

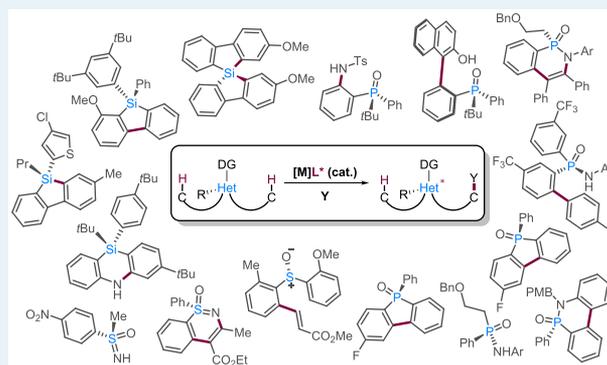
# Generation of Heteroatom Stereocenters by Enantioselective C–H Functionalization

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**ABSTRACT:** C–H functionalization has been established as an efficient way to generate molecular complexity. The formation of stereogenic carbon atoms by asymmetric C–H functionalization has seen tremendous progress over the past decade. More recently, the direct catalytic modification of C–H bonds has been powerfully applied to the formation of noncarbon stereogenic centers, which constitute a key design element of biologically active molecules and chiral ligands for asymmetric catalysis. This area was opened by a seminal report describing enantioselective C–H functionalization for the formation of a silicon stereocenter. It rapidly expanded with advances in the enantioselective formation of phosphorus(V) centers. Moreover, enantioselective routes to chiral sulfur atoms in the oxidation states IV (sulfoxides) and VI (sulfoximines) have been disclosed. Herein, we discuss methods of using selective functionalization of C–H bonds to generate a remote heteroatom stereogenic center via an inner-sphere C–H activation mechanism.

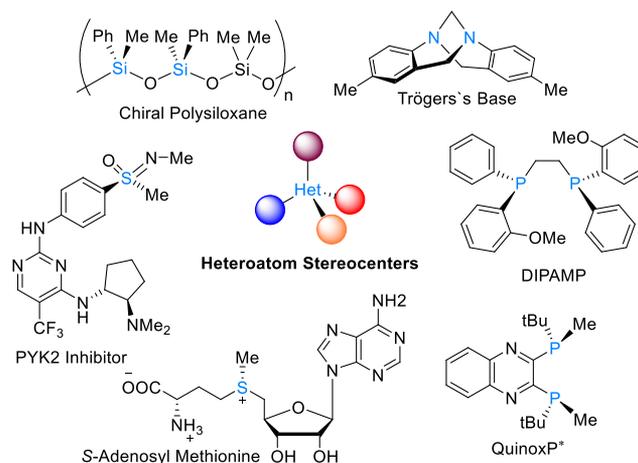
**KEYWORDS:** C–H functionalization, asymmetric catalysis, heteroatom stereocenters, heterocycles, homogenous catalysis



## 1. INTRODUCTION

The direct functionalization of unactivated carbon–hydrogen (C–H) bonds remains a challenge in organic synthesis and continues to give impetus for innovation in chemical reaction development. While the boundaries of what is considered an unactivated C–H bond, translating to nonaddressable by established methodologies, have been continuously pushed over the past decades, the task of selectivity plays an increasingly important role.<sup>1</sup> Assembling chiral molecules by utilizing enantioselective functionalization of C–H bonds has been established as an efficient way to generate molecular complexity.<sup>2</sup> Tremendous progress has been achieved in the formation of stereogenic carbon atoms using asymmetric C–H functionalization. Besides the well-known point chirality of the tetrahedral carbon atom, several heteroatoms can display stereogenicity. Challenges in applying C–H functionalization strategies used for the generation of carbon centered chirality to the synthesis of heteroatom stereocenters are associated with lower racemization barriers, in particular for nitrogen containing compounds and elongated carbon heteroatom bond lengths, as found for carbon phosphorus and carbon sulfur bonds, influencing the outcome of enantioselective transformations.

Heteroatom stereogenic compounds are present in a variety of naturally occurring compounds and also in pharmaceuticals and functional materials (Figure 1).<sup>3</sup> Silicon stereocenters are not present in nature, but stereogenic silicon atoms are introduced in materials with unique physicochemical proper-



**Figure 1.** Heteroatom stereocenters in bioactive compounds and fine chemicals.

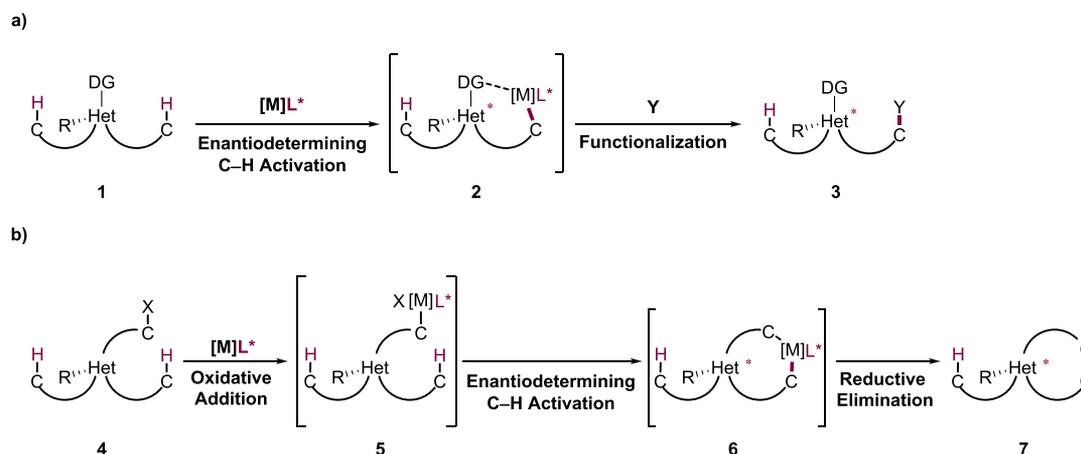
ties.<sup>4</sup> Furthermore, the higher homologue germanium can be stereogenic. The group five element nitrogen displays stereogenicity if the rapid Walden inversion is locked, as found in Tröger's base.<sup>5</sup> The higher homologue phosphorus has a significantly higher inversion barrier, and stereogenic phosphor

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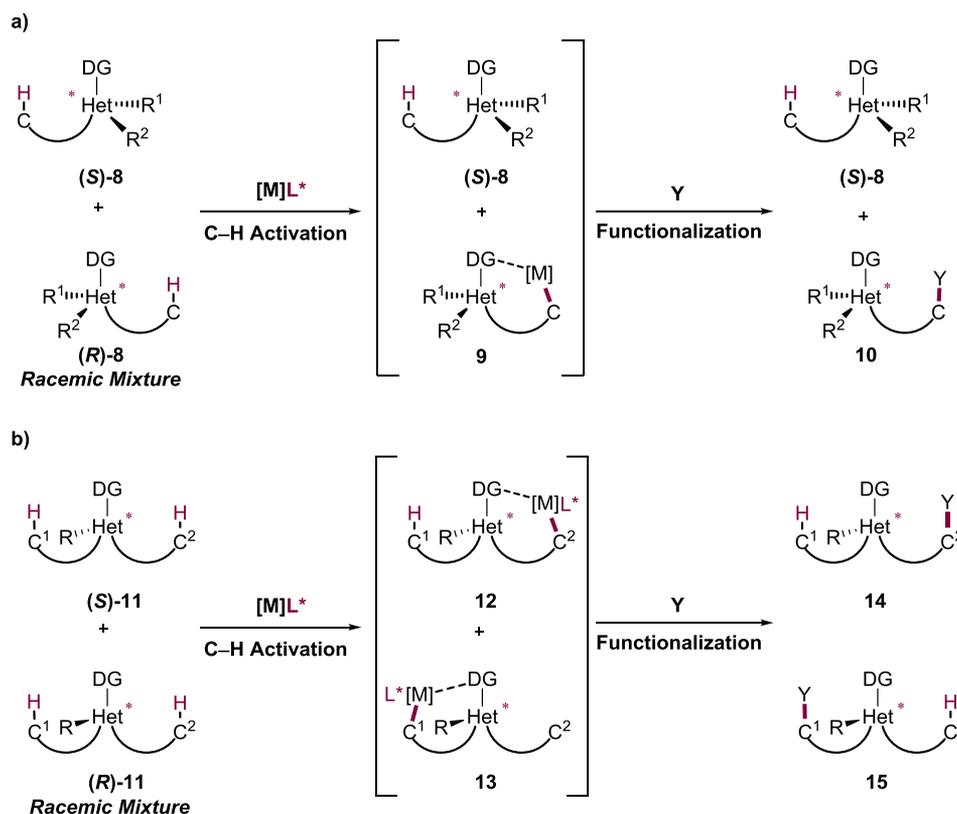
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Scheme 1. Desymmetrization Approaches: (a) Directing Group Mediated C–H Functionalization, (b) Oxidative Addition, C–H Functionalization Sequence



Scheme 2. Resolution Approaches for Enantioselective C–H Activation to Form Heteroatom Stereocenters: (a) Kinetic Resolution, (b) Parallel Kinetic Resolution



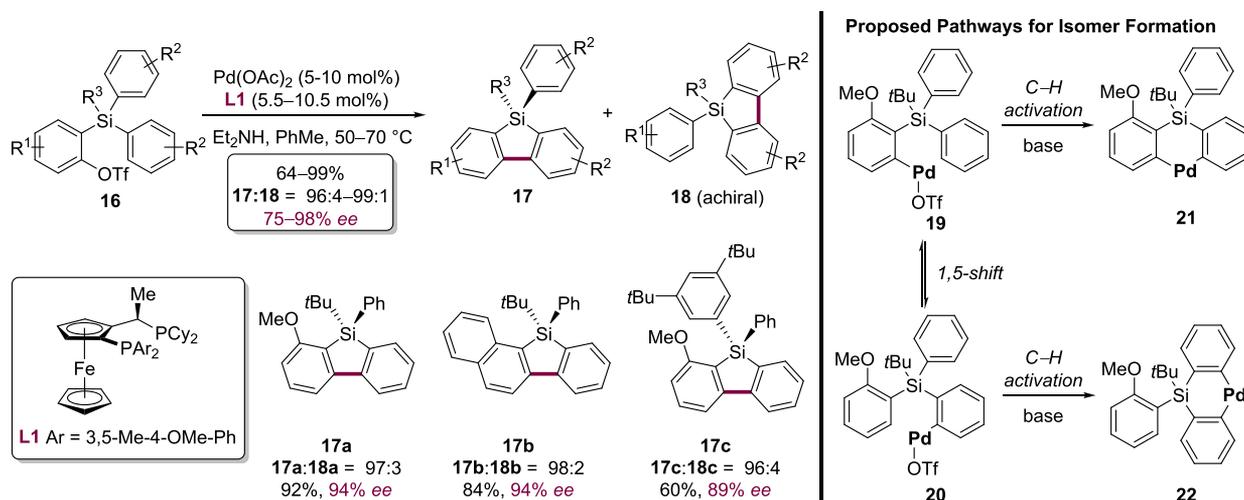
atoms are part of various bioactive compounds.<sup>6</sup> Additionally, *P*-stereogenic ligand scaffolds are extensively used in asymmetric catalysis.<sup>7</sup> Stereogenic sulfur atoms play an important role in general metabolism,<sup>8</sup> and an increasing number of new pharmaceuticals contain sulfur stereocenters.<sup>9</sup>

Recently enantioselective C–H functionalization has emerged as new tool to assemble these intriguing chiral compounds more efficiently. This review deals with enantioselective C–H functionalizations to form heteroatom stereocenters operating via an inner-sphere type mechanism.<sup>10</sup>

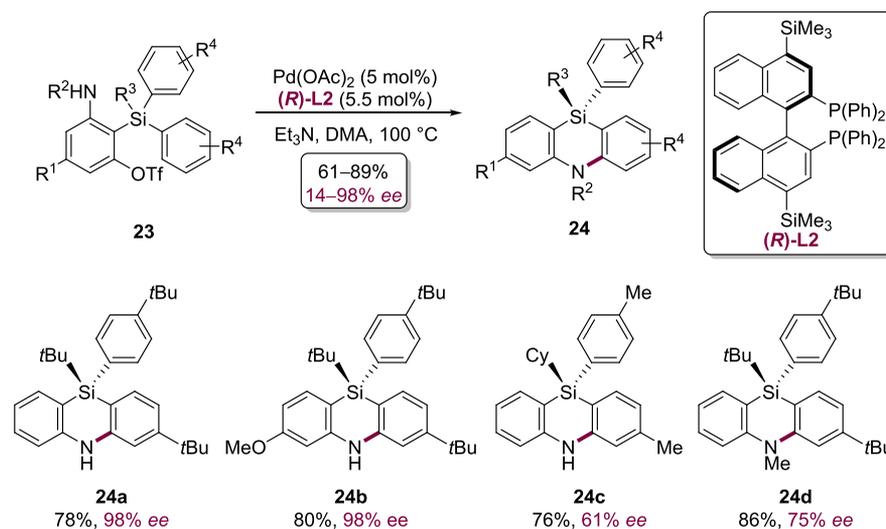
One approach to obtain heteroatom-centered chirality is the desymmetrizing C–H activation of substrates with a prochiral

heteroatom (Scheme 1). The functionality containing the heteroatom can be used as a directing group in combination with a transition metal catalyst to achieve desymmetrization (Scheme 1a). Organoheteroatom compound 1 is converted, in an enantiodetermining C–H activation, to intermediate metallacycle 2, containing a heteroatom stereocenter. Subsequent inter- or intramolecular functionalization gives the chiral product 3. Conceptually different is the use of a prefunctionalized starting material, not relying on a directing group (Scheme 1b). Oxidative addition of a transition metal catalyst into the carbon–(pseudo)halogen bond of 4 gives intermediate 5, which is converted in an enantio-determining

Scheme 3. Pd-Catalyzed Intramolecular C–H Functionalization Approach to Dibenzosiloles



Scheme 4. Pd-Catalyzed Synthesis of 5,10-Dihydrophenazasilines via Enantioselective 1,5-Palladium Migration



C–H activation to form metallacycle **6**. Upon reductive elimination, the chiral product **7** is released via formation of a five- or six-membered ring.

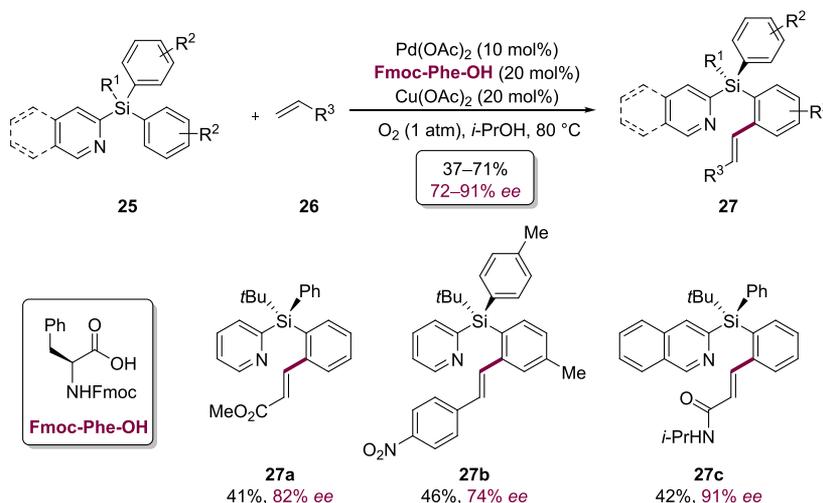
Additionally racemic heteroatom stereogenic starting materials can be applied in kinetic resolutions, thereby overcoming the limitation of a symmetrically substituted starting material in the desymmetrization approach. Kinetic resolutions use chiral catalysts interacting differently with each substrate enantiomer (Scheme 2). The enantiomers (*S*)-**8** and (*R*)-**8** are recognized by a chiral catalyst, resulting in different reaction rates for each enantiomer (Scheme 2a).<sup>11</sup> One enantiomer reacts faster and forms the product **10** in maximum 50% yield. The remaining starting material (*S*)-**8** is in an ideal case reisolated in enantiopure form. A parallel kinetic resolution takes advantage of different chemo-, regio-, or stereoselectivity for the reaction of each enantiomer of a racemic mixture with a reaction partner (Scheme 2b).<sup>12</sup> The enantiomers (*S*)-**11** and (*R*)-**11** are in this case converted to two different products. In the shown example, different regioselectivity is observed for each enantiomer, and the products **14** and **15** can be obtained in maximum 50% yield.

The present review covers catalytic enantioselective C–H functionalizations for the generation of heteroatom stereocenters until July 2019. We have grouped the reports by the formed stereogenic atom, which are the formation of stereogenic silicon, phosphorus, and sulfur atoms. C–H functionalization of heteroatom compounds, which rely on diastereoselective, auxiliary controlled transformations, are beyond the scope of this review. Grouped information on this topic can be found in a review by Cui, Xu and co-workers.<sup>13</sup>

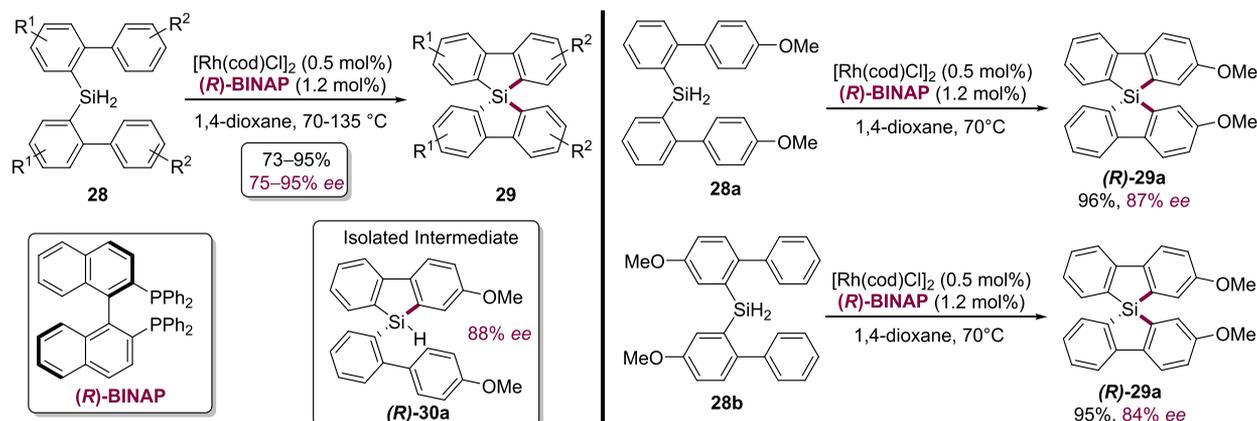
## 2. FORMATION OF SILICON STEROCENTERS

Silicon-containing molecules find wide application in a variety of materials. Large  $\pi$ -conjugated systems with unique optoelectronic properties allow applications as light-emitting diodes and solar cells.<sup>4a,14</sup> Furthermore, silicon is also introduced in bioactive compounds and marketed drugs.<sup>15</sup> Acting as carbon isosteres, organosilicon structures express unique physicochemical properties and potential medicinal applications.<sup>16</sup> In contrast to ubiquitous carbon stereocenters found in biomolecules, silicon-stereogenic compounds are not present in nature, and the synthesis of chiral organosilanes,

## Scheme 5. Pd(II)-Catalyzed C–H Olefination of Tetrasubstituted Silanes



## Scheme 6. Rh-Catalyzed Asymmetric Synthesis of Spirosilabifluorenes



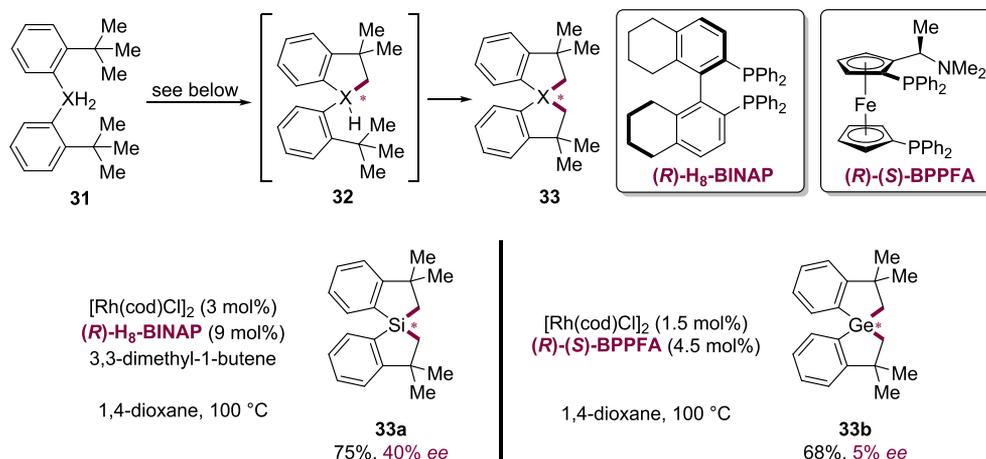
containing a stereocenter at silicon has been a challenge.<sup>17</sup> Over the past decade, significant progress in development of catalytic asymmetric methodologies to form silicon stereocenters has been made, but the known strategies are still limited in number and generality.<sup>18</sup> The application of C–H functionalization strategies enabled more efficient access to silicon stereogenic compounds in a catalytic enantioselective way.

In 2012, Shintani, Hayashi and co-workers reported the first catalytic enantioselective approach toward *Si* stereocenters applying functionalization of C(sp<sup>2</sup>)–H bonds (Scheme 3).<sup>19</sup> The work drew upon Shimizu's Pd(0)/Pd(II)-catalyzed approach to silicon-bridged biaryls.<sup>20</sup> A Pd–Josiphos-type catalyst enabled the desymmetrization of triarylsilanes **16** to yield the silicon-stereogenic dibenzosiloles **17** in high chemo- and enantioselectivity. The formation of the undesired achiral dibenzosilole **18** was largely suppressed by applying chiral bidentate phosphine ligand **L1**. Ortho-substituted substrates gave products with a high yield and enantioselectivity (**17a** and **17b**). Additionally, a tetraaryl silane was a competent substrate delivering the product **17c** in 60% yield and 89% ee. Furthermore, a pathway for the formation of the undesired dibenzosilole **18** was proposed. The oxidative addition product **19** can undergo a 1,5-Pd migration to give **20**. Both **19** and **20** undergo base-assisted intramolecular C–H activation to yield

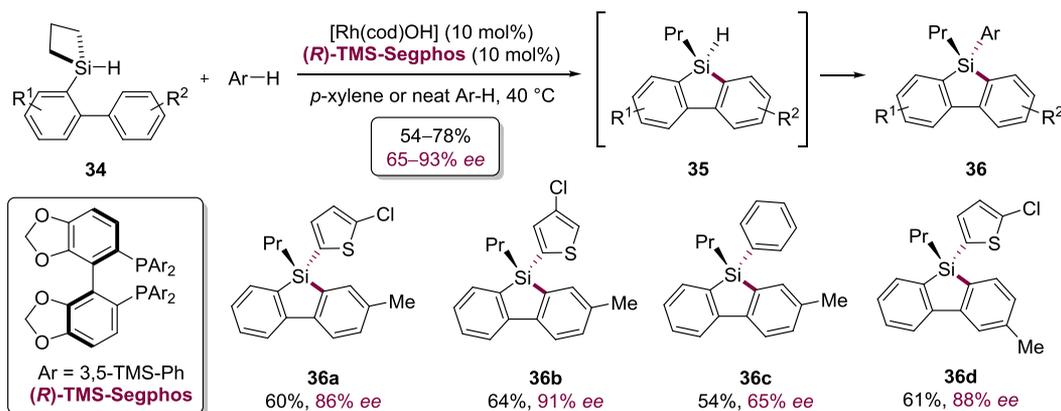
different six-membered palladacycles **21** and **22**; reductive elimination delivers the products **17a** and **18a**.

Building upon these findings, Shintani, Nozaki and co-workers utilized the 1,5-Pd migration to achieve enantioselective C–H functionalization of **23**. The application of a 4,4'-disubstituted BINAP ligand<sup>21</sup> (*R*)-**L2** and Pd(OAc)<sub>2</sub> enabled the formation of silicon-stereogenic 5,10-dihydrophenazasilines **24** in good yield and high enantioselectivity (Scheme 4).<sup>22</sup> A variety of different aryl substituents were tolerated, and the products were obtained in excellent enantioselectivity (e.g., **24a** and **24b**). Introducing a less bulky alkyl substituent on the silicon atom or the use of the corresponding secondary amine resulted in moderate selectivity (**24c** and **24d**). Mechanistic investigations suggested 1,5-Pd migration as the enantio-determining step and deprotonation/reductive elimination sequence as turnover-limiting.

Recently, Cui, Xu and co-workers reported a Pd(II)-catalyzed C–H olefination of tetrasubstituted silanes (Scheme 5).<sup>23</sup> The application of a silicon tethered pyridine directing group<sup>24</sup> enabled the C–H desymmetrization of prochiral silanes **25** in good enantioselectivity. Intermolecular functionalization was achieved using Pd(OAc)<sub>2</sub>, and a survey of different monoprotected amino acids proved Fmoc-Phe-OH as optimal.<sup>25</sup> Silanes containing bulky alkyl substituents were converted with different electron-deficient olefins **26** to obtain

Scheme 7. Rh-Catalyzed Sequential C(sp<sup>3</sup>)-H Bond Activation

## Scheme 8. Tandem Desymmetrization of Silacyclobutanes/Intermolecular Dehydrogenative Silylation



the silicon-stereogenic products in moderate yield and good ee (e.g., 27a–27c). In addition to methyl acrylate (e.g., 27a), styrenes (e.g., 27b) and acrylamides (e.g., 27c) were also suitable reaction partners. In general, substrates equipped with a quinoline directing group (e.g., 27c) were converted in higher ee.

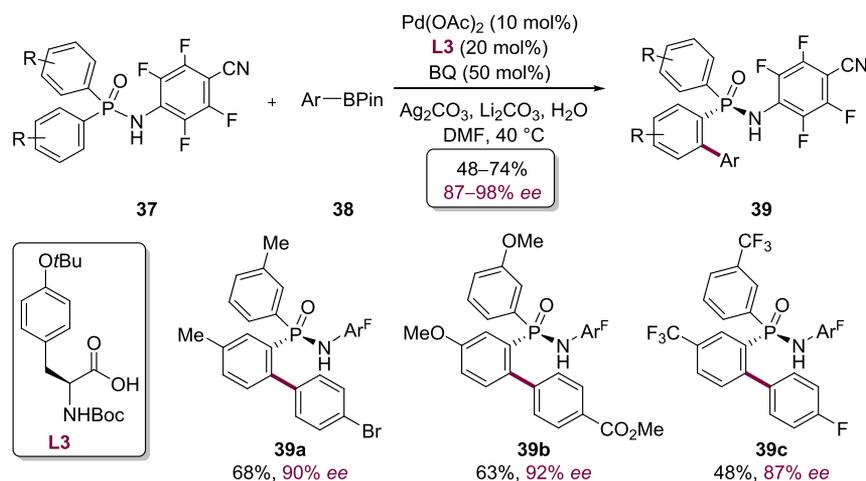
In 2013, Kuninobu, Takai and co-workers disclosed the Rh-catalyzed asymmetric synthesis of spirocyclic compounds with a quaternary silicon atom in high yield and enantioselectivity (Scheme 6).<sup>26</sup> Cyclization of bis(biphenylsilanes) 28 using  $[\text{Rh}(\text{cod})\text{Cl}]_2$  and (R)-BINAP delivered a silicon stereogenic intermediate, which is converted in a second C–H functionalization to the axial chiral spirobifluorenes 29. Detailed mechanistic studies in collaboration with the Murai group included the isolation of intermediate (R)-30a in 88% ee.<sup>27</sup> This could be converted under the same reaction conditions to the spirobifluorene (R)-29a without a loss of ee, suggesting that the absolute configuration is determined in the first silylative cyclization. Intriguingly, the cyclization of 28a and 28b led to the same product enantiomer (R)-29a in comparable yield and ee, highlighting that, in this case, the substitution pattern of the biphenyl moieties did not affect the enantioselectivity.

Takai, Murai and co-workers extended this methodology for functionalization of more challenging C(sp<sup>3</sup>)-H bonds, however only with poor enantio-control (Scheme 7).<sup>28</sup> In a single example, 2-fold dehydrogenative C(sp<sup>3</sup>)-H bond

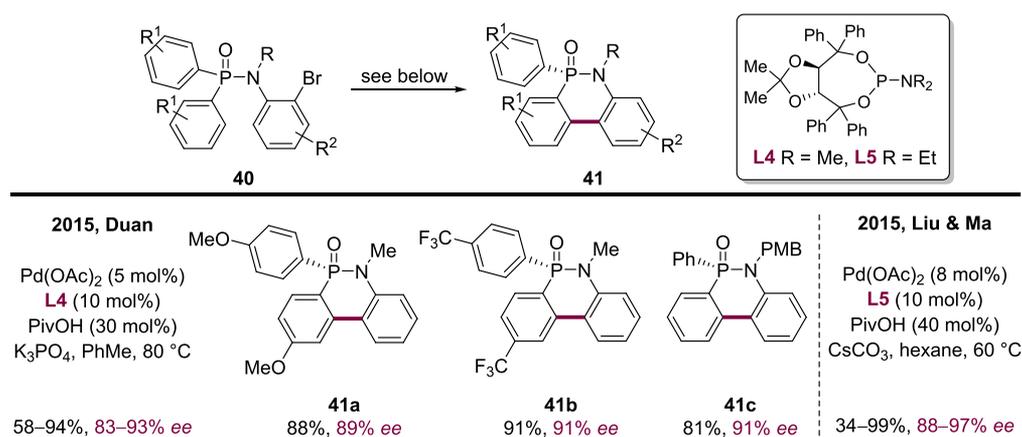
silylation of silane 31a led via 32a to spirobifluorene 33a in 75% yield and 40% ee using  $[\text{Rh}(\text{cod})\text{Cl}]_2$  and (R)-H<sub>8</sub>-BINAP. To achieve high levels of reactivity, the application of hydrogen acceptors was necessary. The addition of 3,3-dimethyl-1-butene enabled a significantly reduced reaction temperature and increased conversion and yield. Furthermore, silicon could be replaced by germanium to obtain chiral spirogermabiindane 33b. Among a variety of chiral phosphine ligands, (R)-(S)-BPPFA performed best, giving the product 33b with moderate yield (68%) and low ee (5%). In this case, the addition of a hydrogen acceptor did not result in improved yields.

In 2017, He and co-workers reported a Rh-catalyzed tandem silacyclobutane (SCB) desymmetrization/C–H silylation and intermolecular dehydrogenative silylation to form dibenzosiloles (Scheme 8).<sup>29</sup> SCB activation has been extensively studied previously in a variety of transition metal catalyzed transformations.<sup>30</sup> In an enantio-determining Si–C bond activation, SCBs 34 are converted via intermediate silane 35 to form products 36 bearing a quaternary silicon stereocenter. This work represents a rare example where C–H activation is not the enantiodetermining step to achieve formation of a heteroatom stereocenter. The application of  $[\text{Rh}(\text{cod})\text{OH}]$  and (R)-TMS-Segphos enabled the formation of dibenzosiloles 36 in good yield and high enantioselectivity. Both 2-chloro- and 3-chlorothiophene were compatible arene partners, delivering 36a and 36b, respectively, in high enantioselectivity.

## Scheme 9. Desymmetrizing C–H Arylation for the Synthesis of Phosphinamides



## Scheme 10. Pd-Catalyzed Enantioselective C–H Arylation of Phosphinic Amides



Unsubstituted benzene was also converted, albeit in moderate yield and selectivity (**36c**). Meta-substituted biaryl silanes were suitable substrates delivering **36d** with 88% ee. Although the isolation of intermediate **35** failed, a series of control experiments suggested that the SCB opening/C–H silylation occurs first with subsequent intermolecular dehydrogenative silylation to form **36**. The formation of intermediate **35** is stereoselective, and the subsequent dehydrogenative coupling is stereospecific and independent of the ligand chirality.

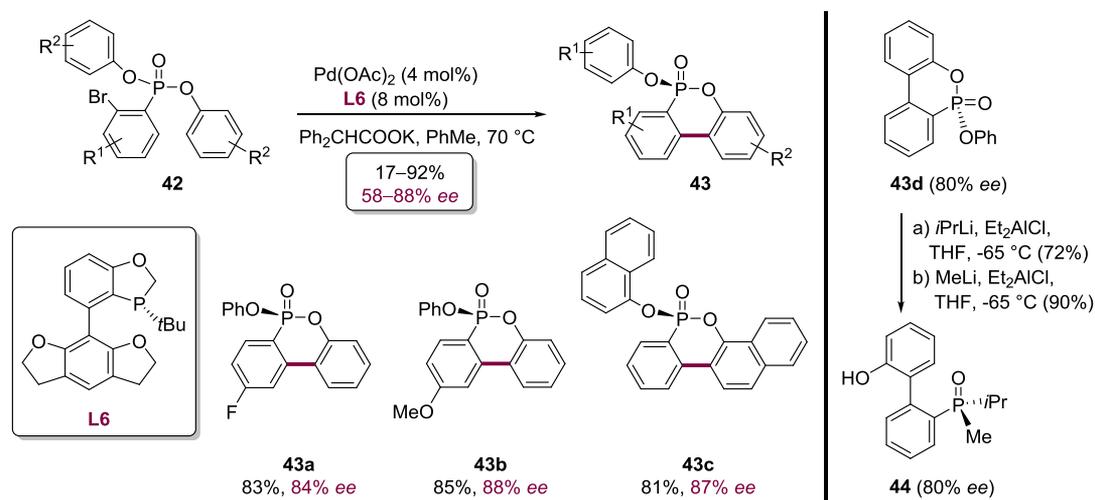
## 3. FORMATION OF PHOSPHORUS STEREOCENTERS

Organophosphorus compounds bearing a stereocenter at phosphorus are found in bioactive molecules and materials,<sup>31</sup> but the main role of chiral phosphorus compounds is in the application as robust and versatile ligand scaffolds, or as organocatalysts in asymmetric catalysis.<sup>32</sup> Typically, chiral P(III) compounds are used as ligands in transition-metal catalysis,<sup>7</sup> and P(V) compounds serve as Lewis base<sup>33</sup> and Brønsted acid catalysts.<sup>34</sup> While in many cases different types of chirality are placed within the backbone of the ligand, the introduction of a stereogenic center on phosphorus can be advantageous because of its closer proximity to the catalytic center.<sup>35</sup> The comparably low number of *P*-chiral ligands is associated with the challenges in their synthesis, often relying on a variety of resolution techniques.<sup>36</sup> Catalytic asymmetric methods exist but are still limited in scope and efficiency.<sup>37</sup>

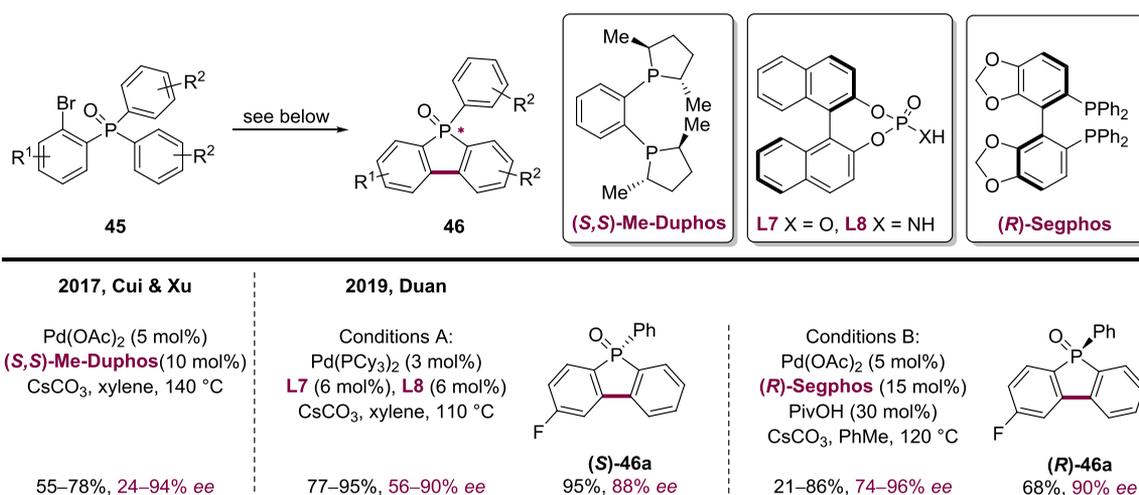
Recently, the application of C–H functionalization technology for the synthesis of organophosphorus compounds has led to a variety of new *P*-stereogenic compounds, which were previously inaccessible.

In 2015, the Han group presented a Pd(II)-catalyzed desymmetrization C–H arylation strategy to access *P*-chiral phosphinamides (Scheme 9).<sup>38</sup> The work is built on the racemic transformation, previously reported by the same group.<sup>39</sup> According to the proposed mechanism, the phosphinamide of **37** serves as directing group guiding the ortho C–H metalation. Additionally the authors observed an important role of DMF, facilitating the C–H activation event. Hypothesizing that stereoinduction is feasible if a strongly coordinating DMF-like chiral ligand is applied, a variety of amino acid derivatives were explored.<sup>25</sup> The use of Pd(OAc)<sub>2</sub> and **L3** enabled the formation of *P*-stereogenic phosphinamides **39** in good yield and high enantioselectivity. Ag<sub>2</sub>CO<sub>3</sub> serves as the oxidant while 1,4-benzoquinone (BQ) was proposed to assist reductive elimination.<sup>39</sup> The addition of 40 equiv of water in anhydrous DMF was crucial to improving both yield and enantioselectivity. Further studies revealed a positive influence of polar protic additives on the enantioselectivity.<sup>40</sup> This observation was rationalized by stabilization of a transition-state through an H-bonding network provided by the additive. Meta-substituted diaryl phosphinamides **37a–37c** reacted smoothly, and both electron-donating and electron-

## Scheme 11. Biaryl Phosphonates Synthesis by Intramolecular Pd-Catalyzed C–H Arylation



## Scheme 12. Pd-Catalyzed Enantioselective Synthesis of Dibenzophosphole Oxides



withdrawing groups were tolerated (**39b** and **39c**). Furthermore, boronic esters decorated with halogen and ester functionalities (**39a** and **39b**) were suitable substrates for this transformation, delivering the products in good yield and high ee.

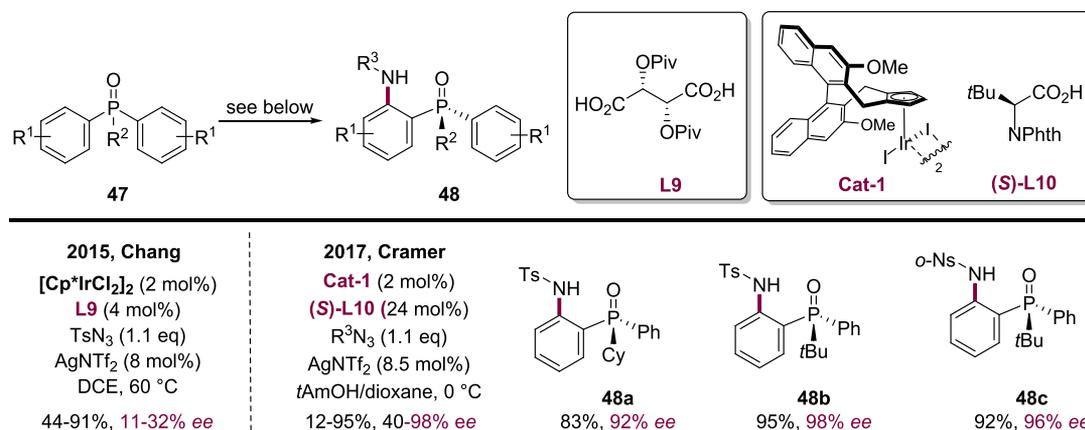
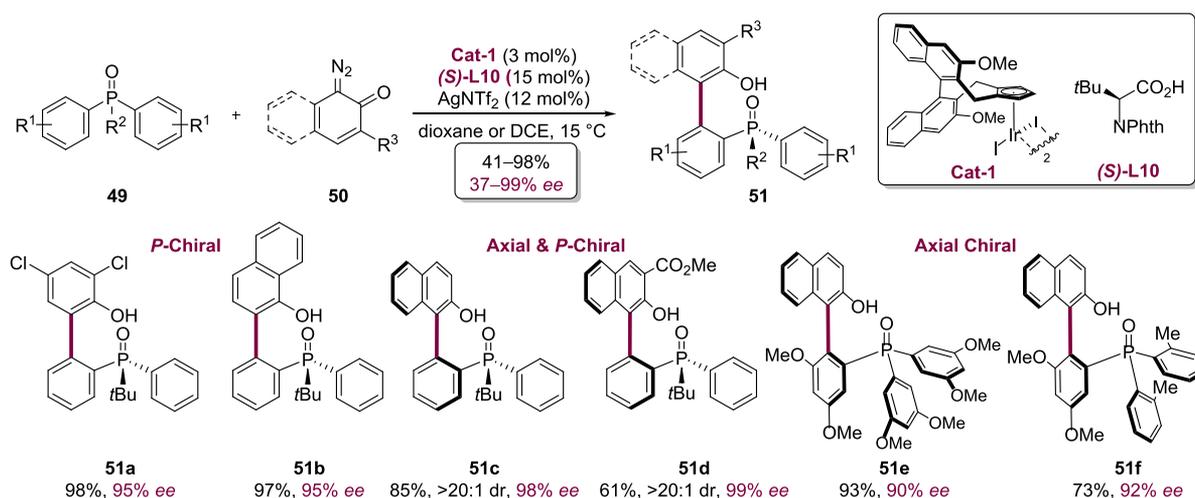
By applying an intramolecular Pd(0)/Pd(II) C–H arylation strategy, Duan and co-workers achieved, in 2015, the enantioselective formation of *P*-chiral phosphinic amides (Scheme 10).<sup>41</sup> Cyclization was accomplished by using *N*-(*o*-bromoaryl)-diarylphosphinic amides **40** and Pd(OAc)<sub>2</sub> in combination with TADDOL-derived phosphoramidite **L4**.<sup>42</sup> Substrates substituted with both electron-donating and electron-withdrawing groups were well tolerated, delivering the products in high yield and high enantioselectivity (**41a** and **41b**). Furthermore, phosphinic amide containing a cleavable *N*-PMB protecting group reacted smoothly, and the corresponding product **41c** was obtained in 81% yield and 91% ee. Additionally the obtained products could be converted into *P*-chiral biphenyl monophosphine ligands via the addition of organolithium compounds and P–N bond cleavage. Shortly after this report Liu, Ma and co-workers reported the same transformation, also applying Pd(OAc)<sub>2</sub> in combination with a similar TADDOL-derived phosphoramidite **L5**, obtaining the

*P*-chiral products in very high yields (up to 99%) and enantioselectivity (up to 97% ee).<sup>43</sup>

After these two reports, the Tang group reported a similar Pd(0)/Pd(II) C–H arylation strategy for the formation *P*-chiral biaryl phosphonates (Scheme 11).<sup>44</sup> Various *o*-bromoaryl phosphonates **42** were cyclized to form **43** using Pd(OAc)<sub>2</sub> and a new modification of the *P*-chiral monophosphorus ligand BI-DIME **L6**.<sup>45</sup> The enantioselectivity of the reaction was further improved by fine-tuning the base, and Ph<sub>2</sub>CHCOOK proved optimal. Both electron-poor and electron-rich phosphonates were converted to the products (**43a** and **43b**) in good yield and enantioselectivity. In addition, condensed arenes were well tolerated, delivering the product in good yield and enantioselectivity (**43c**). Product **43d** was converted to *P*-chiral phosphine oxide **44** by 2-fold sequential alkyllithium addition. The aryloxy substituent displacement on the phosphonate occurred stereospecifically, and by reversing the order of addition of the alkyllithium reagent the opposite enantiomer of the phosphine oxide **44** could be obtained.

In a related work, Cui, Xu and co-workers disclosed an enantioselective synthesis of phosphole oxides (Scheme 12).<sup>46</sup> A combination of Pd(OAc)<sub>2</sub> and **(S,S)-Me-Duphos** enabled

Scheme 13. Enantioselective Ir-Catalyzed C–H Amidation of Phosphine Oxides

Scheme 14. C–H Arylation to Access *P*- and Axially Chiral Biaryl Phosphine Oxides

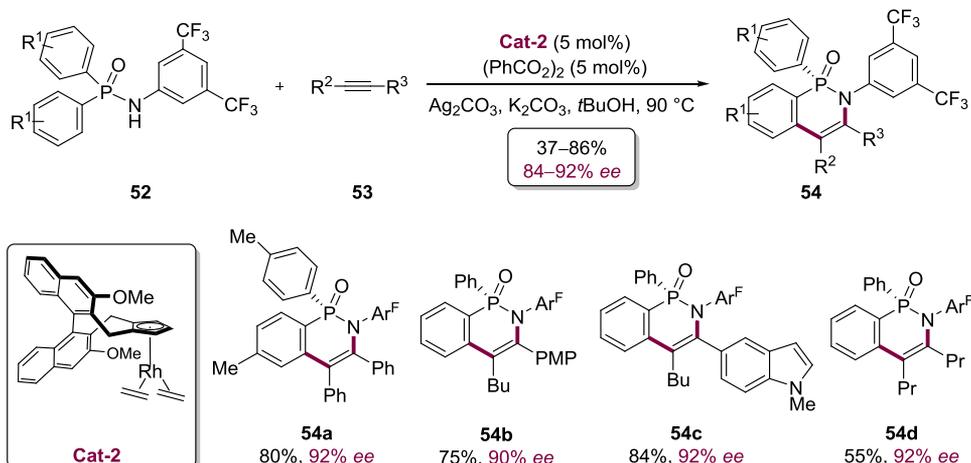
Pd(0)/Pd(II) C–H arylation of different *o*-bromoaryl phosphine oxides **45**. The cyclized products **46** were obtained in moderate yield and enantioselectivity. Superior results on the same transformation were reported recently by the Duan group.<sup>47</sup> Two catalytic systems were developed and applied for the formation of both enantiomers of the corresponding dibenzophosphole oxides **46**. A Pd-catalyst containing an achiral phosphine ligand (Pd(PCy<sub>3</sub>)<sub>2</sub>) and a chiral BINOL-phosphoric acid/amide mixture (L7/ L8 = 1/1) proved optimal to achieve good enantioselectivity. Dibenzophosphole oxide (*S*)-**46a** was obtained in 95% yield and 88% ee. Furthermore, a nonlinear effect was observed for this catalytic system, and the involvement of more than one phosphoric acid/amide in the enantioselective C–H palladation step was suggested. The second set of conditions relied on the use of Pd(OAc)<sub>2</sub> and (*R*)-Segphos in combination with pivalic acid. Dibenzophosphole oxide (*R*)-**46a** was obtained in moderate yield and high enantioselectivity under these conditions.

In 2015, the Chang group demonstrated a dual role of a carboxylic acid additive in an Ir-catalyzed enantioselective C–H amidation of diaryl phosphine oxides **47** (Scheme 13).<sup>48</sup> The methodology drew upon their earlier report on the development of a diastereoselective auxiliary controlled transformation.<sup>49</sup> The combination of [Cp\*IrCl<sub>2</sub>]<sub>2</sub> and AgNTf<sub>2</sub> to generate a dicationic iridium complex, and the tartaric acid derivative L9 as a chiral ligand, gave the C–H

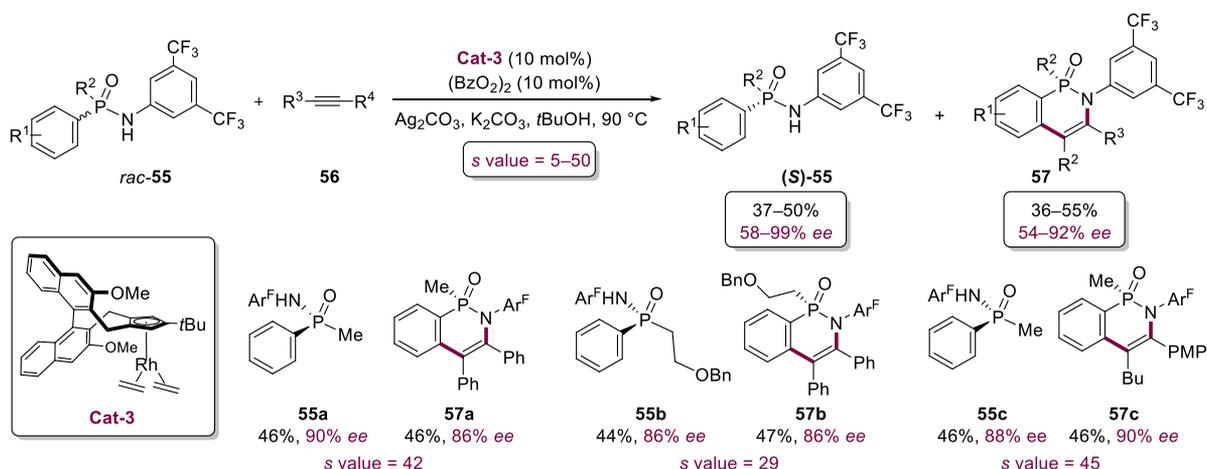
amidated phosphine oxides **48** in good yields and low enantioselectivity using tosyl azide as the amidation reagent. Mechanistic studies suggested that the chiral acid takes part in the rate-limiting and enantio-determining concerted metalation deprotonation (CMD) step.<sup>48,50</sup> Subsequently, Cramer and co-workers showcased that high levels of enantio-control are feasible using a combination of readily modifiable Cp<sup>x</sup>Ir(III) complexes<sup>51</sup> and a chiral carboxylic acid. Applying **Cat-1** together with *tert*-leucine derived (*S*)-L10 gave the products **48** in high yield and very high enantioselectivity.<sup>52</sup> An extensive investigation of chiral carboxylic acids revealed a strong cooperative effect between the Cp<sup>x</sup> ligand and phthaloyl *tert*-leucine (*S*)-L10 delivering phosphine oxide **48a** in 83% yield and 92% ee. Application of the opposite enantiomer (*R*)-L10 resulted in significantly lower reactivity and erosion of enantioselectivity (15% yield and 20% ee for **48a**), highlighting the strong matched–mismatched effect between the Cp<sup>x</sup> ligand and the chiral acid. Phosphine oxides bearing a *tert*-butyl substituent were converted to the C–H amidated products in excellent enantioselectivity (**48b** and **48c**). The readily cleavable *o*-nosyl group could be introduced easily delivering product **48c** in 92% yield and 96% ee.

In 2018, the Cramer group employed the Cp<sup>x</sup>Ir(III)/chiral carboxylic acid system to achieve C–H arylation of phosphine oxides **49**, providing access to *P*- and axially chiral products **51** (Scheme 14).<sup>53</sup> The use of quinone diazides **50** in an Ir-

## Scheme 15. Rh-Catalyzed Enantiotopic C–H Activation of Phosphinamides



## Scheme 16. Rh-Catalyzed Kinetic Resolution of Phosphinic Amides



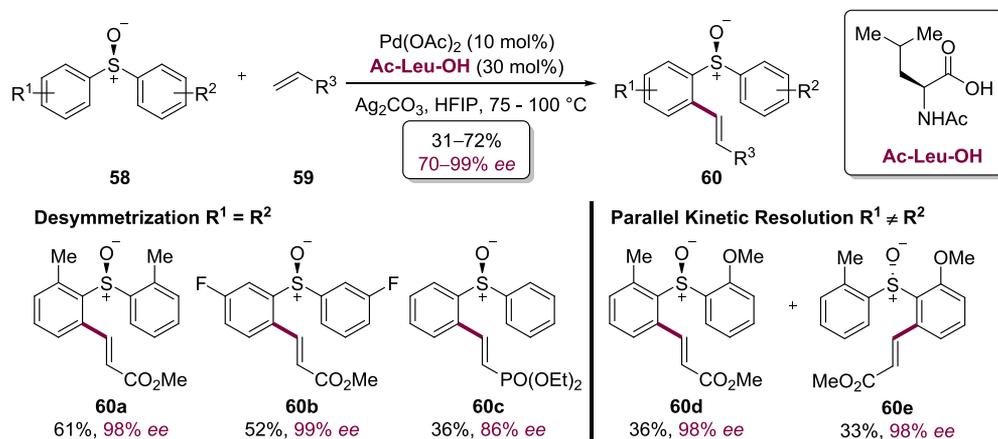
catalyzed racemic arylation was reported previously by Yang and co-workers.<sup>54</sup> Application of the powerful combination of  $\text{Cp}^*\text{Ir(III)}$  **Cat-1** and **(S)-L10** enabled the formation of *P*-chiral biaryl phosphine oxides in excellent yield and enantioselectivity (**51a** and **51b**). Introduction of ortho-substituted diazides generated a stable chiral axis, delivering products with both axial and *P*-chirality in excellent diastereo- and enantioselectivity (**51c** and **51d**). The protocol was also applicable for the enantioselective synthesis of purely axial chiral phosphine oxides (**51e** and **51f**), underlining that the chiral  $\text{Cp}^*$  ligand also has a bearing on the formation of the atropchiral biaryl axis. The obtained products could be reduced to the corresponding phosphines and hence serve as access to chiral monodentate MOP-type ligands.<sup>55</sup>

In 2017, Sun and Cramer reported a desymmetrization of phosphinamides **52** generating *P*-chiral cyclic products **54** (Scheme 15).<sup>56</sup> The first example of a  $\text{Rh(III)}$ -catalyzed enantiodetermining C–H activation, and subsequent trapping with internal alkynes **53**, enabled the formation of the annulated products **54** in high enantioselectivity.<sup>57</sup> Reducing the reversibility of the C–H activation was crucial to obtaining high ee. This was achieved by adding the inorganic base  $\text{K}_2\text{CO}_3$ , which efficiently mitigated the reversibility of the enantio-determining step. By applying atropchiral **Cat-2** and  $\text{Ag}_2\text{CO}_3$  as the stoichiometric oxidant, a variety of differently

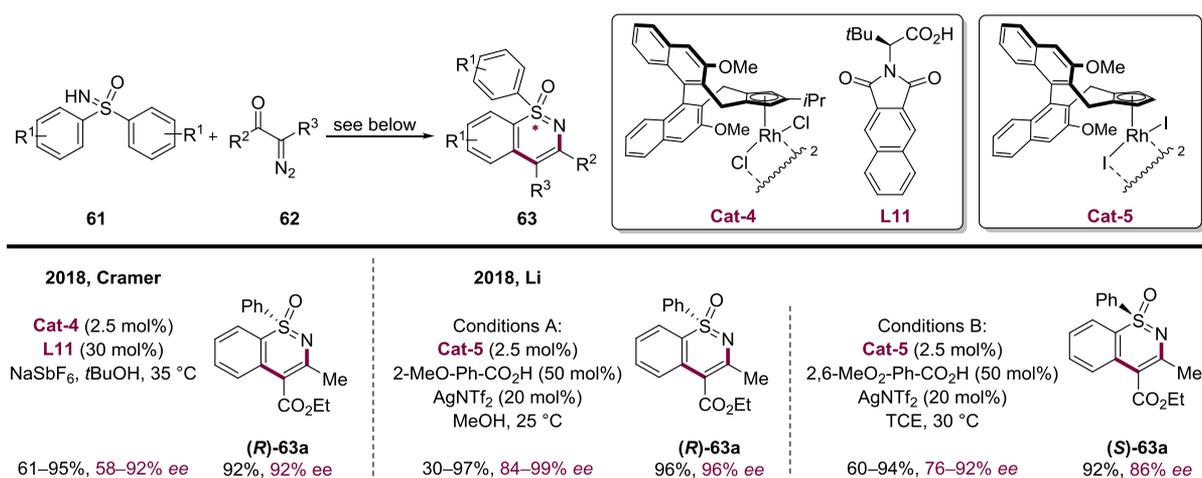
substituted diaryl phosphinamides were converted in good yield and high enantioselectivity.<sup>58</sup> The alkyne acceptors could be readily exchanged. Diaryl (e.g., **54a**) and unsymmetrical substituted alkynes (e.g., **54b** and **54c**) were capable substrates delivering the products with high ee. Additionally, the regioselectivity for unsymmetrical alkynes was >20:1 in all cases, outperforming the achiral  $\text{Cp}^*\text{Rh(III)}$  catalyst, for which poor to modest regioselectivity was observed. Dialkyl alkynes were converted in high enantioselectivity as well, albeit with lower yield (e.g., **54d**). Furthermore, highly enantiospecific reduction of the *P(V)* products **54** to valuable *P(III)*-chiral compounds was achieved under carefully optimized conditions.

Sun and Cramer further extended this methodology to alkyl, aryl phosphinic amides to obtain enantioenriched products through a kinetic resolution process (Scheme 16).<sup>59</sup> Chiral phosphinic amides **55** were selectively converted into **57** due to a difference in cyclometalation rates (see Scheme 2a). Crucial for a sufficient rate difference of the two starting material enantiomers was the development of new trisubstituted  $\text{Cp}^*$  ligands (**Cat-3**).<sup>60</sup> The application of **Cat-3** enabled the resolution of phosphinic amides **55**, delivering highly enantioenriched starting material **(S)-55** and cyclized products **57** with  $s$  values<sup>61</sup> up to 50. Different aryl substituents had little influence on the reaction performance delivering the products in high enantioselectivity (e.g., **55a** and **57a**). Longer

Scheme 17. Pd-Catalyzed Enantioselective C–H Functionalization of Diaryl Sulfoxides



Scheme 18. Rh-Catalyzed Enantioselective C–H Functionalization of Sulfoximines



alkyl chains decorated with a benzyl ether group (e.g., **55b** and **57b**) and unsymmetrically substituted alkynes (e.g., **55c** and **57c**) were suitable reaction partners delivering the products with high selectivity. Furthermore, product **57a** was successfully applied as a Lewis-base catalyst in an enantioselective reductive aldol reaction.

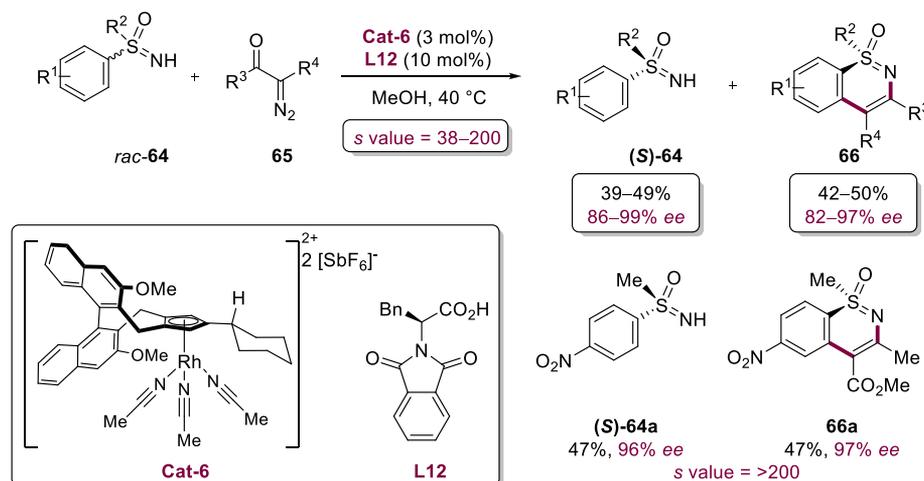
#### 4. FORMATION OF SULFUR STEREOCENTERS

Biomolecules containing sulfur stereocenters are ubiquitous in nature and play an important role in the chemical reactions of general metabolism.<sup>8</sup> In particular, chiral sulfonium ions, sulfoxides (both oxidation state IV), and sulfoximines (oxidation state VI) bind stereoselectively with enzymes in metabolic processes. Because of the significant bioactivity, an increasing number of marketed drugs and bioactive compounds entering clinical trials contain sulfoxides and sulfoximines in enantiopure form.<sup>9,62</sup> Furthermore, chiral sulfoximines can improve pharmacokinetic properties, compared to commonly introduced sulfone and sulfonamide derivatives.<sup>63</sup> In addition, chiral sulfoxides are of high importance in stereoselective synthesis. Sulfoxides serve as efficient and versatile chiral auxiliaries for the formation of C–C and C–X bonds<sup>64</sup> or as chiral ligands in asymmetric catalysis.<sup>65</sup> Traditional methods to access enantiopure organo-sulfur compounds include diastereoselective transformations, various resolution techniques, and biocatalytic reactions.<sup>64,66</sup>

Methods to access compounds containing a sulfur stereocenter in a catalytic asymmetric fashion are still limited in scope and efficiency.<sup>64,67</sup> Recently, C–H activation technology has been applied to efficiently access chiral sulfoxides and sulfoximines.

In 2018, Wang and co-workers introduced a Pd(II)-catalyzed enantioselective C–H olefination of diaryl sulfoxides (Scheme 17).<sup>68</sup> A survey of a range of different monoprotected amino acids<sup>25</sup> revealed Ac-Leu-OH as the optimal ligand for this transformation. Desymmetrization of prochiral diaryl sulfoxides **58** gave the alkenylated products (**60a**–**60c**) in moderate yield and high enantioselectivity. Both ortho-substituted and electron-poor sulfoxides were converted with excellent enantioselectivity (**60a** and **60b**). Aside from methyl acrylate, diethyl vinyl phosphonate was also a competent reaction partner delivering the product **60c** with good ee. The yields were reflective of moderate conversion rates, most likely due to strong coordination of the sulfoxides to palladium, resulting in possible deactivation of the catalyst. The remaining starting materials were recovered without significant loss. Additionally, nonsymmetric diaryl sulfoxides **58** were converted in a parallel kinetic resolution (see Scheme 2b) to deliver two products from the racemic starting materials. Diaryl sulfoxides with two different ortho substituents reacted to give products **60d** and **60e** in excellent enantioselectivity. Mechanistic studies confirmed that a regiodivergent parallel kinetic resolution was operative.

Scheme 19. Kinetic Resolution of Sulfoximines via Rh-Catalyzed C–H Functionalization



In 2018, the desymmetrization of sulfoximines under Rh(III)-catalyzed C–H functionalization was reported independently by the Cramer group and by the Li group (Scheme 18).<sup>69</sup> Symmetric diaryl sulfoximines **61** were converted applying diazo compounds **62** to form chiral-at-sulfur 1,2-benzothiazines **63** using different modifications of Cp<sup>x</sup>Rh(III) catalysts. Sun and Cramer applied their trisubstituted Cp<sup>x</sup> ligand (**Cat-4**) in combination with *tert*-leucine-derived ligand **L11** to obtain the annulated products in high yield and enantioselectivity (e.g., **63a**).<sup>59,60</sup> A variety of different diazo compounds proved to be capable reaction partners for this transformation, delivering the products in high ee. However, application of less reactive diazo compounds led to decreased enantioselectivity. As the trapping of the diazo reaction partner occurs after the enantio-determining C–H activation, no influence on the ee was expected. Reversibility of the C–H activation step was suggested to explain the observed inferior results for less reactive diazo compounds. Li and co-workers applied another Cp<sup>x</sup>Rh(III) catalyst **Cat-5** in combination with differently substituted benzoic acid derivatives achieving an enantiodivergent desymmetrization of sulfoximines **61**. The use of **Cat-5** and 2-methoxybenzoic acid gave benzothiazine (*R*)-**63a** in very high yield and enantioselectivity. Interestingly, when applying 2,6-dimethoxybenzoic acid, the opposite product enantiomer (*S*)-**63a** was obtained in moderate selectivity, which could be further improved to 86% ee by changing the solvent to tetrachloroethane. Additionally, the coupling of sulfoximines with  $\alpha$ -diazo malonates was achieved using modified reaction conditions.

Further extending this methodology, Brauns and Cramer recently presented the kinetic resolution of chiral sulfoximines (Scheme 19).<sup>70</sup> Addressing the limitations of two identical aryl substituents, the kinetic resolution (see Scheme 2a) allowed for the conversion of racemic aryl alkyl substituted sulfoximines **64** to cyclic benzothiazines **66** and additionally provided with enantioenriched acyclic starting materials (*S*)-**64**. Screening of different trisubstituted Cp<sup>x</sup>Rh(III) catalysts and carboxylic acids revealed **Cat-6** in combination with phenylalanine-derived acid **L12** as optimal, delivering the products **66** in excellent selectivity. A variety of different aryl and alkyl substituted sulfoximines **64** were tolerated, and *p*-nitroaryl methyl sulfoximine **64a** was resolved with an excellent *s* value<sup>61</sup> and very high enantioselectivity for both the acyclic

starting material (*S*)-**64a** and the annulated sulfoximine **66a**. Additionally, **64a** was successfully converted to a known precursor of a proline-rich tyrosine kinase 2 (PYK2) inhibitor, currently undergoing clinical trials.<sup>9b</sup>

## 5. CONCLUSIONS AND FUTURE PERSPECTIVES

The application of enantioselective C–H functionalization strategies has provided efficient access to valuable chiral heteroatom scaffolds over the past seven years. The reported structures include bioactive molecules currently in clinical trials and chiral ligand scaffolds, which could be applied in asymmetric catalysis. The majority of the methodologies were published from 2015 onward, and the formation of sulfur stereogenic centers via enantioselective C–H functionalization was initiated only in 2018, highlighting room for further developments.

Approaches so far relied mainly on the desymmetrizing C(sp<sup>2</sup>)-H activation of prochiral substrates with formation of a heteroatom stereocenter in a distal position. Enantioselective C(sp<sup>3</sup>)-H activation has developed rapidly over the past years, enabling functionalization in closer proximity to the formed stereocenter.<sup>2b</sup> Application of these recent activation strategies to the formation of heteroatom stereocenters would enable access to more diverse, previously inaccessible product scaffolds. Another area of active research within enantioselective C–H functionalization is the application of 3d transition-metal catalysts.<sup>2c,d</sup> The base metal complexes can serve as worthwhile alternative catalysts for established methodologies but can also provide complementary reactivity to the presented noble metal complexes. Hence, the introduction of 3d transition-metal catalysis would also provide a greater diversity in accessible stereogenic heteroatom molecules. Given the great importance of chiral heteroatom scaffolds, in particular in drug discovery, we expect enantioselective C–H functionalization strategies to play an increasingly important role in target-oriented synthesis, to access complex structures containing chiral heteroatoms more efficiently.

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## Notes

The authors declare no competing financial interest.

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