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Article

Singlet Carbenes Are Stereoinductive Main Group Ambiphiles

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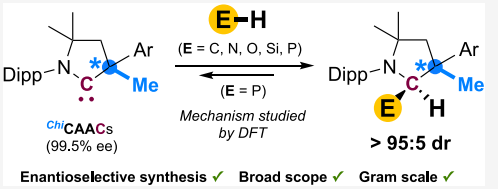
ABSTRACT: Stereogenic units are a critical source of molecular complexity, but their stereoselective formation via main group ambiphiles—which are suitable for derivatizing a wide scope of functionalities—is largely unexplored. Herein, using chiral cyclic (alkyl)(amino)carbenes (^{Chi}CAACs), we study stereoinduction during the oxidative addition of E−H σ-bonds (E = C, N, O, Si, P). Through computational modeling, the relationship between stereochemical outcome and mechanism is elucidated, providing insight into when and why ^{Chi}CAACs exhibit excellent stereoselectivities. Altogether, these results demonstrate the potential for chiral main group ambiphiles to generate stereogenic units in a highly controlled manner opening avenues for applying "metal-like" reactivity in metal-free asymmetric syntheses.



INTRODUCTION

Stereogenic units are crucial sources of molecular complexity, playing a pivotal role in a wide range of chemical processes and biological mechanisms. Harnessing their formation with precision has fueled relentless advancements in asymmetric synthesis, a field that continues to drive innovation at the forefront of modern chemistry.[1,2] Among these, chiral singlet carbenes have gained considerable recognition as powerful tools for asymmetric catalysis.[3,4] Thanks to their unique stereoelectronic properties and high modularity, these species have proven effective not only as chiral ligands in transition-metal (TM) catalysis,[5] but also as chiral organocatalysts.[6] Recently, their applications have expanded beyond traditional strategies, finding new roles as TM-surrogates. Akin to electron-rich TMs, their distinct stereoelectronic properties can be leveraged to promote oxidative σ-bond insertions at carbon,[7] as well as the reverse reaction—reductive σ-bond eliminations.[8] Individually, these fundamental steps represent significant milestones for main group ambiphiles,[9] which also include constrained phosphines,[10] silylenes,[11] and other heavier analogues.[12] Collectively, they unlock unexplored avenues in catalysis.[8,10d,13]

To the best of our knowledge the stereoselective reactivity of main group ambiphiles, which holds potential for the broad synthesis of stereogenic units is hitherto largely uncharted. Building on our recent report on CPL-active molecular propellers,[14] we sought to explore the intermolecular formation of stereogenic units using cyclic(alkyl)(amino)carbene ambiphiles. A key step in the synthesis of these propellers (i.e., an intramolecular oxidative addition at carbon) proceeds with limited stereocontrol, yielding a mixture of diastereomers (Scheme 1).[15] We envisaged that extending this reactivity to an intermolecular oxidative addition would provide a broader context for systematic investigations of stereochemical factors governing activations at chiral main group ambiphiles. Herein, using a combined synthetic and theoretical approach we report the stereoselective oxidative addition of E−H σ-bonds (E = C, N, O, Si, P) at carbon. To achieve this task, we have devised a methodology to access persistent, configurationally stable and enantiopure cyclic(alkyl)(amino)carbenes (^{Chi}CAACs) in multigram quantities. Notably, our results demonstrate that chiral carbenes are powerful stereoinductive ambiphiles exhibiting excellent thermodynamic and kinetic control.

RESULTS AND DISCUSSION

To begin this study, we first considered the reaction of a terminal alkyne (i.e., phenyl-acetylene) with the bulky and enantiopure (*L*)-menthyl cyclic(alkyl)(amino)carbene (^{Menth}CAAC) derived from the chiral pool.[16] However, in this case the carbene insertion into the C(sp)−H bond resulted in a 50:50 mixture of diastereomers (see Supporting Information for details). We attributed this result to the conformational flexibility of the menthyl group which is known to interfere with stereoinduction.[17] To circumvent this problem we devised a general route to conformationally rigid enantiopure CAACs.[18] Racemic chiral CAAC iminium salts (***rac*)-1** are readily available on a multigram scale.[19] Selective reduction with $LiAlH_4$ afforded the CAAC-H_2 racemate (*rac*)-**2** in nearly quantitative yield.[20a] Using preparative chiral HPLC, both enantiomers (***R*)-2** and (***S*)-2** were separated and isolated in excellent yield and high enantiopurity (>98.5% ee; First eluted (***R*)-2**; second eluted (***S*)-

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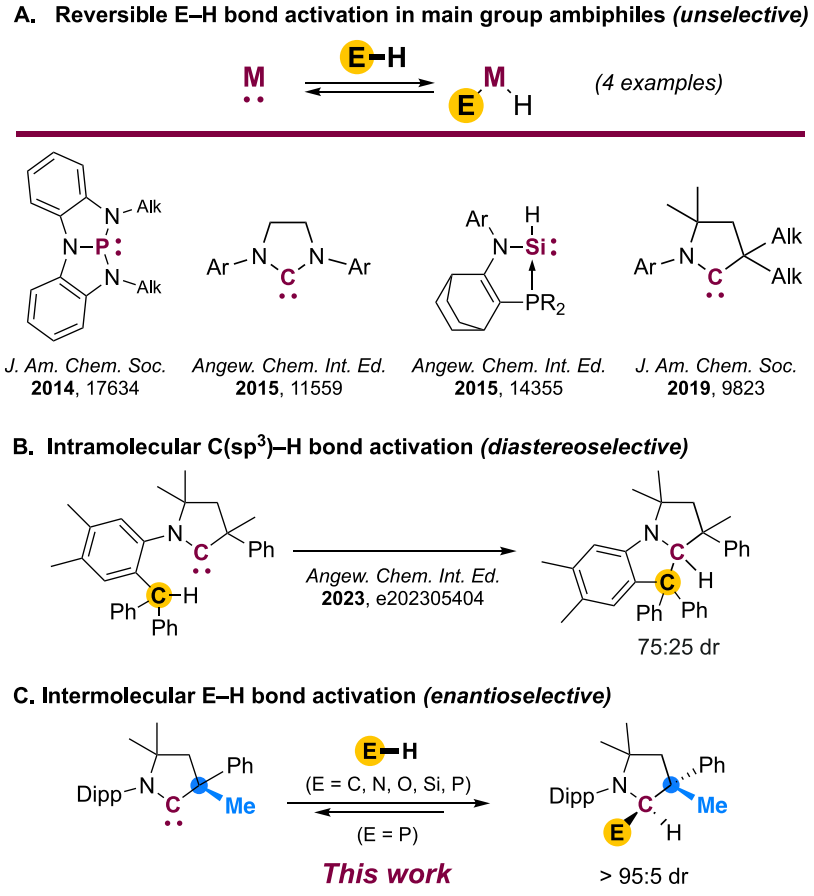
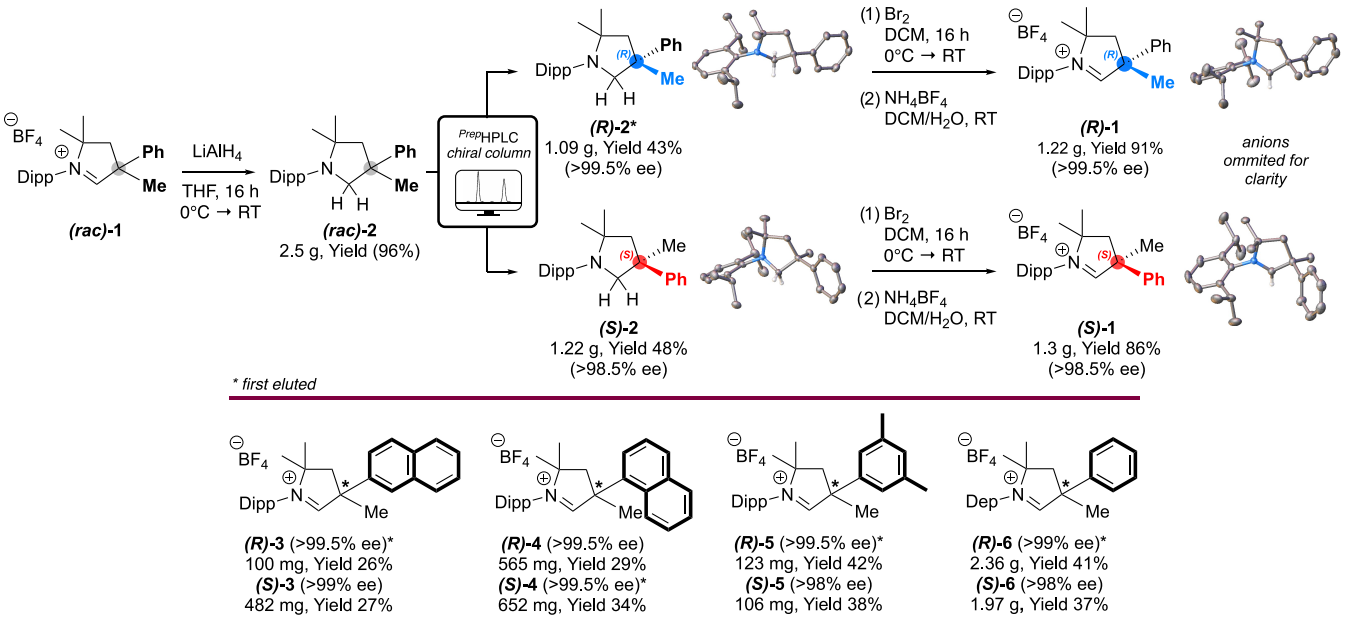
Scheme 1. Stereoselective E–H Insertion Reactions with Carbenoids and CAACs



Scheme 2. Preparation and Characterization of Chiral CAAC Precursors



2). Electronic circular dichroism (ECD) confirmed the mirror-image spectra of both enantiomers, (*R*)-**2** and (*S*)-**2**, and their absolute configuration was established by X-ray diffraction (see SI for details). Subsequent reoxidation with bromine followed by anion exchange with ammonium tetrafluoroborate yielded (*R*)-**1** and (*S*)-**1** in excellent yield (>70% over 3 steps) without loss of enantiopurity (Scheme 2).[20b] We evaluated the generality of this method, which also allowed for the preparation of both *R* and *S* salts **3**–**6** with excellent enantioselectivities. The absolute configuration of iminium salts was assigned by single crystal X-ray diffraction (see SI for details).

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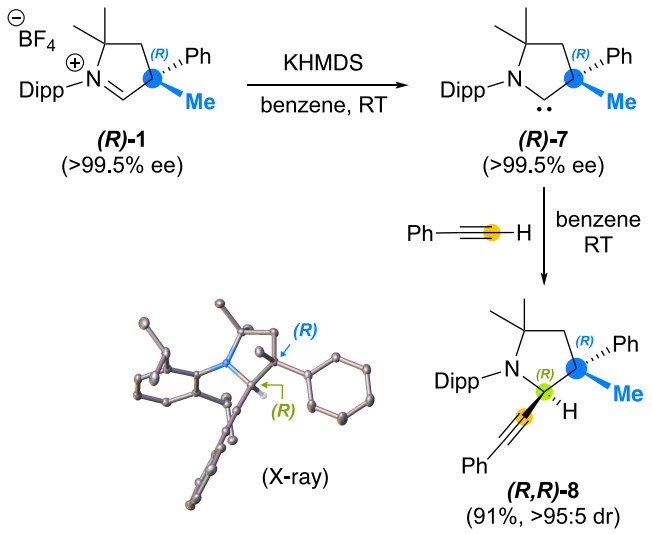
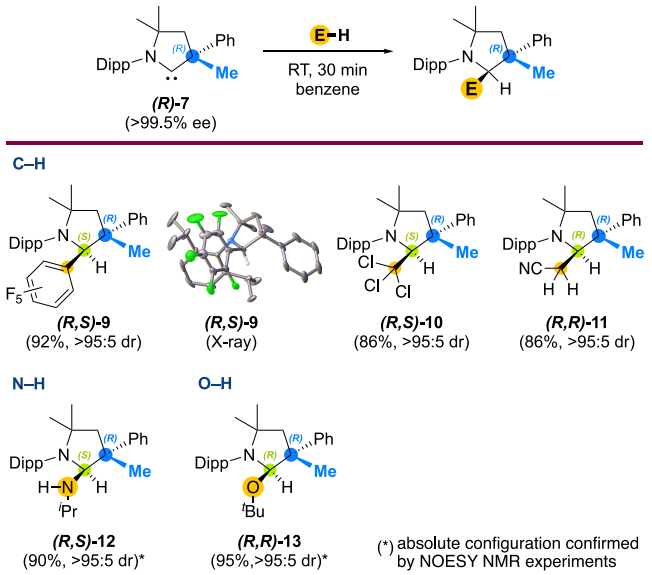
C−H, N−H, and O−H Bond Activation. With these configurationally rigid chiral CAACs (^{Chi}CAAC) in hand, we looked at their reactivity with phenyl acetylene. In marked contrast with ^{Menth}CAAC, reaction of free ^{Chi}CAAC (*R*)-7 (obtained by deprotonation of (*R*)-**1** with KHMDS) led to the selective formation of adduct (*R,R*)-**8** (>95:5 dr) resulting from the diastereoselective oxidative addition of the carbene into the alkyne C(sp)−H bond (Scheme 3). X-ray diffraction analysis

Scheme 3. Enantioselective Oxidative Addition of ^{Chi}CAAC (*R*)-7 into the C(sp)−H Bond of Phenylacetylene



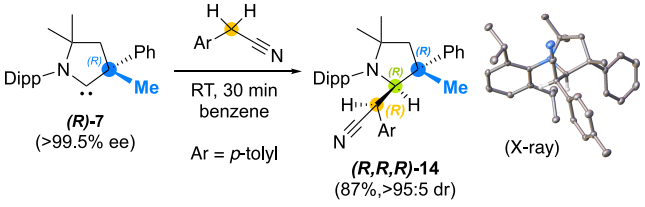
established the absolute configuration of **8** and revealed the *anti*-orientation of the alkyne fragment relative to the α-carbon phenyl substituent. This result underscores the importance of controlling the chiral pocket around the carbene center. We also considered C(sp^2)−H bonds using pentafluorobenzene (*R,S*)-**9**, C(sp^3)−H bonds using chloroform **10** and acetonitrile **11**, N−H bonds with isopropyl amine **12** and O−H bonds with *tert*-butanol **13** (Scheme 4). In all cases, excellent diastereoselectivities (>95:5 dr) in favor of the *anti*-oxidative addition product were observed (established by NOESY experiments and confirmed by DFT; see SI for details).

Scheme 4. Enantioselective Oxidative Addition of ^{Chi}CAAC (*R*)-7 into E−H Bonds (E = C, N, O)



Encouraged by this efficient creation of stereochemical complexity, we envisaged that this process might permit simultaneous control over the configuration of multiple stereocenters, such as with prochiral E−H bonds. To test this hypothesis, ^{Chi}CAAC (*R*)-7 was reacted with 4-methylbenzyl cyanide (Scheme 5). Gratifyingly, we observed the clean

Scheme 5. Enantioselective Reaction of ^{Chi}CAAC (*R*)-7 with Prochiral 4-Methylbenzyl Cyanide



formation of β-amino nitrile (*R,R,R*)-**14** which was obtained in good yield (87%) and high diastereoselectivity (>95:5 dr). We confirmed the absolute configuration by X-ray diffraction analysis. This result showcases the extensive control that the ^{Chi}CAAC scaffold can exert over stereochemical outcomes at positions remote to the stereogenic α-carbon. It is worth mentioning that chiral β-amino nitriles are important intermediates in the synthesis of biologically active compounds.[21] In that regard, this approach, which involves the direct diastereoselective C(sp^3)−H insertion of an amino-carbene into prochiral alkyl nitriles, represents a new methodology for their preparation.[22]

To obtain further insight into the stereoselectivity of this reaction, we modeled the free energy profile of the proposed mechanism using density functional theory (DFT) at the ωB97X-V/def2-mTZVPP/SMD(Benzene)//r2SCAN-3c/CPCM (Benzene) level of theory (Figure 1).[23] Note, for simplicity, benzyl cyanide was modeled in place of 4-methylbenzyl cyanide. The reaction proceeds with the formation of **INT2**, a transient contact ion-pair between an iminium cation and an α-cyano carbanion, through **TS1**. Subsequent nucleophilic addition via **TS2** ($\Delta G^{\ddagger}$ = +15.7 kcal/mol) leads to the observed diastereomer (*R,R,R*)-**14** (ΔG =

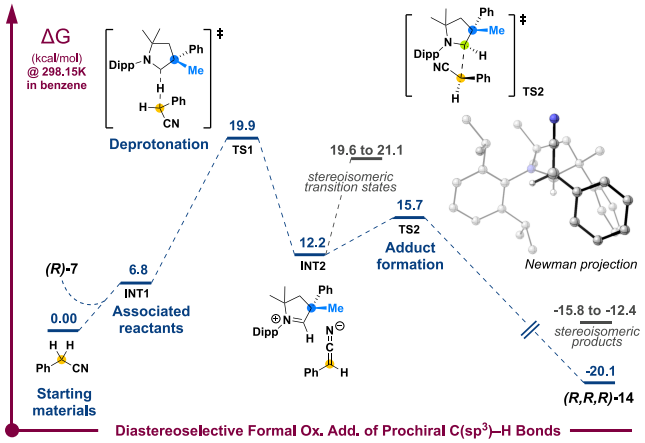


Figure 1. DFT free energy profile of the reaction between ^{Chi}CAAC (*R*)-7 and benzylcyanide.

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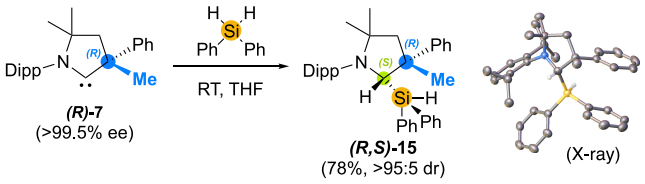
−20.1 kcal/mol). Curious as to when stereoinduction arises along the reaction coordinate, we modeled the other diastereoisomers of **INT1**, **INT2**, and **TS2**. Interestingly, there is no indication of significant stereoinduction before C−C bond formation begins in TS2 (see SI for details). However, the formation of (***R,R,R***)**-14** is strongly favored both kinetically ($\Delta\Delta G^{\ddagger} \leq -3.9$ kcal/mol) and thermodynamically ($\Delta\Delta G \leq -4.3$ kcal/mol), in agreement with the excellent experimentally observed diastereoselectivity. Importantly, this suggests that the stereochemical outcome of oxidative addition at carbon may be acutely sensitive to the nature of the stereocenter-forming transition state, which may change with the identity of the E−H bond (vide infra).

Si−H Bond Activation. Organosilanes are valuable substances in organic synthesis and medicinal chemistry but also in materials science where carbenes have been used to modulate the properties of silicon surfaces.[24,25] From the perspective of asymmetric synthesis, silanes have several similarities with C(sp^3) carbon atoms (i.e., tetrahedral geometry), but also present some key differences (i.e., electronegativity, covalent radius and potential hypervalency) which can impart significant challenges in enantioselective transformations.[26] To probe the diastereoselective oxidative addition of carbenes to silanes, ^{Chi}CAAC (***R***)**-7** was reacted with diphenylsilane in THF solution (Scheme 6). In this case, we

Scheme 6. Enantioselective Oxidative Addition of (*R*)-7 into Diphenylsilane



obtained the corresponding adduct (***R,S***)**-15** in excellent yield and selectivity (>95:5 dr). Confirming its absolute configuration by X-ray diffraction revealed the *syn*-orientation of the silane fragment with respect to the α-carbon phenyl substituent which contrasted with our results so far. To rationalize this divergent outcome, we modeled the free energy profile for the formation of (***R,S***)**-15**. As shown in Figure 2 and in agreement with existing

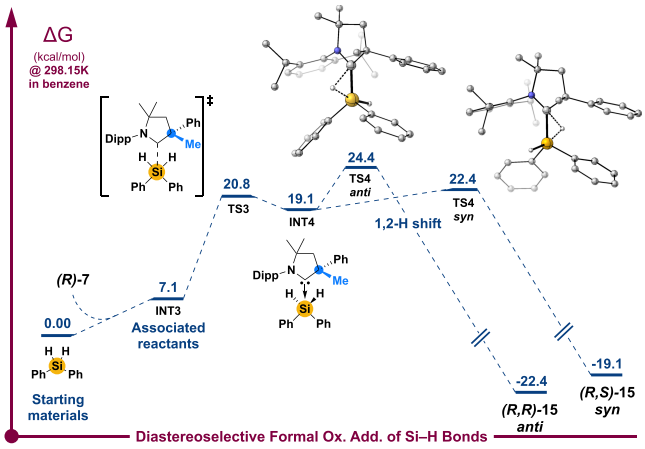
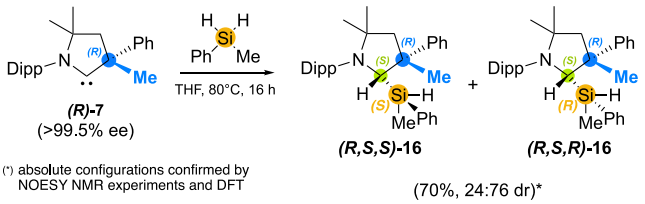


Figure 2. DFT free energy profile of the reaction between ^{Chi}CAAC (*R*)-7 and diphenylsilane.

literature,[27] we propose that the reaction proceeds via the formation of pentacoordinate carbene-silane complex **INT4** through **TS3**, which rearranges via 1,2-hydride shift through transition states **TS4** ***anti*** or ***syn*** to yield (***R,S***)**-15** or (***R,R***)**-15**, respectively. Interestingly (***R,S***)**-15** is kinetically favored ($\Delta\Delta G^{\ddagger}$ = −2.0 kcal/mol) but thermodynamically disfavored ($\Delta\Delta G$ = +3.3 kcal/mol). This can be rationalized by the mechanism for Si−H insertion, wherein the smaller half of the E−H bond, hydrogen, is the nucleophile in the stereocenter-forming transition state, **TS4**. Evidently, the ^{Chi}CAAC scaffold directs the nucleophile, whether E or H, toward the less hindered side of the carbene center, *anti* to the phenyl. Thus, for Si−H bonds, in which the electrons are polarized toward hydrogen, the silane substituent ultimately ends up *syn* to the phenyl, contrasting with the outcomes for C−H, N−H, O−H, and P−H (vide infra) addition. Finally, although (***R,S***)**-15** is the kinetic product, the high barrier to regenerating the silicate ($\Delta G^{\ddagger}$ = 41.5 kcal/mol) prevents equilibration to the thermodynamic product. Si-stereogenic silanes have been prepared via TM-catalyzed carbene insertion reactions, but uncatalyzed variants using free carbenes remain unexplored so far. Inspired by our results with prochiral C−H bonds, we extended this study to prochiral Si−H bonds. Reaction of ^{Chi}CAAC (***R***)**-7** with methylphenylsilane produced adduct **16** as a mixture of (*R,S,S*) and (*R,S,R*) diastereomers in a 76:24 ratio (Scheme 7). Although not fully

Scheme 7. Enantioselective Oxidative Addition of (*R*)-2 into Prochiral Si−H Bonds



diastereoselective, the good diastereoselectivity observed with diphenylsilane and the prochiral 4-methylbenzyl cyanide suggest that, in the appropriate steric environment, prochiral silanes could undergo fully diastereoselective bond insertion with main group ambiphiles.

P−H Bond Activation. Phosphines are another important class of molecules which shine as ligands in transition metal catalysis or as organocatalysts in enantioselective transformations.[28] We performed the reaction of ^{Chi}CAAC (***R***)**-7** with diphenylphosphine in THF at room temperature and obtained adduct **17** as a mixture of (R,R) and (R,S) diastereomers in a 60:40 ratio (confirmed by ^{31}P and ^{1}H NMR spectroscopy; Scheme 8).[29] Provided a suitable steric environment, the oxidative addition of CAACs to phosphines is thermally reversible.[8] In that respect, ^{Chi}CAAC (***R***)**-7** can be seen as a midpoint between the very bulky adamantyl CAAC and the very small dimethyl CAAC.[19] We thus hypothesized that the steric profile of (**R**)-7 could facilitate a reversible reductive elimination/oxidative addition equilibrium to favor the thermodynamic isomer. Gratifyingly, heating the reaction mixture at 80 °C for 18 h led to the diastereoselective formation of adduct (***R,R***)**-17** (>95:5 dr) which was confirmed by XRD analysis and 2D-NMR spectroscopy (See SI for details). DFT calculations support a mechanism an-alogous to that found in our earlier studies on reductive elimination at carbon (Figure 3).[8b] After formation of the iminium phosphide **INT5** through

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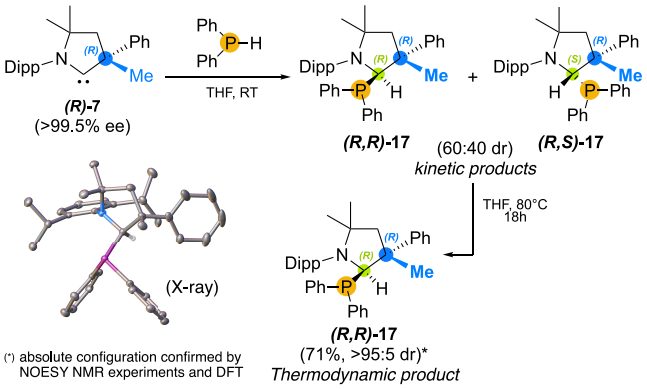
Scheme 8. Enantioselective Oxidative Addition of ^{Chi}CAAC (*R*)-7 into P−H Bonds



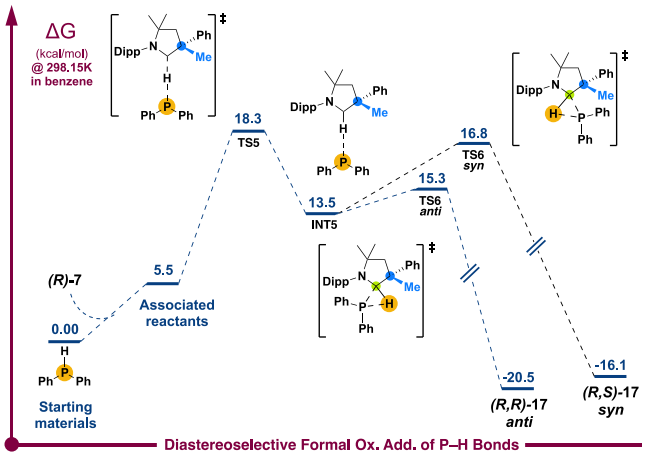
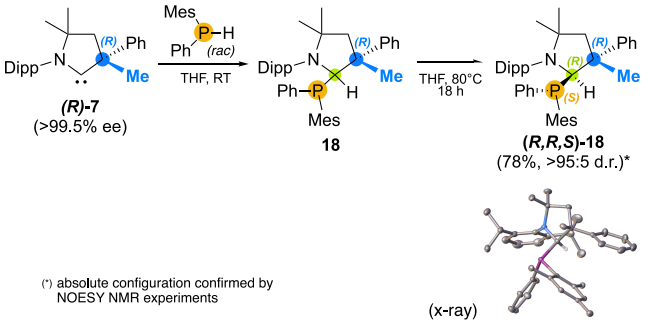


Figure 3. DFT free energy profile of the reaction between ^{Chi}CAAC (*R*)-7 and diphenylphosphine.

TS5, both stereoisomers are accessible through transition states **TS6*syn*** and **TS6*anti*** relatively close in energy ($\Delta\Delta G^{\ddagger}$ = 1.5 kcal/mol). In line with the observed kinetic product distribution, the kinetically favored (***R,R*)-17** dominates, albeit slightly. However, unlike in Si−H insertion, regeneration of the preceding intermediate from (***R,S*)-17** is thermally accessible, allowing equilibration of the mixture toward enantiopure (***R,R*)-17**. This outcome is somewhat surprising, since P−H insertion of diphenylphosphine is significantly less kinetically selective than the analogous Si−H insertion for diphenylsilane. However, analysis of the transition state geometries provides some insights. In Si−H bond insertion, the nucleophile is positioned much closer to the carbene carbon (δ_{avg}(C···H) = 1.95 Å, δ_{avg}(C···P) = 3.25 Å) than in the P−H bond insertion. The more compact nature of the product-determining transition state—which cannot be fully attributed to the smaller covalent radius of hydrogen (0.31 Å) compared to phosphorus (1.07 Å)—likely e- e superior kinetic selectivity observed in Si−H insertion. A similar phenomenon is at play with the mechanistically analogous second-row E−H insertion reactions, which generally feature less hindered substrates than diphenylphosphine, yet exhibit superior kinetic selectivity. Inspection of the transition states for C−H insertion of benzyl cyanide reveals a δ_{avg}(C···C) of 2.87 Å, a reflection of the smaller covalent radius of carbon (0.76 Å) relative to phosphorus.

Despite the growing notoriety of chiral carbenes,[3,5] chiral phosphines remain a cornerstone of asymmetric catalysis, enabling a wide range of sophisticated enantioselective transformations.[28] Among them, *P*-stereogenic phosphorus ligands stand out for their ability to promote highly enantioselective transformations.[30] Building on our experimental and computational results with diphenylphosphine, we reasoned that ^{Chi}CAACs could provide a platform for accessing *P*-stereogenic phosphines. In this scenario, we envisioned that asymmetric equilibration of the diastereomeric mixture, facilitated by reversible C−P bond formation, could lead to an enantioenriched phosphine, due to the thermodynamically favored diastereomer acting as a "sink."[31] This strategy, if successful, would represents an exciting uncatalyzed strategy to prepare *P*-stereogenic phosphines.[32] Following that reasoning we explored the reaction of ^{Chi}CAAC (***R***)-7 with (*rac*)-*P*(mesityl)-(phosphine) in THF at room temperature (Scheme 9). Under

Scheme 9. Reaction of ^{Chi}CAAC (*R*)-7 with (*rac*)-P(Ph)(Mes)−H Allows for the Preparation of Enantiopure *P*-Stereogenic Phosphine



these conditions rapid formation of adduct **18** as a mixture of two diastereoisomers was observed by NMR spectroscopy. We tentatively assigned the absolute configuration of the minor stereoisomer as (R,*S*,*R*) based on two-dimensional (2D) NMR measurements and DFT-based NMR chemical shift calculations (See SI). Gratifyingly, heating this mixture at 80 °C for 2 h enabled a clean equilibration to diastereomerically pure, *P*-stereogenic (***R,R,S*)-18** (>95:5 dr), the absolute configuration of which was confirmed by ^{1}H−^{1}H NOESY NMR.

CONCLUSIONS

Herein, by leveraging a new route to readily accessible enantiopure cyclic (alkyl)(amino)carbenes (^{Chi}CAACs), we investigated factors governing stereoinduction in the oxidative addition of E−H σ-bonds (E = C, N, O, Si, P) to chiral carbon ambiphiles. Our results reveal that these carbenes serve as powerful synthons for constructing stereochemical complexity, exemplified by their ability to precisely control the formation of two stereocenters with prochiral reagents. Notably, their capacity to direct stereochemistry at silicon and phosphorus centers underscores their broader potential in asymmetric synthesis. DFT calculations confirm the intimate connection between the structure of the product-determining transition states and reaction thermodynamics with the observed stereoselectivities under either kinetic or thermodynamic control. This relationship is particularly evident in the stereoselectivity observed in Si−H and P−H bond activation pathways. Altogether, this work positions chiral ambiphilic carbenes as a new paradigm in asymmetric synthesis, with far-reaching implications for organic chemistry, catalysis, and materials science. We believe these findings extend to other main group

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ambiphiles, an area still largely unexplored in enantioselective transformations.

■ ASSOCIATED CONTENT

Data Availability Statement

All computational data underlying this study are openly available for download, free of charge, from the UC San Diego Library Digital Collections at DOI: 10.6075/J0154HDK.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c03845.

Experimental procedures, analytical data (^{1}H, ^{13}C, ^{31}P, ^{19}F NMR, HRMS), computational details and DFT-optimized structures (PDF) CIF/PLATON report (PDF)

Accession Codes

Deposition Numbers 2385234−2385239, 2385854−2385856, 2401279−2401282, and 2428557−2428558 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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