 786 (m), 508 (s); LRMS [ESI<sup>+</sup>, TOF] 195.1(5), 326.1(8), 519.3(100), 520.3(38), 537.3(10), 659.3(9), 843.6(3); Anal. Calcd.

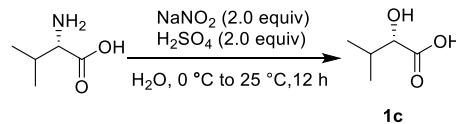
for  $\text{C}_{35}\text{H}_{38}\text{N}_2\text{O}_2\cdot0.1\text{H}_2\text{O}$ : C, 81.05; H, 7.38; N, 5.40. Found: C, 80.35; H, 7.08; N, 5.43; HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_{35}\text{H}_{39}\text{N}_2\text{O}_4$  519.3016, found 519.3012; TLC  $R_f$  0.26 (silica gel, hexanes/EtOAc, 8:2, UV,  $\text{KMnO}_4$ );  $[\alpha]_D^{24}$  +152.6 ( $c$  = 1.0, 100%  $\text{CHCl}_3$ ).



37 49

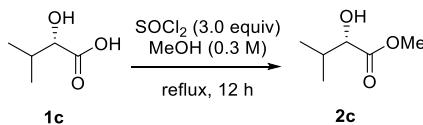
**Preparation of (4*R*,4'*R*)-2,2'-(Propane-2,2-diyl)bis(4-(2,6-dimethylphenyl)-5,5-dimethyl-4,5-dihydrooxazole) (**49**).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **37** (0.24 g, 0.50 mmol) and xylenes (12 mL) under nitrogen. The mixture was heated to reflux in a 160 °C oil bath using a condenser connected to a Dean–Stark apparatus which was itself connected to Schlenk flask. Once the bisamide alcohol dissolved completely then  $\text{Ti}(\text{O}i\text{-Pr})_4$  (0.028 g, 0.030 mL, 20 mol %) was added to the solution in one portion. The reaction mixture was refluxed for 12 h with removal of the water byproduct. After the reaction mixture was cooled to room temperature, the solution was concentrated by rotary evaporation (60 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm  $\varnothing$  × 15 cm column) eluting with *n*-hexane (95%)/EtOAc, 7:3 to afford **49** (0.18 g, 82%) as a white solid. Recrystallization from *n*-hexane (95%) afforded 0.17 g (78%) of analytically pure **49** as a white solid. Data for **49**: mp 105–107 °C (*n*-hexane (95%));  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.05–7.00 (m, 2H, HC(11)), 6.99–6.92 (m, 4H, HC(10,10')), 5.36 (s, 2H, HC(4)), 2.36 (d,  $J$  = 16.9 Hz, 12H, HC(9,9')), 1.62 (s, 6H, HC(1)), 1.56 (s, 6H, HC(6)), 1.09 (s, 6H, HC(6'));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  167.3 (C(3)), 138.1 (C(8)), 136.5 (C(7)), 135.0 (C(8')), 130.5 (C(10)), 128.4 (C(10')), 127.1 (C(11)), 86.7 (C(5)), 75.1 (C(4)), 38.9 (C(2)), 30.8 (C(6)), 23.7 (C(6')), 22.9 (C(1)), 22.0 (C(9')), 21.7 (C(9)); IR (neat) 2973 (s), 1739 (s), 1654 (m), 1466 (s), 1385 (s), 1263 (s), 1124 (m), 1010 (s), 973 (s), 916 (s), 837 (s), 767 (m), 736 (s); LRMS [ESI<sup>+</sup>, TOF] 399.2(6), 447.3(100), 448.3(37), 449.3(8), 450.3(2); Anal.  $\text{C}_{29}\text{H}_{39}\text{N}_2\text{O}_2$  (446.623): C, 77.99; H, 8.58; N, 6.27. Found: C, 77.62; H, 8.46; N, 6.32; HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_{29}\text{H}_{39}\text{N}_2\text{O}_2$  447.3003, found 447.3012; TLC  $R_f$  0.44 (silica gel, hexanes/EtOAc, 8:2, UV,  $\text{KMnO}_4$ );  $[\alpha]_D^{24}$  +188.3 ( $c$  = 1.0,  $\text{CHCl}_3$ ).

**Synthesis of Bisoxazoline Ligands with an Isopropyl Substituent at the C(5)-position.**



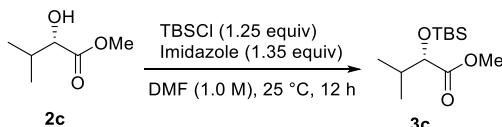
**Preparation of (S)-2-Hydroxy-3-methylbutanoic Acid (**1c**).** L-Valine (8.78 g, 75.0 mmol) was placed into a 300 mL, three-necked flask containing an egg-shaped stir bar (50.8 × 19.1 mm), and water (75 mL) was added. The flask was fitted with two addition funnels. In one addition funnel concentrated  $\text{H}_2\text{SO}_4$  (14.71 g, 8.0 mL, 150.0 mmol, 2.0 equiv) was added. To the other addition funnel a solution of  $\text{NaNO}_2$  (10.35 g, 150 mmol, 2.0 equiv) dissolved in  $\text{H}_2\text{O}$  (25 mL) was added. The reaction vessel was cooled to 0 °C using an ice bath, and the acid was added dropwise with stirring for 2 min. After the L-valine dissolved, the sodium nitrite solution was added dropwise by syringe, and the rate of addition of the acid was adjusted similarly so as to maintain the internal temperature below 0 °C. After the addition was complete, the mixture was stirred at 0 °C for 1 h and then was stirred at 25 °C for 12 h. After this time, the reaction mixture was transferred to 500 mL separatory funnel and was extracted with ethyl acetate (3 × 100 mL). The organic layers were combined, washed with brine (1 × 100 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary

evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by recrystallization with hot hexane (300 mL) to afford **1c** (5.80 g, 65%) as a white crystalline solid. The spectroscopic data for **1c** matched the literature values.<sup>116</sup> Data for **1c**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.11 (d, *J* = 3.6 Hz, 1H), 2.11 (septd, *J* = 6.8, 3.5 Hz, 1H), 1.03 (d, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H).

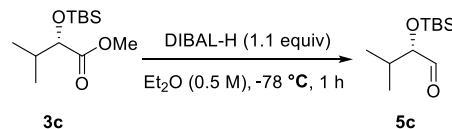


*Preparation of Methyl (S)-2-Hydroxy-3-methylbutanoate (2c).*

A 250 mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **1c** (5.80 g, 49.1 mmol) and MeOH (distilled, 120 mL) under nitrogen. The solution was cooled in an ice bath for 10 min, and SOCl<sub>2</sub> (17.52 g, 10.74 mL, 147.3 mmol, 3.0 equiv) was added dropwise by syringe over 5 min at 0 °C. The mixture was heated to reflux using a condenser in a 75 °C oil bath for 12 h. After the solution was cooled to 25 °C, the volatile components are removed by rotary evaporation (30 °C, 50 mbar). The resulting residue was diluted with ethyl acetate (200 mL) and satd aq NaHCO<sub>3</sub> (200 mL) was added slowly because of evolution of gas. The mixture was transferred to a 500 mL separatory funnel, and the organic layer was removed. The aqueous layer was extracted with ethyl acetate (3 × 100 mL), and the organic layers were combined, washed with brine (1 × 100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by trituration with hot hexane (300 mL) to afford (4.40 g, 68%) **2c** as a colorless oil. The spectroscopic data for **2c** matched the literature values.<sup>116</sup> Data for **2c**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.02 (dd, *J* = 6.0, 3.6 Hz, 1H), 3.76 (s, 3H), 2.78 (d, *J* = 6.1 Hz, 1H), 2.04 (septd, *J* = 6.9, 3.6 Hz, 1H), 0.99 (d, *J* = 6.9 Hz, 4H), 0.83 (d, *J* = 6.9 Hz, 4H).

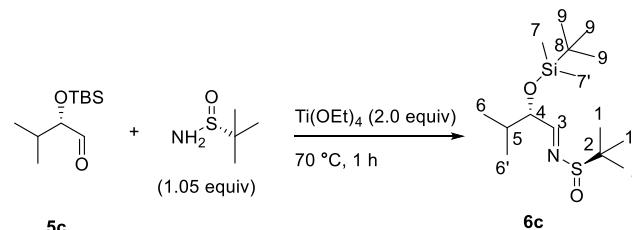


*Preparation of Methyl (S)-2-((tert-Butyldimethylsilyl)oxy)-3-methylbutanoate (3c).* A 250 mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **2c** (4.40 g, 33.3 mmol), TBSCl (6.27 g, 41.6 mmol, 1.25 equiv), imidazole (3.06 g, 44.95 mmol, 1.35 equiv), and DMF (SDS, 45 mL) under nitrogen. The mixture was stirred at 25 °C for 12 h. The resulting mixture was diluted in Et<sub>2</sub>O (200 mL), transferred to 500 mL separatory funnel, washed with water (3 × 100 mL) and brine (1 × 100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/EtOAc, 9:1 to afford **3c** (7.50 g, 92%) as a colorless oil. The spectroscopic data for **3c** matched the literature values.<sup>117</sup> Data for **3c**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 3.86 (d, *J* = 4.7 Hz, 1H), 3.58 (s, 3H), 1.99–1.86 (m, 1H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.81 (s, 9H), 0.78 (d, *J* = 6.8 Hz, 3H), −0.06 (s, 3H), −0.07 (s, 3H).

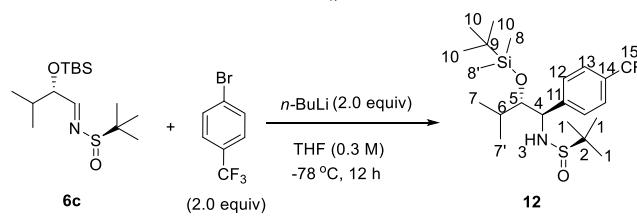


*Preparation of (S)-2-((tert-Butyldimethylsilyl)oxy)-3-methylbutanal (5c).* A 250 mL, three-necked round-bottomed flask equipped with nitrogen inlet, an egg-shaped stir bar (50.8 × 19.1 mm), an internal temperature probe, and two rubber septa was charged with **3c** (7.60 g, 31.0 mmol) and Et<sub>2</sub>O (60 mL, SDS) under nitrogen. The solution was cooled to −78 °C using a cryocooler in an *i*-PrOH bath, and DIBAL-H (1.0 M in heptane, 34.1 mL, 34.1 mmol, 1.1 equiv) was added dropwise by syringe to maintain the internal temperature below −70 °C. The solution was stirred at −78 °C for 1 h, and then reaction was quenched with H<sub>2</sub>O (6 mL). The mixture was slowly warmed to 25 °C. The mixture was stirred for additional 1 h. Then the mixture was filtered through a fritted glass funnel (7.5 mm diameter) containing Celite into a 250 mL filter flask. The Celite cake was washed with Et<sub>2</sub>O (2 × 75 mL). The combined filtrates were transferred to a 250 mL separatory funnel, washed with water (1 × 100 mL) and brine (1 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/Et<sub>2</sub>O, 7:3 to afford **5c** (5.40 g, 80%) as a colorless oil. The spectroscopic data for **5c** matched the literature values.<sup>111</sup> Data for **5c**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.58 (s, 1H), 3.71 (dd, *J* = 4.9, 2.2 Hz, 1H), 2.07–1.96 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 9 H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 6H).

equiv) was added dropwise by syringe to maintain the internal temperature below −70 °C. The solution was stirred at −78 °C for 1 h, and then reaction was quenched with H<sub>2</sub>O (6 mL). The mixture was slowly warmed to 25 °C. The mixture was stirred for additional 1 h. Then the mixture was filtered through a fritted glass funnel (7.5 mm diameter) containing Celite into a 250 mL filter flask. The Celite cake was washed with Et<sub>2</sub>O (2 × 75 mL). The combined filtrates were transferred to a 250 mL separatory funnel, washed with water (1 × 100 mL) and brine (1 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/Et<sub>2</sub>O, 7:3 to afford **5c** (5.40 g, 80%) as a colorless oil. The spectroscopic data for **5c** matched the literature values.<sup>111</sup> Data for **5c**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.58 (s, 1H), 3.71 (dd, *J* = 4.9, 2.2 Hz, 1H), 2.07–1.96 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 9 H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 6H).

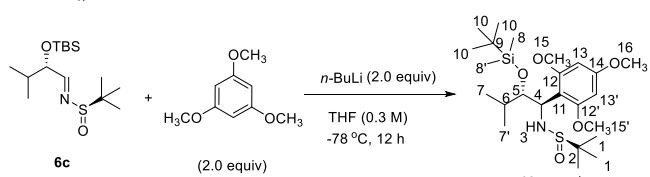


*Preparation of (R)-N-((S,E)-2-((tert-Butyldimethylsilyl)oxy)-3-methylbutylidene)-2-methylpropane-2-sulfonamide (6c).* A 100 mL, one-necked Schlenk flask with an egg-shaped stir bar (38.1 × 15.9 mm) was charged with **5c** (4.98 g, 23.05 mmol), (*R*)-2-methylpropane-2-sulfonamide (2.93 g, 24.20 mmol, 1.05 equiv), and titanium(IV) ethoxide (10.51 g, 9.66 mL, 46.1 mmol, 2.0 equiv) under nitrogen. The mixture was stirred in a 70 °C oil bath for 60 min and then was diluted with ethyl acetate (50 mL). The resulting solution was poured into a 200 mL Erlenmeyer flask with a stir bar and brine (5 mL), and the vial was rinsed with ethyl acetate (2 × 25 mL) to help the transfer. The suspension was stirred at 25 °C for 10 min and then filtered through a fritted glass funnel (7.5 mm diameter) containing Celite. The Celite cake was washed with ethyl acetate (2 × 100 mL). The combined filtrates were transferred to a 250 mL separatory funnel, washed with water (1 × 100 mL) and brine (1 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/EtOAc, 9:1 to afford **6c** (6.93 g, 94%) as a yellow oil. Data for **6c**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.88 (d, *J* = 5.3 Hz, 1H, HC(3)), 4.12 (t, *J* = 5.1 Hz, 1H, HC(4)), 1.93–1.79 (m, 1H, HC(5)), 1.15 (s, 9H, HC(1)), 0.89 (dd, *J* = 6.9, 2.5 Hz, 6H, HC(6)), 0.84 (s, 9H, HC(9)), 0.01 (s, 3H, HC(7')), −0.04 (s, 3H, HC(7)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 171.6 (C(3)), 78.8 (C(4)), 56.7 (C(2)), 33.8 (C(5)), 25.8 (C(9)), 22.5 (C(1)), 18.8 (C(6')), 18.1 (C(8)), 17.9 (C(6)), −4.2 (C(7')), −4.9 (C(7)); IR (neat) 2958 (m), 2930 (m), 2859 (w), 1622 (w), 1472 (m), 1388 (w), 1363 (m), 1253 (m), 1139 (w), 1090 (s), 1006 (w), 938 (w), 860 (m), 837 (s), 776 (s), 683 (w), 665 (w), 584 (w), 501 (w); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>15</sub>H<sub>34</sub>NO<sub>2</sub>SSi 320.2076, found 320.2080; TLC *R*<sub>f</sub> 0.50 (silica gel, hexanes/EtOAc, 9:1, UV, KMnO<sub>4</sub>).



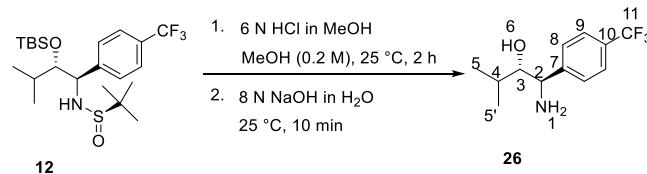
*Preparation of (R)-N-((2S)-2-((tert-Butyldimethylsilyl)oxy)-3-methyl-1-(4-(trifluoromethyl)phenyl)butyl)-2-methylpropane-2-sulfonamide (12).* A 100 mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1 × 15.9 mm) was charged with

bromo-4-(trifluoromethyl)benzene (3.15 g, 1.96 mL, 14.0 mmol, 2.0 equiv) and THF (17 mL) under nitrogen. The solution was cooled to  $-78^{\circ}\text{C}$  using a cryocooler in an *i*-PrOH bath, and *n*-butyllithium (0.89 g, 8.8 mL, 1.6 M in hexane, 14.0 mmol, 2.0 equiv) was added dropwise by syringe. The resulting solution was stirred at  $-78^{\circ}\text{C}$  using a cryocooler in *i*-PrOH bath for 1 h. Then another 50 mL Schlenk flask containing an egg-shaped stir bar (19.1  $\times$  9.5 mm) was charged with **6c** (2.23 g, 7.0 mmol) and THF (17 mL) under nitrogen and was cooled to  $-78^{\circ}\text{C}$  using a cryocooler in an *i*-PrOH bath. The *N*-sulfinyl imine solution was transferred to the organolithium solution using a syringe dropwise over 5 min. The resulting mixture was stirred at  $-78^{\circ}\text{C}$  using a cryocooler in an *i*-PrOH bath for 12 h. The reaction was quenched by the addition of satd aq  $\text{NH}_4\text{Cl}$  solution (50 mL) at  $-78^{\circ}\text{C}$  and then was slowly warmed to  $25^{\circ}\text{C}$ . The mixture was transferred to a 250 mL separatory funnel. The organic layer was removed, the aqueous layer was extracted with ethyl acetate (3  $\times$  50 mL), and the organic layers were combined, washed with brine (1  $\times$  100 mL), dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation ( $30^{\circ}\text{C}$ , 50 mbar). The dr of the crude product was  $>99:1$  by  $^1\text{H}$  NMR analysis. The crude product was purified by column chromatography (silica, 4 cm  $\varnothing$   $\times$  12 cm column) eluting with hexanes/EtOAc, 1:1 to afford **13** (4.60 g, 78%) as a yellow solid. Data for **13**: mp 97–99  $^{\circ}\text{C}$  (hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.97 (d,  $J$  = 10.6 Hz, 2H, HC(13,13')), 4.76 (t,  $J$  = 9.6 Hz, 1H, HC(4)), 4.48 (d,  $J$  = 10.1 Hz, 1H, HN(3)), 3.80 (d,  $J$  = 9.2 Hz, 1H, HC(5)), 3.70 (s, 3H, HC(15)), 3.67 (s, 3H, HC(16)), 3.62 (s, 3H, HC(15')), 2.29 (sept,  $J$  = 6.7 Hz, 1H, HC(6)), 0.90 (d,  $J$  = 6.7 Hz, 3H, HC(7)), 0.85 (d,  $J$  = 7.1 Hz, 3H, HC(7')), 0.83 (s, 9H, HC(1)), 0.61 (s, 9H, HC(10)),  $-0.21$  (s, 3H, HC(8)),  $-0.81$  (s, 3H, HC(8'));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  160.3 (C(14)), 158.9 (C(12)), 158.6 (C(12')), 110.7 (C(11)), 90.7 (C(13)), 90.6 (C(13')), 77.8 (C(5)), 55.6 (C(2)), 55.4 (C(16)), 55.1 (C(15)), 55.0 (C(15')), 54.5 (C(4)), 29.1 (C(6)), 25.8 (C(10)), 21.8 (C(1)), 21.4 (C(7')), 18.0 (C(9)), 14.2 (C(7)),  $-4.1$  (C(8)),  $-5.5$  (C(8')); IR (neat) 2957 (w), 2856 (w), 2231 (w), 1608 (m), 1592 (m), 1497 (w), 1465 (m), 1419 (w), 1363 (w), 1331 (w), 1250 (w), 1221 (m), 1204 (m), 1151 (m), 1124 (s), 1105 (m), 1061 (s), 1009 (w), 951 (m), 924 (m), 909 (m), 858 (m), 831 (s), 813 (m), 773 (s), 729 (s), 671 (w), 644 (m), 601 (w), 558 (m), 465 (w); HRMS (ESI)  $m/z$  (M + H) $^+$  calcd for  $\text{C}_{24}\text{H}_{46}\text{NO}_3\text{SSi}$  488.2859, found 488.2866; TLC  $R_f$  0.17 (silica gel, hexanes/EtOAc, 7:3, UV,  $\text{KMnO}_4$ ).

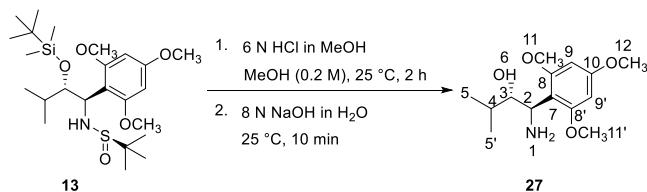


*Preparation of (R)-N-((1*R*,2*S*)-2-((tert-Butyldimethylsilyl)oxy)-3-methyl-1-(2,4,6-trimethoxyphenyl)butyl)-2-methylpropane-2-sulfonamide (13).* A 100 mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1  $\times$  15.9 mm) was charged with 1,3,5-trimethoxybenzene (4.03 g, 24.0 mmol, 2.0 equiv) and THF (30 mL) under nitrogen. The solution was cooled to 0  $^{\circ}\text{C}$  using an ice bath, and *n*-butyllithium (1.53 g, 15.0 mL, 1.6 M in hexane, 24.0 mmol, 2.0 equiv) was added dropwise by syringe. The resulting mixture was slowly warmed to 25  $^{\circ}\text{C}$  and was stirred at 25  $^{\circ}\text{C}$  for 3 h. Then the organolithium solution was cooled to  $-78^{\circ}\text{C}$  using a cryocooler in an *i*-PrOH bath, and the temperature was monitored using an internal temperature probe. Then another 50 mL Schlenk flask containing an egg-shaped stir bar (19.1  $\times$  9.5 mm) was charged with **6c** (3.83 g, 12.0 mmol) and THF (30 mL) under nitrogen and was cooled to  $-78^{\circ}\text{C}$  using a cryocooler in an *i*-PrOH bath. The *N*-sulfinyl imine solution was transferred to the organolithium solution using a syringe dropwise over 5 min. The resulting mixture was stirred at  $-78^{\circ}\text{C}$  using a cryocooler in *i*-PrOH bath for 12 h. The reaction was quenched by the addition of satd aq  $\text{NH}_4\text{Cl}$  solution (50 mL) at  $-78^{\circ}\text{C}$  and slowly warmed to

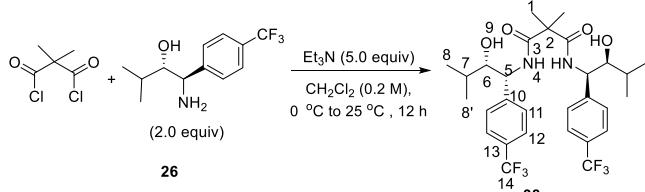
25  $^{\circ}\text{C}$ . The mixture was transferred to a 250 mL separatory funnel. The organic layer was removed, the aqueous layer was extracted with ethyl acetate (3  $\times$  60 mL), and the organic layers were combined, washed with brine (1  $\times$  100 mL), dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30  $^{\circ}\text{C}$ , 50 mbar). The dr of the crude product was  $>99:1$  by  $^1\text{H}$  NMR analysis. The crude product was purified by column chromatography (silica, 4 cm  $\varnothing$   $\times$  12 cm column) eluting with hexanes/EtOAc, 1:1 to afford **13** (4.60 g, 78%) as a yellow solid. Data for **13**: mp 97–99  $^{\circ}\text{C}$  (hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.97 (d,  $J$  = 10.6 Hz, 2H, HC(13,13')), 4.76 (t,  $J$  = 9.6 Hz, 1H, HC(4)), 4.48 (d,  $J$  = 10.1 Hz, 1H, HN(3)), 3.80 (d,  $J$  = 9.2 Hz, 1H, HC(5)), 3.70 (s, 3H, HC(15)), 3.67 (s, 3H, HC(16)), 3.62 (s, 3H, HC(15')), 2.29 (sept,  $J$  = 6.7 Hz, 1H, HC(6)), 0.90 (d,  $J$  = 6.7 Hz, 3H, HC(7)), 0.85 (d,  $J$  = 7.1 Hz, 3H, HC(7')), 0.83 (s, 9H, HC(1)), 0.61 (s, 9H, HC(10)),  $-0.21$  (s, 3H, HC(8)),  $-0.81$  (s, 3H, HC(8'));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  160.3 (C(14)), 158.9 (C(12)), 158.6 (C(12')), 110.7 (C(11)), 90.7 (C(13)), 90.6 (C(13')), 77.8 (C(5)), 55.6 (C(2)), 55.4 (C(16)), 55.1 (C(15)), 55.0 (C(15')), 54.5 (C(4)), 29.1 (C(6)), 25.8 (C(10)), 21.8 (C(1)), 21.4 (C(7')), 18.0 (C(9)), 14.2 (C(7)),  $-4.1$  (C(8)),  $-5.5$  (C(8')); IR (neat) 2957 (w), 2856 (w), 2231 (w), 1608 (m), 1592 (m), 1497 (w), 1465 (m), 1419 (w), 1363 (w), 1331 (w), 1250 (w), 1221 (m), 1204 (m), 1151 (m), 1124 (s), 1105 (m), 1061 (s), 1009 (w), 951 (m), 924 (m), 909 (m), 858 (m), 831 (s), 813 (m), 773 (s), 729 (s), 671 (w), 644 (m), 601 (w), 558 (m), 465 (w); HRMS (ESI)  $m/z$  (M + H) $^+$  calcd for  $\text{C}_{24}\text{H}_{46}\text{NO}_3\text{SSi}$  488.2859, found 488.2866; TLC  $R_f$  0.17 (silica gel, hexanes/EtOAc, 7:3, UV,  $\text{KMnO}_4$ ).



*Preparation of (1*R*,2*S*)-1-Amino-3-methyl-1-(4-(trifluoromethyl)phenyl)butan-2-ol (26).* A 250 mL, one-necked Schlenk flask with an egg-shaped stir bar (50.8  $\times$  19.1 mm) was charged with **12** (2.32 g, 5.0 mmol) and methanol (10 mL) under nitrogen. HCl (6 N) in MeOH (50 mL) was added dropwise by syringe. The reaction was stirred for 2 h at 25  $^{\circ}\text{C}$ , and then the solvent was removed by rotary evaporation (30  $^{\circ}\text{C}$ , 50 mbar). The crude solid was suspended in ethyl acetate (30 mL), and 8 N NaOH in  $\text{H}_2\text{O}$  (75 mL) was added while the solution was stirred vigorously. The solution was stirred for 10 min and then was transferred to a 500 mL separatory funnel. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2  $\times$  50 mL). pH paper was used to check the neutralization of the solution (pH = 7). The organic layers were combined, dried over anhydrous  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30  $^{\circ}\text{C}$ , 50 mbar). The crude product was purified by column chromatography (silica, 4 cm  $\varnothing$   $\times$  12 cm column) eluting with MeOH/EtOAc, 2:8 to afford **26** (0.98 g, 80%) as a white solid. Data for **26**: mp 139–141  $^{\circ}\text{C}$  (MeOH/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.63–7.58 (m, 4H, HC(8,9)), 4.86 (s, 1H, HO(6)), 3.94 (d,  $J$  = 5.7 Hz, 1H, HC(2)), 3.45 (t,  $J$  = 6.1 Hz, 1H, HC(3)), 1.70–1.46 (m, 1H, HC(4)), 0.99 (d,  $J$  = 6.8 Hz, 3H, HC(5)), 0.94 (d,  $J$  = 6.7 Hz, 3H, HC(5'));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  148.7 (C(7)), 129.8 (C-F, 2J<sub>C-F</sub> = 31.3 Hz, C(10)), 129.8 (C-F, 3J<sub>C-F</sub> = 3.8 Hz, C(9)), 125.8 (C-F, 1J<sub>C-F</sub> = 270.0 Hz, C(11)), 80.8 (C(3)), 58.4 (C(2)), 31.3 (C(4)), 20.1 (C(5)), 17.7 (C(5'));  $^{19}\text{F}$ NMR (471 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$   $-59.87$ ; IR (neat) 2931 (w), 2291 (w), 1617 (w), 1424 (w), 1364 (w), 1326 (s), 1162 (m), 1108 (s), 1065 (s), 1018 (s), 974 (m), 924 (w), 887 (m), 857 (m), 843 (s), 781 (m), 747 (m), 700 (w), 678 (m), 610 (s), 586 (m), 526 (w), 496 (w); HRMS (ESI)  $m/z$  (M + H) $^+$  calcd for  $\text{C}_{12}\text{H}_{17}\text{NOF}_3$  248.1261, found 248.1262; TLC  $R_f$  0.35 (silica gel, MeOH/EtOAc, 2:8, UV,  $\text{KMnO}_4$ ).

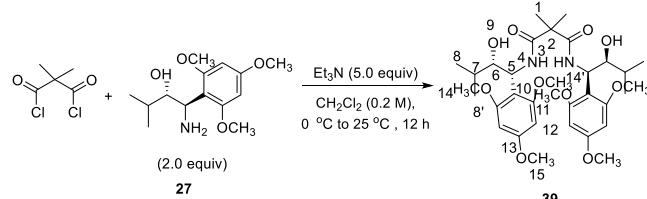


**Preparation of (1*R*,2*S*)-1-Amino-3-methyl-1-(2,4,6-trimethoxyphenyl)butan-2-ol (27).** A 250 mL, one-necked Schlenk flask with an egg-shaped stir bar (50.8 × 19.1 mm) was charged with 13 (3.90 g, 8.0 mmol) and methanol (15 mL) under nitrogen. HCl (6 N) in MeOH (80 mL) was added dropwise by syringe. The reaction was stirred for 2 h at 25 °C, and then the solvent was removed rotary evaporation (30 °C, 50 mbar). The crude solid was suspended in ethyl acetate (30 mL), and 8 N NaOH in H<sub>2</sub>O (120 mL) was added while the solution was stirred vigorously. The solution was stirred for 10 min and then was transferred to a 500 mL separatory funnel. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 75 mL). pH paper was used to check the neutralization of the solution (pH = 7). The organic layers were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm Ø × 12 cm column) eluting with MeOH/EtOAc, 2:8 to afford 27 (1.70 g, 77%) as a white solid. The compound 27 was crystallized from EtOAc at -35 °C. Data for 27: mp 107–109 °C (MeOH/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.05 (s, 2H, HC(9,9')), 4.36 (d, *J* = 7.9 Hz, 1H, HC(2)), 3.70 (d, *J* = 6.6 Hz, 9H, HC(11,11',12)), 3.57 (dd, *J* = 7.9, 4.0 Hz, 1H, HC(3)), 2.19 (s, 3H, HN, HO(1,6)), 1.85–1.79 (m, 1H, HC(4)), 0.90 (d, *J* = 7.1 Hz, 3H, HC(5)), 0.84 (d, *J* = 6.9 Hz, 3H, HC(5')); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 160.0 (C(10)), 158.9 (C(8,8')), 111.3 (C(7)), 90.9 (C(9)), 78.5 (C(3)), 55.5 (C(11,11')), 55.0 (C(12)), 49.5 (C(2)), 29.7 (C(4)), 20.3 (C(5)), 15.3 (C(5')); IR (neat) 3353 (w), 2952 (m), 1589 (s), 1491 (w), 1455 (m), 1437 (m), 1414 (m), 1375 (m), 1337 (w), 1270 (w), 1220 (m), 1202 (s), 1181 (m), 1166 (m), 1148 (s), 1120 (s), 1058 (m), 1039 (m), 1016 (m), 1001 (m), 961 (s), 816 (s), 794 (m), 635 (m), 567 (m), 528 (m); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>29</sub>H<sub>37</sub>N<sub>2</sub>O<sub>4</sub>F<sub>6</sub> 591.2650, found 591.2658; TLC *R*<sub>f</sub> 0.33 (silica gel, hexanes/EtOAc, 6:4, UV, KMnO<sub>4</sub>).

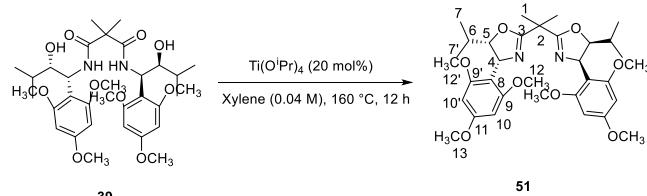


**Preparation of N<sup>1</sup>,N<sup>3</sup>-Bis((1*R*,2*S*)-2-hydroxy-3-methyl-1-(4-(trifluoromethyl)phenyl)butyl)-2,2-dimethylmalonamide (38).** A 50 mL Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with 26 (0.74 g, 3.0 mmol, 2.0 equiv), Et<sub>3</sub>N (0.75 g, 1.04 mL, 7.5 mmol, 5.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (10 mL) under nitrogen. The solution was cooled to 0 °C using an ice bath, and 2,2-dimethylmalonyl dichloride (0.25 g, 0.19 mL, 1.5 mmol) was added dropwise by syringe over 2 min. The resulting mixture was slowly warmed to 25 °C and was stirred at 25 °C for 12 h. The mixture was transferred to a 125 mL separatory funnel. The reaction mixture was washed with water (1 × 50 mL) and then brine (1 × 50 mL). The organic layer was removed, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 mL), and the organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm Ø × 15 cm column) eluting with hexanes/EtOAc, 1:1 to afford 38 (0.74 g, 83%) as a white solid. Data for 38: mp 175–177 °C (hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.62 (d, *J* = 7.9 Hz, 2H, HC(4)), 7.49 (d, *J* = 7.7 Hz, 4H, HC(12)), 7.40 (d, *J* = 7.8 Hz, 4H, HC(11)), 5.04 (dd, *J* = 8.1, 4.3 Hz, 2H, HC(5)), 3.58–3.39

(m, 2H, HC(6)), 2.63 (d, *J* = 5.8 Hz, 2H, HO(9)), 1.37 (s, 6H, HC(1)), 1.36–1.29 (m, 2H, HC(7)), 0.93 (d, *J* = 6.5 Hz, 6H, HC(8)), 0.87 (d, *J* = 6.4 Hz, 6H, HC(8')); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 172.7 (C(3)), 142.5 (C(10)), 129.9 (C–F, 2J<sub>C–F</sub> = 32.5 Hz, C(13)), 128.6 (C(11)), 125.3 (C–F, 3J<sub>C–F</sub> = 3.8 Hz, C(12)), 124.1 (C–F, 1J<sub>C–F</sub> = 270.0 Hz, C(14)), 120.8 (C(6)), 78.8 (C(5)), 49.4 (C(2)), 30.7 (C(7)), 23.7 (C(1)), 19.1 (C(8)), 18.3 (C(8')); <sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>) –62.64; IR (neat) 2916 (s), 2848 (s), 1738 (m), 1662 (w), 1518 (w), 1472 (m), 1366 (m), 1328 (m), 1229 (w), 1217 (m), 1164 (w), 1125 (m), 1069 (w), 1019 (w), 847 (w), 730 (w), 719 (m), 618 (w), 528 (w); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>29</sub>H<sub>37</sub>N<sub>2</sub>O<sub>4</sub>F<sub>6</sub> 591.2650, found 591.2658; TLC *R*<sub>f</sub> 0.33 (silica gel, hexanes/EtOAc, 6:4, UV, KMnO<sub>4</sub>).

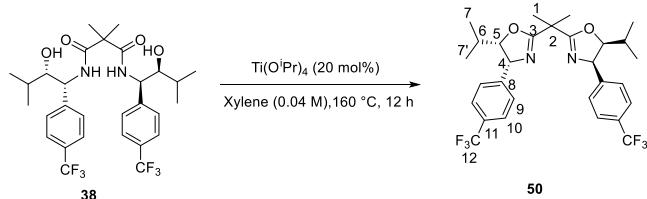


**Preparation of N<sup>1</sup>,N<sup>3</sup>-Bis((1*R*,2*S*)-2-hydroxy-3-methyl-1-(2,4,6-trimethoxyphenyl)butyl)-2,2-dimethylmalonamide (39).** A 50 mL Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with 27 (1.45 g, 5.4 mmol, 2.0 equiv), Et<sub>3</sub>N (1.36 g, 1.87 mL, 13.5 mmol, 5.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (15 mL) under nitrogen. The solution was cooled to 0 °C using an ice bath, and 2,2-dimethylmalonyl dichloride (0.45 g, 0.35 mL, 2.7 mmol) was added dropwise by syringe over 2 min. The resulting mixture was slowly warmed to 25 °C and was stirred at 25 °C for 12 h. The mixture was transferred to a 125 mL separatory funnel. The reaction mixture was washed with water (1 × 50 mL) and then brine (1 × 50 mL). The organic layer was removed, and then the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 mL), and the organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm Ø × 15 cm column) eluting with hexanes/EtOAc, 3:7 to afford 39 (1.4 g, 81%) as a white solid. Data for 39: mp 68–70 °C (hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.98 (d, *J* = 9.5 Hz, 2H, HC(4)), 6.08 (s, 4H, HC(12)), 5.70 (t, *J* = 8.5 Hz, 2H, HC(5)), 3.79 (s, 12H, HC(14,14')), 3.76 (s, 6H, HC(15)), 3.59 (ddd, *J* = 10.0, 5.0 Hz, 2H, HC(6)), 1.80 (d, *J* = 5.7 Hz, 2H, HO(9)), 1.69 (qqd, *J* = 17.5, 10.0, 7.0, 3.0 Hz, 2H, HC(7)), 1.35 (s, 6H, HC(1)), 0.99 (d, *J* = 6.8 Hz, 6H, HC(8)), 0.95 (d, *J* = 6.7 Hz, 6H, HC(8')); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 172.3 (C(3)), 160.6 (C(13)), 159.1 (C(11)), 107.4 (C(10)), 91.1 (C(12)), 78.1 (C(6)), 55.9 (C(14,15)), 55.3 (C(14')), 49.4 (C(2)), 47.4 (C(5)), 29.8 (C(7)), 23.7 (C(1)), 20.5 (C(8)), 15.3 (C(8')); IR (neat) 3450 (w), 2969 (w), 2840 (w), 1739 (m), 1666 (m), 1608 (s), 1591 (m), 1498 (s), 1454 (s), 1419 (m), 1365 (m), 1331 (m), 1219 (s), 1204 (s), 1149 (s), 1120 (s), 1059 (m), 1035 (m), 999 (m), 950 (m), 920 (m), 813 (m), 728 (m), 634 (m), 547 (m), 527 (m); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>51</sub>H<sub>81</sub>N<sub>2</sub>O<sub>10</sub> 635.3549, found 635.3544; TLC *R*<sub>f</sub> 0.16 (silica gel, hexanes/EtOAc, 1:1, UV, KMnO<sub>4</sub>).



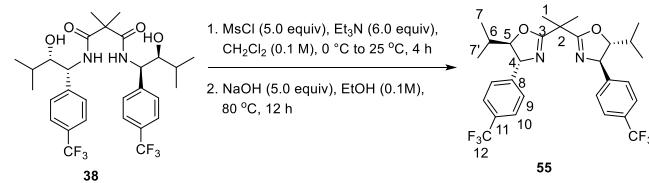
**Preparation of (4*R*,4*'S*,5*S*,5*'S*)-2,2'-(Propane-2,2-diyl)bis(5-isopropyl-4-(2,4,6-trimethoxyphenyl)-4,5-dihydrooxazole) (51).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with 39 (0.31 g, 0.50 mmol) and xylenes (12 mL) under nitrogen. The mixture was heated to reflux

in a 160 °C oil bath using a condenser connected to a Dean–Stark apparatus which was itself connected to Schlenk flask. Once the bisamide alcohol dissolved completely then  $\text{Ti(O-i-Pr)}_4$  (0.028 g, 0.030 mL, 20 mol %) was added to the solution in one portion. The reaction mixture was refluxed for 12 h with removal of the water byproduct. After the reaction mixture was cooled to room temperature, the solution was concentrated by rotary evaporation (60 °C, 50 mbar). The crude product was purified by column chromatography (silica neutralized with triethylamine, 1 cm  $\varnothing$   $\times$  15 cm column) eluting with *n*-hexane (95%)/EtOAc, 3:7 to afford **51** (0.25 g, 85%) as a white solid. Recrystallization from *n*-hexane (95%)/Et<sub>2</sub>O (1:1) afforded 0.23 g (80%) of analytically pure **51** as a white solid. Data for **51**: mp 134–136 °C (*n*-hexane (95%)/Et<sub>2</sub>O); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>);  $\delta$  6.05 (s, 4H, HC(10,10')), 5.74 (d,  $J$  = 10.4 Hz, 2H, HC(4)), 4.06 (t,  $J$  = 10.5 Hz, 2H, HC(5)), 3.74 (s, 6H, HC(13)), 3.73 (s, 6H, HC(12)), 3.67 (s, 6H, HC(12')), 1.63 (dqq,  $J$  = 10.5, 6.6, 6.5 Hz, 2H, HC(6)), 1.54 (s, 6H, HC(1)), 0.97 (d,  $J$  = 6.5 Hz, 6H, HC(7)), 0.50 (d,  $J$  = 6.6 Hz, 6H, HC(7')); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>);  $\delta$  169.9 (C(3)), 161.0 (C(9)), 160.6 (C(11)), 158.8 (C(9')), 107.3 (C(8)), 90.9 (C(10)), 90.2 (C(10')), 88.5 (C(5)), 61.0 (C(6)), 55.7 (C(4)), 55.2 (C(13)), 54.9 (C(12)), 38.9 (C(12')), 28.7 (C(2)), 24.3 (C(1)), 20.7 (C(7')), 19.1 (C(7)); IR (neat) 1657 (s), 1633 (s), 1603 (s), 1596 (s), 1417 (s), 1326 (S), 1223 (s), 1137 (s), 1117 (m), 1074 (s), 990 (s), 939 (s), 895 (s), 775 (m), 518 (s); LRMS [ESI<sup>+</sup>, TOF] 204.1(2), 335.1(4), 309.3(3), 599.3(100), 600.3(39), 601.3(9), 602.3(2); Anal. Calcd for C<sub>33</sub>H<sub>46</sub>N<sub>2</sub>O<sub>8</sub> (598.725): C, 66.20; H, 7.74; N, 4.68. Found: C, 66.11; H, 7.68; N, 4.85; HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>33</sub>H<sub>47</sub>N<sub>2</sub>O<sub>8</sub> 599.3320, found 599.3332; TLC *R<sub>f</sub>* 0.29 (silica gel, hexanes/EtOAc, 1:9, UV, KMnO<sub>4</sub>);  $[\alpha]_D^{24}$  +187.7 ( $c$  = 1.0, CHCl<sub>3</sub>).



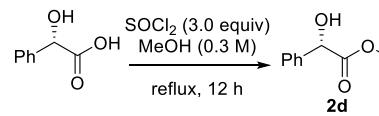
**Preparation of (4*R*,4*R*',5*R*,5*S*)-2,2'-(Propane-2,2-diyl)bis(5-*iso*propyl-4-(4-(trifluoromethyl)phenyl)-4,5-dihydrooxazole) (50).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9  $\times$  6.35 mm) was charged with **38** (0.29 g, 0.50 mmol) and xylenes (12 mL) under nitrogen. The mixture was heated to reflux in a 160 °C oil bath using a condenser connected to a Dean–Stark apparatus which was itself connected to a Schlenk flask. Once the bisamide alcohol dissolved completely then  $\text{Ti(O-i-Pr)}_4$  (0.028 g, 0.030 mL, 20 mol %) was added to the solution in one portion. The reaction mixture was refluxed for 12 h with removal of the water byproduct. After the reaction mixture was cooled to room temperature, the solution was concentrated by rotary evaporation (60 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm  $\varnothing$   $\times$  15 cm column) eluting with *n*-hexane (95%)/EtOAc, 1:1 to afford **50** (0.22 g, 80%) as a white solid. Recrystallization from *n*-hexane (95%) afforded 0.21 g (77%) of analytically pure **50** as a white solid. Data for **50**: mp 99–101 °C (*n*-hexane (95%)); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.52 (d,  $J$  = 8.2 Hz, 4H, HC(10)), 7.38 (d,  $J$  = 8.1 Hz, 4H, HC(9)), 5.17 (d,  $J$  = 9.1 Hz, 2H, HC(4)), 4.38 (t,  $J$  = 9.4 Hz, 2H, HC(5)), 1.67 (s, 6H, HC(1)), 1.56 (dqq,  $J$  = 9.4, 6.6, 6.6 Hz, 2H, HC(6)), 0.99 (d,  $J$  = 6.6 Hz, 6H, HC(7)), 0.68 (d,  $J$  = 6.6 Hz, 6H, HC(7')); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  171.0 (C(3)), 141.8 (C(8)), 129.8 (C–F, 2J<sub>C–F</sub> = 32.8 Hz, C(11)), 129.1 (C(9)), 125.1 (C–F, 3J<sub>C–F</sub> = 3.8 Hz, C(10)), 124.1 (C–F, 1J<sub>C–F</sub> = 272.1 Hz, C(12)), 120.94 (C(5)), 90.5 (C(4)), 71.1 (C(2)), 39.3 (C(6)), 24.5 (C(1)), 19.9 (C(7')), 18.9 (C(7)); <sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>) –62.58; IR (neat) 2967 (s), 1665 (s), 1646 (s), 1621 (s), 1467 (s), 1326 (S), 1232 (s), 1157 (s), 1121 (m), 1099 (m), 989 (s), 900 (s), 868 (s), 731 (m), 500 (s); LRMS [ESI<sup>+</sup>, TOF] 344.1(1), 553.2(1), 555.2(100), 556.2(32), 573.2(8), 574.2(3); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>29</sub>H<sub>33</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub> 555.2438, found 555.2446; TLC *R<sub>f</sub>* 0.19 (silica gel, hexanes/EtOAc, 9:1, UV, KMnO<sub>4</sub>);  $[\alpha]_D^{24}$  +193.4 ( $c$  = 1.0, CHCl<sub>3</sub>). Anal. Calcd for C<sub>29</sub>H<sub>33</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub> (554.566): C, 62.81; H, 5.82; N, 5.05. Found: C, 62.88; H, 5.75; N, 5.31.

+ H)<sup>+</sup> calcd for C<sub>29</sub>H<sub>33</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub> 555.2455, found 555.2446; TLC *R<sub>f</sub>* 0.21 (silica gel, hexanes/EtOAc, 7:3, UV, KMnO<sub>4</sub>);  $[\alpha]_D^{24}$  +193.6 ( $c$  = 1.0, CHCl<sub>3</sub>). Anal. Calcd for C<sub>29</sub>H<sub>33</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub> (554.566): C, 62.56; H, 5.82; N, 5.05. Found: C, 62.48; H, 5.90; N, 5.08.



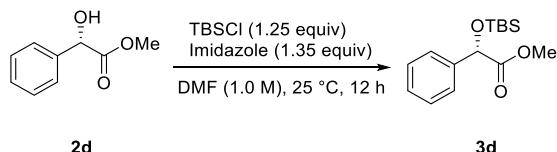
**Preparation of (4*R*,4*R*',5*R*,5*R*)-2,2'-(Propane-2,2-diyl)bis(5-*iso*propyl-4-(4-(trifluoromethyl)phenyl)-4,5-dihydrooxazole) (55).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9  $\times$  6.35 mm) was charged with **38** (0.29 g, 0.50 mmol), Et<sub>3</sub>N (0.30 g, 0.41 mL, 3.0 mmol, 6.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (5 mL) under nitrogen. The solution was cooled to 0 °C using an ice bath, and methanesulfonyl chloride (0.28 g, 0.19 mL, 2.5 mmol, 5.0 equiv) was added dropwise by syringe over 2 min. The mixture was quenched with H<sub>2</sub>O (1 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (5  $\times$  2 mL portions). The organic layers were combined and concentrated by rotary evaporation (30 °C, 50 mbar). A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9  $\times$  6.35 mm) was charged with the residue, and ethanol (5 mL). NaOH (0.10 g, 2.5 mmol, 5.0 equiv) in water (0.5 mL) was added dropwise. The mixture was heated to reflux using a condenser in 85 °C oil bath for 12 h. After the solution was cooled to 25 °C, the volatile components were removed by rotary evaporation (30 °C, 50 mbar). The resulting residue was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The mixture was transferred to a 60 mL separatory funnel. The reaction mixture was washed with water (1  $\times$  5 mL) and then brine (1  $\times$  5 mL). The organic layer was removed, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  10 mL), and the organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub> (0.30 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm  $\varnothing$   $\times$  15 cm column) eluting with *n*-hexane (95%)/EtOAc, 1:1 to afford **55** (0.22 g, 81%) as a white solid. Recrystallization from *n*-hexane (95%) afforded 0.21 g (76%) of analytically pure **55** as a white solid. Data for **55**: mp 89–91 °C (*n*-hexane (95%)); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>);  $\delta$  7.53 (d,  $J$  = 8.3 Hz, 4H, HC(10)), 7.37 (d,  $J$  = 8.2 Hz, 4H, HC(9)), 4.90 (d,  $J$  = 6.1 Hz, 2H, HC(4)), 4.16 (t,  $J$  = 6.2 Hz, 2H, HC(5)), 1.95 (dqq,  $J$  = 7.7, 7.7, 6.2 Hz, 2H, HC(6)), 1.69 (s, 6H, HC(1)), 1.11–0.93 (m, 12H, HC(7')); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>);  $\delta$  170.5 (C(3)), 147.0 (C(8)), 130.2 (C–F, 2J<sub>C–F</sub> = 31.5 Hz, C(11)), 127.3 (C(9)), 125.7 (C–F, 1J<sub>C–F</sub> = 3.8 Hz, C(10)), 124.2 (C–F, 1J<sub>C–F</sub> = 272.2 Hz, C(12)), 123.1 (C(5)), 93.0 (C(4)), 39.3 (C(2)), 32.7 (C(6)), 24.4 (C(1)), 17.6 (C(7')), 17.3 (C(7)); <sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>) –62.58; IR (neat) 2973 (s), 1650 (s), 1620 (s), 1519 (s), 1416 (s), 1325 (S), 1228 (s), 1128 (m), 1114 (m), 1067 (m), 980 (s), 905 (s), 867 (s), 724 (s), 512 (s); LRMS [ESI<sup>+</sup>, TOF] 215.1(1), 306.1(1), 553.5(1), 555.2(100), 556.2(32), 573.2(8), 574.2(3); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>29</sub>H<sub>33</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub> 555.2438, found 555.2446; TLC *R<sub>f</sub>* 0.19 (silica gel, hexanes/EtOAc, 9:1, UV, KMnO<sub>4</sub>);  $[\alpha]_D^{24}$  +193.4 ( $c$  = 1.0, CHCl<sub>3</sub>). Anal. Calcd for C<sub>29</sub>H<sub>33</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub> (554.566): C, 62.81; H, 5.82; N, 5.05. Found: C, 62.88; H, 5.75; N, 5.31.

#### Synthesis of Bisoxazoline Ligands with a Phenyl Substituent at the C(5)-Position.

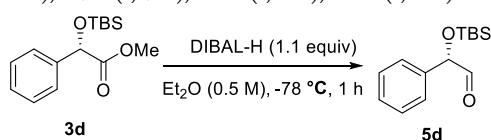


**Preparation of Methyl (S)-2-Hydroxy-2-phenylacetate (2d).** A 250 mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8  $\times$  19.1 mm) was charged with (S)-2-hydroxy-2-phenylacetic acid (7.60 g, 50.0 mmol) and MeOH (distilled, 120 mL) under nitrogen. The solution was cooled in an ice bath for 10 min, and SOCl<sub>2</sub> (17.84 g, 10.94 mL, 150.0 mmol, 3.0 equiv) was added

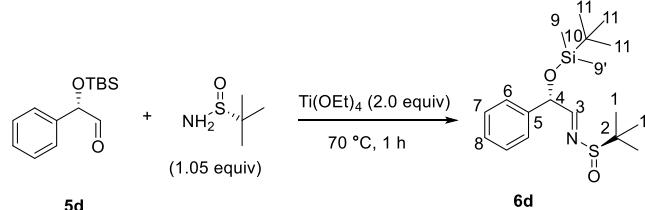
dropwise by syringe over 5 min at 0 °C. The mixture was heated to reflux using a condenser in 75 °C oil bath for 12 h. After the solution was cooled to 25 °C, the volatile components are removed by rotary evaporation (30 °C, 50 mbar). The resulting residue was diluted with ethyl acetate (200 mL), and satd aq NaHCO<sub>3</sub> (200 mL) was added slowly because of the evolution of gas. The mixture was transferred to a 500 mL separatory funnel, and the organic layer was removed. The aqueous layer was extracted with ethyl acetate (3 × 100 mL), and the organic layers were combined, washed brine (1 × 100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by column chromatography (silica, 4 cm ø × 15 cm column) eluting with hexanes/EtOAc, 7:3 to afford **2d** (7.25 g, 87%) as a white solid. The spectroscopic data for **2d** matched the literature values.<sup>93</sup> Data for **2d**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.43–7.40 (m, 2H), 7.40–7.33 (m, 3H), 5.18 (d, *J* = 5.1 Hz, 1H), 3.74 (s, 3H), 3.65 (d, *J* = 5.2 Hz, 1H).



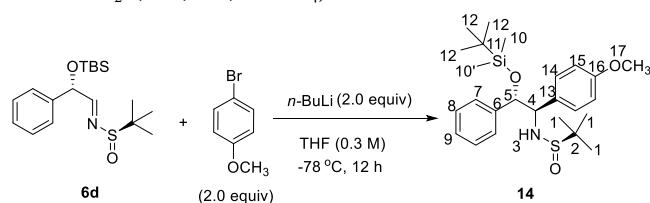
**Preparation of Methyl (S)-2-((tert-Butyldimethylsilyl)oxy)-2-phenylacetate (3d).** A 250 mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **2d** (7.24 g, 43.6 mmol), TBSCl (8.21 g, 54.5 mmol, 1.25 equiv), imidazole (4.00 g, 58.86 mmol, 1.35 equiv), and DMF (SDS, 45 mL) under nitrogen. The mixture was stirred at 25 °C for 12 h. The resulting mixture was diluted in Et<sub>2</sub>O (200 mL), transferred to 500 mL separatory funnel, washed with water (3 × 100 mL) and brine (1 × 100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/Et<sub>2</sub>O, 9:1 to afford **3d** (11.00 g, 92%) as a colorless oil. The spectroscopic data for **3d** matched the literature values.<sup>118</sup> Data for **3d**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.50 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.41–7.24 (m, 3H), 5.28 (s, 1H), 3.67 (s, 3H), 0.96 (s, 9H), 0.15 (s, 3H), 0.07 (s, 3H).



**Preparation of (S)-2-((tert-Butyldimethylsilyl)oxy)-3-methylbutanal (5d).** A 250 mL, three-necked round-bottomed flask equipped with nitrogen inlet, an egg-shaped stir bar (50.8 × 19.1 mm), an internal temperature probe, and two rubber septa was charged with **3d** (10.99 g, 39.2 mmol) and Et<sub>2</sub>O (80 mL, SDS) under nitrogen. The solution was cooled to -78 °C using a cryocooler in an *i*-PrOH bath, and DIBAL-H (1.0 M in heptane, 43.12 mL, 43.12 mmol, 1.1 equiv) was added dropwise by syringe to maintain the internal temperature below -70 °C. The solution was stirred at -78 °C for 1 h and then reaction was quenched with H<sub>2</sub>O (6 mL). The mixture was slowly warmed to 25 °C. The mixture was stirred for additional 1 h. Then the mixture was filtered through a fritted glass funnel (7.5 mm diameter) containing Celite into a 250 mL filter flask. The Celite cake was washed with Et<sub>2</sub>O (2 × 75 mL). The combined filtrates were transferred to a 250 mL separatory funnel, washed with water (1 × 100 mL) and brine (1 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm  $\varnothing$  × 12 cm column) eluting with hexanes/Et<sub>2</sub>O, 9:1 to afford **5d** (8.60 g, 88%) as a yellow oil. The spectroscopic data for **5d** matched the literature values.<sup>118</sup> Data for **5d**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.54 (d, *J* = 2.3 Hz, 1H), 7.48–7.28 (m, 5H), 5.04 (d, *J* = 2.2 Hz, 1H), 0.98 (s, 9H), 0.15 (s, 3H), 0.07 (s, 3H).

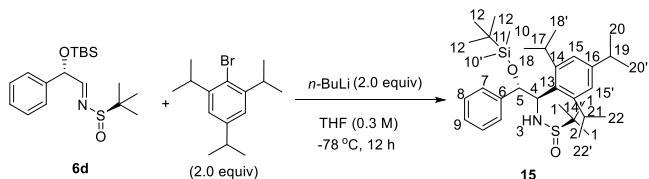


**Preparation of (R)-N-((S,E)-2-((tert-Butyl(dimethylsilyl)oxy)-2-phenylethylidene)-2-methylpropane-2-sulfonamide (6d).** A 100 mL, one-necked Schlenk flask with an egg-shaped stir bar (38.1 × 15.9 mm) was charged with **5d** (8.61 g, 34.4 mmol), (R)-2-methylpropane-2-sulfonamide (4.37 g, 36.12 mmol, 1.05 equiv), and titanium(IV) ethoxide (15.60 g, 14.4 mL, 68.8 mmol, 2.0 equiv) under nitrogen. The mixture was stirred in a 70 °C oil bath for 60 min and then was diluted with ethyl acetate (50 mL). The resulting solution was poured into a 200 mL Erlenmeyer flask with a stir bar and brine (10 mL), and the vial was rinsed with ethyl acetate (2 × 25 mL) to help the transfer. The suspension was stirred at 25 °C for 10 min and then filtered through a fritted glass funnel (7.5 mm diameter) containing Celite. The Celite cake was washed with ethyl acetate (2 × 100 mL). The combined filtrates were transferred to a 250 mL separatory funnel, washed with water (1 × 100 mL) and brine (1 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm Ø × 12 cm column) eluting with hexanes/Et<sub>2</sub>O, 8:2 to afford **6d** (11.00 g, 89%) as a yellow oil. Data for **6d**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.00 (d, *J* = 4.9 Hz, 1H), HC(3)), 7.40 (d, *J* = 7.4 Hz, 2H), HC(6)), 7.33 (t, *J* = 7.5 Hz, 2H), HC(7)), 7.26 (t, *J* = 7.4 Hz, 1H), HC(8)), 5.50 (d, *J* = 4.9 Hz, 1H), HC(4)), 1.06 (s, 9H), HC(1)), 0.92 (s, 10H), HC(11)), 0.10 (s, 3H), HC(9)), 0.03 (s, 3H), HC(9')); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 169.6 (C(3)), 139.8 (C(5)), 128.5 (C(7)), 128.1 (C(8)), 126.3 (C(6)), 76.8 (C(4)), 57.3 (C(2)), 25.7 (C(11)), 22.3 (C(1)), 18.2 (C(10)), -4.6 (C(9)), -4.7 (C(9')); IR (neat) 2956 (w), 2929 (w), 2858 (w), 1624 (w), 1472 (w), 1454 (w), 1390 (w), 1363 (m), 1254 (m), 1193 (w), 1088 (s), 1066 (s), 1027 (w), 1006 (w), 939 (w), 867 (s), 836 (s), 777 (s), 756 (m), 699 (s), 665 (m), 581 (m), 511 (m), 456 (w); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>18</sub>H<sub>32</sub>NO<sub>2</sub>SSi 354.1918, found 354.1923; TLC *R*<sub>f</sub> 0.45 (silica gel, hexanes/Et<sub>2</sub>O, 7:3, UV, KMnO<sub>4</sub>).

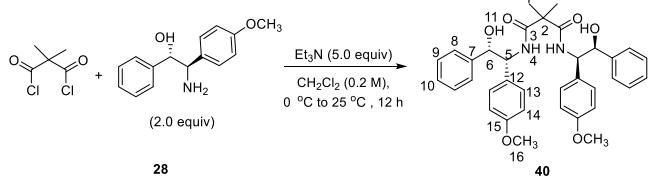


**Preparation of (R)-N-((1*R*,2*S*)-2-((tert-Butyl(dimethylsilyl)oxy)-1-(4-methoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfonamide (14).** A 100 mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1 × 15.9 mm) was charged with 1-bromo-4-methoxybenzene (3.74 g, 2.50 mL, 20.0 mmol, 2.0 equiv) and THF (30 mL) under nitrogen. The solution was cooled to -78 °C using a cryocooler in an *i*-PrOH bath, and *n*-butyllithium (1.28 g, 12.50 mL, 1.6 M in hexane, 20.0 mmol, 2.0 equiv) was added dropwise by syringe. The resulting solution was stirred at -78 °C using a cryocooler in an *i*-PrOH bath for 1 h. Then another 50 mL Schlenk flask containing an egg-shaped stir bar (19.1 × 9.5 mm) was charged with **6d** (3.53 g, 10.0 mmol) and THF (30 mL) under nitrogen and was cooled to -78 °C using a cryocooler in an *i*-PrOH bath. The *N*-sulfinyl imine solution was transferred to the organolithium solution using a syringe dropwise over 5 min. The resulting mixture was stirred at -78 °C using a cryocooler in *i*-PrOH bath for 12 h. The reaction was quenched by the addition of satd aq NH<sub>4</sub>Cl solution (100 mL) at -78 °C and then was slowly warmed to 25 °C. The mixture was transferred to a 250 mL separatory funnel. The organic layer was removed, the aqueous layer

was extracted with ethyl acetate ( $3 \times 75$  mL), and the organic layers were combined, washed with brine ( $1 \times 100$  mL), dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation ( $30^\circ\text{C}$ , 50 mbar). The dr of the crude product was 98:2 by  $^1\text{H}$  NMR analysis. The crude product was purified by column chromatography (silica, 4 cm  $\phi \times 12$  cm column) eluting with hexanes/EtOAc, 7:3 to afford **14** (4.61 g, 76%) as a white solid. Data for **14**: mp 103–105  $^\circ\text{C}$  (hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27–7.19 (m, 3H, HC(7,9)), 7.12 (dd,  $J = 7.3, 2.2$  Hz, 2H, HC(8)), 7.05 (d,  $J = 8.6$  Hz, 2H, HC(14)), 6.77 (d,  $J = 8.7$  Hz, 2H, HC(15)), 4.75 (d,  $J = 6.0$  Hz, 1H, HC(5)), 4.46 (dd,  $J = 6.0, 2.4$  Hz, 1H, HC(4)), 3.74 (s, 3H, HC(17)), 3.69 (d,  $J = 1.8$  Hz, 1H, HN(3)), 1.10 (s, 9H, HC(1)), 0.80 (s, 9H, HC(12)), –0.14 (s, 3H, HC(10)), –0.29 (s, 3H, HC(10'));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.0 (C(16)), 140.3 (C(6)), 130.1 (C(13)), 129.9 (C(14)), 128.8 (C(9)), 127.8 (C(7)), 127.2 (C(8)), 113.0 (C(15)), 79.2 (C(5)), 63.6 (C(4)), 55.2 (C(2)), 55.0 (C(17)), 25.5 (C(12)), 22.4 (C(1)), 17.8 (C(11)), –4.9 (C(10)), –5.4 (C(10')); IR (neat) 2955 (w), 2929 (w), 2857 (w), 1612 (w), 1586 (w), 1513 (m), 1472 (m), 1389 (w), 1363 (w), 1303 (w), 1249 (s), 1173 (m), 1069 (s), 1035 (m), 1009 (m), 985 (w), 911 (m), 828 (s), 777 (s), 731 (s), 700 (s), 673 (m), 635 (m), 602 (m), 570 (m), 479 (w); HRMS (ESI)  $m/z$  (M + H) $^+$  calcd for  $\text{C}_{25}\text{H}_{40}\text{NO}_3\text{SSi}$  462.2490, found 462.2498; TLC  $R_f$  0.47 (silica gel, hexanes/EtOAc, 7:3; UV,  $\text{KMnO}_4$ ).

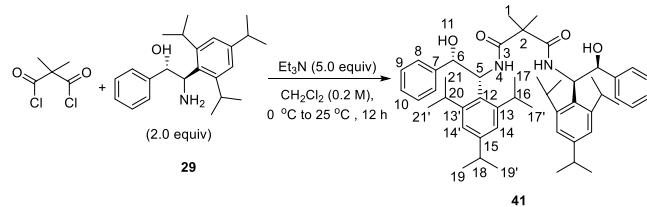


(200 mL) was added while the solution was stirred vigorously. The solution was stirred for 10 min and then was transferred to a 500 mL separatory funnel. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). pH paper was used to check the neutralization of the solution (pH = 7). The organic layers were combined, dried over anhydrous  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The  $^1\text{H}$  NMR analysis of crude product showed the removal of chiral auxiliary only while the TBS group was still intact. The crude residue was moved to the next step of removal of TBS group without further purification. A 250 mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with the crude residue and THF (50 mL) under nitrogen. Tetra-*n*-butylammonium fluoride (5.20 g, 20.0 mL, 1.0 M in THF, 20.0 mmol, 2.0 equiv) was added dropwise by syringe. The mixture was heated to reflux using a condenser in a 60 °C oil bath for 12 h. After the solution was cooled to 25 °C, the volatile components are removed by rotary evaporation (30 °C, 50 mbar). The resulting residue is diluted with ethyl acetate (100 mL) and water (100 mL). The mixture was transferred to a 250 mL separatory funnel, and the organic layer was removed. The aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the organic layers were combined, washed with brine (1 × 100 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by column chromatography (silica, 4 cm  $\varnothing$  × 15 cm column) eluting with hexanes/Et<sub>2</sub>O, 1:1 to afford **29** (3.00 g, 87%) as a white solid. The compound was further recrystallized with hot hexane (30 mL) to afford **29** (2.80 g, 82%) as a white crystalline solid. Data for **29**: mp 149–151 °C (hexanes);  $^1\text{H}$  NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.61 (d,  $J$  = 7.3 Hz, 2H, HC(5)), 7.46 (t,  $J$  = 7.5 Hz, 2H, HC(6)), 7.38 (t,  $J$  = 7.3 Hz, 1H, HC(7)), 7.19 (d,  $J$  = 1.7 Hz, 1H, HC(11)), 7.11 (d,  $J$  = 2.0 Hz, 1H, HC(11')), 5.05 (d,  $J$  = 9.4 Hz, 1H, HC(3)), 4.74 (d,  $J$  = 9.4 Hz, 1H, HC(2)), 4.26 (sept,  $J$  = 6.6 Hz, 1H, HC(13)), 3.56 (sept,  $J$  = 6.6 Hz, 1H, HC(15)), 2.96 (sept,  $J$  = 6.8 Hz, 1H, HC(17)), 1.87 (s, 1H, HO (8)), 1.45 (d,  $J$  = 6.8 Hz, 3H, HC(18)), 1.38 (dd,  $J$  = 9.8, 6.8 Hz, 6H, HC(16,16')), 1.34 (d,  $J$  = 6.9 Hz, 6H, HC(14,14')), 1.30 (d,  $J$  = 6.8 Hz, 3H, HC(18')), 1.21 (s, 2H, HN(1));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  149.2 (C(12)), 148.5 (C(10')), 148.0 (C(10)), 142.7 (C(4)), 131.8 (C(9)), 128.5 (C(6)), 128.0 (C(7)), 127.1 (C(5)), 12.7 (C(11')), 121.3 (C(11)), 78.0 (C(3)), 57.2 (C(2)), 34.1 (C(15)), 29.8 (C(17)), 29.3 (C(13)), 25.2 (C(18)), 25.1 (C(16')), 25.0 (C(16)), 24.4 (C(14')), 24.0 (C(14)), 23.9 (C(18)); IR (neat) 3555 (s), 3310 (s), 2954 (s), 2926 (s), 2867 (s), 1607 (s), 1569 (s), 1492 (s), 1455 (s), 1380 (s), 1361 (s), 1264 (s), 1201 (s), 1155 (s), 1102 (s), 1078 (s), 1040 (s), 913 (s), 880 (s), 563 (s), 499 (s); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>23</sub>H<sub>34</sub>NO 340.2644, found 340.2640; TLC  $R_f$  0.36 (silica gel, hexanes/Et<sub>2</sub>O, 8:2, UV, KMnO<sub>4</sub>).

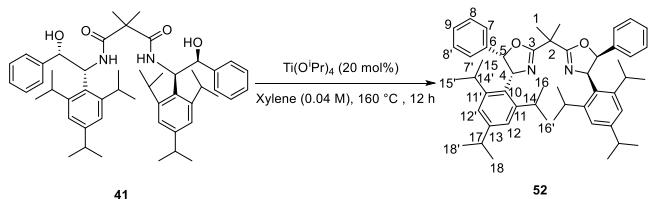


**Preparation of N<sup>1</sup>,N<sup>3</sup>-Bis((1R,2S)-2-hydroxy-1-(4-methoxyphenyl)-2-phenylethyl)-2,2-dimethylmalonamide (40).** A 50 mL Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **28** (1.28 g, 5.2 mmol, 2.0 equiv), Et<sub>3</sub>N (1.31 g, 1.8 mL, 13.0 mmol, 5.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (20 mL) under nitrogen. The solution was cooled to 0 °C using an ice bath, and 2,2-dimethylmalonyl dichloride (0.43 g, 0.34 mL, 2.6 mmol) was added dropwise by syringe over 2 min. The resulting mixture was warmed slowly to 25 °C and was stirred at 25 °C for 12 h. The mixture was transferred to a 125 mL separatory funnel. The reaction mixture was washed with water (1 × 50 mL) and then brine (1 × 50 mL). The organic layer was removed, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 mL), and the organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The organic layer was removed, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 mL), and the organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The resulting residue is diluted with ethyl acetate (100 mL) and water (100 mL). The mixture was transferred to a 250 mL separatory funnel, and the organic layer was removed. The aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the organic layers were combined, washed with brine (1 × 100 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford **40** (1.05 g, 70%) as a white solid. Data for **40**: mp 179–181 °C (hexanes/Et<sub>2</sub>O);  $^1\text{H}$  NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.30 (d,  $J$  = 8.3 Hz, 2H, HC(4)), 7.27–7.21 (m, 6H HC(8,10)), 7.09–7.02 (m, 4H HC(9)), 6.85 (d,  $J$  = 8.7 Hz, 4H HC(13)), 6.68 (d,  $J$  = 8.6 Hz, 4H HC(14)), 5.21 (dd,  $J$  = 8.3, 4.4 Hz, 2H HC(6)), 5.00 (t,  $J$  = 4.3 Hz, 2H HC(5)), 3.75 (s, 6H HC(16)), 3.49 (d,  $J$  = 4.4 Hz, 2H, HC(11)), 1.34 (s, 6H, HC(1));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  173.2 (C(3)), 158.9 (C(15)), 139.7 (C(7)), 129.2 (C(12)), 128.7 (C(13)), 128.0 (C(10)), 127.8 (C(8)), 126.6 (C(9)), 113.5 (C(14)), 76.5 (C(5)), 58.8 (C(6)), 55.1 (C(16)), 49.6 (C(2)), 23.6 (C(1)); IR (neat) 3307 (w), 2936 (w), 1652 (m), 1634 (m), 1614 (m), 1512 (s), 1455 (m), 1395 (w), 1288 (m), 1249 (s), 1178 (s), 1114 (w), 1033 (s), 912 (m), 866 (w), 814 (m), 777 (w), 756 (m), 730 (m), 697 (s), 574 (s), 532 (s); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>35</sub>H<sub>39</sub>N<sub>2</sub>O<sub>6</sub> 583.2807, found 583.2808; TLC  $R_f$  0.49 (silica gel, hexanes/Et<sub>2</sub>O, 3:7, UV, KMnO<sub>4</sub>).

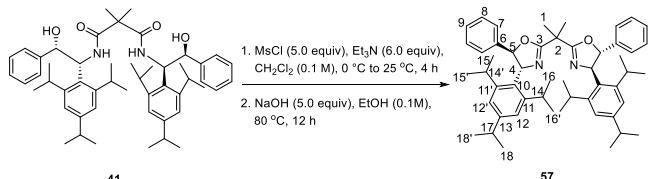
combined, dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm  $\varnothing$  × 15 cm column) eluting with hexanes/Et<sub>2</sub>O, 3:7 to afford **40** (1.05 g, 70%) as a white solid. Data for **40**: mp 179–181 °C (hexanes/Et<sub>2</sub>O);  $^1\text{H}$  NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.30 (d,  $J$  = 8.3 Hz, 2H, HC(4)), 7.27–7.21 (m, 6H HC(8,10)), 7.09–7.02 (m, 4H HC(9)), 6.85 (d,  $J$  = 8.7 Hz, 4H HC(13)), 6.68 (d,  $J$  = 8.6 Hz, 4H HC(14)), 5.21 (dd,  $J$  = 8.3, 4.4 Hz, 2H HC(6)), 5.00 (t,  $J$  = 4.3 Hz, 2H HC(5)), 3.75 (s, 6H HC(16)), 3.49 (d,  $J$  = 4.4 Hz, 2H, HC(11)), 1.34 (s, 6H, HC(1));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  173.2 (C(3)), 158.9 (C(15)), 139.7 (C(7)), 129.2 (C(12)), 128.7 (C(13)), 128.0 (C(10)), 127.8 (C(8)), 126.6 (C(9)), 113.5 (C(14)), 76.5 (C(5)), 58.8 (C(6)), 55.1 (C(16)), 49.6 (C(2)), 23.6 (C(1)); IR (neat) 3307 (w), 2936 (w), 1652 (m), 1634 (m), 1614 (m), 1512 (s), 1455 (m), 1395 (w), 1288 (m), 1249 (s), 1178 (s), 1114 (w), 1033 (s), 912 (m), 866 (w), 814 (m), 777 (w), 756 (m), 730 (m), 697 (s), 574 (s), 532 (s); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>35</sub>H<sub>39</sub>N<sub>2</sub>O<sub>6</sub> 583.2807, found 583.2808; TLC  $R_f$  0.49 (silica gel, hexanes/Et<sub>2</sub>O, 3:7, UV, KMnO<sub>4</sub>).



**Preparation of N<sup>1</sup>,N<sup>3</sup>-Bis((1R,2S)-2-hydroxy-1-(2,4,6-triisopropylphenyl)-2-phenylethyl)-2,2-dimethylmalonamide (41).** A 50 mL Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **29** (2.04 g, 6.0 mmol, 2.0 equiv), Et<sub>3</sub>N (1.52 g, 2.09 mL, 15.0 mmol, 5.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (20 mL) under nitrogen. The solution was cooled to 0 °C using an ice bath, and 2,2-dimethylmalonyl dichloride (0.50 g, 0.39 mL, 3.0 mmol) was added dropwise by syringe over 2 min. The resulting mixture was warmed slowly to 25 °C and was stirred at 25 °C for 12 h. The mixture was transferred to a 125 mL separatory funnel. The reaction mixture was washed with water (1 × 50 mL) and then brine (1 × 50 mL). The organic layer was removed, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 mL), and the organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The organic layer was removed, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 mL), and the organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The resulting residue is diluted with ethyl acetate (100 mL) and then brine (1 × 50 mL). The organic layer was removed, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 mL), and the organic layers were combined, washed with brine (1 × 100 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford **41** (2.00 g, 85%) as a white solid. The compound was further recrystallized with hot hexane (20 mL) to afford **41** (1.90 g, 80%) as a white crystalline solid. Data for **41**: mp 201–203 °C (hexanes);  $^1\text{H}$  NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.41 (d,  $J$  = 7.0 Hz, 4H, HC(8)), 7.34 (t,  $J$  = 7.4 Hz, 4H, HC(9)), 7.29 (t,  $J$  = 7.2 Hz, 2H, HC(10)), 6.98 (d,  $J$  = 8.3 Hz, 4H, HC(4,14')), 6.89 (s, 2H, HC(14)), 5.76 (t,  $J$  = 8.8 Hz, 2H, HC(5)), 4.88 (d,  $J$  = 9.1 Hz, 2H, HC(6)), 3.64 (sept,  $J$  = 6.7, 6.2 Hz, 2H, HC(18)), 2.93 (sept,  $J$  = 6.6, 6.2 Hz, 2H, HC(16)), 2.85 (sept,  $J$  = 6.9 Hz, 2H, HC(20)), 1.88 (s, 2H, HC(11)), 1.31 (d,  $J$  = 6.7 Hz, 6H, HC(19)), 1.28–1.23 (m, 18H, HC(17,21,21')), 1.19 (d,  $J$  = 6.7 Hz, 6H, HC(19')), 0.80 (d,  $J$  = 6.7 Hz, 6H, HC(17')), 0.74 (s, 6H, HC(1));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  172.2 (C(3)), 149.2 (C(15)), 148.2 (C(13)), 147.1 (C(13')), 141.1 (C(7)), 129.0 (C(12)), 128.5 (C(9)), 128.4 (C(10)), 127.2 (C(8)), 123.0 (C(14')), 121.8 (C(14)), 77.7 (C(6)), 54.2 (C(5)), 48.8 (C(2)), 34.2 (C(20)), 30.8 (C(16)), 29.5 (C(18)), 24.8 (C(19')), 24.8 (C(17')), 24.4 (C(17)), 24.1 (C(21,21')), 24.0 (C(19)), 23.9 (C(1)); IR (neat) 3413 (s), 2958 (s), 2923 (s), 2867 (s), 1668 (s), 1609 (s), 1505 (s), 1456 (s), 1382 (s), 1363 (s), 1316 (s), 1249 (s), 1187 (s), 1103 (s), 1052 (s), 1038 (s), 909 (s), 877 (s), 847 (s), 756 (s), 622 (s), 472 (s); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>51</sub>H<sub>71</sub>N<sub>2</sub>O<sub>4</sub> 775.5427, found 775.5414; TLC  $R_f$  0.27 (silica gel, hexanes/Et<sub>2</sub>O, 8:2, UV, KMnO<sub>4</sub>).

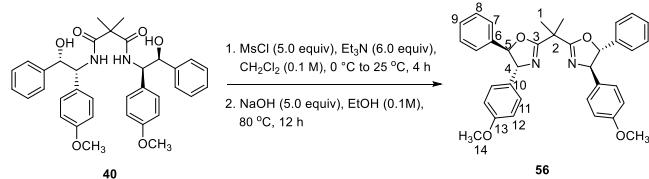


**Preparation of (4*R*,4*R*',5*S*,5*S*)-2,2'-(Propane-2,2-diyl)bis(5-phenyl-4-(2,4,6-triisopropylphenyl)-4,5-dihydrooxazole) (52).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **41** (0.38 g, 0.50 mmol) and xylenes (12 mL) under nitrogen. The mixture was heated to reflux in a 160 °C oil bath using a condenser connected to a Dean–Stark apparatus which was itself connected to Schlenk flask. Once the bisamide alcohol dissolved completely then  $\text{Ti}(\text{O}i\text{-Pr})_4$  (0.028 g, 0.030 mL, 20 mol %) was added to the solution in one portion. The reaction mixture was refluxed for 12 h with removal of the water byproduct. After the reaction mixture was cooled to room temperature, the solution was concentrated by rotary evaporation (60 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm  $\phi$  × 15 cm column) eluting with *n*-hexane (95%)/  $\text{Et}_2\text{O}$ , 1:1 to afford **52** (0.33 g, 88%) as a white solid. Recrystallization from *n*-hexane (95%) afforded 0.30 g (82%) of analytically pure **52** as a white solid. Data for **52**: mp 157–159 °C (*n*-hexane (95%)).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.10 (m, 6H, HC(7)), 7.02–7.01 (m, 4H, HC(7',8)), 6.96–6.95 (m, 2H, HC(8',9)), 6.72 (s, 2H, HC(12)), 6.18 (d,  $J$  = 11.8 Hz, 2H, HC(12')), 6.07 (d,  $J$  = 11.8 Hz, 2H, HC(4)), 3.27 (sept,  $J$  = 6.9 Hz, 2H, HC(5)), 2.80 (sept,  $J$  = 6.9 Hz, 2H, HC(14)), 2.56 (sept,  $J$  = 6.7 Hz, 2H, HC(17)), 1.92 (s, 6H, HC(14')), 1.44 (d,  $J$  = 6.8 Hz, 6H, HC(1)), 1.38 (d,  $J$  = 6.7 Hz, 6H, HC(16,16')), 1.19 (dd,  $J$  = 6.9, 5.0 Hz, 18H, HC(15,15',18)), 0.24 (d,  $J$  = 6.8 Hz, 6H, HC(18));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  166.7 (C(3)), 149.5 (C(11')), 148.0 (C(13)), 146.2 (C(11)), 138.2 (C(6)), 127.9 (C(10)), 127.6 (C(7)), 126.8 (C(8)), 125.5 (C(8')), 122.5 (C(12)), 120.3 (C(9)), 82.8 (C(5)), 70.6 (C(4)), 39.5 (C(2)), 34.1 (C(17)), 30.5 (C(14)), 29.9 (C(14')), 26.4 (C(15)), 25.5 (C(16)), 24.3 (C(1)), 24.1 (C(18)), 24.0 (C(15')), 23.8 (C(16')), 23.1 (C(18')); IR (neat) 2958 (s), 1674 (s), 1660 (s), 1451 (s), 1363 (s), 1323 (s), 1134 (s), 1111 (s), 979 (s), 911 (s), 878 (s), 732 (s), 548 (s); LRMS [ESI<sup>+</sup>, TOF] 173.1(2), 263.9(1), 417.1(5), 686.1(12), 739.5(100), 740.5(57), 741.5(17); Anal. Calcd for  $\text{C}_{51}\text{H}_{67}\text{N}_2\text{O}_2$  (739.079): C, 82.88; H, 9.00; N, 3.79. Found: C, 82.54; H, 8.91; N, 3.92; HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_{51}\text{H}_{67}\text{N}_2\text{O}_2$  739.5220, found 739.5203; TLC  $R_f$  0.63 (silica gel, hexanes/EtOAc, 9:1, UV, KMnO<sub>4</sub>);  $[\alpha]_D^{24}$  +148.3 ( $c$  = 1.0,  $\text{CHCl}_3$ ).



**Preparation of (4*R*,4*R*',5*R*,5*R*)-2,2'-(Propane-2,2-diyl)bis(5-phenyl-4-(2,4,6-triisopropylphenyl)-4,5-dihydrooxazole) (57).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **41** (0.38 g, 0.50 mmol),  $\text{Et}_3\text{N}$  (0.30 g, 0.41 mL, 3.0 mmol, 6.0 equiv), and  $\text{CH}_2\text{Cl}_2$  (5 mL) under nitrogen. The solution was cooled to 0 °C using an ice bath, and methanesulfonyl chloride (0.28 g, 0.19 mL, 2.5 mmol, 5.0 equiv) was added dropwise by syringe over 2 min. The mixture was quenched with  $\text{H}_2\text{O}$  (1 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (5 × 2 mL portions). The organic layers were combined, and concentrated by rotary evaporation (30 °C, 50 mbar). A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with the residue and ethanol (5 mL).  $\text{NaOH}$  (0.10 g, 2.5 mmol, 5.0 equiv) in water (0.5 mL) was added dropwise. The mixture was heated to reflux using a condenser in 85 °C oil bath for 12 h. After the solution was cooled to 25 °C, the volatile components are removed by rotary evaporation (30 °C, 50 mbar). The resulting residue is diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL). The mixture was transferred to a 60 mL separatory funnel. The reaction mixture was washed with water (1 × 5 mL) and then brine (1 × 5 mL). The organic layer was removed, and then the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 × 10 mL) and the organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$  (0.30 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica neutralized with triethylamine, 1 cm  $\phi$  × 15 cm column) eluting with *n*-hexane (95%)/ EtOAc, 1:1 to afford **57** (0.23 g, 85%) as a white solid. Data for **57**: mp 41–43 °C (*n*-hexane (95%)/ EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 (s, 10H, HC(7,8,9)), 7.19 (d,  $J$  = 8.6 Hz, 4H, HC(12)), 6.85 (d,  $J$  = 8.7 Hz, 4H, HC(11)), 5.28 (d,  $J$  = 7.5 Hz, 2H, HC(5)), 5.05 (d,  $J$  = 7.5 Hz, 2H, HC(4)), 3.79 (s, 6H,

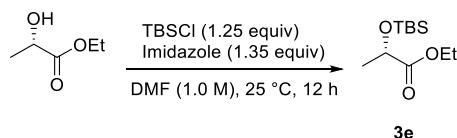
components are removed by rotary evaporation (30 °C, 50 mbar). The resulting residue is diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL). The mixture was transferred to a 60 mL separatory funnel. The reaction mixture was washed with water (1 × 5 mL) and then brine (1 × 5 mL). The organic layer was removed, the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 × 10 mL), and the organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$  (0.30 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm  $\phi$  × 15 cm column) eluting with *n*-hexane (95%)/  $\text{Et}_2\text{O}$ , 1:1 to afford **57** (0.18 g, 80%) as a white solid. Recrystallization from anhydrous  $\text{Et}_2\text{O}$  afforded 0.17 g (75%) of analytically pure **57** as a white solid. Data for **57**: mp 219–221 °C ( $\text{Et}_2\text{O}$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 (s, 10H, HC(7,8,9)), 6.98 (s, 4H, HC(12)), 5.62 (d,  $J$  = 10.1 Hz, 2H, HC(4)), 5.48 (d,  $J$  = 10.1 Hz, 2H, HC(5)), 2.85 (sept,  $J$  = 7.4, 6.8 Hz, 6H, HC(14,14',17)), 1.82 (s, 6H, HC(1)), 1.23 (d,  $J$  = 6.8 Hz, 12H, HC(17,17')), 1.18 (d,  $J$  = 4.7 Hz, 12H, HC(18,18')), 0.91 (s, 12H, HC(16,16'));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.2 (C(3)), 148.1 (C(11,13)), 140.6 (C(10)), 130.1 (C(6)), 128.7 (C(8)), 128.4 (C(9)), 126.3 (C(7)), 122.1 (C(12,12')), 89.0 (C(5)), 74.3 (C(4)), 39.2 (C(2)), 34.1 (C(4,14')), 28.8 (C(13)), 24.5 (C(16,16')), 24.1 (C(1)), 24.0 (C(17,17')), 24.0 (C(18,18')); IR (neat) 2926 (s), 1663 (s), 1607 (s), 1457 (s), 1383 (s), 1362 (s), 1313 (S), 1221 (s), 1140 (s), 1111 (s), 967 (s), 917 (s), 881 (s), 852 (s), 760 (s), 555 (s); LRMS [ESI<sup>+</sup>, TOF] 141.9(1), 228.1(8), 445.7(1), 725.5(1), 739.5(100), 740.5(53), 741.5(17); Anal. Calcd for  $\text{C}_{51}\text{H}_{67}\text{N}_2\text{O}_2$  (739.079): C, 82.88; H, 9.00; N, 3.79. Found: C, 82.64; H, 8.97; N, 4.02; HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_{51}\text{H}_{67}\text{N}_2\text{O}_2$  739.5225, found 739.5203; TLC  $R_f$  0.46 (silica gel, hexanes/EtOAc, 9:1, UV, KMnO<sub>4</sub>);  $[\alpha]_D^{24}$  +148.3 ( $c$  = 1.0,  $\text{CHCl}_3$ ).



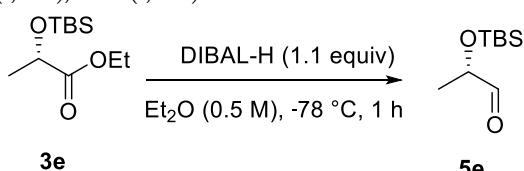
**Preparation of (4*R*,4*R*',5*R*,5*R*)-2,2'-(Propane-2,2-diyl)bis(4-(4-methoxyphenyl)-5-phenyl-4,5-dihydrooxazole) (56).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **40** (0.29 g, 0.50 mmol),  $\text{Et}_3\text{N}$  (0.30 g, 0.41 mL, 3.0 mmol, 6.0 equiv), and  $\text{CH}_2\text{Cl}_2$  (5 mL) under nitrogen. The solution was cooled to 0 °C using an ice bath, and methanesulfonyl chloride (0.28 g, 0.19 mL, 2.5 mmol, 5.0 equiv) was added dropwise by syringe over 2 min. The mixture was quenched with  $\text{H}_2\text{O}$  (1 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (5 × 2 mL portions). The organic layers were combined and concentrated by rotary evaporation (30 °C, 50 mbar). A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with the residue and ethanol (5 mL).  $\text{NaOH}$  (0.10 g, 2.5 mmol, 5.0 equiv) in water (0.5 mL) was added dropwise. The mixture was heated to reflux using a condenser in 85 °C oil bath for 12 h. After the solution was cooled to 25 °C, the volatile components are removed by rotary evaporation (30 °C, 50 mbar). The resulting residue is diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL). The mixture was transferred to a 60 mL separatory funnel. The reaction mixture was washed with water (1 × 5 mL) and then brine (1 × 5 mL). The organic layer was removed, and then the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 × 10 mL) and the organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$  (0.30 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica neutralized with triethylamine, 1 cm  $\phi$  × 15 cm column) eluting with *n*-hexane (95%)/ EtOAc, 1:1 to afford **56** (0.23 g, 85%) as a white solid. Data for **56**: mp 41–43 °C (*n*-hexane (95%)/ EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 (s, 10H, HC(7,8,9)), 7.19 (d,  $J$  = 8.6 Hz, 4H, HC(12)), 6.85 (d,  $J$  = 8.7 Hz, 4H, HC(11)), 5.28 (d,  $J$  = 7.5 Hz, 2H, HC(5)), 5.05 (d,  $J$  = 7.5 Hz, 2H, HC(4)), 3.79 (s, 6H,

HC(14)), 1.86 (s, 6H, HC(1));  $^{13}\text{C}\{\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.5 (C(3)), 159.2 (C(13)), 140.5 (C(6)), 134.3 (C(10)), 128.9 (C(9)), 128.4 (C(8)), 128.0 (C(12)), 125.9 (C(7)), 114.2 (C(11)), 89.5 (C(4)), 78.2 (C(5)), 55.4 (C(14)), 39.4 (C(2)), 24.9 (C(1)); IR (neat) 2933 (s), 1655 (m), 1611 (s), 1611 (m), 1455 (s), 1386 (s), 1302 (s), 1243 (w), 1174 (m), 1140 (m), 1106 (m), 967 (s), 970 (m), 887 (s), 824 (m), 781 (s), 590 (m); LRMS [ESI $^+$ , TOF] 116.9(1), 226.0(8), 340.1(21), 547.2(100), 548.2(42), 565.2(22), 566.2(9); Anal. Calcd for  $\text{C}_{35}\text{H}_{34}\text{N}_2\text{O}_4$  (546.654): C, 76.90; H, 6.27; N, 5.12. Found: C, 76.65; H, 6.07; N, 5.27; HRMS (ESI)  $m/z$  (M + H) $^+$  calcd for  $\text{C}_{35}\text{H}_{35}\text{N}_2\text{O}_4$  547.2595, found 547.2597; TLC  $R_f$  0.50 (silica gel, hexanes/EtOAc, 7:3, UV, KMnO<sub>4</sub>);  $[\alpha]_D^{24}$  +177.6 ( $c$  = 1.0,  $\text{CHCl}_3$ ).

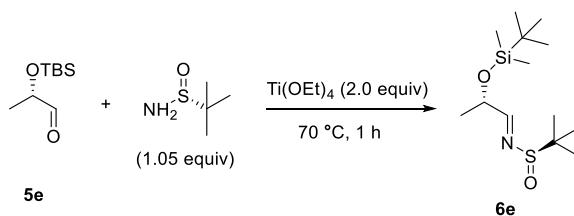
**Synthesis of Bisoxazoline Ligands with a Methyl Substituent at the C(5)-Position.**



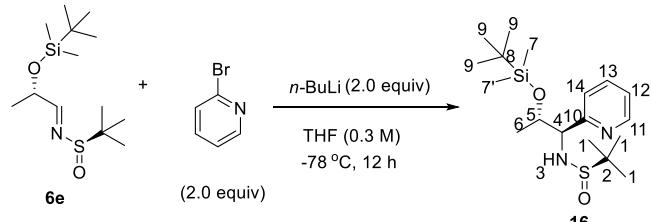
**Preparation of Ethyl (S)-2-((tert-Butyldimethylsilyl)oxy)propanoate (3e).** A 250 mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8  $\times$  19.1 mm) was charged with ethyl (S)-2-hydroxypropanoate (5.90 g, 50.0 mmol), TBSCl (9.42 g, 62.5 mmol, 1.25 equiv), imidazole (4.59 g, 67.5 mmol, 1.35 equiv), and DMF (SDS, 50 mL) under nitrogen. The mixture was stirred at 25 °C for 12 h. The resulting mixture was diluted in  $\text{Et}_2\text{O}$  (200 mL) transferred to 500 mL separatory funnel, washed with water (3  $\times$  100 mL) and brine (1  $\times$  100 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm  $\phi$   $\times$  12 cm column) eluting with hexanes/ $\text{Et}_2\text{O}$ , 7:3 to afford 3e (8.80 g, 89%) as a colorless oil. The spectroscopic data for 3e matched the literature values.<sup>119</sup> Data for 3e:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.25 (q,  $J$  = 6.7 Hz, 1H), 4.16–4.08 (m, 2H), 1.34 (d,  $J$  = 6.8 Hz, 3H), 1.22 (t,  $J$  = 7.2 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H).



**Preparation of (S)-2-((tert-Butyldimethylsilyl)oxy)propanal (5e).** A 250 mL, three-necked round-bottomed flask equipped with nitrogen inlet, an egg-shaped stir bar (50.8  $\times$  19.1 mm), an internal temperature probe, and two rubber septa was charged with 3e (10.00 g, 45.8 mmol) and  $\text{Et}_2\text{O}$  (100 mL, SDS) under nitrogen. The solution was cooled to -78 °C using a cryocooler in an *i*-PrOH bath and DIBAL-H (1.0 M in heptane, 50.38 mL, 50.38 mmol, 1.1 equiv) was added dropwise by syringe to maintain the internal temperature below -70 °C. The solution was stirred at -78 °C for 1 h, and then reaction was quenched with  $\text{H}_2\text{O}$  (7 mL). The mixture was slowly warmed to 25 °C. The mixture was stirred for additional 1 h. Then, the mixture was filtered through a fritted glass funnel (7.5 mm diameter) containing Celite into a 250 mL filter flask. The Celite cake was washed with  $\text{Et}_2\text{O}$  (2  $\times$  100 mL). The combined filtrates were transferred to a 250 mL separatory funnel, washed with water (1  $\times$  100 mL) and brine (1  $\times$  100 mL), dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm  $\phi$   $\times$  12 cm column) eluting with hexanes/ $\text{Et}_2\text{O}$ , 9:1 to afford 5e (7.10 g, 82%) as a yellow oil. The spectroscopic data for 5e matched the literature values.<sup>119</sup> Data for 5e:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.61 (d,  $J$  = 1.2 Hz, 1H), 4.09 (qd,  $J$  = 6.8, 1.3 Hz, 1H), 1.28 (d,  $J$  = 6.8 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 6H), 0.09 (s, 6H).



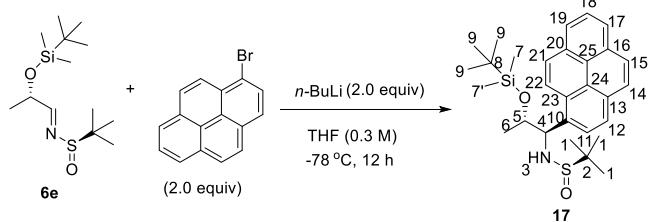
**Preparation of (R)-N-((S,E)-2-((tert-Butyldimethylsilyl)oxy)propylidene)-2-methylpropane-2-sulfonamide (6e).** A 100 mL, one-necked Schlenk flask with an egg-shaped stir bar (38.1  $\times$  15.9 mm) was charged with 5e (7.10 g, 37.7 mmol), (R)-2-methylpropane-2-sulfonamide (4.79 g, 39.58 mmol, 1.05 equiv), and titanium(IV) ethoxide (17.09 g, 15.78 mL, 75.4 mmol, 2.0 equiv) under nitrogen. The mixture was stirred in a 70 °C oil bath for 60 min and then was diluted with ethyl acetate (50 mL). The resulting solution was poured into a 200 mL Erlenmeyer flask with a stir bar and brine (10 mL), and the vial was rinsed with ethyl acetate (2  $\times$  25 mL) to help the transfer. The suspension was stirred at 25 °C for 10 min and then filtered through a fritted glass funnel (7.5 mm diameter) containing Celite. The Celite cake was washed with ethyl acetate (2  $\times$  100 mL). The combined filtrates were transferred to a 250 mL separatory funnel, washed with water (1  $\times$  100 mL) and brine (1  $\times$  100 mL), dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm  $\phi$   $\times$  12 cm column) eluting with hexanes/ $\text{Et}_2\text{O}$ , 7:3 to afford 6e (8.80 g, 89%) as a colorless oil. The spectroscopic data for 6e matched the literature values.<sup>103</sup> Data for 6e:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.92 (d,  $J$  = 3.8 Hz, 1H), 4.54 (qd,  $J$  = 6.6, 3.8 Hz, 1H), 1.29 (d,  $J$  = 6.6 Hz, 3H), 1.14 (s, 9H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).



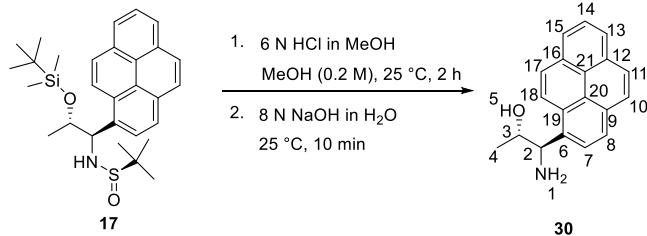
**Preparation of (R)-N-((1R,2S)-2-((tert-Butyldimethylsilyl)oxy)-1-(pyridin-2-yl)propyl)-2-methylpropane-2-sulfonamide (16).** A 100 mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1  $\times$  15.9 mm) was charged with 2-bromopyridine (3.16 g, 1.90 mL, 20.0 mmol, 2.0 equiv) and THF (25 mL) under nitrogen. The solution was cooled to -78 °C using a cryocooler in an *i*-PrOH bath, and *n*-butyllithium (1.28 g, 12.5 mL, 1.6 M in hexane, 20.0 mmol, 2.0 equiv) was added dropwise by syringe. The resulting solution was stirred at -78 °C using a cryocooler in an *i*-PrOH bath for 1 h. Then another 50 mL Schlenk flask containing an egg-shaped stir bar (19.1  $\times$  9.5 mm) was charged with 6e (2.91 g, 10.0 mmol), and THF (25 mL) under nitrogen and was cooled to -78 °C using a cryocooler in an *i*-PrOH bath. The N-sulfinyl imine solution was transferred to the organolithium solution using a syringe dropwise over 5 min. The resulting mixture was stirred at -78 °C using a cryocooler in an *i*-PrOH bath for 12 h. The reaction was quenched by the addition of satd aq  $\text{NH}_4\text{Cl}$  solution (50 mL) at -78 °C and then was slowly warmed to 25 °C. The mixture was transferred to a 250 mL separatory funnel. The organic layer was removed, the aqueous layer was extracted with ethyl acetate (3  $\times$  50 mL), and the organic layers were combined, washed with brine (1  $\times$  100 mL), dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The dr of the crude product was 95:5 by  $^1\text{H}$  NMR analysis. The crude product was purified by column chromatography (silica, 4 cm  $\phi$   $\times$  12 cm column) eluting with MeOH/EtOAc, 0.5:9.5 to afford 16 (3.30 g, 89%) as a colorless oil. Data for 16:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.57–8.49 (m, 1H, HC(11)), 7.61 (td,  $J$  = 7.7, 1.8 Hz, 1H, HC(13)), 7.29 (d,  $J$  = 7.9 Hz, 1H, HC(14)), 7.15 (ddd,  $J$  = 7.5, 4.9, 1.1 Hz, 1H,

HC(12)), 4.47 (t,  $J$  = 5.2 Hz, 1H, HC(4)), 4.39 (d,  $J$  = 5.1 Hz, 1H, HC(3)), 4.24 (qd,  $J$  = 6.2, 5.1 Hz, 1H, HC(5)), 1.19 (s, 9H, HC(1)), 1.08 (d,  $J$  = 6.3 Hz, 3H, HC(6)), 0.84 (s, 9H, HC(9)), 0.02 (s, 3H, HC(7')), -0.04 (s, 3H, HC(7));  $^{13}\text{C}\{\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.3 (C(10)), 149.0 (C(11)), 135.9 (C(13)), 123.3 (C(14)), 122.3 (C(12)), 71.5 (C(5)), 65.4 (C(4)), 56.0 (C(2)), 25.8 (C(9)), 22.6 (C(1)), 19.5 (C(6)), 18.0 (C(8)), -4.4 (C(7')), -4.8 (C(7)); IR (neat) 2954 (s), 2929 (s), 1472 (s), 1436 (s), 1361 (s), 1253 (s), 1134 (s), 1010 (s), 918 (m), 830 (m), 809 (s), 774 (s), 748 (s), 668 (s), 634 (s), 588 (s), 527 (s); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_{18}\text{H}_{35}\text{N}_2\text{O}_2\text{SSi}$  371.2184, found 371.2189; TLC  $R_f$  0.37 (silica gel, MeOH/EtOAc, 0.5:9.5, UV, KMnO<sub>4</sub>).

*Preparation of (R)-N-((1R,2S)-2-((tert-Butyldimethylsilyloxy)-1-(pyren-1-yl)propyl)-2-methylpropane-2-sulfonamide (17).*

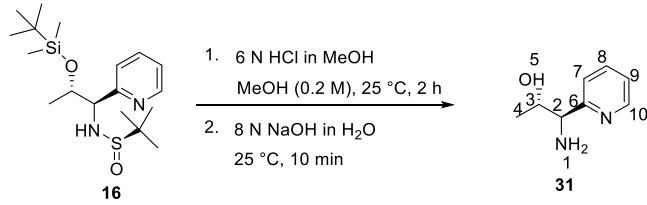


A 100 mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1  $\times$  15.9 mm) was charged with 1-bromo-1,4-dihydronaphthalene (5.62 g, 20.0 mmol, 2.0 equiv) and THF (25 mL) under nitrogen. The solution was cooled to -78 °C using a cryocooler in an *i*-PrOH bath and *n*-butyllithium (1.28 g, 12.5 mL, 1.6 M in hexane, 20.0 mmol, 2.0 equiv) was added dropwise by syringe. The resulting solution was stirred at -78 °C using a cryocooler in an *i*-PrOH bath for 1 h. Then another 50 mL Schlenk flask containing an egg-shaped stir bar (19.1  $\times$  9.5 mm) was charged with **6e** (2.91 g, 10.0 mmol), and THF (25 mL) under nitrogen and was cooled to -78 °C using a cryocooler in an *i*-PrOH bath. The *N*-sulfinyl imine solution was transferred to the organolithium solution using a syringe dropwise over 5 min. The resulting mixture was stirred at -78 °C using a cryocooler in an *i*-PrOH bath for 12 h. The reaction was quenched by the addition of satd aq NH<sub>4</sub>Cl solution (50 mL) at -78 °C and then was slowly warmed to 25 °C. The mixture was transferred to a 250 mL separatory funnel. The organic layer was removed, the aqueous layer was extracted with ethyl acetate (3  $\times$  50 mL), and the organic layers were combined, washed with brine (1  $\times$  100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The dr of the crude product was 99:1 by <sup>1</sup>H NMR analysis. The crude product was purified by column chromatography (silica, 4 cm  $\phi$   $\times$  12 cm column) eluting with hexanes/EtOAc, 1:1 to afford **17** (4.0 g, 80%) as a white solid. Data for **17**: mp 132–134 °C (hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  8.42–8.31 (m, 1H, HC(12)), 8.27–8.14 (m, 5H, HC(15,18,19,21,22)), 8.09 (s, 2H, HC(11,14)), 8.01–7.98 (m, 1H, HC(17)), 5.37 (s, 2H, HC(3,4)), 4.34 (s, 1H, HC(5)), 1.21 (s, 3H, HC(6)), 1.02 (s, 9H, HC(1)), 0.53 (s, 9H, HC(9)), -0.17 (s, 3H, HC(7)), -0.45 (s, 3H, HC(7'));  $^{13}\text{C}\{\text{H}\}$  NMR (126 MHz, DMSO-d<sub>6</sub>)  $\delta$  134.7 (C(10)), 130.8 (C(16)), 130.1 (C(20)), 129.7 (C(13)), 128.7 (C(23)), 127.3 (C(21)), 127.0 (C(25)), 126.0 (C(12)), 125.1 (C(14)), 124.8 (C(15,18)), 124.5 (C(11)), 124.0 (C(22)), 123.8 (C(17,19)), 122.8 (C(24)), 71.5 (C(5)), 59.6 (C(4)), 55.1 (C(2)), 25.3 (C(9)), 22.2 (C(1)), 20.5 (C(6)), 17.2 (C(8)), -4.9 (C(7)), -5.4 (C(7')); IR (neat) 3433 (w), 3133 (w), 2951 (w), 2852 (w), 1461 (w), 1392 (w), 1365 (w), 1250 (m), 1185 (w), 1123 (m), 1090 (m), 1077 (s), 1011 (s), 923 (m), 847 (s), 834 (s), 817 (s), 777 (s), 756 (m), 716 (m), 683 (m), 664 (m), 629 (m), 500 (m), 466 (m); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_{29}\text{H}_{40}\text{NO}_2\text{SSi}$  494.2554, found 494.2549; TLC  $R_f$  0.46 (silica gel, hexanes/EtOAc, 7:3, UV, KMnO<sub>4</sub>).



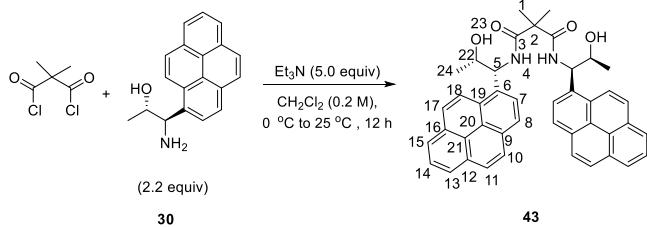
*Preparation of (1R,2S)-1-Amino-1-(pyren-1-yl)propan-2-ol (30).*

A 250 mL, one-necked Schlenk flask with an egg-shaped stir bar (50.8  $\times$  19.1 mm) was charged with **17** (3.95 g, 8.0 mmol) and methanol (10 mL) under nitrogen. HCl (6 N) in MeOH (80 mL) was added dropwise by syringe. The mixture was stirred for 2 h at 25 °C, and then the solvent was removed rotary evaporation (30 °C, 50 mbar). The crude solid was suspended in ethyl acetate (50 mL), and 8 N NaOH in H<sub>2</sub>O (120 mL) was added while the solution was stirred vigorously. The solution was stirred for 10 min and then was transferred to a 500 mL separatory funnel. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2  $\times$  50 mL). pH paper was used to check the neutralization of the solution (pH = 7). The organic layers were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm  $\phi$   $\times$  12 cm column) eluting with MeOH/EtOAc, 1:1 to afford **30** (1.70 g, 76%) as a white solid. Data for **30**: mp 139–141 °C (MeOH/EtOAc); <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  8.50 (d,  $J$  = 9.4 Hz, 1H, (13)), 8.39 (d,  $J$  = 8.0 Hz, 1H, (18)), 8.27 (d,  $J$  = 8.0 Hz, 1H, (11)), 8.25–8.21 (m, 2H, (8,15)), 8.18 (d,  $J$  = 9.3 Hz, 1H, (14)), 8.14–8.08 (m, 2H, (7,17)), 8.02 (t,  $J$  = 7.6 Hz, 1H, (10)), 5.10 (d,  $J$  = 4.5 Hz, 1H, (2)), 4.16–4.09 (m, 1H, (3)), 1.00 (d,  $J$  = 6.3 Hz, 3H, (4));  $^{13}\text{C}\{\text{H}\}$  NMR (126 MHz, DMSO-d<sub>6</sub>)  $\delta$  138.4 (C(6)), 130.9 (C(9)), 130.2 (C(12)), 129.3 (C(16)), 127.8 (C(19)), 127.4 (C(21)), 126.9 (C(8)), 126.5 (C(17)), 125.9 (C(10)), 124.9 (C(11)), 124.9 (C(7)), 124.7 (C(14)), 124.6 (C(20)), 124.2 (C(18)), 123.9 (C(15)), 123.2 (C(13)), 70.3 (C(2)), 56.3 (C(3)), 17.4 (C(4)); IR (neat) 3360 (w), 2962 (w), 1583 (w), 1456 (w), 1373 (w), 1185 (w), 1141 (w), 1117 (m), 1077 (w), 1027 (w), 955 (m), 935 (s), 868 (m), 850 (s), 835 (s), 808 (m), 769 (m), 746 (m), 715 (s), 682 (m), 647 (m), 621 (m), 529 (w), 501 (m); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_{19}\text{H}_{18}\text{NO}$  276.1396, found 276.1388; TLC  $R_f$  0.26 (silica gel, MeOH/EtOAc, 2:8, UV, KMnO<sub>4</sub>).

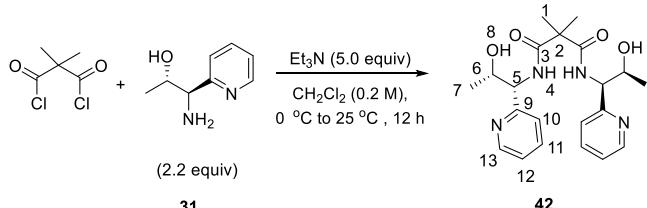


*Preparation of (1R,2S)-1-Amino-1-(pyridin-2-yl)propan-2-ol (31).* A 250 mL, one-necked Schlenk flask with an egg-shaped stir bar (50.8  $\times$  19.1 mm) was charged with **16** (2.96 g, 8.0 mmol) and methanol (10 mL) under nitrogen. HCl (6 N) in MeOH (80 mL) was added dropwise by syringe. The mixture was stirred for 2 h at 25 °C, and then the solvent was removed rotary evaporation (30 °C, 50 mbar). The crude solid was suspended in ethyl acetate (50 mL), and 8 N NaOH in H<sub>2</sub>O (120 mL) was added while the solution was stirred vigorously. The solution was stirred for 10 min and then was transferred to a 500 mL separatory funnel. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2  $\times$  50 mL). pH paper was used to check the neutralization of the solution (pH = 7). The organic layers were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm  $\phi$   $\times$  12 cm column) eluting with MeOH/EtOAc, 1:1 to afford **31** (0.86 g, 71%) as a colorless oil. Data for **31**: <sup>1</sup>H NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.51 (d,  $J$  = 4.7 Hz, 1H, (10)), 7.65 (td,  $J$  = 7.6, 1.6 Hz, 1H, (8)), 7.29 (d,  $J$  = 7.8

Hz, 1H, (7)), 7.17 (dd,  $J$  = 7.4, 5.0 Hz, 1H, (9)), 4.06–3.98 (m, 1H, (3)), 3.87 (d,  $J$  = 4.6 Hz, 1H, (2)), 2.37 (s, 3H, (1,15)), 1.04 (d,  $J$  = 6.4 Hz, 3H, (4));  $^{13}\text{C}\{\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  162.3 (C(6)), 148.9 (C(10)), 122.7 (C(7)), 122.3 (C(9)), 71.6 (C(3)), 60.8 (C(2)), 19.5 (C(4)); IR (neat) 3271 (s), 2999 (s), 1592 (s), 1473 (s), 1372 (s), 1199 (s), 1077 (s), 1017 (s), 995 (s), 939 (s), 864 (s), 816 (s), 797 (s), 754 (s), 677 (s), 621 (m), 585 (s), 561 (s); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_8\text{H}_{13}\text{N}_2\text{O}$  153.1031, found 153.1028; TLC  $R_f$  0.32 (silica gel, MeOH/EtOAc, 1:1, UV, KMnO<sub>4</sub>).

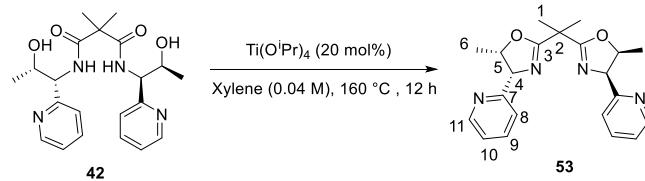


**Preparation of  $N^1$ -((1*R*,2*S*)-1-(4,5*a*1-Dihydropyren-1-yl)-2-hydroxypropyl)- $N^3$ -((1*R*,2*S*)-2-hydroxy-1-(pyren-1-yl)propyl)-2,2-dimethylmalonamide (43).** A 50 mL Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **30** (1.70 g, 6.18 mmol, 2.2 equiv), Et<sub>3</sub>N (1.42 g, 1.95 mL, 14.0 mmol, 5.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (20 mL) under nitrogen. The solution was cooled to 0 °C using an ice bath, and 2,2-dimethylmalonyl dichloride (0.46 g, 0.36 mL, 2.81 mmol) was added dropwise by syringe over 2 min. The resulting mixture was warmed slowly to 25 °C and was stirred at 25 °C for 12 h. The mixture was transferred to a 125 mL separatory funnel. The reaction mixture was washed with water (1 × 50 mL) and then brine (1 × 50 mL). The organic layer was removed, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 mL), and the organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub> (5 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm  $\phi$  × 15 cm column) eluting with hexanes/EtOAc, 1:9 to afford **43** (1.58 g, 87%) as a white solid. Data for **43**: mp 230–232 °C (hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  8.41 (d,  $J$  = 9.3 Hz, 2H, HC(15)), 8.20 (d,  $J$  = 7.5 Hz, 2H, HC(11)), 8.12 (d,  $J$  = 7.5 Hz, 2H, HC(13)), 8.09–7.94 (m, 6H, HC(8,14,17)), 7.82 (d,  $J$  = 8.9 Hz, 2H, HC(7)), 7.78–7.72 (m, 4H, HC(10,18)), 7.67 (d,  $J$  = 7.7 Hz, 2H, HN(4)), 6.14 (dd,  $J$  = 7.7, 4.6 Hz, 2H, HC(5)), 4.38 (s, 2H, HC(22)), 2.45 (s, 2H, HO(23)), 1.55 (s, 6H, HC(1)), 1.05 (d,  $J$  = 6.3 Hz, 6H, HC(24));  $^{13}\text{C}\{\text{H}\}$  NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  173.8 (C(3)), 132.4 (C(6)), 131.7 (C(9)), 131.0 (C(12)), 130.9 (C(16)), 129.4 (C(19)), 128.2 (C(20)), 127.7 (C(21)), 127.6 (C(13)), 126.4 (C(17)), 125.7 (C(10)), 125.4 (C(11)), 125.2 (C(7)), 125.1 (C(14)), 125.0 (C(18)), 124.3 (C(8)), 123.0 (C(15)), 70.5 (C(22)), 54.7 (C(5)), 50.1 (C(2)), 24.1 (C(1)), 19.5 (C(24)); IR (neat) 3400 (s), 2958 (s), 1668 (s), 1660 (s), 1574 (s), 1519 (s), 1476 (s), 1348 (s), 1299 (s), 1185 (s), 1150 (s), 1083 (s), 981 (s), 865 (s), 848 (s), 753 (s), 622 (s), 497 (s); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_{43}\text{H}_{39}\text{N}_2\text{O}_4$  647.2930, found 647.2910; TLC  $R_f$  0.26 (silica gel, hexanes//Et<sub>2</sub>O, 1:9, UV, KMnO<sub>4</sub>).

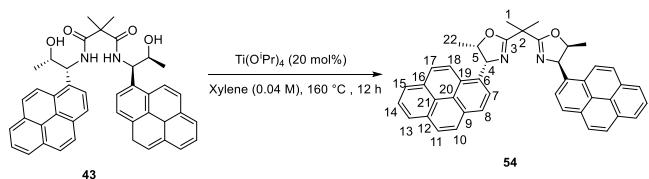


**Preparation of  $N^1,N^3$ -Bis((1*R*,2*S*)-2-Hydroxy-1-(pyridin-2-yl)propyl)-2,2-dimethylmalonamide (42).** A 50 mL Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **31** (0.86 g, 5.65 mmol, 2.2 equiv), Et<sub>3</sub>N (1.29 g, 1.78 mL, 12.85 mmol, 5.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (18 mL) under nitrogen. The solution was cooled to 0 °C using an ice bath, and 2,2-

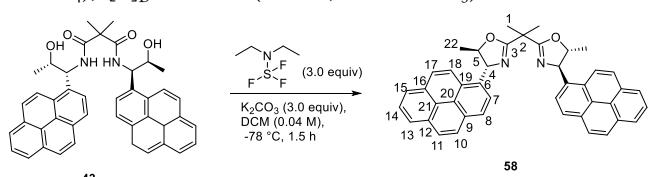
dimethylmalonyl dichloride (0.42 g, 0.32 mL, 2.57 mmol) was added dropwise by syringe over 2 min. The resulting mixture was warmed slowly to 25 °C and was stirred at 25 °C for 12 h. The mixture was transferred to a 125 mL separatory funnel. The reaction mixture was washed with water (1 × 50 mL) and then brine (1 × 50 mL). The organic layer was removed, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 mL), and the organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub> (5 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm  $\phi$  × 15 cm column) eluting with MeOH/EtOAc, 2:8 to afford **42** (0.66 g, 65%) as a colorless oil. Data for **42**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.50 (d,  $J$  = 4.8 Hz, 2H, HC(13)), 8.00 (d,  $J$  = 6.8 Hz, 2H, HN(4)), 7.66 (td,  $J$  = 7.7, 1.7 Hz, 2H, HC(11)), 7.29 (d,  $J$  = 7.8 Hz, 2H, HC(10)), 7.22 (dd,  $J$  = 7.4, 5.0 Hz, 2H, HC(12)), 5.05 (dd,  $J$  = 7.5, 3.7 Hz, 2H, HC(5)), 4.36 (s, 2H, HO(8)), 4.21–4.12 (m, 2H, HC(6)), 1.52 (s, 6H, HC(1)), 1.04 (d,  $J$  = 6.5 Hz, 6H, HC(7));  $^{13}\text{C}\{\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.8 (C(3)), 157.2 (C(9)), 148.6 (C(13)), 137.1 (C(11)), 123.7 (C(12)), 122.8 (C(10)), 70.8 (C(6)), 58.4 (C(5)), 49.9 (C(2)), 23.7 (C(1)), 19.2 (C(7)); IR (neat) 3353 (s), 2975 (s), 2244 (s), 1657 (s), 1607 (s), 1594 (s), 1502 (s), 1484 (s), 1351 (s), 1293 (s), 1179 (s), 1130 (s), 1094 (s), 982 (s), 882 (s), 826 (s), 727 (s), 683 (s), 589 (m); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_{21}\text{H}_{29}\text{N}_4\text{O}_4$  401.2202, found 401.2189; TLC  $R_f$  0.44 (silica gel, MeOH/EtOAc, 2:8, UV, KMnO<sub>4</sub>).



**Preparation of (4*R*,4'*R*,5*S*,5'*S*)-2,2'-(Propane-2,2-diyli)bis(5-methyl-4-(pyridin-2-yl)-4,5-dihydrooxazole) (53).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **42** (0.40 g, 1.0 mmol) and xylenes (24 mL) under nitrogen. The mixture was heated to reflux in a 160 °C oil bath using a condenser connected to a Dean–Stark apparatus which was itself connected to Schlenk flask. Once the bisamide alcohol dissolved completely then Ti(O<sup>i</sup>Pr)<sub>4</sub> (0.056 g, 0.060 mL, 20 mol %) was added to the solution in one portion. The reaction mixture was refluxed for 12 h with removal of the water byproduct. After the reaction mixture was cooled to room temperature, the solution was concentrated by rotary evaporation (60 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm  $\phi$  × 15 cm column) eluting with MeOH/EtOAc, 1:9 to afford **53** (0.19 g, 53%) as a white solid. Recrystallization from *n*-hexane (95%)/Et<sub>2</sub>O, 1:1 afforded 0.15 g (43%) of analytically pure **53** as a white solid. Data for **53**: mp 127–129 °C (*n*-hexane (95%)/Et<sub>2</sub>O);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.54 (d,  $J$  = 4.0 Hz, 2H(11)), 7.64 (td,  $J$  = 7.7, 1.8 Hz, 2H(9)), 7.44 (d,  $J$  = 7.9 Hz, 2H(8)), 7.16 (ddd,  $J$  = 7.6, 4.8, 1.2 Hz, 2H(10)), 5.45 (d,  $J$  = 9.9 Hz, 2H(4)), 5.19–5.13 (m, 2H(5)), 1.70 (s, 6H(1)), 0.82 (d,  $J$  = 6.5 Hz, 6H(6));  $^{13}\text{C}\{\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8 (C(7)), 159.0 (C(11)), 149.0 (C(9)), 136.4 (C(10)), 122.2 (C(8)), 80.4 (C(5)), 73.3 (C(4)), 39.1 (C(2)), 24.2 (C(1)), 16.7 (C(6)); IR (neat) 2985 (s), 2970 (s), 2926 (s), 1653 (s), 1603 (s), 1571 (s), 1451 (s), 1384 (s), 1323 (s), 1191 (s), 1115 (s), 999 (s), 906 (s), 890 (s), 726 (s), 537 (s); LRMS [ESI<sup>+</sup>, TOF] 118.0(3), 230.1(3), 321.1(2), 365.1(100), 366.1(25), 383.2(11), 513.3(1); Anal. Calcd for  $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_2$  (364.450): C, 69.21; H, 6.64; N, 15.37. Found: C, 68.81; H, 6.47; N, 15.26; HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_{21}\text{H}_{25}\text{N}_4\text{O}_2$  365.1964, found 365.1978; TLC  $R_f$  0.19 (silica gel, MeOH/EtOAc, 2:8, UV, KMnO<sub>4</sub>);  $[\alpha]_D^{24}$  +40.2 ( $c$  = 1.0, 100% CHCl<sub>3</sub>).



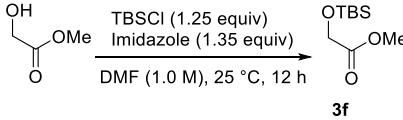
**Preparation of (4*R*,5*S*)-4-(4,5a1-Dihydropyren-1-yl)-5-methyl-2-(2-(4*R*,5*S*)-5-methyl-4-(pyren-1-yl)-4,5-dihydrooxazol-2-yl)propan-2-yl)-4,5-dihydrooxazole (54).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **43** (0.32 g, 0.50 mmol) and xylenes (12 mL) under nitrogen. The mixture was heated to reflux in a 160 °C oil bath using a condenser connected to a Dean–Stark apparatus which was itself connected to Schlenk flask. Once the bisamide alcohol dissolved completely then  $\text{Ti(O}^{\text{i}}\text{Pr})_4$  (0.028 g, 0.030 mL, 20 mol %) was added to the solution in one portion. The reaction mixture was refluxed for 12 h with removal of the water byproduct. After the reaction mixture was cooled to room temperature, the solution was concentrated by rotary evaporation (60 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm  $\phi$  × 15 cm column) eluting with *n*-hexane (95%)/EtOAc, 7:3 to afford **54** (0.33 g, 64%) as a white solid. Recrystallization from anhydrous toluene afforded 0.17 g (58%) of analytically pure **54** as a white solid. Data for **54**: mp 233–235 °C (toluene);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.27 (d,  $J$  = 7.9 Hz, 2H, HC(15)), 8.21–8.19 (m, 6H, HC(11,13,14)), 8.16–8.10 (m, 4H, HC(8,17)), 8.08–8.04 (m, 4H, HC(7,18)), 8.04–7.99 (m, 2H, HC(10)), 6.45 (d,  $J$  = 9.9 Hz, 2H, HC(4)), 5.57–5.45 (m, 2H, HC(5)), 1.94 (s, 6H, HC(1)), 0.70 (d,  $J$  = 6.5 Hz, 6H, HC(22));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.2 (C(3)), 132.5 (C(6)), 131.4 (C(9)), 130.7 (C(12,16)), 128.2 (C(19)), 128.1 (C(20,21)), 127.7 (C(13)), 127.1 (C(17)), 126.0 (C(10)), 125.5 (C(11)), 125.4 (C(7)), 125.1 (C(14)), 124.9 (C(18)), 124.8 (C(15)), 122.4 (C(8)), 80.5 (C(5)), 68.8 (C(4)), 39.4 (C(2)), 24.5 (C(1)), 17.0 (C(22)); IR (neat) 2968 (s), 1660 (s), 1613 (s), 1586 (s), 1449 (s), 1363 (s), 1325 (s), 1137 (s), 1114 (s), 984 (s), 909 (s), 871 (s), 738 (s), 513 (s); LRMS [ESI<sup>+</sup>, TOF] 241.2(2), 611.2(100), 612.2(49), 613.2(11), 629.2(5), 630.2(3), 631.4(2); Anal. Calcd for  $\text{C}_{43}\text{H}_{36}\text{N}_2\text{O}_2$  (739.280): C, 84.56; H, 5.61; N, 4.59. Found: C, 84.41; H, 5.57; N, 4.73; HRMS (ESI)  $m/z$  (M-H)<sup>+</sup> calcd for  $\text{C}_{43}\text{H}_{35}\text{N}_2\text{O}_2$  611.2711, found 611.2699; TLC  $R_f$  0.26 (silica gel, hexanes/EtOAc, 7:3; UV,  $\text{KMnO}_4$ );  $[\alpha]_D^{24}$  −422.7 ( $c$  = 1.0, 100%  $\text{CHCl}_3$ ).



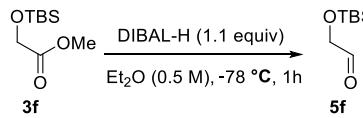
**Preparation of (4*R*,5*R*)-4-(4,5a1-Dihydropyren-1-yl)-5-methyl-2-(2-(4*R*,5*R*)-5-methyl-4-(pyren-1-yl)-4,5-dihydrooxazol-2-yl)propan-2-yl)-4,5-dihydrooxazole (58).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **43** (0.32 g, 0.5 mmol) and  $\text{CH}_2\text{Cl}_2$  (12 mL) under nitrogen. The solution was cooled to −78 °C using a cryocooler in an *i*-PrOH and diethylaminosulfur trifluoride (0.24 g, 0.19 mL, 1.5 mmol, 3.0 equiv) was added dropwise by syringe. The resulting solution was stirred at −78 °C using a cryocooler in *i*-PrOH for 1.5 h. Then,  $\text{K}_2\text{CO}_3$  (0.20 g, 1.5 mmol, 3.0 equiv) was added in one portion at −78 °C, and the mixture was slowly warmed to 25 °C. The reaction was quenched by the addition of satd aq  $\text{NaHCO}_3$  solution (2 mL). The mixture was transferred to a 60 mL separatory funnel. The organic layer was removed, the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 × 10 mL), and the organic layers were combined, washed with brine (1 × 10 mL), dried over  $\text{Na}_2\text{SO}_4$  (1 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm  $\phi$  × 15 cm column) eluting with *n*-hexane (95%)/EtOAc, 7:3 to afford **58** (0.21 g, 71%) as a white solid. Recrystallization from anhydrous toluene afforded 0.20 g (67%) of analytically pure **58** as a

yellow solid. Data for **58**: mp 227–229 °C (toluene);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.31 (d,  $J$  = 9.3 Hz, 2H HC(15)), 8.20–8.15 (m, 4H HC(11,13)), 8.12–8.10 (m, 4H HC(8,14)), 8.06–8.04 (m, 4H HC(7,17)), 8.02–7.99 (m, 4H HC(10,18)), 5.91 (d,  $J$  = 6.2 Hz, 2H HC(4)), 4.75 (quint,  $J$  = 6.2 Hz, 2H HC(5)), 1.91 (s, 6H HC(1)), 1.75 (d,  $J$  = 6.2 Hz, 6H, HC(22));  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.2 (C(3)), 135.5 (C(6)), 131.4 (C(9)), 130.6 (C(12)), 130.6 (C(16)), 128.0 (C(19)), 127.8 (C(21)), 127.5 (C(20)), 127.2 (C(13)), 125.9 (C(17)), 125.3 (C(10)), 125.3 (C(11)), 125.0 (C(7)), 124.9 (C(14)), 124.4 (C(18)), 122.2 (C(8)), 84.7 (C(15)), 73.0 (C(5)), 39.3 (C(2)), 24.4 (C(1)), 21.1 (C(22)); IR (neat) 2980 (s), 2956 (s), 1655 (s), 1610 (s), 1585 (s), 1455 (s), 1379 (s), 1321 (s), 1134 (s), 1114 (s), 979 (s), 914 (s), 875 (s), 750 (s), 522 (s); LRMS [ESI<sup>+</sup>, TOF] 241.1(4), 611.2 (100), 612.2(53), 629.2(41), 630.2(17), 631.2(6); Anal. Calcd for  $\text{C}_{43}\text{H}_{36}\text{N}_2\text{O}_2$  (739.280): C, 84.56; H, 5.61; N, 4.59. Found: C, 84.49; H, 5.52; N, 4.71; HRMS (ESI)  $m/z$  (M-H)<sup>+</sup> calcd for  $\text{C}_{43}\text{H}_{35}\text{N}_2\text{O}_2$  611.2701, found 611.2699; TLC  $R_f$  0.30 (silica gel, hexanes/EtOAc, 7:3; UV,  $\text{KMnO}_4$ );  $[\alpha]_D^{24}$  −32.5 ( $c$  = 1.0, 100%  $\text{CHCl}_3$ ).

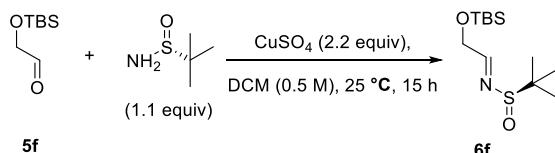
**Synthesis of Bisoxazoline Ligands with No Substituent at the C(5)-Position.**



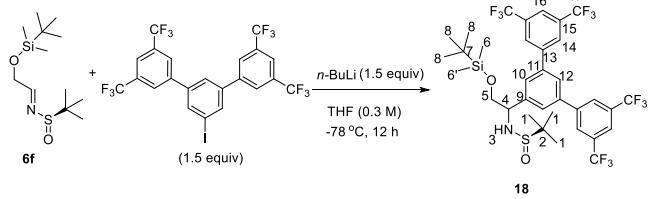
**Preparation of Methyl 2-((tert-Butyldimethylsilyloxy)acetate (3f).** A 250 mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with methyl 2-hydroxyacetate (4.50 g, 50.0 mmol), TBSCl (9.42 g, 62.5 mmol, 1.25 equiv), imidazole (4.59 g, 67.5 mmol, 1.35 equiv), and DMF (SDS, 50 mL) under nitrogen. The mixture was stirred at 25 °C for 12 h. The resulting mixture was diluted in  $\text{Et}_2\text{O}$  (200 mL) and transferred to a 500 mL separatory funnel, washed with water (3 × 100 mL) and brine (1 × 100 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm  $\phi$  × 12 cm column) eluting with hexanes/ $\text{Et}_2\text{O}$ , 9:1 to afford **3f** (9.30 g, 90%) as a colorless oil. The spectroscopic data for **3f** matched the literature values.<sup>120</sup> Data for **3f**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.13 (s, 2H), 3.61 (s, 3H), 0.81 (s, 9H), −0.01 (s, 6H).



**Preparation of (S)-2-((tert-Butyldimethylsilyloxy)propanal (5f).** A 250 mL, three-necked round-bottomed flask equipped with nitrogen inlet, an egg-shaped stir bar (50.8 × 19.1 mm), an internal temperature probe and two rubber septa was charged with **3f** (9.35 g, 45.8 mmol) and  $\text{Et}_2\text{O}$  (100 mL, SDS) under nitrogen. The solution was cooled to −78 °C using a cryocooler in an *i*-PrOH bath and DIBAL-H (1.0 M in heptane, 50.38 mL, 50.38 mmol, 1.1 equiv) was added dropwise by syringe to maintain the internal temperature below −70 °C. The solution was stirred at −78 °C for 1 h and then reaction was quenched with  $\text{H}_2\text{O}$  (7 mL). The mixture was slowly warmed to 25 °C. The mixture was stirred for additional 1 h. Then the mixture was filtered through a fritted glass funnel (7.5 mm diameter) containing Celite into a 250 mL filter flask. The Celite cake was washed with  $\text{Et}_2\text{O}$  (2 × 100 mL). The combined filtrates were transferred to a 250 mL separatory funnel, washed with water (1 × 100 mL) and brine (1 × 100 mL), dried over  $\text{Na}_2\text{SO}_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm  $\phi$  × 12 cm column) eluting with hexanes/ $\text{Et}_2\text{O}$ , 7:3 followed by distillation (1.33 mbar, 35–55 °C) afforded **5f** (6.5 g, 82%) as a colorless oil. The spectroscopic data for **5f** matched the literature values.<sup>121</sup> Data for **5f**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.69 (s, 1H), 4.20 (s, 2H), 0.92 (s, 9H), 0.10 (s, 6H).

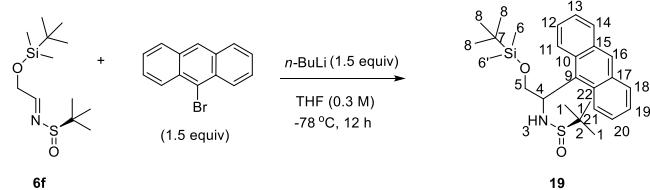


**Preparation of (R,E)-N-(2-((tert-Butyldimethylsilyl)oxy)-ethylidene)-2-methylpropane-2-sulfonamide (6f).** A 250 mL, one-necked Schlenk flask with an egg-shaped stir bar (50.8 × 19.1 mm) was charged with 5f (6.50 g, 37.3 mmol), (R)-2-methylpropane-2-sulfonamide (4.97 g, 41.03 mmol, 1.1 equiv), CuSO<sub>4</sub> (13.10 g, 82.06 mmol, 2.2 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (SDS, 80 mL) under nitrogen. The anhydrous CuSO<sub>4</sub> (white color) was prepared by heating CuSO<sub>4</sub>·5H<sub>2</sub>O (blue) in vacuum oven (1.33 mbar, 300 °C) for 5 days. The mixture was stirred at 25 °C for 15 h and then diluted with CH<sub>2</sub>Cl<sub>2</sub> (SDS, 50 mL). The suspension was filtered through a fritted glass funnel (7.5 mm diameter) containing Celite. The Celite cake was washed with CH<sub>2</sub>Cl<sub>2</sub> (2 × 100 mL). The combined filtrates were concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm Ø × 12 cm column) eluting with hexanes/EtOAc, 7:3 to afford 6f (8.90 g, 86%) as a colorless oil. The spectroscopic data for 6f matched the literature values.<sup>122</sup> Data for 6f: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.99 (t, *J* = 3.1 Hz, 1H), 4.47 (d, *J* = 3.1 Hz, 2H), 1.13 (s, 9H), 0.85 (s, 9H), 0.03 (s, 6H).



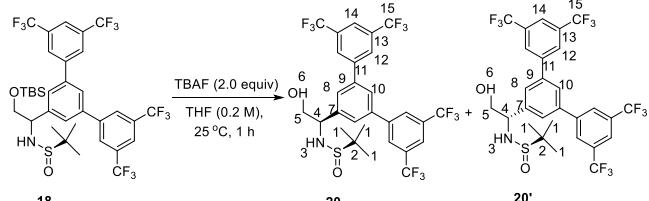
**Preparation of (R)-N-(2-((tert-Butyldimethylsilyl)oxy)-1-(3,3",5,5"-tetrakis(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-yl)-ethyl)-2-methylpropane-2-sulfonamide (18).** A 100 mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1 × 15.9 mm) was charged with 5'-iodo-3,3",5,5"-tetrakis(trifluoromethyl)-1,1':3',1"-terphenyl (4.71 g, 7.5 mmol, 1.5 equiv) and THF (20 mL) under nitrogen. The solution was cooled to -78 °C using a cryocooler in an *i*-PrOH bath, and *n*-butyllithium (0.48 mg, 1.69 mL, 1.6 M in hexane, 7.5 mmol, 1.5 equiv) was added dropwise by syringe. The resulting solution was stirred at -78 °C using a cryocooler in an *i*-PrOH bath for 1 h. Then another 50 mL Schlenk flask containing an egg-shaped stir bar (19.1 × 9.5 mm) was charged with 6f (1.39 g, 5.0 mmol), and THF (20 mL) under nitrogen and was cooled to -78 °C using a cryocooler in an *i*-PrOH bath. The *N*-sulfinyl imine solution was transferred to the organolithium solution using a syringe dropwise over 5 min. The resulting mixture was stirred at -78 °C using a cryocooler in an *i*-PrOH bath for 12 h. The reaction was quenched by the addition of satd aq NH<sub>4</sub>Cl solution (50 mL) at -78 °C and then was slowly warmed to 25 °C. The mixture was transferred to a 250 mL separatory funnel. The organic layer was removed, the aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the organic layers were combined, washed with brine (1 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The dr of the crude product was 67:33 by <sup>1</sup>H NMR analysis. The crude product was purified by column chromatography (silica, 4 cm Ø × 12 cm column) eluting with hexanes/EtOAc, 7:3 to afford 18 (3.50 g, 90%) as a white solid comprising a mixture of diastereomers. Data for 18: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.04 (s, 1.37H, HC(14)), 8.03 (s, 2.52H, HC(14)), 7.92 (s, 1.26H, HC(16)), 0.66 (s, 1H, HC(16)), 7.70 (d, *J* = 1.6 Hz, 0.69H, HC(10)), 7.69 (t, *J* = 1.7 Hz, 0.59H, HC(12)), 7.67 (t, *J* = 1.5 Hz, 0.39H, HC(12)), 7.66 (d, *J* = 1.6 Hz, 1.19H, HC(10)), 4.73 (ddd, *J* = 8.4, 4.0, 1.5 Hz, 0.62H, HC(4)), 4.60 (dd, *J* = 10.5, 4.5 Hz, 0.37H, HC(4)), 4.40 (d, *J* = 1.6 Hz, 0.61H, HN(3)), 4.24 (d, *J* = 6.0 Hz, 0.36H, HN(3)), 4.01 (d, *J* = 4.5 Hz, 0.12H, HC(5)), 3.98 (d, *J* = 4.5 Hz, 0.23H, HC(5)), 3.95–3.90 (m, 0.89H, HC(5)),

3.73 (dd, *J* = 10.0, 8.8 Hz, 0.62H, HC(5)), 1.30 (s, 5.55H, HC(1)), 1.25 (s, 3.27H, HC(1)), 0.92 (s, 5.69H, HC(8)), 0.86 (s, 3.29H, HC(8)), 0.11 (s, 1.86H, HC(6')), 0.08 (s, 1.92H, HC(6)), 0.03 (s, 1.05H, HC(6')), 0.00 (s, 1.06H, HC(6)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 143.3 (C(11)), 142.7 (C(11)), 142.6 (C(9)), 141.7 (C(9)), 140.0 (C(13)), 139.9 (C(13)), 132.6 (C-F, 2J<sub>C-F</sub> = 33.4 Hz, C(15)), 132.5 (C-F, 2J<sub>C-F</sub> = 33.4 Hz, C(15)), 127.6 (C(10)), 127.5 (C-F, 3J<sub>C-F</sub> = 2.8 Hz, C(14)), 127.4 (C(10)), 125.9 (C(12)), 125.9 (C(12)), 123.4 (C-F, 1J<sub>C-F</sub> = 273.3 Hz, C(17)), 123.4 (C-F, 1J<sub>C-F</sub> = 273.2 Hz, C(17)), 121.7 (C-F, 3J<sub>C-F</sub> = 3.8 Hz, C(16)), 121.7 (C-F, 3J<sub>C-F</sub> = 3.8 Hz, C(16)), 67.7 (C(5)), 67.3 (C(5)), 60.3 (C(4)), 59.3 (C(4)), 56.7 (C(2)), 55.8 (C(2)), 25.8 (C(8)), 25.8 (C(8)), 22.6 (C(1)), 18.2 (C(7)), -5.1 (C(6')), -5.4 (C(6)), -5.4 (C(6')), -5.4 (C(6)); <sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>) δ -62.82, -62.76; IR (neat) 2931 (s), 1620 (s), 1463 (s), 1369 (s), 1171 (s), 1128 (m), 1107 (m), 1070 (s), 1005 (s), 899 (s), 878 (s), 836 (s), 777 (s), 735 (s), 706 (s), 682 (m), 639 (s), 518 (s); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>34</sub>H<sub>38</sub>NO<sub>2</sub>F<sub>12</sub>SSi 780.2226, found 780.2201; TLC *R*<sub>f</sub> 0.33 (hexanes/EtOAc, 7.5:2.5, UV, KMnO<sub>4</sub>).

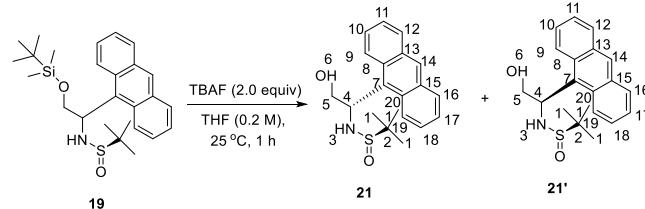


**Preparation of (R)-N-(1-(Anthracen-9-yl)-2-((tert-butyldimethylsilyl)oxy)ethyl)-2-methylpropane-2-sulfonamide (19).** A 100 mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1 × 15.9 mm) was charged with 9-bromoanthracene (5.14 g, 20.0 mmol, 2.0 equiv) and THF (25 mL) under nitrogen. The solution was cooled to -78 °C using a cryocooler in an *i*-PrOH bath, and *n*-butyllithium (1.28 g, 13.0 mL, 1.6 M in hexane, 20.0 mmol, 2.0 equiv) was added dropwise by syringe. The resulting solution was stirred at -78 °C using a cryocooler in *i*-PrOH bath for 1 h. Then another 50 mL Schlenk flask containing an egg-shaped stir bar (19.1 × 9.5 mm) was charged with 6f (2.77 g, 10.0 mmol) and THF (25 mL) under nitrogen and was cooled to -78 °C using a cryocooler in an *i*-PrOH bath. The *N*-sulfinyl imine solution was transferred to the organolithium solution using a syringe dropwise over 5 min. The resulting mixture was stirred at -78 °C using a cryocooler in an *i*-PrOH bath for 12 h. The reaction was quenched by the addition of satd aq NH<sub>4</sub>Cl solution (50 mL) at -78 °C and slowly warmed to 25 °C. The mixture was transferred to a 250 mL separatory funnel. The organic layer was removed, the aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the organic layers were combined, washed with brine (1 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The dr of the crude product was 69:31 by <sup>1</sup>H NMR analysis. The crude product was purified by column chromatography (silica, 4 cm Ø × 12 cm column) eluting with hexanes/EtOAc, 8:2 to afford 19 (4.09 g, 90%) as a yellow solid comprising a mixture of diastereomers. Data for 19: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.05–8.32 (m, 3H, HC(11,16,21)), 8.01–8.00 (m, 2H, HC(14,18)), 7.62–7.38 (m, 4H, HC(12,13,19,20)), 6.16–6.08 (m, 1H, HC(4)), 4.65 (s, 0.24H, HC(3)), 4.56 (t, *J* = 10.5 Hz, 0.25H, HC(5)), 4.48 (dd, *J* = 10.1, 6.7 Hz, 0.76H, HC(5)), 4.24 (dd, *J* = 10.1, 6.7 Hz, 0.77H, HC(5)), 4.01 (s, 0.76H, HC(3)), 3.84 (dd, *J* = 10.1, 6.7 Hz, 0.76H, HC(5)), 1.25 (s, 7H, HC(1)), 1.19 (s, 2H, HC(1)), 0.98 (s, 2H, HC(8)), 0.72 (s, 7H, HC(8)), 0.13 (s, 1H, HC(6')), 0.12 (s, 1H, HC(6)), -0.14 (s, 2H, HC(6')), -0.32 (s, 2H, HC(6)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 132.0 (C(15)), 131.5 (C(17)), 131.1 (C(10)), 130.9 (C(22)), 130.6 (C(22)), 129.9 (C(9)), 129.7 (C(9)), 129.5 (C(16)), 129.4 (C(16)), 129.2 (C(14)), 128.8 (C(18)), 127.4 (C(13)), 127.1 (C(19)), 126.76 (C(19)), 126.0 (C(12)), 125.3 (C(12)), 125.1 (C(20)), 124.7 (C(20)), 124.0 (C(11)), 123.3 (C(21)), 66.6 (C(5)), 65.1 (C(5)), 56.2 (C(2)), 55.3 (C(2)), 55.1 (C(4)), 54.8

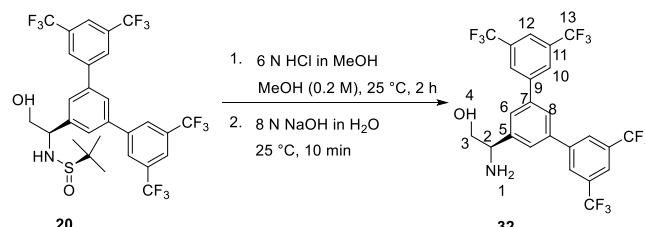
(C(4)), 26.0 (C(8)), 25.7 (C(8)), 22.8 (C(1)), 22.7 (C(1)), 18.3 (C(7)), 18.1 (C(7)), -5.0 (C(6')), -5.2 (C(6)), -5.4 (C(6')), -5.6 (C(6)); IR (neat) 2952 (s), 2927 (s), 2855 (s), 1624 (s), 1524 (s), 1470 (s), 1388 (s), 1252 (s), 1158 (s), 1067 (m), 1011 (s), 886 (s), 832 (w), 775 (m), 729 (m), 695 (s), 600 (s), 5 (s); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>26</sub>H<sub>38</sub>NO<sub>2</sub>F<sub>12</sub>SSI 456.2396, found 456.2393; TLC  $R_f$  0.34 (hexanes/EtOAc, 7.5:2.5, UV, KMnO<sub>4</sub>).



**Preparation of (R)-N-(2-Hydroxy-1-(3,3',5,5"-tetraakis(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-yl)ethyl)-2-methylpropane-2-sulfonamide (20).** A 100 mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1 × 15.9 mm) was charged with 18 (3.70 g, 4.74 mmol) and THF (30 mL) under nitrogen. Tetra-*n*-butylammonium fluoride (2.48 g, 9.49 mL, 1.0 M in THF, 9.49 mmol, 2.0 equiv) was added dropwise by syringe. The mixture was stirred at 25 °C for 1 h. The mixture was transferred to a 125 mL separatory funnel and washed with water (1 × 30 mL). The organic layer was removed, the aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the organic layers were combined, washed with brine (1 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The dr of the crude product was 2:1 by <sup>1</sup>H NMR analysis. The crude product was purified by automatic flash column chromatography (ISCO, 350 g) eluting with IPA/CH<sub>2</sub>Cl<sub>2</sub>, 0:1 gradient to 0.5:9.5 to afford 21 (1.94 g, 63%) and 21' (0.87 g, 28%) as yellow solids. The compound 21 was crystallized by slow vapor diffusion of *n*-pentane into benzene. Data for 21 (major isomer): mp 188–190 °C (IPA/CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.53 (s, 2H, HC(8,19)), 8.41 (s, 1H, HC(14)), 7.99–7.97 (m, 2H, HC(12,16)), 7.52–7.38 (m, 4H, HC(10,11,17,18)), 6.15 (td,  $J$  = 7.2, 2.9 Hz, 1H, HC(4)), 4.47–4.34 (m, HC(5)), 4.24 (d,  $J$  = 2.3 Hz, 1H, HN(3)), 4.20–4.09 (m, 1H, HC(5)), 3.06 (s, 1H, HO(6)), 1.19 (s, 9H, HC(1)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 130.7 (C(13,15)), 130.4 (C(8,20)), 129.6 (C(7)), 129.0 (C(12,14,16)), 124.9 (C(9,10,11,17,18,19)), 66.0 (C(5)), 56.3 (C(2)), 55.1 (C(4)), 22.8 (C(1)); IR (neat) 3300 (s), 1444 (s), 1363 (s), 1321 (s), 1158 (s), 1074 (s), 1058 (s), 915 (s), 882 (s), 859 (s), 835 (s), 786 (s), 653 (m), 548 (s); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>20</sub>H<sub>24</sub>NO<sub>2</sub>S 342.1519, found 342.1528; TLC  $R_f$  0.46 (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9.5:0.5, UV, KMnO<sub>4</sub>). Data for 21' (minor isomer): mp 194–196 °C (IPA/CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.94–8.53 (m, 2H, HC(8,9)), 8.46 (s, 1H, HC(14)), 8.06–7.99 (m, 2H, HC(12,16)), 7.57–7.38 (m, 4H, HC(10,11,17,18)), 6.27 (d,  $J$  = 9.9 Hz, 1H, HC(4)), 4.93 (s, 1H, HN(3)), 4.59–4.51 (m, 1H, HC(5)), 4.02 (dd,  $J$  = 11.8, 4.2 Hz, 1H, HC(5)), 1.17 (s, 9H, HC(1)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 131.8 (C(13,15)), 129.5 (C(8,20)), 129.0 (C(7)), 128.6 (C(14)), 127.2 (C(12,16)), 126.8 (C(11,17)), 124.9 (C(10,18)), 123.4 (C(9,19)), 65.0 (C(5)), 56.9 (C(2)), 55.8 (C(4)), 22.8 (C(1)); IR (neat) 3403 (s), 2958 (s), 1471 (s), 1391 (s), 1241 (s), 1161 (s), 1066 (s), 1037 (m), 961 (s), 889 (s), 853 (s), 837 (s), 793 (s), 647 (s), 550 (s); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>20</sub>H<sub>24</sub>NO<sub>2</sub>S 342.1526, found 342.1528; TLC  $R_f$  0.44 (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9.5:0.5, UV, KMnO<sub>4</sub>).

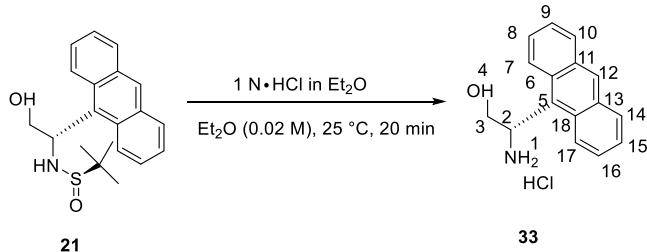


**Preparation of (R)-N-1-(Anthracen-9-yl)-2-hydroxyethyl)-2-methylpropane-2-sulfonamide (21).** A 125 mL one-necked Schlenk flask containing an egg-shaped stir bar (38.1 × 15.9 mm) was charged with 19 (4.09 g, 8.98 mmol) and THF (60 mL) under nitrogen. Tetra-*n*-butylammonium fluoride (4.69 g, 17.98 mL, 1.0 M in THF, 17.96 mmol, 2.0 equiv) was added dropwise by syringe. The mixture was stirred at 25 °C for 1 h. The mixture was transferred to a 250 mL separatory funnel and washed with water (1 × 60 mL). The organic layer was removed, the aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the organic layers were combined, washed with brine (1 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The dr of the crude product was 69:31 by <sup>1</sup>H NMR analysis. The crude product was purified by automatic flash column chromatography (ISCO, 350 g) eluting with IPA/CH<sub>2</sub>Cl<sub>2</sub>, 0:1 gradient to 0.5:9.5 to afford 21 (1.94 g, 63%) and 21' (0.87 g, 28%) as yellow solids. The compound 21 was crystallized by slow vapor diffusion of *n*-pentane into benzene. Data for 21 (major isomer): mp 188–190 °C (IPA/CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.53 (s, 2H, HC(8,19)), 8.41 (s, 1H, HC(14)), 7.99–7.97 (m, 2H, HC(12,16)), 7.52–7.38 (m, 4H, HC(10,11,17,18)), 6.15 (td,  $J$  = 7.2, 2.9 Hz, 1H, HC(4)), 4.47–4.34 (m, HC(5)), 4.24 (d,  $J$  = 2.3 Hz, 1H, HN(3)), 4.20–4.09 (m, 1H, HC(5)), 3.06 (s, 1H, HO(6)), 1.19 (s, 9H, HC(1)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 130.7 (C(13,15)), 130.4 (C(8,20)), 129.6 (C(7)), 129.0 (C(12,14,16)), 124.9 (C(9,10,11,17,18,19)), 66.0 (C(5)), 56.3 (C(2)), 55.1 (C(4)), 22.8 (C(1)); IR (neat) 3300 (s), 1444 (s), 1363 (s), 1321 (s), 1158 (s), 1074 (s), 1058 (s), 915 (s), 882 (s), 859 (s), 835 (s), 786 (s), 653 (m), 548 (s); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>20</sub>H<sub>24</sub>NO<sub>2</sub>S 342.1519, found 342.1528; TLC  $R_f$  0.46 (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9.5:0.5, UV, KMnO<sub>4</sub>). Data for 21' (minor isomer): mp 194–196 °C (IPA/CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.94–8.53 (m, 2H, HC(8,9)), 8.46 (s, 1H, HC(14)), 8.06–7.99 (m, 2H, HC(12,16)), 7.57–7.38 (m, 4H, HC(10,11,17,18)), 6.27 (d,  $J$  = 9.9 Hz, 1H, HC(4)), 4.93 (s, 1H, HN(3)), 4.59–4.51 (m, 1H, HC(5)), 4.02 (dd,  $J$  = 11.8, 4.2 Hz, 1H, HC(5)), 1.17 (s, 9H, HC(1)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 131.8 (C(13,15)), 129.5 (C(8,20)), 129.0 (C(7)), 128.6 (C(14)), 127.2 (C(12,16)), 126.8 (C(11,17)), 124.9 (C(10,18)), 123.4 (C(9,19)), 65.0 (C(5)), 56.9 (C(2)), 55.8 (C(4)), 22.8 (C(1)); IR (neat) 3403 (s), 2958 (s), 1471 (s), 1391 (s), 1241 (s), 1161 (s), 1066 (s), 1037 (m), 961 (s), 889 (s), 853 (s), 837 (s), 793 (s), 647 (s), 550 (s); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>20</sub>H<sub>24</sub>NO<sub>2</sub>S 342.1526, found 342.1528; TLC  $R_f$  0.44 (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9.5:0.5, UV, KMnO<sub>4</sub>).

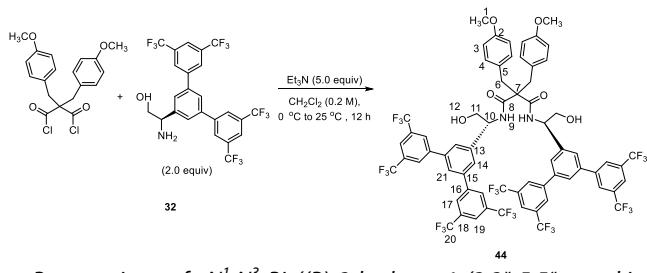


**Preparation of (R)-2-Amino-2-(3,3',5,5"-tetraakis(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-yl)ethan-1-ol (32).** A 250 mL, one-necked Schlenk flask with an egg-shaped stir bar (50.8 × 19.1 mm) was charged with 20 (1.90 g, 2.8 mmol) and methanol (5 mL) under nitrogen. HCl (6 N) in MeOH (28 mL) was added dropwise by syringe. The mixture was stirred for 2 h at 25 °C, and then the solvent was removed rotary evaporation (30 °C, 50 mbar). The crude solid was suspended in ethyl acetate (50 mL),

and 8 N NaOH in H<sub>2</sub>O (42 mL) was added while the solution was stirred vigorously. The solution was stirred for 10 min and then was transferred to a 500 mL separatory funnel. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). pH paper was used to check the neutralization of the solution (pH = 7). The organic layers were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (5 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm Ø × 12 cm column) eluting with MeOH/EtOAc, 1:9 to afford **32** (1.2 g, 80%) as a white solid. Data for **32**: mp 177–179 °C (MeOH/EtOAc); <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 8.35 (s, 4H, HC(10)), 7.98 (s, 3H, HC(6,8)), 7.84 (s, 2H, HC(12)), 4.18 (t, *J* = 6.2 Hz, 1H, HC(2)), 3.82 (dd, *J* = 10.9, 5.4 Hz, 1H, HC(3)), 3.73 (dd, *J* = 10.9, 7.0 Hz, 1H, HC(3)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CD<sub>3</sub>OD) δ 146.2 (C(7)), 141.3 (C(5)), 138.5 (C(9)), 133.3 (C–F, 2J<sub>C–F</sub> = 33.4 Hz, C(12)), 128.9 (C–F, 2J<sub>C–F</sub> = 4.0 Hz, C(10)), 127.8 (C(6)), 126.3 (C(8)), 124.9 (C–F, 1J<sub>C–F</sub> = 272.5 Hz, C(13)), 122.1 (C–F, 3J<sub>C–F</sub> = 3.8 Hz, C(12)), 68.4 (C(3)), 58.5 (C(2)); <sup>19</sup>FNMR (471 MHz, CD<sub>3</sub>OD) –64.19; IR (neat) 1595 (s), 1372 (s), 1288 (m), 1278 (m), 1229 (s), 1157 (m), 1112 (m), 1051 (s), 925 (m), 878 (s), 844 (s), 768 (s), 705 (s), 682 (m), 535 (s); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>24</sub>H<sub>16</sub>NOF<sub>12</sub> 562.1025, found 562.1040; TLC *R*<sub>f</sub> 0.6 (silica gel, MeOH/EtOAc, 1:9, UV, KMnO<sub>4</sub>).

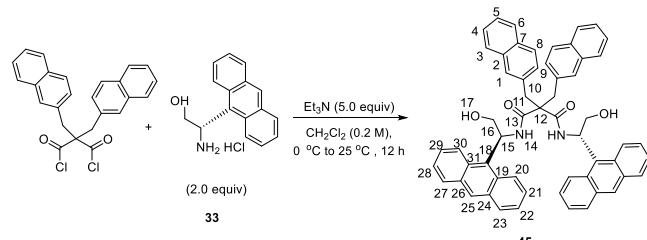


**Preparation of (S)-2-Amino-2-(anthracen-9-yl)ethan-1-ol hydrogen Chloride (33).** A 250 mL, one-necked Schlenk flask with an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **21** (0.72 g, 2.13 mmol), and Et<sub>2</sub>O (100 mL) under nitrogen. HCl (1 N) in Et<sub>2</sub>O (85.2 mL) was added dropwise by syringe. The mixture was stirred for 20 min at 25 °C. Then the mixture was filtered through a fritted glass funnel (7.5 mm diameter). The solids were washed with Et<sub>2</sub>O (2 × 50 mL) and dried in high vacuum (1.33 mbar) to afford **33** (0.44 g, 89%) as a white solid. Data for **33**: mp 230–232 °C (MeOH/EtOAc); <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 8.61 (s, 1H, HC(12)), 8.41–8.39 (m, 2H, HC(7,17)), 8.11–8.09 (m, Hz, 2H, HC(10,14)), 7.69–7.66 (m, 2H, HC(8,16)), 7.55–7.52 (m, 2H, HC(9,15)), 5.96 (dd, *J* = 9.9, 5.0 Hz, 1H, HC(2)), 4.75–4.54 (m, 1H, HC(3)), 4.07 (dd, *J* = 12.0, 5.0 Hz, 1H, HC(3)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CD<sub>3</sub>OD) δ 132.9 (C(11,13)), 131.5 (C(18)), 131.4 (C(6)), 131.0 (C(5)), 129.2 (C(12)), 128.5 (C(10,14)), 126.2 (C(9,15)), 125.7 (C(8,16)), 123.9 (C(7,17)), 63.3 (C(3)), 54.2 (C(2)); IR (neat) 3047 (s), 2844 (s), 1623 (s), 1518 (s), 1481 (s), 1259 (s), 1218 (s), 1189 (s), 1157 (s), 1003 (s), 955 (s), 884 (s), 843 (s), 786 (s), 763 (s), 625 (s), 535 (s); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>16</sub>H<sub>16</sub>NO 238.1230, found 238.1232; TLC *R*<sub>f</sub> 0.29 (silica gel, MeOH/EtOAc, 1:9, UV, KMnO<sub>4</sub>).



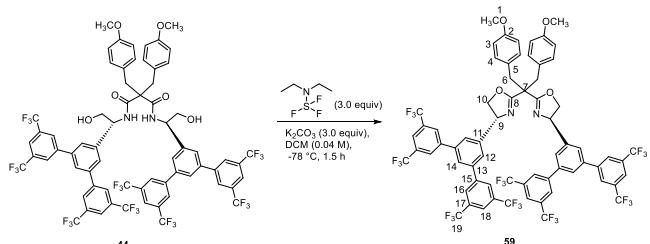
**Preparation of N<sup>1</sup>,N<sup>3</sup>-Bis((R)-2-hydroxy-1-(3,3",5,5"-tetraakis-(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-yl)ethyl)-2,2-bis(4-methoxybenzyl)malonamide (44).** A 50 mL Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged

with **32** (1.12 g, 2.0 mmol, 2.0 equiv), Et<sub>3</sub>N (0.50 g, 0.69 mL, 10.0 mmol, 5.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (8 mL) under nitrogen. The solution was cooled to 0 °C using an ice bath, and 2,2-dimethylmalonyl dichloride (0.38 g, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added dropwise by syringe over 2 min. The resulting mixture was warmed slowly to 25 °C and was stirred at 25 °C for 12 h. The mixture was transferred to a 60 mL separatory funnel. The reaction mixture was washed with water (1 × 25 mL) and then brine (1 × 25 mL). The organic layer was removed, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 15 mL), and the organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub> (2 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm Ø × 15 cm column) eluting with hexanes/EtOAc, 7:3 to afford **44** (1.11 g, 78%) as a white solid. Data for **44**: mp 124–126 °C (hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.10 (d, *J* = 7.4 Hz, 2H, HN(9)), 7.97 (s, 8H, HC(17)), 7.90 (s, 4H, HC(19)), 7.64 (s, 2H, HC(21)), 7.45 (d, *J* = 1.7 Hz, 4H, HC(14)), 6.99 (d, *J* = 8.6 Hz, 4H, HC(4)), 6.42 (d, *J* = 8.6 Hz, 4H, HC(3)), 5.25 (dd, *J* = 11.5, 5.7 Hz, 2H, HC(10)), 3.90 (dd, *J* = 11.3, 4.1 Hz, 2H, HC(11)), 3.84 (dd, *J* = 11.3, 5.8 Hz, 2H, HC(11)), 3.43 (s, 6H, HC(1)), 3.38 (d, *J* = 14.4 Hz, 2H, HC(6)), 3.31 (d, *J* = 14.4 Hz, 2H, HC(6)), 2.37 (s, 2H, HO(12)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>) δ 172.8 (C(8)), 158.6 (C(2)), 142.2 (C(15)), 141.5 (C(13)), 140.0 (C(16)), 132.5 (C–F, 2J<sub>C–F</sub> = 33.9 Hz, C(18)), 130.5 (C(4)), 127.9 (C(5)), 127.5 (C–F, 1J<sub>C–F</sub> = 3.8 Hz, C(17)), 126.3 (C(14)), 125.6 (C(21)), 123.3 (C–F, 1J<sub>C–F</sub> = 273.2 Hz, C(20)), 121.8 (C–F, 3J<sub>C–F</sub> = 3.9 Hz, C(19)), 113.6 (C(3)), 66.2 (C(11)), 59.9 (C(7)), 55.7 (C(10)), 54.8 (C(1)), 43.0 (C(6)); <sup>19</sup>FNMR (471 MHz, CDCl<sub>3</sub>) –62.80; IR (neat) 3396 (w), 1650 (s), 1613 (s), 1614 (m), 1513 (s), 1465 (s), 1393 (s), 1275 (m), 1171 (m), 1036 (s), 898 (s), 873 (m), 735 (w), 705 (m), 682 (m), 518 (s); HRMS (ESI) *m/z* (M + H)<sup>+</sup> calcd for C<sub>67</sub>H<sub>47</sub>F<sub>24</sub>N<sub>2</sub>O<sub>6</sub> 1431.3120, found 1431.3051; TLC *R*<sub>f</sub> 0.27 (silica gel, hexanes/EtOAc, 7:3, UV, KMnO<sub>4</sub>).

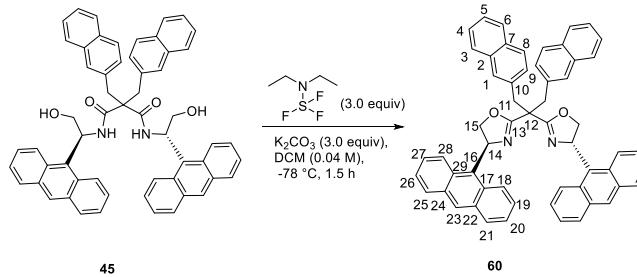


**Preparation of N<sup>1</sup>,N<sup>3</sup>-Bis((R)-2-hydroxy-1-(3,3",5,5"-tetraakis-(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-yl)ethyl)-2,2-bis(4-methoxybenzyl)malonamide (45).** A 50 mL Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **33** (0.44 g, 1.85 mmol, 2.0 equiv), Et<sub>3</sub>N (0.46 g, 0.63 mL, 9.25 mmol, 5.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (8 mL) under nitrogen. The solution was cooled to 0 °C using an ice bath, and 2,2-bis(naphthalen-2-ylmethyl)malonyl dichloride (0.38 g, 0.92 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added dropwise by syringe over 2 min. The resulting mixture was warmed slowly to 25 °C and was stirred at 25 °C for 12 h. The mixture was transferred to a 60 mL separatory funnel. The reaction mixture was washed with water (1 × 25 mL) and then brine (1 × 25 mL). The organic layer was removed, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 15 mL), and the organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub> (2 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm Ø × 15 cm column) eluting with hexanes/EtOAc, 1:1 to afford **45** (0.62 g, 82%) as a yellow solid. Data for **45**: mp 153–155 °C (hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.36 (d, *J* = 4.8 Hz, 2H, HC(14)), 8.18 (s, 2H, HC(25)), 7.80–7.78 (m, 6H, HC(6,20,30)), 7.49 (d, *J* = 8.2 Hz, 2H, HC(8)), 7.33–7.07 (m, 18H, HC(3,4,21,22,23,27,28,29)), 6.99–6.97 (m, 4H, HC(1,9)), 6.20 (dt, *J* = 8.5, 4.5 Hz, 2H, HC(15)), 4.39–4.33 (m, 2H, HC(16)), 3.99 (s, 2H, HC(17)), 3.76–3.68 (m, *J* = 10.9, 2H, HC(16)), 3.54 (d, *J* = 14.1 Hz, 2H, HC(11)), 3.29 (d, *J* = 14.1 Hz, 2H, HC(11));

$^{13}\text{C}\{\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  174.0 (C(13)), 133.1 (C(2)), 133.0 (C(7)), 132.3 (C(24,26)), 131.6 (C(19,31)), 129.6 (C(10,18)), 129.0 (C(29)), 128.9 (C(28)), 128.2 (C(9)), 128.0 (C(5)), 127.6 (C(22)), 127.4 (C(21)), 126.6 (C(4)), 126.1 (C(3)), 125.8 (C(23,27)), 125.0 (C(13)), 123.5 (C(20,30)), 67.5 (C(16)), 59.3 (C(12)), 54.4 (C(15)), 44.3 (C(10)); IR (neat) 3321 (s), 2925 (s), 1661 (s), 1623 (s), 1504 (s), 1445 (s), 1367 (s), 1236 (s), 1157 (s), 1032 (s), 886 (s), 859 (s), 788 (s), 601 (s); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_{57}\text{H}_{47}\text{N}_2\text{O}_4$  823.3535, found 823.3536; TLC  $R_f$  0.13 (silica gel, hexanes/EtOAc, 7:3, UV, KMnO<sub>4</sub>).

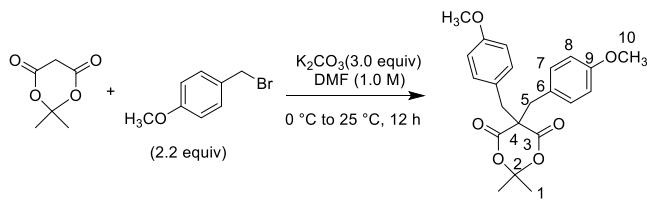


**Preparation of (4R,4'R)-2,2'-(1,3-Bis(4-methoxyphenyl)propane-2,2-diyli)bis(4-(3,3",5,5"-tetrakis(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-yl)-4,5-dihydrooxazole) (59).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with 44 (0.71 g, 0.5 mmol) and  $\text{CH}_2\text{Cl}_2$  (12 mL) under nitrogen. The solution was cooled to -78 °C using a cryocooler in an *i*-PrOH, and diethylaminosulfur trifluoride (0.24 g, 0.19 mL, 1.5 mmol, 3.0 equiv) was added dropwise by syringe. The resulting solution was stirred at -78 °C using a cryocooler in *i*-PrOH for 1.5 h. Then  $\text{K}_2\text{CO}_3$  (0.20 g, 1.5 mmol, 3.0 equiv) was added in one portion at -78 °C, and the mixture was slowly warmed to 25 °C. The reaction was quenched by the addition of satd aq  $\text{NaHCO}_3$  solution (2 mL). The mixture was transferred to a 60 mL separatory funnel. The organic layer was removed, the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 × 10 mL), and the organic layers were combined, washed with brine (1 × 10 mL), dried over  $\text{Na}_2\text{SO}_4$  (1 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm  $\phi$  × 15 cm column) eluting with hexanes/EtOAc, 9:1 to afford 59 (0.64 g, 92%) as a white solid. Recrystallization from hexanes/Et<sub>2</sub>O afforded 0.60 g (87%) of analytically pure 59 as a white solid. Data for 59: mp 119–121 °C (hexanes/EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99 (s, 8H, HC(16)), 7.89 (s, 4H, HC(18)), 7.64 (s, 2H, HC(14)), 7.49 (s, 4H, HC(12)), 7.25 (d,  $J$  = 8.6 Hz, 4H, HC(4)), 6.71 (d,  $J$  = 8.6 Hz, 4H, HC(3)), 5.34 (dd,  $J$  = 10.1, 7.1 Hz, 2H, HC(9)), 4.73–4.52 (m, 2H, HC(10)), 4.21–4.05 (m, 2H, HC(10)), 3.64 (s, 6H, HC(1)), 3.52 (d,  $J$  = 14.0 Hz, 2H, HC(6)), 3.36 (d,  $J$  = 14.0 Hz, 2H, HC(6));  $^{13}\text{C}\{\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  168.8 (C(8)), 158.7 (C(2)), 145.0 (C(13)), 142.5 (C(11)), 139.9 (C(5)), 132.4 (C–F,  $2J_{\text{C}-\text{F}}$  = 33.4 Hz, C(17)), 131.5 (C(4)), 128.4 (C(5)), 127.4 (C–F,  $3J_{\text{C}-\text{F}}$  = 2.5 Hz, C(16)), 126.2 (C(12)), 125.4 (C(14)), 123.4 (C–F,  $1J_{\text{C}-\text{F}}$  = 273.2 Hz, C(19)), 121.7 (C–F,  $3J_{\text{C}-\text{F}}$  = 3.9 Hz, C(18)), 113.6 (C(3)), 74.7 (C(10)), 69.2 (C(9)), 55.1 (C(1)), 49.5 (C(7)), 39.7 (C(6));  $^{19}\text{F}$ NMR (471 MHz,  $\text{CDCl}_3$ ) –62.75; IR (neat) 2904 (s), 1655 (s), 1612 (s), 1465 (s), 1393 (s), 1369 (s), 1323 (s), 1275 (m), 1169 (m), 1107 (m), 1037 (s), 961 (s), 899 (s), 824 (s), 706 (s), 537 (s); LRMS [ESI<sup>+</sup>, TOF] 637.3(1), 1395.2(100), 1395.2(5), 1396.2(72), 1397.2(27), 1398.3(9); Anal. Calcd for  $\text{C}_{67}\text{H}_{42}\text{F}_{24}\text{N}_2\text{O}_4$  (1394.280): C, 57.68; H, 3.03; N, 2.01. Found: C, 57.59; H, 3.02; N, 2.12, HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_{67}\text{H}_{43}\text{F}_{24}\text{N}_2\text{O}_4$  1395.2898, found 1395.2840; TLC  $R_f$  0.23 (silica gel, hexanes/EtOAc, 9:1, UV, KMnO<sub>4</sub>);  $[\alpha]_D^{24}$  +89.5 ( $c$  = 1.0, 100% CHCl<sub>3</sub>).



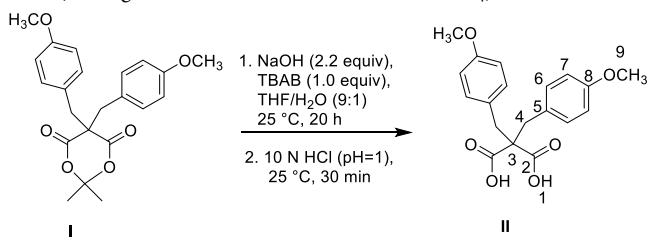
**Preparation of (4S,4'R)-2,2'-(1,3-Di(naphthalen-2-yl)propane-2,2-diyli)bis(4-(anthracen-9-yl)-4,5-dihydrooxazole) (60).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with 45 (0.41 g, 0.5 mmol) and  $\text{CH}_2\text{Cl}_2$  (12 mL) under nitrogen. The solution was cooled to -78 °C using a cryocooler in an *i*-PrOH, and diethylaminosulfur trifluoride (0.24 g, 0.19 mL, 1.5 mmol, 3.0 equiv) was added dropwise by syringe. The resulting solution was stirred at -78 °C using a cryocooler in *i*-PrOH for 1.5 h. Then  $\text{K}_2\text{CO}_3$  (0.20 g, 1.5 mmol, 3.0 equiv) was added in one portion at -78 °C, and the mixture was slowly warmed to 25 °C. The reaction was quenched by the addition of satd aq  $\text{NaHCO}_3$  solution (2 mL). The mixture was transferred to a 60 mL separatory funnel. The organic layer was removed, the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 × 10 mL), and the organic layers were combined, washed with brine (1 × 10 mL), dried over  $\text{Na}_2\text{SO}_4$  (1 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm  $\phi$  × 15 cm column) eluting with hexanes/EtOAc, 9:1 to afford 60 (0.36 g, 92%) as a yellow solid. Recrystallization from pentanes/toluene afforded 0.35 g (90%) of analytically pure 60 as a yellow solid. Data for 60: mp 148–150 °C (pentanes/toluene);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.50 (s, 2H, HC(23)), 8.46–8.45 (m, 4H, HC(18,28)), 8.06–8.04 (m, 4H, HC(21,25)), 7.98–7.89 (m, 6H, HC(1,3,6)), 7.82–7.76 (m, 2H, HC(8)), 7.63 (dd,  $J$  = 8.4, 1.4 Hz, 2H, HC(9)), 7.58–7.51 (m, 4H, HC(4,5)), 7.49–7.38 (m, 8H, HC(19,20,26,27)), 6.67 (t,  $J$  = 11.2 Hz, 2H, HC(14)), 4.99 (dd,  $J$  = 11.4, 8.3 Hz, 2H, HC(15)), 4.82 (dd,  $J$  = 10.9, 8.3 Hz, 2H, HC(15)), 4.02 (d,  $J$  = 14.0 Hz, 2H, HC(11)), 3.69 (d,  $J$  = 14.1 Hz, 2H, HC(11));  $^{13}\text{C}\{\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  167.6 (C(13)), 134.5 (C(2)), 133.5 (C(7)), 132.6 (C(17,29)), 131.8 (C(22,24)), 130.6 (C(3)), 129.8 (C(10)), 129.6 (C(21,25)), 128.9 (C(23)), 128.8 (C(9)), 127.8 (C(8)), 127.7 (C(1)), 127.7 (C(6)), 126.1 (C(26)), 126.0 (C(20)), 125.7 (C(4,5)), 124.8 (C(19,27)), 124.1 (C(18,28)), 73.4 (C(15)), 65.6 (C(14)), 49.5 (C(12)), 40.5 (C(11)); IR (neat) 2904 (s), 1655 (s), 1612 (s), 1465 (s), 1393 (s), 1369 (s), 1323 (s), 1275 (m), 1169 (m), 1107 (m), 1037 (s), 961 (s), 899 (s), 824 (s), 706 (s), 537 (s); LRMS [ESI<sup>+</sup>, TOF] 376.3(8), 585.2(8), 787.3(100), 788.3(62), 789.3(27), 849.2(12), 850.2(9); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $\text{C}_{57}\text{H}_{43}\text{N}_2\text{O}_2$  787.3332, found 787.3325; TLC  $R_f$  0.19 (silica gel, hexanes/EtOAc, 9:1, UV, KMnO<sub>4</sub>);  $[\alpha]_D^{24}$  +195.7 ( $c$  = 1.0, 100% CHCl<sub>3</sub>). Anal. Calcd for  $\text{C}_{57}\text{H}_{42}\text{N}_2\text{O}_2$  (786.320): C, 86.99; H, 5.38; N, 3.56. Found: C, 86.78; H, 5.40; N, 3.74.

**Preparation of Various Bridging Substituents on Malonyl Dichloride.**

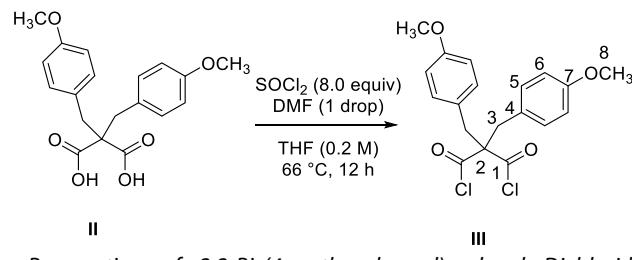


**Preparation of 5,5-Bis(4-Methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (I).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with 2,2-dimethyl-1,3-dioxane-4,6-dione (0.86 g, 6.0 mmol) and DMF (SDS, 6 mL) under nitrogen. The mixture was cooled to 0 °C in an ice

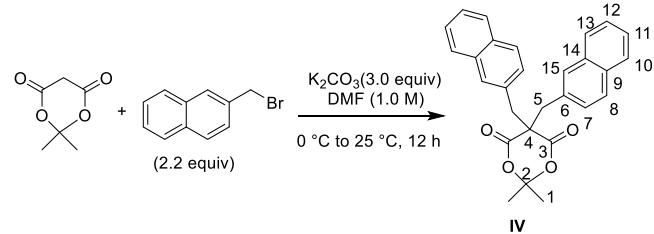
bath, and  $K_2CO_3$  (2.48 g, 18.0 mmol, 3.0 equiv) was added in one portion. 1-(Chloromethyl)-4-methoxybenzene (2.07 g, 1.79 mL, 13.2 mmol, 2.2 equiv) was added slowly under nitrogen flow over 5 min. The mixture was slowly warmed to 25 °C and stirred at 25 °C for 12 h. After 12 h, the mixture was diluted in EtOAc (15 mL) and transferred to a 125 mL separatory funnel with 80 mL of water. The organic layer was removed. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the organic layers were combined, washed with satd aq  $NaHCO_3$  (20 mL) and brine (1 × 30 mL), dried over anhydrous  $Na_2SO_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by column chromatography (silica, 3 cm  $\phi$  × 15 cm column) eluting with hexanes/EtOAc, 7:3 to afford **I** (2.00 g, 87%) as a white solid. The compound was further recrystallized with hot hexane (20 mL) to afford **I** (1.93 g, 84%) as a white solid. Data for **I**: mp 180–182 °C (hexanes);  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.09 (d,  $J$  = 8.8 Hz, 4H), HC(7)), 6.78 (d,  $J$  = 8.7 Hz, 4H), HC(8)), 3.72 (s, 6H), HC(10)), 3.35 (s, 4H), HC(5)), 0.70 (s, 6H, HC(1));  $^{13}C\{^1H\}$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  168.5 (C(3)), 159.2 (C(9)), 131.2 (C(7)), 127.0 (C(6)), 114.1 (C(8)), 105.8 (C(2)), 60.4 (C(4)), 55.2 (C(10)), 44.1 (C(5)), 28.8 (C(1)); IR (neat) 1732 (s), 1611 (m), 1512 (s), 1452 (m), 1365 (m), 1247 (s), 1176 (s), 1120 (m), 1094 (m), 1028 (s), 957 (m), 823 (s), 730 (m), 686 (m), 553 (m), 523 (s); HRMS (ESI)  $m/z$  (M + Na)<sup>+</sup> calcd for  $C_{24}H_{24}O_6$  407.1485, found 407.1471; TLC  $R_f$  0.40 (silica gel, hexanes/EtOAc, 8:2, UV,  $KMnO_4$ ).



**Preparation of 2,2-Bis(4-methoxybenzyl)malonic Acid (II).** A 50 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **I** (1.92 g, 5.0 mmol), granulated NaOH (0.44 g, 11.00 mmol, 2.2 equiv), tetra-*n*-butylammonium bromide (1.61 g, 5.00 mmol, 1.0 equiv), and a mixture of THF/H<sub>2</sub>O (18 mL/2 mL). The mixture was stirred at 25 °C for 20 h. After 20 h, the mixture was acidified to pH = 1 using 10 N HCl and was stirred for 30 min. The mixture was diluted in EtOAc (15 mL) and transferred to a 125 mL separatory funnel. The organic layer was removed. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the organic layers were combined, washed with water (20 mL) and brine (1 × 30 mL), dried over anhydrous  $Na_2SO_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by column chromatography (silica, 3 cm  $\phi$  × 15 cm column) eluting with hexanes/EtOAc, 1:1 to afford **II** (1.40 g, 80%) as a white solid. Data for **II**: mp 131–133 °C (hexanes/EtOAc);  $^1H$  NMR (500 MHz,  $CD_3OD$ )  $\delta$  7.15 (d,  $J$  = 8.5 Hz, 4H, HC(6)), 6.73 (d,  $J$  = 10.0 Hz, 4H, HC(7)), 3.69 (s, 6H, HC(9)), 3.18 (s, 4H, HC(4));  $^{13}C\{^1H\}$  NMR (126 MHz,  $CD_3OD$ )  $\delta$  180.3 (C(2)), 159.7 (C(8)), 131.6 (C(6)), 130.8 (C(5)), 114.3 (C(7)), 62.7 (C(3)), 55.5 (C(9)), 44.8 (C(4)); IR (neat) 2936 (w), 2837 (w), 1731 (m), 1611 (m), 1583 (w), 1512 (s), 1460 (m), 1302 (m), 1247 (s), 1177 (s), 1115 (m), 1029 (s), 908 (m), 828 (s), 779 (m), 732 (s), 665 (m), 638 (m), 600 (m), 556 (m), 518 (m); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for  $C_{19}H_{18}O_6$  345.1351, found 345.1338; TLC  $R_f$  0.22 (silica gel, MeOH/EtOAc, 0.5:9.5, UV,  $KMnO_4$ ).

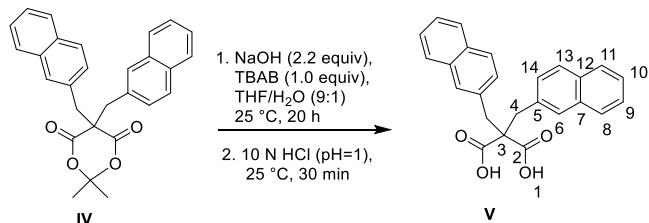


**Preparation of 2,2-Bis(4-methoxybenzyl)malonyl Dichloride (III).** A 50 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **II** (1.40 g, 4.1 mmol), DMF (SDS, 1 drop), and THF (SDS, 20 mL) under nitrogen. The solution was cooled in an ice bath for 10 min, and  $SOCl_2$  (3.90 g, 2.4 mL, 33.0 mmol, 8.0 equiv) was added dropwise by syringe over 5 min at 0 °C. The flask was fitted with a condenser, and the mixture was heated to reflux using in 66 °C oil bath for 12 h. After the solution was cooled to 25 °C, the volatile components were removed by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by recrystallization with hot hexanes (15 mL) to afford **III** (1.20 g, 80%) as a white solid. Data for **III**: mp 111–113 °C (hexanes);  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.23 (d,  $J$  = 8.1 Hz, 4H, HC(5)), 6.90 (d,  $J$  = 8.2 Hz, 4H, HC(6)), 3.83 (s, 6H, HC(8)), 3.40 (s, 4H), HC(3));  $^{13}C\{^1H\}$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  170.5 (C(1)), 159.3 (C(7)), 131.4 (C(5)), 124.9 (C(4)), 114.2 (C(6)), 79.4 (C(2)), 55.2 (C(8)), 37.8 (C(3)); IR (neat) 2965 (w), 2940 (w), 2840 (w), 1892 (w), 1797 (s), 1610 (m), 1582 (w), 1513 (s), 1466 (m), 1448 (m), 1441 (m), 1330 (w), 1303 (m), 1257 (s), 1182 (s), 1122 (w), 1044 (s), 1031 (s), 956 (w), 939 (w), 913 (s), 867 (m), 840 (s), 824 (s), 812 (s), 777 (s), 765 (s), 721 (m), 686 (s), 647 (m), 635 (w), 569 (m), 547 (m), 522 (s); HRMS (ESI)  $m/z$  (M)<sup>+</sup> calcd for  $C_{19}H_{18}O_4Cl_2$  380.0577, found 380.0582; TLC  $R_f$  0.46 (silica gel, hexanes/EtOAc, 9:1, UV,  $KMnO_4$ ).

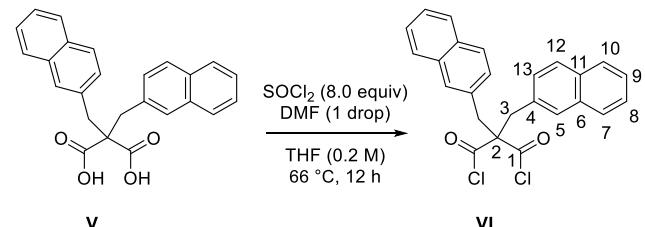


**Preparation of 2,2-Dimethyl-5,5-bis(naphthalen-2-ylmethyl)-1,3-dioxane-4,6-dione (IV).** A 25 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with 2,2-dimethyl-1,3-dioxane-4,6-dione (0.86 g, 6.0 mmol) and DMF (SDS, 6 mL) under nitrogen. The mixture was cooled to 0 °C in an ice bath, and  $K_2CO_3$  (2.48 g, 18.0 mmol, 3.0 equiv) was added in one portion. 2-(Bromomethyl)naphthalene (2.92 g, 13.2 mmol, 2.2 equiv) was added slowly under nitrogen flow over 5 min. The mixture was slowly warmed to 25 °C and stirred at 25 °C for 12 h. After 12 h, the mixture was diluted in EtOAc (15 mL) and transferred to a 125 mL separatory funnel with 80 mL of water. The organic layer was removed. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the organic layers were combined, washed with satd aq  $NaHCO_3$  (20 mL) and brine (1 × 30 mL), dried over anhydrous  $Na_2SO_4$  (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by column chromatography (silica, 3 cm  $\phi$  × 15 cm column) eluting with hexanes/EtOAc, 8:2 to afford **IV** (2.20 g, 85%) as a white solid. The compound was further recrystallized with hot hexane (20 mL) to afford **IV** (2.10 g, 82%) as a white solid. Data for **IV**: mp 184–186 °C (hexanes);  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.82 (d,  $J$  = 7.8 Hz, 2H, HC(10)), 7.79–7.77 (m, 4H, HC(8,13)), 7.73 (s, 2H, HC(15)), 7.50–7.42 (m, 4H, HC(11,12)), 7.36 (d,  $J$  = 8.5 Hz, 2H, HC(7)), 3.69 (s, 4H, HC(5)), 0.44 (s, 6H, HC(1));  $^{13}C\{^1H\}$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  168.4 (C(3)), 133.4 (C(9)), 132.7 (C(6)), 132.3 (C(14)), 129.3 (C(7)), 128.6 (C(15)), 128.0 (C(8)), 128.0 (C(10)), 127.6 (C(13)), 126.3

(C(11)), 126.2 (C(12)), 105.9 (C(2)), 60.0 (C(4)), 45.3 (C(5)), 28.7 (C(1)); IR (neat) 1768 (w), 1731 (m), 1600 (w), 1507 (w), 1439 (w), 1390 (w), 1355 (m), 1269 (s), 1200 (m), 1158 (w), 1097 (m), 1049 (m), 950 (m), 903 (m), 864 (m), 825 (s), 757 (s), 746 (s), 700 (m), 645 (m), 479 (s); HRMS (ESI)  $m/z$  (M + Na)<sup>+</sup> calcd for C<sub>28</sub>H<sub>24</sub>O<sub>4</sub> 447.1569, found 447.1572; TLC  $R_f$  0.42 (silica gel, hexanes/EtOAc, 9:1, UV, KMnO<sub>4</sub>).



**Preparation of 2,2-Bis(naphthalen-2-ylmethyl)malonic Acid (V).** A 50 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with IV (2.10 g, 4.95 mmol), granulated NaOH (0.43 g, 10.89 mmol, 2.2 equiv), tetra-n-butylammonium bromide (1.59 g, 4.95 mmol, 1.0 equiv), and mixture of THF/H<sub>2</sub>O (18 mL/2 mL). The mixture was stirred at 25 °C for 20 h. After 20 h, the mixture was acidified to pH = 1 using 10 N HCl and was stirred for 30 min. The mixture was diluted in EtOAc (15 mL) transferred to a 125 mL separatory funnel. The organic layer was removed. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the organic layers were combined, washed with water (20 mL) and brine (1 × 30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by column chromatography (silica, 3 cm  $\phi$  × 15 cm column) eluting with hexanes/EtOAc, 1:1 to afford V (1.50 g, 78%) as a white solid. Data for V: mp 179–181 °C (hexanes/EtOAc); <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  7.81–7.65 (m, 8H, HC(6,8,11,13)), 7.45–7.32 (m, 6H, HC(9,10,14)), 5.12 (s, 2H, HC(1)), 3.43 (s, 4H, HC(4)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CD<sub>3</sub>OD)  $\delta$  175.3 (C(2)), 135.2 (C(12)), 134.7 (C(7)), 133.8 (C(5)), 129.9 (C(16)), 129.1 (C(14)), 128.7 (C(13)), 128.6 (C(11)), 128.5 (C(8)), 126.9 (C(10)), 126.6 (C(9)), 61.4 (C(3)), 41.0 (C(4)); IR (neat) 2444 (w), 1725 (w), 1645 (w), 1599 (m), 1481 (m), 1448 (m), 1421 (m), 1329 (w), 1229 (m), 1207 (m), 1125 (w), 1062 (w), 1034 (w), 934 (m), 899 (m), 859 (m), 833 (w), 819 (s), 790 (m), 779 (m), 747 (s), 665 (m), 648 (m), 593 (w), 555 (w), 519 (w), 476 (s); HRMS (ESI)  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>25</sub>H<sub>21</sub>O<sub>4</sub> 385.1449, found 385.1440; TLC  $R_f$  0.38 (silica gel, MeOH/EtOAc, 0.5:9.5, UV, KMnO<sub>4</sub>).



**Preparation of 2,2-Bis(naphthalen-2-ylmethyl)malonyl Dichloride (VI).** A 50 mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with V (1.50 g, 3.0 mmol), DMF (SDS, 1 drop), and THF (SDS, 20 mL) under nitrogen. The solution was cooled in an ice bath for 10 min, and SOCl<sub>2</sub> (3.70 g, 2.3 mL, 31.0 mmol, 8.0 equiv) was added dropwise by syringe over 5 min at 0 °C. The mixture was heated to reflux using a condenser in 66 °C oil bath for 12 h. After the solution was cooled to 25 °C, the volatile components are removed by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by recrystallization with hexanes/Et<sub>2</sub>O, 1:1 to afford VI (1.20 g, 75%) as a white solid. Data for VI: mp 135–137 °C (hexanes/Et<sub>2</sub>O); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.02–7.84 (m, 6H, HC(10,12,7)), 7.74 (s, 2H, HC(5)), 7.65–7.54 (m, 4H, HC(8,9)), 7.42 (dd, *J* = 8.5, 2.0 Hz, 2H, HC(13)), 3.69 (s,

4H, HC(3)); <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  170.6 (C(1)), 133.3 (C(6)), 132.8 (C(11)), 130.5 (C(4)), 129.8 (C(5)), 128.6 (C(7)), 127.9 (C(12)), 127.8 (C(10)), 127.6 (C(13)), 126.6 (C(9)), 126.5 (C(8)), 79.1 (C(2)), 38.8 (C(3)); IR (neat) 1794 (m), 1509 (w), 1432 (w), 1062 (w), 1042 (w), 958 (w), 930 (m), 916 (m), 890 (w), 854 (m), 814 (s), 774 (m), 762 (m), 745 (m), 696 (m), 682 (m), 579 (m), 510 (m), 471 (s); HRMS (ESI)  $m/z$  (M + Na)<sup>+</sup> calcd for C<sub>25</sub>H<sub>18</sub>O<sub>2</sub>Cl<sub>2</sub> 420.0674, found 420.0683; TLC  $R_f$  0.50 (silica gel, hexanes/Et<sub>2</sub>O, 9.9:0.1, UV, KMnO<sub>4</sub>).

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.0c02899>.

Crystallographic coordinates and structural factors for 20, 21, 27, and 37 along with <sup>1</sup>H and <sup>13</sup>C NMR spectra for all compounds (PDF)

### Accession Codes

CCDC 2039471–2039472, 2048488, and 2050220 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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