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Expedited Synthesis of Axially Chiral 3-Monosilyl and 3,3′-Bis-silyl Biphenols, Binaphthols, and Phosphoramidites Enabled by Catalytic Two-Fold C−H Silylation with a Traceless Acetal Directing Group

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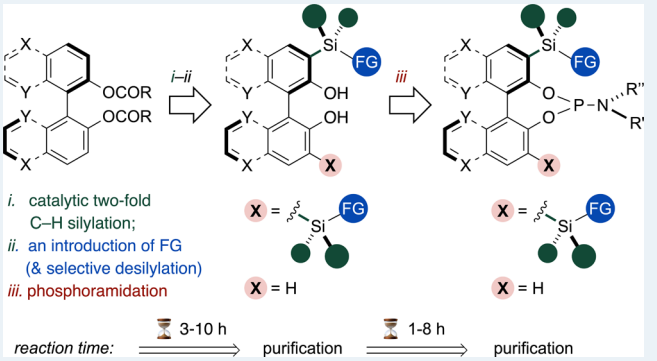
ABSTRACT: The design and development of supporting ligands have significantly propelled the discovery of new catalytic reactions and the improvement of existing ones. Among these, axially chiral biphenols and 1,1′-binaphthalene-2,2′-diol (BINOL) are some of the most privileged ligands used in a wide array of enantioselective reactions. Despite the well-established benefits of structural modifications to biphenol and BINOL scaffolds, particularly at their 3,3′-positions—for enhancing reactivity and stereofidelity in catalytic asymmetric transformations—only a limited number of 3,3′-bis-functionalized biphenols and BINOLs are currently available. Here, we report a unified strategy to rapidly access a range of axially chiral 3-monosilyl and 3,3′ bis-silyl-substituted and biphenols and BINOLs as well as their corresponding 3-monosilyl and 3,3′ bis-silyl BINOL-based phosphoramidites. This approach involves traceless acetal-directed, catalytic two-fold C−H silylation of axially chiral biaryls, coupled with selective monoprotodesilylation, expanding the versatility of catalytic C−H functionalization in ligand design and development. Scope studies on the augmentation of the topological space of potentially stereoselectivity-amplifying 3,3′-bis-silyl substituents in axially chiral biphenols and BINOLs were achieved through C−H silylation of biphenols and BINOLs using various dihydrosilanes, as well as the derivatization of 3,3′-silanes, leading to functionalized silane-substituted biphenols and BINOLs. Lastly, the phosphoramidation of newly synthesized 3-monosilyl and 3,3′ bis-silyl BINOL and biphenols with dichlorophosphinamine provided a series of 3-monosilyl and 3,3′ bis-silyl BINOL-based phosphoramidites. The efficiency of this synthetic approach is underscored by its short synthetic steps, expedited reaction times, and minimal purification, making it versatile for the synthesis of a wide array of organosilicon-functionalized axially chiral biaryls and phosphoramidites.



KEYWORDS: *C−H silylation, binaphthol, biphenol, phosphoramidite, transition-metal catalysis*

INTRODUCTION

Supporting ligands play an increasingly crucial role in modern transition-metal catalysis.[1−5] Structural modifications to supporting ligands that transform a metal catalyst's overall architecture through metal−ligand coordination dictate both the reactivity and stereofidelity of catalytic transformations.[6−9] In recent decades, the design and development of ligands have significantly propelled the discovery of new catalytic reactions and the improvement of existing ones. Specifically, to construct biologically relevant molecules that possess chirality and exist as enantio-enriched forms,[10,11] the successful development of asymmetric catalysis demands a large and readily available set of chiral catalyst libraries for rapid reaction screening and optimization.

Axially chiral biphenols **1** have been among the most privileged ligands in a wide array of asymmetric reactions (Figure 1a).[12,13] The 6,6′-substituents in biphenols rotationally impede the aryl−aryl linkage, thereby inducing axial chirality. Recent studies have shown that structural modifications to biphenol and binaphthol scaffolds, particularly at their 3,3′-positions (e.g., **2**), significantly impact stereoselectivity in various asymmetric reactions.[12−14] The two phenolic groups present in axially chiral biphenols and binaphthols serve as key anchoring points for a diverse range of main and transition metals. This feature allows for the modification of their functions, transforming them into chiral Lewis acids or phosphorus ligands (e.g., **3**).[15−17] Ojima demonstrated that chiral 3,3′-bis-functionalized biphenol-based phosphoramidites, formed through structure and function modifications,

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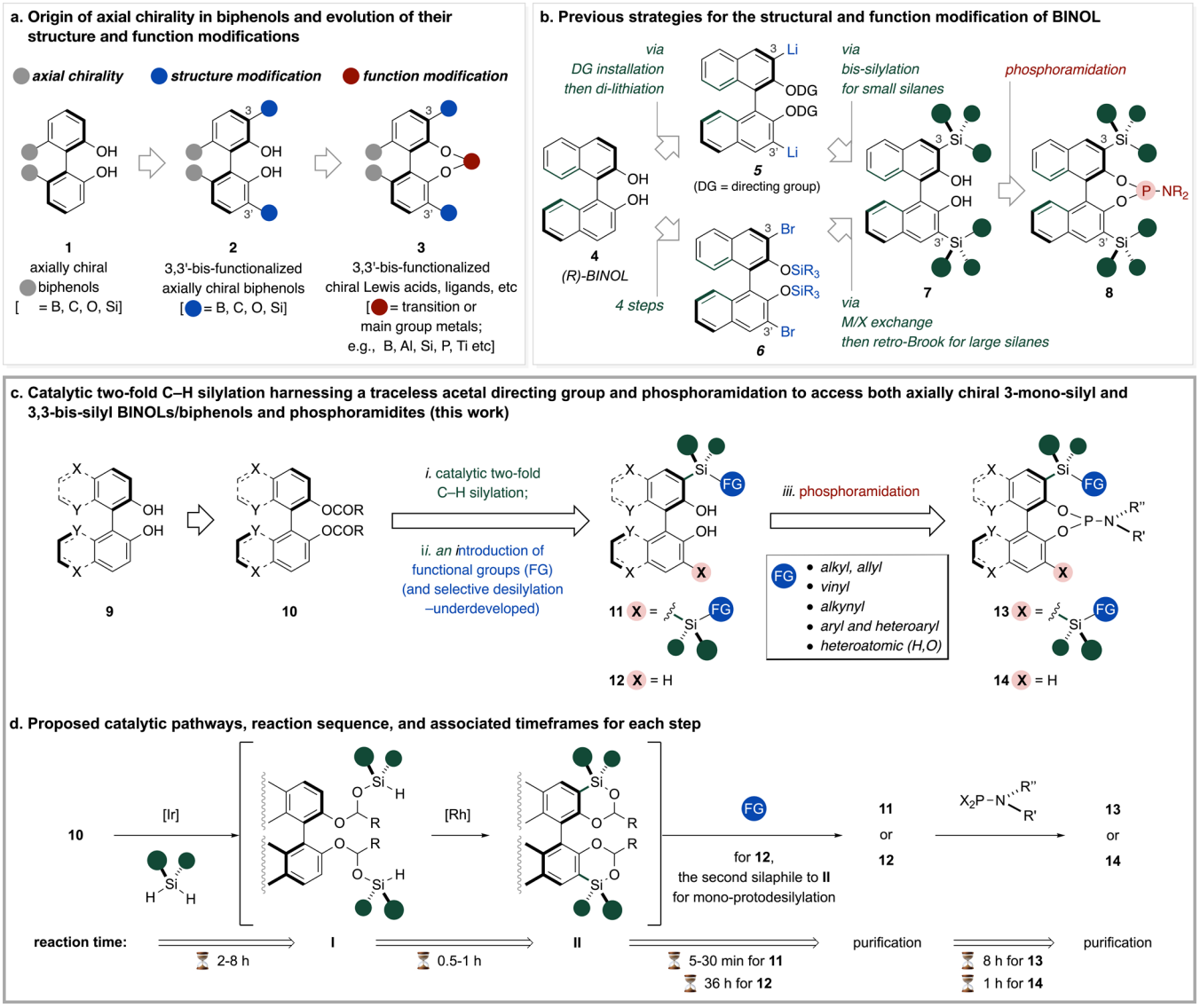

Figure 1. (a) Origin of axial chirality in biphenols and evolution of their structure and function modifications. (b) Previous stoichiometric methods for a synthesis of 3,3′-bis-silyl BINOLs/biphenols. (c) Synthetic strategies toward design and development of axially chiral 3-mono- and 3,3′-bis-silyl BINOLs/biphenols and 3-mono- and 3,3′-bis-functionalized BINOL/biphenol-based phosphoramidites. (d) Proposed reaction sequence and timeframes of traceless acetal-directed, two-fold catalytic C−H silylation and phosphoramidation.

outperformed 3,3′-bis-hydro-biphenol-based phosphoramidites in terms of enantioselectivity.[18]

1,1′-Binaphthalene-2,2′-diol (BINOL) **4** has been one of the most privileged ligands in a wide array of asymmetric reactions (Figure 1b).[12,13,19,20] Despite the established benefits from axially chiral 3,3′-bis-functionalized scaffolds, only a limited number of 3,3′-bis-functionalized biphenols and binaphthols **7** are available.[18,21,22] In fact, only 3,3′-bis(triphenyl silyl) binaphthol is available in Sigma-Aldrich, but its price is substantially high compared to BINOL. Furthermore, to the best of our knowledge, 3,3′-bis-silyl BINOL-based phosphoramidite ligands **8** are not commercially available.[23]

The synthesis of 3,3′-bis-silyl BINOLs typically employs one of two methods. Sterically less demanding silanes can be introduced to a BINOL scaffold by Snieckus' dilithiation of MOM-protected binaphthol using excess alkyl lithium base, followed by treatment with halosilane (Figure 1b).[24] Yamamoto's five step sequence, developed to address the scope limitations of Snieckus' method, leveraged a metal−halogen exchange, followed by a retro-Brook rearrangement (Figure 1b).[25] While this strategy can host hindered organosilanes, it encounters challenges due to the limited availability of appropriate halosilanes.[21,25] These two current strategies lack the capability to generate a large library of axially chiral 3,3′-bis-silyl biphenol/binaphthol ligands in an efficient manner. This drawback arises from several factors, including multistep reaction sequences, the use of strong basic conditions, multiple purifications of various intermediates, and a limited silane scope.

We envisioned catalytic strategies for the rapid and modular synthesis of a library of axially chiral 3,3′-bis- and 3-monosilyl BINOLs and biphenols (**11** and **12**), as well as their corresponding 3,3′-bis-silyl and 3-monosilyl BINOL and biphenol-based phosphoramidites (**13** and **14**) (Figure 1c).[26,27] Our strategy implements traceless acetal-directed, catalytic 2-fold C−H silylation of axially chiral BINOLs and biphenols **10**, followed by the introduction of sterically and electronically tunable functional groups onto the newly formed

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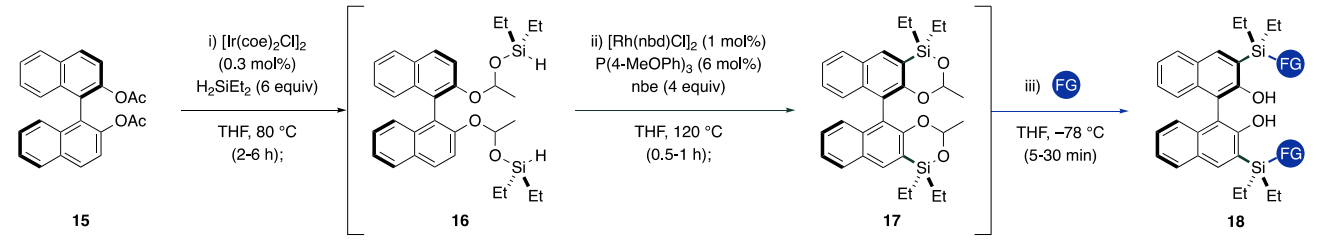
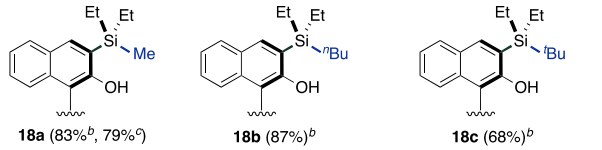
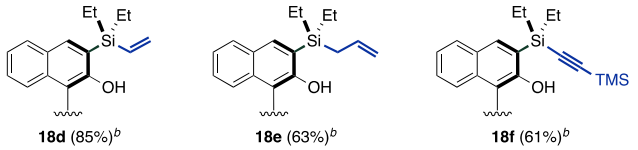
Table 1. Synthesis of 3,3′-Bis-Silyl BINOLs via Catalytic Two-Fold C−H Silylation with a Traceless Acetal Directing Group[a]



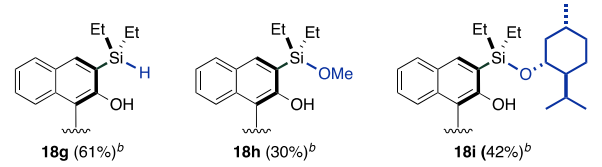
a. alkyl substituents



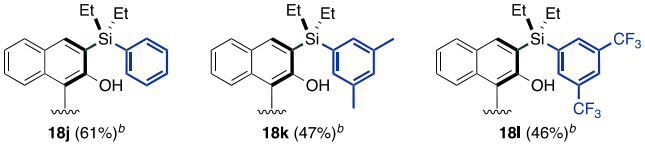
b. vinyl, allyl, and alkynyl substituents



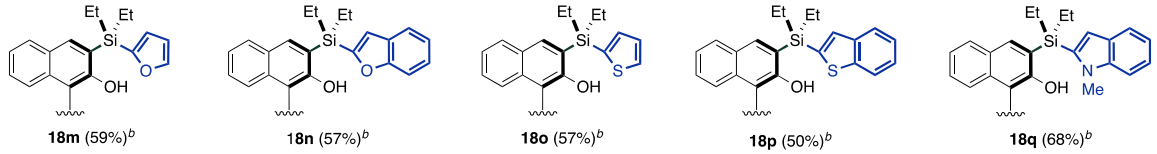
c. hydrogen and heteroatomic substituents



d. aryl substituents



e. heterocyclic substituents



[a]Conditions: (i) **15** (0.2 mmol), $[Ir(coe)_2Cl]_2$ (0.3 mol %), H_2SiEt_2 (6 equiv), THF (1 M), 80 °C. (ii) $[Rh(nbd)Cl]_2$ (1 mol %), $P(4\text{-}OMePh)_3$ (6 mol %), nbe (4 equiv), THF (1 M), 120 °C. (iii) nucleophile (6 equiv), THF (2 M),−78 °C. [b]Isolation yield. [c]10 mmol of **15** was used.

3,3′-bis-silyl groups, concomitantly removing the acetal directing groups.[28] Furthermore, a selective synthesis of 3-monosilyl BINOLs and biphenol **12** from **10** was also envisaged. The challenge arises from the synthetic intricacy of installing orthogonal directing and protecting groups on two phenols, exacerbated by the scarcity of a controlled mono-*ortho*-silylation process for BINOLs and biphenols.

Proposed catalytic pathways, reaction sequences, and associated timeframes for each step are depicted in Figure 1d. Specifically, the bis-hydrosilyl acetal in intermediate **I**, prepared via Ir-catalyzed two-fold hydrosilylation of diesters **10**, serves as a two-atom tether enabling site-specific C−H silylation to produce bisdioxasilines **II**. Within the same reaction vessel, a series of sterically and electronically varied anionic functional groups add to an electrophilic silicon center in **II**, resulting in the expulsion of aldehydes—which could further engage with a second nucleophile. This reaction cascade ultimately produces axially chiral 3,3′-bis-silyl BINOLs and biphenols **11** without the acetal directing groups. The three-step, one-pot reactions can be achieved within 3 to 10 h and require one purification. On the other hand, we hypothesize that 3-monosilyl BINOLs and biphenols **12** can be accessed via kinetically controlled selective monoprotodesilylation of **11** using second silaphiles (e.g., metal fluorides or alkoxides). Despite potential challenge associated with non-selective protodesilylation, phosphoramidation of **11** and **12** with dichlorophosphinamine provides 3,3′-bis-silyl and 3-monosilyl BINOL/biphenol-based phosphoramidites **13** and **14**. We anticipate that the proposed reaction scheme not only expands the versatility of C−H functionalization in the context of ligand design and development but also augments the topological space of potentially stereoselectivity-amplifying 3-monosubstituent and 3,3′-bis-substituents within **11**−**14**.

DISCUSSION

Synthesis of 3,3′-Bis-Silyl BINOLs via Catalytic Two-Fold C−H Silylation with a Traceless Acetal Directing Group. Our approach to the expeditious synthesis of axially chiral 3,3′-bis- and 3-monosilyl BINOLs and biphenols (**11** and **12**), as well as their corresponding 3,3′-bis-silyl and 3-monosilyl BINOL and biphenol-based phosphoramidites (**13** and **14**) initially centered on the development of catalytic two-fold C−H silylation of readily available (*R*)-BINOL bis-acetate **15** (Table 1).[26] Dual Ir-catalyzed ester hydrosilylation of **15** afforded bis-silyl acetal **16**. This reaction was generally completed in 2−6 h in THF at 80 °C using 0.3 mol % of catalyst. The succeeding two-fold *ortho*-C−H silylations of **16**, catalyzed by an electron-rich Wilkinson-type Rh catalyst with norbornene (nbe) as a hydrogen acceptor, provided bisdioxasilines **17**. This dual C−H functionalization was completed within 0.5−1 h in THF at 120 °C in a closed vessel. The resulting bisdioxasilines **17** in an inconsequential diastereomeric mixture (ca. 1.6:1.6:1:1.6) were indeed chromatographically stable and could be stored in a refrigerator for a

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few weeks. A double nucleophilic addition of a variety of nucleophiles to **17** was accomplished within 5−30 min, producing diverse 3,3′-bis-silyl BINOLs **18** with moderate to good yields (17 examples, 30−87% yields, 3 to 8 h, over three steps). In the last step, among other nucleophiles, organolithiums were generally found to be optimal for the ring-opening of **17**, because of rapid product formation and minimal protodesilylation vis-à-vis organomagnesium agents. Specifically, alkyl nucleophiles of varying sterics were introduced using their corresponding organolithium reagents to produce compounds **18a−c** with good yields (Table 1a). Vinyl and allyl Grignard nucleophiles provided 3,3′-bis-vinylsilyl BINOLs **18d** and 3,3′-bis-allysilyl BINOLs **18e** with moderate to good yields (Table 1b). The addition of lithium acetylide to **15** furnished 3,3′-bis-diethylalkynylsilyl BINOL **18f** (Table 1b). Subsequently, hydride and heteroatomic nucleophiles were examined (Table 1c). 3,3′-Bis-hydrodiethylsilyl BINOL **18g** was generated using LAH as the hydride nucleophile. The reactions using oxygen nucleophiles yielded **18h** and **18i**, albeit with diminished yields due to competing protodesilylation. An introduction of the arenes and heterocycles into the 3,3′-bis-silyl BINOL scaffold not only alters their steric and electronic nature but also provides an additional metal binding element that controls stereofidelity and reactivity of catalytic transformations. A key to the success of the reactions involving electronically and sterically varied aryl and heteroaromatic organolithium reagents was the timely addition of corresponding anions to the bisdioxasilines **17**, owing to the distinct lifetimes of the reagents (Table 1d,e). Successful examples include lithiated benzene, 3,5-dimethylbenzene, 3,5-ditrifluoromethylbenzene, furan, benzofuran, thiophene, benzothiophene, and indole, leading to corresponding 3,3′-bis-aryl/heteroarylsilyl BINOLs **18j−q** with moderate yields via three steps. Interestingly, these compounds were generally less polar than the precursor, biscyclic silyl acetal bisdioxasilines **17**. This suggests that the installed bis-silyl groups make the bis-phenoxy groups in **18** substantially less basic and thus directly influence the catalytic metal binding site interacting with the bis-phenoxy groups. While most reactions can be done in a one-pot fashion (**15** to **18**), the reactions with LAH, menthol, phenyl, and indole nucleophiles required semipurification of the dioxasiline intermediates **17** (e.g., filtration through a plug of Celite) to minimize monoprotodesilylation.[27]

Enantiomeric Purity of 3,3′-Bis-Silyl BINOLs Formed through Catalytic Two-Fold C−H Silylation with a Traceless Acetal Directing Group. Racemization has been a persistent challenge in the synthesis and modification of axially chiral molecules, necessitating rigorous confirmation of the enantiomeric purity of the resulting functionalized products. Despite the unsuccessful HPLC separation of product **18a** from both (*R*)-BINOL and racemic BINOL, due to the nonpolar nature of 3,3′-bis-silyl BINOLs, we developed a comparative analytical resolution strategy (Figure 2). This strategy involves subjecting optically enriched lithium L-mentholate to **17** derived from both (*R*)-BINOL [(*R*)-**15**] and (*rac*)-BINOL [(*rac*)-**15**], yielding (*R*)-**18-bis-L-menthol** (i.e., **18i**) and (*rac*)-**18-bis-L-menthol**, respectively (Figure 2a).[26,29] Careful ^{1}H NMR analysis of crude reaction mixtures from both reactions revealed that while the reaction using (*rac*)-BINOL produced a diastereomeric mixture of (*R*)-**18-bis-L-menthol** and (*S*)-**18-bis-L-menthol** in a ca. 1:1.03 ratio, the reaction with (*R*)-**15** afforded a single diastereomer, (*R*)-**18-bis-L-menthol**, consistent with one of the previously observed diastereomers from the reaction with (*rac*)-**15** (Figure 2b). These resolution experiments collectively suggest that the two-fold catalytic C−H silylation strategy does not induce racemization of 3,3′-bis-silyl BINOLs **18**.

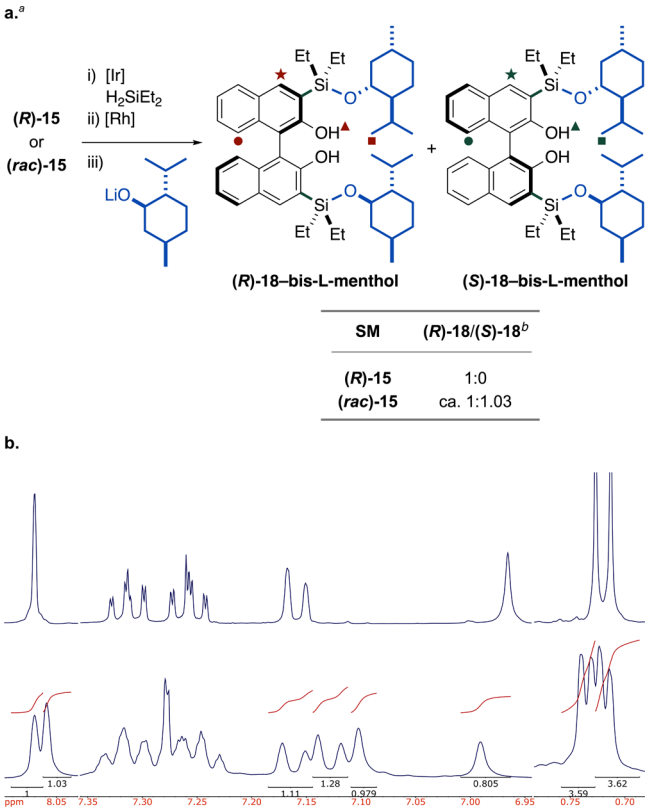

Figure 2. Evaluation of enantiomeric purity of 3,3′-bis-silyl BINOL. (a) Two parallel reactions of optically enriched lithium L-mentholate with (*R*)-**15** and (*rac*)-**15** were carried out, providing (*R*)-**18-bis-L-menthol** (i.e., **18i**) and (*rac*)-**18-bis-L-menthol**, respectively. [a]Conditions: (i) (*R*)-**15** or (*rac*)-**15** (0.2 mmol), $[Ir(coe)_2Cl]_2$ (0.3 mol %), H_2SiEt_2 (6 equiv), THF (1 M), 80 °C. (ii) $[Rh(nbd)Cl]_2$ (1 mol %), $P(4\text{-}OMePh)_3$ (6 mol %), nbe (4 equiv), and THF (1 M), 120 °C. (iii) Lithium L-mentholate (6 equiv), THF (2 M),−78 °C. [b]Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. (b) Top: ^{1}H NMR spectra of (*R*)-**18-bis-L-menthol**. Bottom: ^{1}H NMR spectrum of a mixture of (*R*)-18-bis-L-menthol and (*S*)-18-bis-L-menthol.

Synthesis of 3,3′-Bis-Silyl Biphenols via Catalytic Two-Fold C−H Silylation with a Traceless Acetal Directing Group. We expanded the scope of the 3,3′-bis-silyl biphenol scaffold through catalytic C−H silylation of axially chiral biphenols using a traceless acetal directing group. NMR studies revealed slightly slower reaction kinetics in Ir-catalyzed ester hydrosilylation and diminished efficiency for traceless acetal-directed C−H silylation of biphenols compared to BINOLs, although nucleophilic addition reactions proceeded rapidly (Table 2).[26] In this study, we employed *n*-butyllithium as a nucleophile to react with dioxasilines (e.g., H8-BINOL, 6,6′-dimethoxy-1,1′-biphenyl-2,2′-diol, and bis-dibenzodioxole-2,2′-diol), affording the corresponding 3,3′-bis-silyl biphenols (**18a−c**) in moderate yields.

Synthesis of 3,3′-Bis-Silyl BINOLs with Sterically and Electronically Varied Silane Agents. To broaden the reaction scope, we examined sterically and electronically varied acyclic silane reagents, either commercially available or

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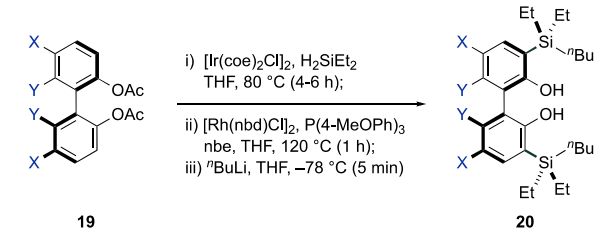
Table 2. Synthesis of 3,3′-Bis-Silyl Biphenols via Catalytic Two-Fold C−H Silylation with a Traceless Acetal Directing Group[a]



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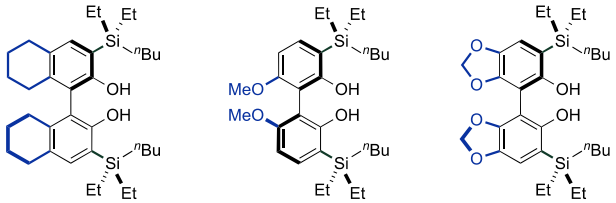
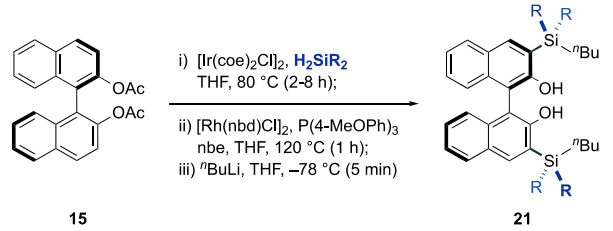


20a (44%)[b] 20b (50%)[b] 20c (39%)[b]

[a]Conditions: (i) **15** (0.2 mmol), $[Ir(coe)_2Cl]_2$ (0.3 mol %), H_2SiEt_2 (6 equiv), THF (1 M), 80 °C. (ii) $[Rh(nbd)Cl]_2$ (1 mol %), P(4-OMePh)$_3$ (6 mol %), nbe (4 equiv), THF (1 M), 120 °C. (iii) ^{n}BuLi (6 equiv), THF (2 M),−78 °C. [b]Isolation yield.

synthesized via reduction of dichlorosilanes using LAH.[26] Dihydrodioctylsilane $[H_2Si(oct)_2]$ and dihydrodiisopropylsilane $[H_2Si^iPr]$ exhibited comparable impediment to the ester hydrosilylation step under the standard iridium catalysis conditions (2−8 h), possibly due to similar A values (ca. 2.1 kcal/mol) (Table 3). In contrast, dihydrodiphenylsilane reacted rapidly with **15** but concomitantly generated disiloxane byproducts. The electron-withdrawing nature of the phenyl groups toward residual water likely contributed to byproduct formation. Overall, the inefficient Ir-catalyzed hyrosilylation of **15** using sterically hindered and electronically withdrawing dihydrosilanes adversely impacted the subsequent Rh-catalyzed, two-fold C−H silylation and nucleophilic addition of ^{n}BuLi, resulting in diminished overall yields of the corresponding 3,3′-bis-silyl BINOLs (**21a−c**).

Table 3. Scope of Dihydrosilanes[a]



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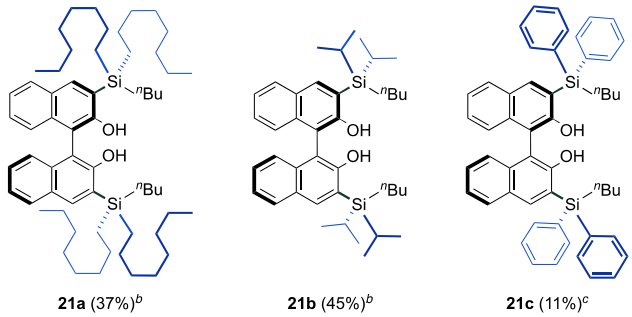
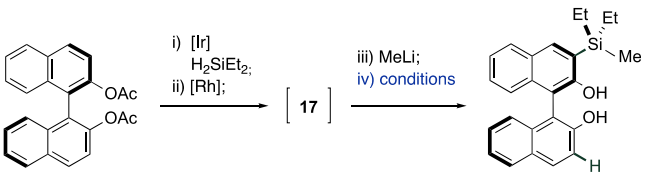


21a (37%)[b] 21b (45%)[b] 21c (11%)[c]

[a]Conditions: (i) **15** (0.2 mmol), $[Ir(coe)_2Cl]_2$ (0.3 mol %), H_2SiR_2 (6 equiv), THF (1M), 80 °C. (ii) $[Rh(nbd)Cl]_2$ (1 mol %), P(4-OMePh)$_3$ (6 mol %), nbe (4 equiv), THF (1 M), 120 °C. (iii) ^{n}BuLi (6 equiv), THF (2 M),−78 °C. [b]Isolation yield. [c]Determined by ^{1}H NMR spectroscopy utilizing an internal standard (mesitylene).

Synthesis of 3-Monosilyl BINOLs. 3-Monosilyl BINOLs were previously accessed through a controlled, directed monometalation using a precise stoichiometric amount of a strong base (e.g., ^{n}BuLi).[30] During our investigation of the two-fold nucleophilic addition of various nucleophiles to bisdioxasilines **17**, we observed monoprotodesilylation of **18**, leading to the formation of 3-monosilyl BINOL **22** over an extended reaction time (Table 4). However, the reaction was incomplete and produced inconsistent results. To optimize the conditions for monoprotodesilylation of 3,3′-bis-silyl BINOL **15**, a variety of silaphiles were surveyed (Table 4). Lithium alkoxides failed to produce the desired product (entries 1 and 2), whereas other basic conditions (e.g., Me_3SiOK, MeLi) and acidic conditions (e.g., HCl) showed improved results (entries 2−5). Ultimately, selective monoprotodesilylation was achieved using TBAF, (entries 6 and 7), although gradual dual protodesilylation, leading to BINOL formation, was observed over time (ca. 10−15%). No evidence of racemization in **22a** was detected in this protocol for selective monoprotodesilylation, as confirmed by chiral HPLC analysis.

Table 4. Synthesis of 3-Monosilyl BINOL via a Sequence of Catalytic Two-Fold C−H Silylation and Selective Monoprotodesilylation[a]



15 22a

entry	reagent[b]	solvent	temp. (°C)[c]	yield (%)[d]
1	^{i}PrOLi	THF	rt	0
2	^{t}BuOLi	THF	rt	0
3	Me_3SiOK	THF	rt	20
4	MeLi	THF	rt	27
5	HCl	THF	100	29
6	TBAF	THF	100	52
7	TBAF	DMF	100	55

[a]Conditions: (i) **15** (0.4 mmol), $[Ir(coe)_2Cl]_2$ (0.3 mol %), H_2SiEt_2 (6 equiv), THF (1 M), 80 °C. (ii) $[Rh(nbd)Cl]_2$ (1 mol %), P(4-OMePh)$_3$ (6 mol %), nbe (4 equiv), THF (1 M), 120 °C. (iii) MeLi (6 equiv), THF (0.4 M),−78 °C to rt. [b]Reagent: 10 equiv. [c]36 h. [d]Isolation yield.

Synthesis of 3,3′-Bis-Silyl BINOL-Based Phosphoramidites. Upon establishing a method for synthesizing various axially chiral 3,3′-bis-silyl BINOLs/biphenols, we explored the phosphoramidation of 3,3′-bis-silyl BINOLs **18** to afford 3,3′-bis-silyl BINOL-based phosphoramidites **23**.[26] Our initial attempt involved reacting **18a** with PCl_3 under basic conditions to form the corresponding phosphorochloridite, followed by the formation of a P−N bond with a secondary amine (e.g., diisopropylamine), aiming to produce **23a**.[31] However, this protocol failed to yield **23a**, as competitive protodesilylation of **18a** was observed during the reaction.

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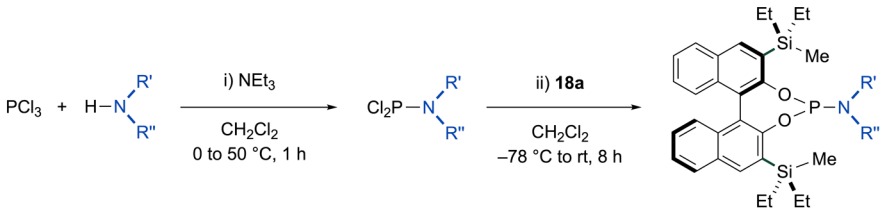
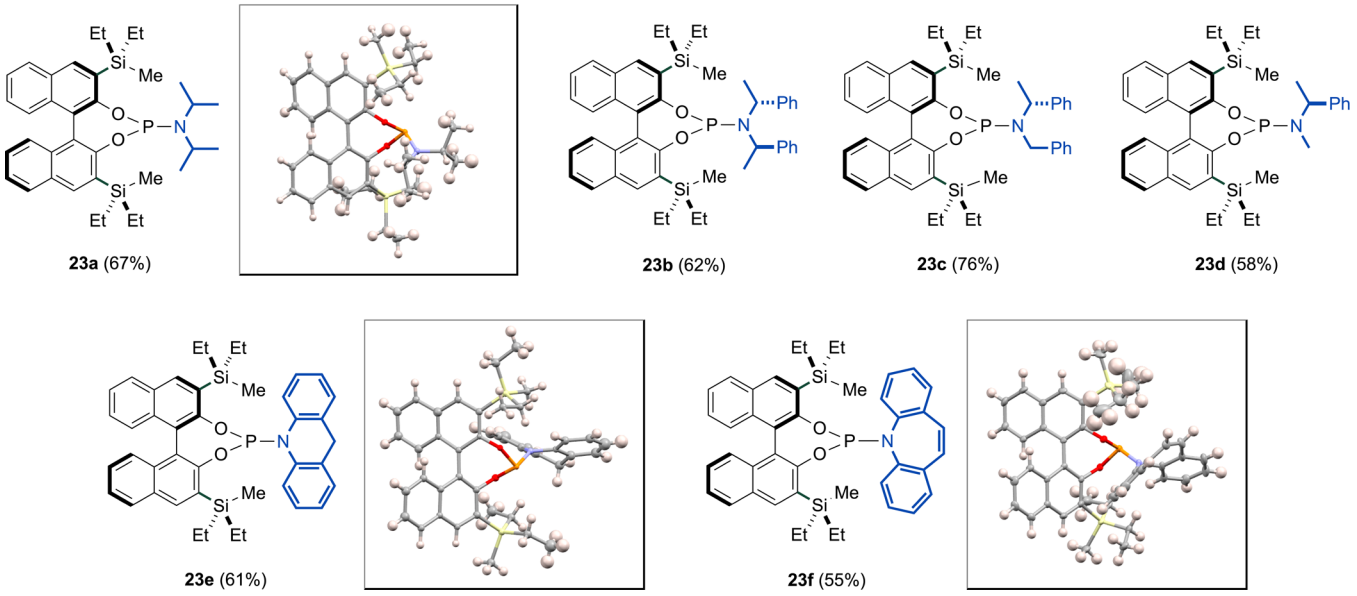
Table 5. Synthesis of 3,3′-Bis-Silyl BINOL-Based Phosphoramidites[a]



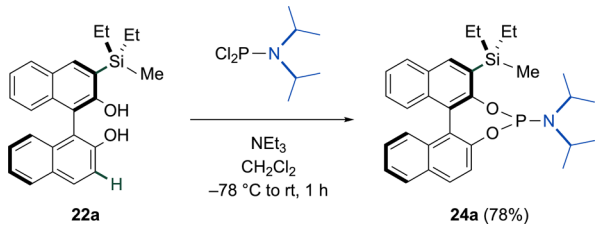


[a]Conditions: (i) R'R"NH (1.1 equiv), PCl_3 (1.1 equiv), NEt_3 (6 equiv), CH_2Cl_2 (1.2 M), 50 °C, 1 h. (ii) **18a** (1 mmol), CH_2Cl_2 (1 M),−78 °C to rt, 8 h.

Alternatively, we reversed the sequence, namely, first forming the P−N bond by reacting a secondary amine with PCl_3 to afford the corresponding dichlorophosphinamine (Table 5). The P−O bonds were then formed through a reaction of dichlorophosphinamine with **18a** under buffered conditions.[32,33] This method successfully generated 3,3′-bis-silyl BINOL-based phosphoramidite **23a** in moderate yield (67%). The added steric bulk of the 3,3′-bis-silyl groups within **18a** was found to reduce the reactivity, impacting the efficiency of P−O bond formation. Using the established phosphoramidation conditions, we expanded the scope of this sequential, traceless acetal-directed dual C−H silylation and phosphoramidation. Additional 3,3′-bis-silyl BINOL-based phosphoramidites (**23b**−**23f**) were synthesized in moderate to good yields (55−76%). X-ray crystallography confirmed the structures of **23a**, **23e**, and **23f**, providing critical insights into the topological arrangement of the two silyl groups within the ligands.

Synthesis of 3-Monosilyl BINOL-Based Phosphoramidite. Next, the axially chiral 3-monosilyl BINOL-based phosphoramidite was prepared through the established protocol described in an earlier section (Scheme 1). Specifically, 3-monosilyl BINOL **22a** reacted with dichlorophosphinamine, prepared by a reaction of diisopropyl amine with PCl_3, under basic conditions to produce 3-monosilyl BINOL-based phosphoramidite **24a** (78% yield). Notably, this reaction with the sterically less encumbered 3-monosilyl BINOL proceeded substantially faster than with the sterically crowded 3,3′-bis-silyl BINOLs (1 h vs 8 h).

Scheme 1. Synthesis of 3-Monosilyl BINOL-Based Phosphoramidite[a]



[a]Conditions: **22a** (0.2 mmol), $Cl_2PN(^iPr)_2$ (1.1 equiv), NEt_3 (4 equiv), CH_2Cl_2 (1 M),−78 °C to rt, 1 h.

Synthetic Applications of 3-Mono- and 3,3′-Bis-Silyl BINOLs. Lastly, our preliminary studies on the application of chiral 3-mono- and 3,3′-bis-silyl BINOLs were carried out (Table 6). Under unoptimized conditions, asymmetric alkynylboration of chalcone **25** with alkynyldiisopropylboronate in the presence of **18a** and **22a** as catalysts afforded β-alkynyl ketone **26** in enantiomeric ratios (er) of 65:35 and 75:25, respectively.[34] The facile association of boronate to 3-monosilyl BINOL and the unique unsymmetric environment provided by **22a**, vis-à-vis sterically more crowded **18a**, likely contributed to the observed selectivity.

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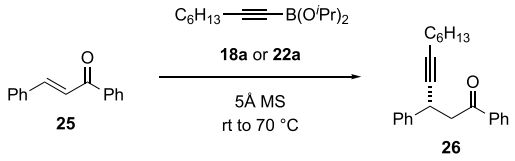
Table 6. Synthetic Applications of 3-Mono- and 3,3′-Bis-Silyl BINOLs[a,b]



catalyst	yield (%)[a]	er
(*R*)-18a	83	65:35
(*R*)-22a	87	75:25

[a]Conditions: **25** (0.2 mmol), **18a**/**22a** (20 mol %), boronate (4 equiv), THF (1 M), 5 Å MS, rt to 70 °C. [b]Isolated yield based on recovered starting material.

CONCLUSIONS

In summary, we have developed a unified synthetic strategy that employs traceless acetal-directed, catalytic two-fold C−H silylation of axially chiral biphenols and BINOLs, coupled with a selective monoprotodesilylation. This method enables rapid access to a range of axially chiral 3-monosilyl and 3,3′ bis-silyl-substituted and biphenols and BINOLs as well as their corresponding 3-monosilyl and 3,3′ bis-silyl BINOL-based phosphoramidites, all achieved with short synthetic steps, expedited reaction times, and minimal purification. Scope studies on dihydrosilanes and the functionalization of 3,3′-silyl moieties from bisdioxasiline intermediates expanded the topological space of potentially stereoselectivity-amplifying 3,3′-bis-silyl substituents in axially chiral biphenols and BINOLs. The enantiomeric purity of 3,3′-bis-silyl BINOLs was confirmed through resolution experiments with lithio L-mentholate, demonstrating that the two-fold catalytic C−H silylation strategy does not induce racemization of the 3,3′-bis-silyl BINOL. Furthermore, we developed a selective monoprotodesilylation protocol using TABF for an efficient synthesis of 3-monosilyl BINOL from 3,3′-bis-silyl BINOL. Finally, phosphoramidation of the newly synthesized 3-monosilyl and 3,3′ bis-silyl BINOLs and biphenols with dichlorophosphinamine provided a series of corresponding 3-monosilyl and 3,3′ bis-silyl BINOL-based phosphoramidites. Preliminary applications of chiral 3-monosilyl and 3,3′-bis-silyl BINOLs in asymmetric alkynylboration of enones were conducted to explore their potential in the development of asymmetric reactions. Further efforts are underway to evaluate the collection of compounds for their applicability in asymmetric reactions.

METHODS

General Procedure for Synthesis of 3,3′-Bis-Silyl Biphenols and BINOLs via Traceless Acetal-Directed Catalytic Two-Fold C−H Silylation. $[Ir(coe)_2Cl]_2$ (0.3 mol %) and biphenol or BINOL diacetates **15** or **19** (1 equiv) were dissolved with THF (1 M) in a flame-dried vial. Dihydrosilane (6 equiv) was added to the mixture. The septum on the vial was replaced with a screw cap with a Teflon liner. The reaction mixture was stirred for 2−8 h at 80 °C. The volatiles were removed *in vacuo* to afford hydrosilyl acetals **16**, which were directly used for a subsequent reaction without further purification. $[Rh(nbd)Cl]_2$ (1 mol %) and $P(4\text{-}OMePh)_3$ (6 mol %) were added to **16** in THF (1 M). The septum on the vial was replaced with a screw cap with a Teflon liner, and the mixture was stirred at 120 °C for 0.5−1 h. The resulting dioxasilines were directly used for a subsequent reaction without further purification or were semipurified through a sequence of the removal of the volatiles, dilution with pentane, filtration through a pad of Celite, and concentration under reduced pressure to afford crude dioxasilinanes **17**. The crude dioxasilinanes **17** (1 equiv) were dissolved in THF (0.2 M), and the mixture was cooled to −78 °C. A corresponding nucleophile (6 equiv) was added slowly to the reaction mixture. After being stirred for 5−30 min at −78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic layer was washed with water and brine and dried over anhydrous sodium sulfate. The combined organic layer was washed with water and brine and dried over anhydrous sodium sulfate. The volatiles were removed under reduced pressure, and the crude mixture was purified by MPLC (hexanes/EtOAc) to afford 3,3′-bis-silyl BINOLs and biphenols **18** or **20**, respectively.

General Procedure for Synthesis of 3-Monosilyl BINOL via Traceless Acetal-Directed Catalytic Two-Fold C−H Silylation Followed by Selective Monoprotodesilylation. $[Ir(coe)_2Cl]_2$ (0.3 mol %) and biphenol or BINOL diacetates **15** or **19** (1 equiv) were dissolved with THF (1 M) in a flame-dried vial. Dihydrosilane (6 equiv) was added to the mixture. The septum on the vial was replaced with a screw cap with a Teflon liner. The reaction mixture was stirred for 2−8 h at 80 °C. The volatiles were removed *in vacuo* to afford hydrosilyl acetals **16**, which were directly used for a subsequent reaction without further purification. $[Rh(nbd)Cl]_2$ (1 mol %) and $P(4\text{-}OMePh)_3$ (6 mol %) were added to **16** in THF (1 M). The septum on the vial was replaced with a screw cap with a Teflon liner, and the mixture was stirred at 120 °C for 0.5−1 h. The resulting dioxasilines were directly used for a subsequent reaction without further purification. MeLi (1.6 M in Et_2O, 6 equiv) was added slowly to the crude dioxasiline **17** in THF (0.4 M) at −78 °C. After being stirred for 5 min at the same temperature, the reaction mixture was warmed to room temperature and diluted with DMF (0.4 M). TBAF (1 M in THF, 10 equiv) was added to the reaction mixture. The mixture was warmed to 100 °C and stirred for 36 h. The reaction mixture was quenched by adding aqueous HCl (1 M) and extracted with Et_2O. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over anhydrous sodium sulfate. The volatiles were removed under reduced pressure, and the crude mixture was purified by MPLC (hexanes/EtOAc) to afford 3-silyl BINOL **22a**.

General Procedure for Synthesis of Synthesis of 3,3′-Bis-Silyl BINOL and 3-Monosilyl BINOL-based Phosphoramidites. A solution of the corresponding secondary amine (1.1 equiv) and triethylamine (6 equiv) in CH_2Cl_2 (1.2 M) was prepared and cooled to 0 °C. Phosphorus trichloride (1.1 equiv) in CH_2Cl_2 (0.22 M) was then added slowly via cannula transfer. The reaction mixture was stirred at 50 °C for 1 h and then cooled to −78 °C. A solution of 3,3′-bis-silyl BINOL **18a** or 3-monosilyl BINOL **22a** (1 equiv) in CH_2Cl_2 (1 M) was added, and the reaction mixture was stirred at rt for 1−8 h. The volatiles were removed under reduced pressure, and the crude material was purified by MPLC (hexanes/EtOAc) to afford the corresponding phosphoramidites **23** or **24a**.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c05927.

Experimental details and spectroscopic characterization data for all compounds (PDF)

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Notes

The authors declare the following competing financial interest(s): The authors declare the following competing financial inter-est(s): UTA has filed patents on the synthesized substances that are described in the paper.

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