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Silyl Fluoride Electrophiles for the Enantioselective Synthesis of Silylated Pyrrolidine Catalysts

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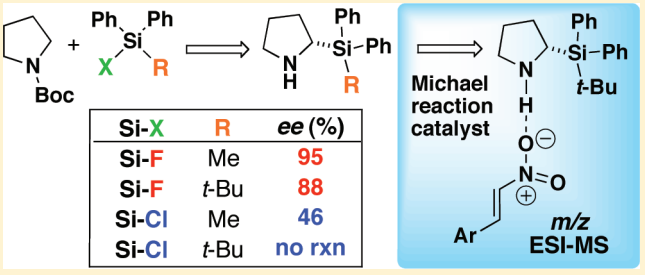
Supporting Information

ABSTRACT: Chiral silylated pyrrolidine catalysts are obtained in high yield and enantioselectivity by sparteine-mediated lithiation of *N*-Boc-pyrrolidine and addition to silyl fluoride electrophiles. The activity and enantioselectivity of a new *tert*-butyldiphenylsilylpyrrolidine catalyst has been demonstrated for various asymmetric Michael reactions at 5 mol % catalyst loading and affords up to 99% ee for asymmetric Michael reactions with aldehydes and nitro-olefins. Acetaldehyde donors proceed with yields up to 77% and enantioselectivities up to 96% ee, avoiding common side reactions that often lower yields. Insight into the mechanism of pyrrolidine-based catalysts is provided by demonstrating ESI mass spectrometry evidence for activation of a nitro acceptor by formation of a hydrogen-bonding adduct with the catalyst amine. Analysis of reaction intermediates using mass spectrometry provides evidence that the pyrrolidine catalyst also plays a role in activating nitro-olefins through hydrogen-bonding.



Si-X	R	*ee* (%)
Si-F	Me	95
Si-F	*t*-Bu	88
Si-Cl	Me	46
Si-Cl	*t*-Bu	no rxn

INTRODUCTION

Enantioselective catalysis provides an efficient method to access chiral molecules for synthetic building blocks, single enantiomer pharmaceuticals, biological screens, and natural products. Traditionally, this field has been dominated by Lewis acid and transition-metal-based catalysts; however, these catalysts tend to be more toxic, expensive, and sensitive to moisture and air. Recently, there has been an interest to develop organocatalysts that have complementary reactivity to existing catalysts, with the advantages of being cheaper to produce and easier to handle. The development of new types of selective organocatalysts continues to gain attention with the rising cost of metals and concerns for environmental sustainability. Organocatalysts are increasingly utilized in diverse synthetic transformations to obtain highly functionalized complex targets.[1−3] The activation mechanism and stereocontrol elements of organocatalysts are of particular interest because they are considered to mimic the active sites of enzymes in biological systems.[4]

We are interested in the design of new catalysts incorporating silicon functional groups to impart steric and/or electronic effects to induce asymmetry.[5] Silicon is positioned directly below carbon on the periodic table and can be utilized in many synthetic transformations that are similar to carbon, while also providing effects and opportunities not available for carbon analogs. Because of the electropositive nature of silicon and the reversal of bond polarity relative to carbon, the incorporation of a silyl group may alter the stabilization of transition states and intermediates when organosilicon species are involved. With a covalent radius approximately 50% larger and bond lengths approximately 20% longer than carbon,[6] silicon can exert a greater steric influence compared to related carbon analogues. Sterically demanding silyl groups are most commonly utilized in protecting group strategies for alcohols where a Si−O bond is formed upon substitution of a silyl electrophile; the formation of a Si−C bond and the corresponding quaternary silyl group can be readily accomplished using the same substitution strategy.[7−9]

Herein we describe the use of silyl fluoride electrophiles for the efficient synthesis of three enantiopure silylated pyrrolidine catalysts including the new sterically demanding *tert*-butyldiphenylsilyl analogue. Although bulky silyl chloride electrophiles are effective silylating agents for the protection of alcohols,[10] their reactivity decreases as the steric interactions around the silicon increase. The increased electrophilicity of a silyl fluoride reagent[11] compared to the silyl chloride reagent allows for enantioselective reactions with sterically demanding silicon centers. We have demonstrated that the silylated pyrrolidines are effective catalysts for the asymmetric Michael addition of aldehydes to nitro-olefins, providing high diastereoselectivity and excellent enantioselectivity.[12,13] Using ESI-MS, new mechanistic insight is provided regarding the Michael reaction through the detection of an adduct suggesting hydrogen-bonding activation of the nitroalkene by the aminocatalyst. While examples of aminocatalysis are widespread in the literature,[14−16] the full details regarding the role of weak stabilizing interactions and steric factors that control selectivity have not been firmly established,[15,17] and thus, silyl variants may improve mechanistic understanding and lead to new reactivity. Our research[18] provides insight regarding this new class of silylated pyrrolidine catalysts,[19,20] as well as an efficient synthetic method to access

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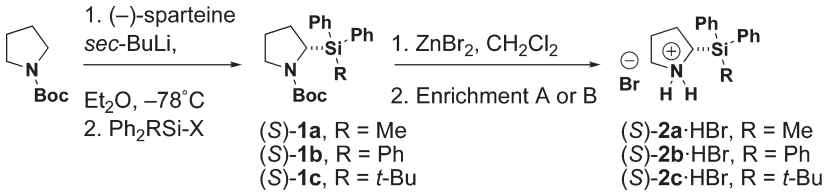
Table 1. Enantioselectivity of Silyl Fluoride Electrophiles for the Synthesis of Silylated Pyrrolidines[a]



entry	Ph_2RSi-X	yield of (*S*)-**1** (%)	yield of (*S*)-**2**·HBr (%)	ee[b] of (*S*)-**2**·HBr (%)	yield enrichment method A (%)	yield enrichment method B (%)	ee[b] enrichment A or B (%)
1	$Ph_2MeSiCl$	84	nd[c]	46	nd	nd	nd
2	Ph_2MeSiF	91	86	95	43	76	99
3	Ph_3SiF	93	85	92	47	69	99
4	Ph_2-*t*-BuSiF	90	86	88	46	68	99

[a] Enrichment method A: recrystallization from 99:2 CH_2Cl_2/MeOH. Enrichment method B: trituration with CH_2Cl_2/hexanes. [b] Determined by HPLC analysis using chiral stationary phase after nitrogen protection with tosylate or benzoyl group; see the Supporting Information for details. [c] nd = not determined.

bulky silylated pyrrolidines with high yields and high enantiopurity in two synthetic steps. This represents the first example of silyl fluoride reagents being utilized in a substitution reaction for enhanced enantioselectivity in the formation of Si−C bonds,[21] which should represent a general strategy for enantioselective synthesis of silicon-containing products for catalysis and biological applications.[22−24]

RESULTS AND DISCUSSION

We have investigated silyl fluoride reagents as effective silylating agents with the goal to establish a general route for the enantioselective formation of C−Si bonds and demonstrate the efficient synthesis of silylated pyrrolidines (such as (*S*)-**2a**−**c**) that incorporate bulky silanes with high enantioselectivity. Silyl fluoride reagents such as diphenylmethylsilyl fluoride and triphenylsilyl fluoride are commercially available, and others can be synthesized in one step from the corresponding silyl chloride reagent.[25] To compare the rate and enantioselectivity between silyl chloride and silyl fluoride electrophiles, we investigated the synthesis of chiral silylpyrrolidines (*S*)-**2a** through (*S*)-**2c** using a (−)-sparteine-mediated asymmetric deprotonation of *N*-Boc-pyrrolidine[26−29] with *sec*-BuLi, followed by addition to a silyl halide reagent (Table 1). Initial use of a silyl chloride electrophile for a moderately sterically hindered diphenylmethylsilyl group afforded high yields of (*S*)-**2a**, but the observed enantioselectivity was very low at only 46% ee after deprotection (entry 1). In contrast, the silyl fluoride variant proceeded efficiently with an increased enantioselectivity of 95% ee (entry 2). The dramatic improvement in enantioselectivity is attributed to the enhanced electrophilicity such that the silylation proceeds at a temperature that is sufficiently low to maintain high configurational stability of the chiral organolithium intermediate. The reduced enantioselectivity with silyl chloride electrophiles suggests that the addition does not proceed until the reaction begins to warm up, which compromises the configurational stability of the organolithium species and degrades the enantioselectivity.[30,31] Although the increased reaction rates for silyl fluoride reagents compared to silyl chloride reagents has been previously reported,[32−34] this is the first example using silyl fluoride reagents as a strategy to enhance enantioselectivity for C−Si bond formation in a substitution reaction.[21,35]

We have also demonstrated that this silyl fluoride synthetic strategy is effective to access the even bulkier triphenylsilyl pyrrolidine (*S*)-**2b** and *tert*-butyldiphenylsilyl pyrrolidine (*S*)-**2c** with high yields and excellent enantioselectivities that are only slightly reduced by the bulkier silanes (92% and 88% ee, entries 3 and 4, respectively). Upon deprotection using $ZnBr_2$[36] and enantioenrichment with a simple trituration in CH_2Cl_2/hexane, (*S*)-**2a**−**c**·HBr are all obtained with 99% ee, with only a slight decrease in yield. Using the same (−)-sparteine-mediated asymmetric deprotonation pathway with chlorotriphenylsilane is known to result in a nearly racemic mixture and 66% yield,[19] and the *tert*-butyldiphenylsilyl chloride is sufficiently bulky such that no reaction is observed. An alternate route to the triphenylsilyl pyrrolidine (*S*)-**2b**, reported by Strohmann and co-workers,[20] employs diphenyldimethoxysilane followed by substitution of the silylether group with phenyllithium. While this synthetic strategy affords excellent enantioselectivity of 99% ee after recrystallization, the overall yield for this sequence was only 34%. Upon investigation of the triisopropylsilyl fluoride reagent, we observed an apparent limit to this strategy, and no reaction was observed. This outcome is attributed to the steric effect in combination with an electronic effect resulting from the replacement of aryl groups with alkyl groups on the silicon.

A comparison of purification methods shows that trituration is the most efficient method of purification while simultaneously enriching the enantiopurity of the catalysts (Table 1). Treatment of catalysts (*S*)-**2a**−**c**·HBr with Amberlyst-A21[37] resin affords the free amine catalysts (*S*)-**2a**−**c** in nearly quantitative yield with no degradation of enantiopurity. The absolute configuration of catalysts (*S*)-**2a**−**c**·HBr was determined by X-ray crystallographic analysis.[38] It should be noted that both the (*R*)- and (*S*)-configurations of the catalyst structures can be readily accessed using the sparteine surrogates described by O'Brien and co-workers.[39,40]

The Michael addition of propionaldehyde to β-nitrostyrene was investigated as a model reaction to compare the catalytic properties of silylated pyrrolidine catalysts (*S*)-**2a**−**c** (Table 2). When catalyst (*S*)-**2a**·HBr is used directly at 10 mol % without adding triethylamine, we observed only low yields (20−30%) after 5 days. Upon addition of triethylamine to generate the free amine catalyst (*S*)-**2a** in situ, the reaction proceeds efficiently to afford the Michael addition product in 1 h favoring the *syn*

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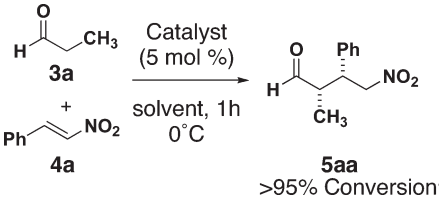
Table 2. Catalyst Comparison for Michael Reaction



entry	catalyst	solvent	dr[b] syn/anti	ee[c] (syn)
1	(*S*)-**2a**·HBr	hexanes	no reaction	
2	(*S*)-**2a**·HBr	hexanes[d]	88:12	81
3	(*S*)-**2a**	hexanes	89:11	82
4	(*S*)-**2a**·HBr	9:1 hexanes/THF[d]	88:12	82
5	(*S*)-**2a**·HBr[e]	9:1 hexanes/THF[d]	93:7	78
6	(*S*)-**2b**·HBr	hexanes[d]	95:5	92
7	(*S*)-**2b**	hexanes	94:6	93
8	(*S*)-**2b**·HBr	9:1 hexanes/THF[d]	97:3	93
9	(*S*)-**2c**·HBr	hexanes[d]	91:9[f]	98
10	(*S*)-**2c**	hexanes	92:8[f]	98
11	(*S*)-**2c**·HBr	9:1 hexanes/THF[d]	92:8[f]	99
12	(*R*)-**7**	hexanes[g]	93:7	99

[a] Conversion calculated using ^{1}H NMR spectroscopy with 3,4,5-trichloropyridine as an internal standard. [b] Determined by ^{1}H NMR analysis of unpurified reaction. [c] Determined by HPLC analysis with OD-H chiral stationary phase. [d] Addition of 5 mol % of Et_3N to reaction. [e] Reaction run with distilled propionaldehyde and 5 mol % of propionic acid added; catalyst (*S*)-**2a**·HBr was 93% ee for this experiment. Reaction time is 3 h. [f] When using distilled propionaldehyde with either 5 or 100 mol % of propionic acid added, a diastereomeric ratio of 94:6−98:2 was obtained. See the Supporting Information for details. [g] Reaction run under literature conditions;[12] structure of (*R*)-**7** shown in Table 3.

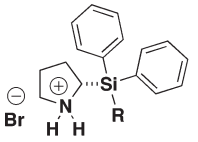
addition product (**5aa**) with 88:12 diastereoselectivity. Optimization experiments revealed that nonpolar solvents such as hexanes are optimal for rate and diastereoselectivity, and catalysts (*S*)-**2a**−**c**·HBr are active with 5 mol % catalyst loading without reducing the reaction rate or stereoselectivity. Comparing the purified free amine catalysts with the triethylamine-treated HBr salts showed no significant change in the rate, selectivity, or yield for the Michael reaction of propionaldehyde with nitrostyrene (Table 2); however, it was noted that the purity of propionaldehyde can effect the diastereoselectivity (entry 5, vide infra). For practical reasons, it was preferred to use triethylamine treatment of (*S*)-**2a-c**·HBr, which is crystalline, for easier handling since the free amine structures are liquids. To increase solubility, THF was also investigated as a 10% cosolvent mixture with hexanes,[19] and comparable yields are observed. On the basis of this preliminary comparison, pyrrolidines (*S*)-**2b**·HBr and (*S*)-**2c**·HBr were identified as the most selective catalysts, with (*S*)-**2c**·HBr imparting the highest enantioselectivity (entries 9−11).

Comparing results for catalyst (*S*)-**2a** in the Michael addition reaction to those previously reported by both Strohmann[20] and Bolm[19] highlights the variations in selectivity observed based on different reaction conditions. While yields are high across all three examples, the reaction times and selectivities for the model reaction of propionaldehyde to nitrostyrene show some variation based on reaction conditions. An 82% ee is reported both here and by Strohmann and co-workers using hexanes solvent systems, whereas Bolm and co-workers reported a higher enantioselectivity of 88% ee using a toluene/THF solvent system. Initially, an 88:12 diastereomeric ratio was observed for (*S*)-**2a**·HBr, but further investigations demonstrated the importance of aldehyde purity on the rate and diastereoselectivity, presumably due to the presence of trace propionic acid when using excess aldehyde. A more optimal 93:7 diastereomeric ratio was obtained using freshly distilled propionaldehyde with 5 mol % of propionic acid added (Table 2, entry 5), which matches the Strohmann and Bolm reports of a 93:7 and 95:5 diastereomeric ratio, respectively. It was noted that the addition of catalytic propionic acid is particularly necessary for faster reaction times of 1−5 h. When comparing product results for the same model reaction using catalyst (*S*)-**2b**,[20] we observe a 97:3 ratio at 0 °C, compared to the 91:9 diastereomeric ratio reported by Strohmann at 4 °C. Thus, diastereoselectivity and reaction time are influenced by the purity or batch of the propionaldehyde, which can account for these variations. For consistently high diastereoselectivity and faster reaction rates, these results indicate that the use of freshly distilled propionaldehyde with 5 mol % of propionic acid is optimal.

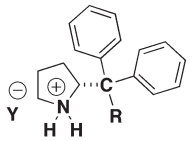
X-ray structure analysis of catalysts (*S*)-**2a**−**c**·HBr provides an opportunity to compare the steric volume of the silyl side chains and analyze the factors that account for the observed selectivity.[41−44] Bond lengths between the pyrrolidine carbon and silicon are approximately 1.91 Å for catalysts (*S*)-**2a-c**·HBr, which is 20% longer than a typical carbon−carbon bond of 1.54 Å (Table 3). Using a simple geometric equation for the volume of an irregular tetrahedron, an estimate for the steric volume of the side chains on pyrrolidine was calculated (Table 3).[45] Using the steric volume alone as a predicting tool for selectivity would suggest that catalysts (*S*)-**2c**·HBr, (*S*)-**6**, and the silyl ether (*R*)-**7** should impart a similar enantio- and diastereoselectivity to the corresponding Michael products. In fact, (*S*)-**2c**·HBr and (*R*)-**7** give very similar results in terms of yield and enantioselectivity (Table 2, entries 11 and 12); however, (*S*)-**6** affords a lower diastereomeric ratio of 78:22.[12,20] These results indicate that steric factors are not solely responsible for catalyst performance. In addition to the steric effects, the silicon may affect secondary weak interactions of the polar intermediates that play a role in stereoselectivity. The electropositive nature of the silicon atom leads to a reversal of charge distribution, and the ability of a silyl group to stabilize a β-silyl carbocation is well-documented.[46−48] An increase in the steric volume correlates with a higher diastereoselectivity, while the presence of a bulky nonplanar substituent, such as a *tert*-butyl or trimethylsilyl ether group, correlates with a higher enantioselectivity. Catalyst (*S*)-**2a** containing a simple methyl group affords products with reduced enantioselectivity as expected due to the smaller steric volume.

The scope of Michael donors and acceptors was then explored with catalyst (*S*)-**2c**·HBr (Tables 4 and 5). The silylated catalyst generally provides high yields and excellent enantio- and diastereocontrol for a variety of donor and acceptor partners. Hydroxy and alkoxy aldehydes have been previously reported for conjugate additions with nitroolefins, generally giving high yields but only moderate to low diastereoselectivity.[49,50] For our system, the free amine catalyst (*S*)-**2c** was necessary for a reasonable reaction rate with the benzyloxyacetaldehdye donor and gives comparable results of both yield and diastereomeric ratio to literature catalysts (Table 4, entry 5).[49] The more challenging branched aldehyde donors proceed with

Table 3. Steric Comparison of Pyrrolidine Catalysts and Correlation to Selectivity Observed in the Michael Reaction of Propionaldehyde to Nitrostyrene[a]



(*S*)-**2a**·HBr, R = Me
(*S*)-**2b**·HBr, R = Ph
(*S*)-**2c**·HBr, R = *t*-Bu

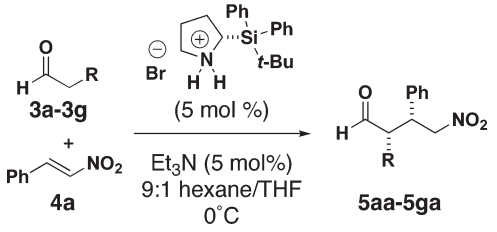


(*S*)-**6**·HCl, Y = Cl, R = Ph
(*R*)-**7**·HBr, Y = Br, R = OTMS

catalyst	X (Si or C)	R =	pyrrolidine C–X bond length (Å)	X–Ph bond length (Å)	X–R bond length (Å)	tetrahedral volume (Å^3)	dr syn/anti	ee (syn)
(*S*)-**2a**·HBr	Si	CH_3	1.91	1.87	1.85	14.87	93:7	78
(*S*)-**2b**·HBr	Si	Ph	1.91	1.87	1.87	28.78	97:3	93
(*S*)-**2c**·HBr	Si	*t*-Bu	1.92	1.88	1.90	19.36	92:8	99
(*S*)-**6**·HCl	C	Ph	1.57	1.55	1.55	21.98	78:22[b]	96[b]
(*R*)-**7**·HBr[c]	C	OTMS	1.54	1.54	1.42	20.27	93:7	99

[a] Product **5aa** selectivity data taken from Table 2 entries 5, 8, 11, and 12. [b] Product **5aa** selectivity data for catalyst (*S*)-**6** reported in the literature.[20] [c] Catalyst (*R*)-**7**·HBr was crystallized as the protonated tetrabromozincate(II) salt monohydrate, with two protonated catalyst units per $ZnBr_4$ unit; see the Supporting Information.

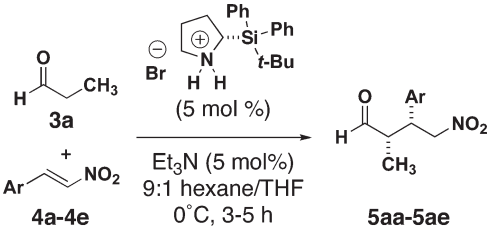
Table 4. Michael Donor Scope with Catalyst (*S*)-2c·HBr



entry	donor R =	5	time (h)	yield (%)	dr[a] (syn/anti)	ee[b] (syn)
1	CH_3	**5aa**	1	87	92:8	99
2	H	**5ba**	96	75	n/a	95
3	*n*-Bu	**5ca**	2	93	93:7	97
4	Bn[c]	**5da**	5	89	94:6	93
5	OBn[d]	**5ea**	8	76	61:39	95
6	$(CH_3)_2$	**5fa**	168	26	n/a	52
7[e]	$(CH_3)_2$	**5fa**	168	30	n/a	56
8	*i*-Pr	**5ga**	168	no reaction		
9[e]	*i*-Pr	**5ga**	96	81	87:13	90[f]

[a] Determined by ^{1}H NMR analysis of unpurified reaction. [b] Determined by HPLC analysis with chiral stationary phase. [c] Chloroform used as solvent. [d] Reaction run using the free amine catalyst (*S*)-**2c** at 10 mol % and without addition of Et_3N. [e] Reaction run at 20 mol % catalyst loading. [f] Determined after reduction to the alcohol using $NaBH_4$.

Table 5. Michael Acceptor Scope with Catalyst (*S*)-2c·HBr



entry	acceptor Ar =	5	yield (%)	dr[a] (syn/anti)	ee[b] (syn)
1	Ph	**5aa**	87	92:8	99
2[c]	4-ClC_6H_4	**5ab**	82	97:3	95
3[c]	2-FC_6H_4	**5ac**	88	98:2	92[d]
4[c]	4-$MeOC_6H_4$	**5ad**	80	98:2	95[e]
5[c]	2-Furyl	**5ae**	96	97:3	92

[a] Determined by ^{1}H NMR analysis of unpurified reaction. [b] Determined by HPLC analysis with chiral stationary phase. [c] Reactions performed with 5 mol % of propionic acid and catalyst (*S*)-**2c**·HBr was 96% ee. [d] Determined after reductive amination to the 2,3-disubstituted pyrrolidine followed by *N*-protection using 4-MeO-benzoyl chloride; see structure **5ac′**. [e] Determined after reduction to the alcohol using $NaBH_4$.

low yield or no reaction (Table 4, entries 6 and 8), and we attribute this dramatically reduced catalytic activity to a slow iminium–enamine formation[51] due to disfavored steric interactions by the increased steric bulk of the silyl chain. While branched substrates are known to exhibit dramatic solvent effects in the Michael reaction (giving yields from 10 to 96% depending only on the solvent used),[52] changing solvent systems showed no effect on the yields with our catalyst. Increasing the catalyst loading to 20 mol % for the branched substrates had minimal effect on the isobutyraldehyde donor, while the longer chain isovaleraldehyde donor became active to afford an 81% yield (Table 4, entries 7 and 9). When investigating the acceptor scope (Table 5), it was noted that consistently high enantioselectivity is observed and the addition reaction typically completes in 3–5 h. These selectivity results are consistent with the literature reports for DFT computational studies for aminocatalysts and also observed experimental results.[53−55]

Using catalyst (*S*)-**2c** with 20 mol % catalyst loading, the Michael reaction with acetaldehyde affords high yields and up to 96% ee for various nitrostyrenes (Table 6). This reaction also

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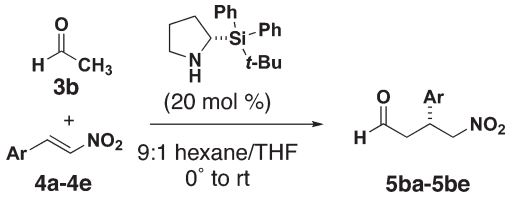
proceeds using 5 mol % catalyst loading, but longer reaction times, up to 4 days, are required (entry 2). The Michael addition of acetaldehyde is known to be a particular challenge due to the formation of significant byproduct.[56,57] List and co-workers have previously reported that prolinol silyl ether catalysts, such as (*R*)-7, are suitable catalysts for acetaldehyde Michael donors; however, using bulkier silyl ethers tends to give lower product conversion with no significant increase in enantioselectivity.[56] Although our earlier experiments suggested no significant advantage to using the silyl pyrrolidine as the free amine catalyst, here with the acetaldehyde reaction we observed that triethylamine conditions promote significant byproduct formation and afford lower product conversion (entry 3). A control experiment where the purified acetaldehyde Michael product **5bc** was combined with triethylamine and excess acetaldehyde showed signs of degradation after 30 min, and within 48 h the Michael product had been completely consumed. Using the free amine silyl pyrrolidine was sufficient to overcome this problem and provide the acetaldehyde products with acceptable yields. Comparing a reaction with freshly distilled acetaldehyde showed no effect on the reaction rate or enantioselectivity; however, a reduced yield was observed with the addition of 20 mol % propionic acid (entry 4 vs 5).

Table 6. Acetaldehyde Scope for Michael Reaction with Catalyst (*S*)-2c·HBr



entry	acceptor Ar =	5	time (h)	yield (%)	ee[a]
1	Ph	**5ba**	3	75	95
2[b]	Ph	**5ba**	96	75	nd
3[c]	Ph	**5ba**	3	56	nd
4	4-ClC_6H_4	**5bb**	3	77	92
5[d]	4-ClC_6H_4	**5bb**	3	43	93
6	2-FC_6H_4	**5bc**	3	76	96
7	4-$MeOC_6H_4$	**5bd**	48	62	92
8	2-Furyl	**5be**	48	63	90

[a] Determined by HPLC analysis on chiral stationary phase after reduction to the alcohol using $NaBH_4$. [b] Reaction run with 5 mol % of catalyst. [c] Reaction run with 20 mol % of catalyst (*S*)-**2c**·HBr in the presence of 20 mol % of Et_3N. [d] Reaction run with 20 mol % of propionic acid added.

The enamine mechanism for aldol and Michael reactions with aminocatalysts has been extensively discussed in the literature.[58,59] To complement the existing mechanistic insight, we monitored the formation of intermediates using ESI-MS where even low concentrations of intermediates containing the catalyst can be directly observed due to the ionization sensitivity of the instrument.[60−62] For this purpose, a 10 μL aliquot from a mixture of catalyst (*S*)-**2c**, nitrostyrene, and propionaldehyde under reaction conditions was diluted into 2 mL of MeOH and injected for MS analysis (positive mode). Immediately after addition of the aldehyde, masses corresponding to enamine formation **8** (*m*/*z* 350.2, calcd; *m*/*z* 350.0 observed), nitro complexation **9** (*m*/*z* 459.2, calcd; *m*/*z* 459.0 observed), and Michael adduct formation **10** (*m*/*z* 499.3, calcd; *m*/*z* 499.4 observed) were observed by ESI-MS (Figure 1).

Of particular note is the observation of *m*/*z* 459 corresponding to the formation of adduct **9**, which indicates a binding interaction between the nitrostyrene and the silylated pyrrolidine catalyst. The formation of this adduct, as observed by ESI-MS, suggests a binding interaction between either the N−H or silicon group from the catalyst and an oxygen on the nitro group. From the literature, both ^1H and ^{29}Si NMR experiments provide evidence for these types of binding interactions between nitroolefins and

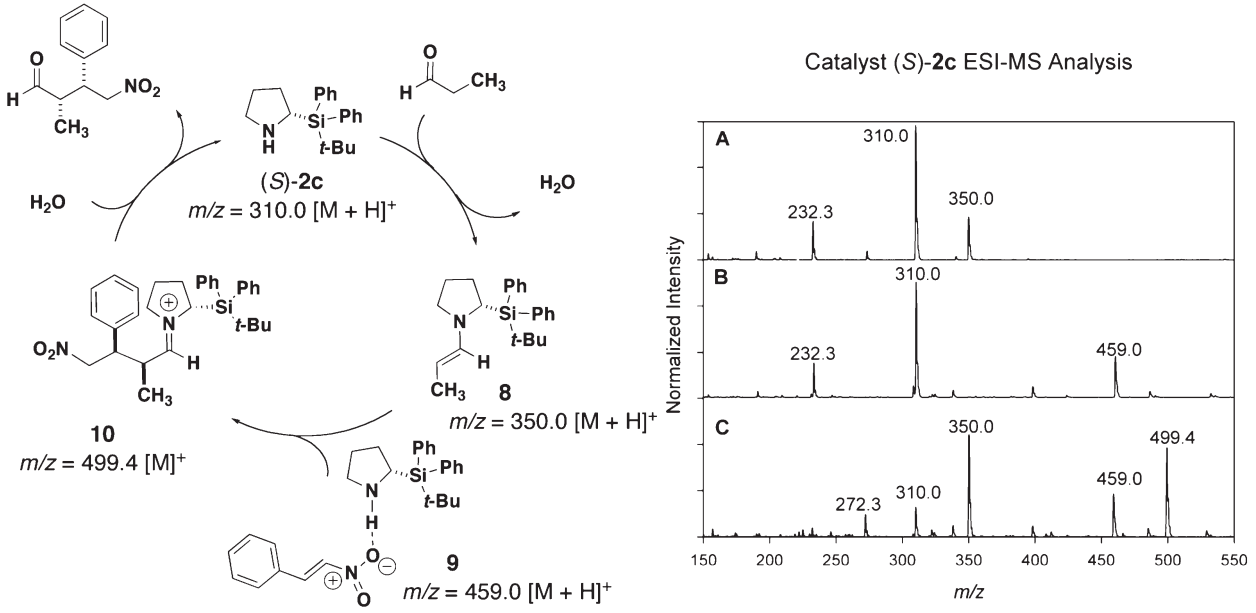


Figure 1. ESI-MS analysis (observed *m*/*z* values) of enamine mechanism and proposed activation of nitro-olefin with catalyst (*S*)-**2c**: (A) enamine observed upon mixing catalyst (*S*)-**2c** with propionaldehyde; (B) observation of hydrogen-bonding complex upon mixing catalyst (*S*)-**2c** with nitrostyrene; (C) reaction mixture with 5 mol % of catalyst (*S*)-**2c.**

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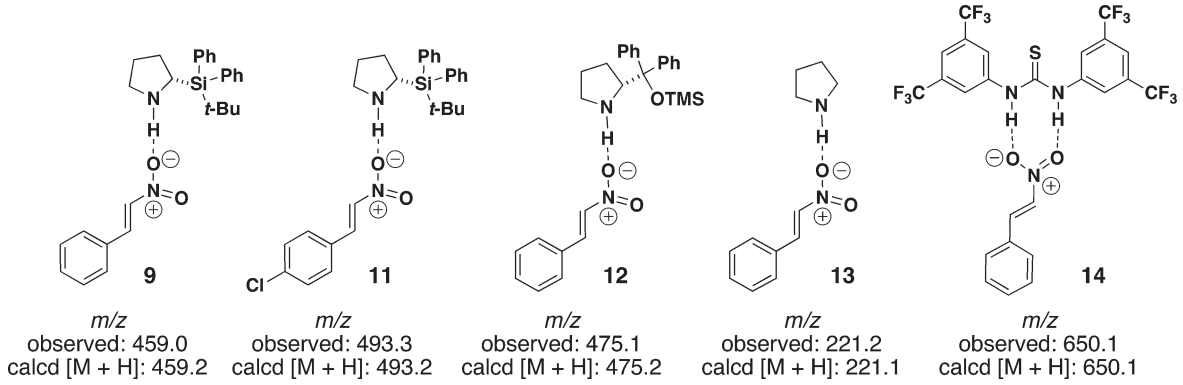

Figure 2. ESI-MS evidence of nitrostyrene binding to pyrrolidines and thioureas.

various binding donors.[15,62] Hydrogen-bonding activation of electrophiles containing nitro groups has been previously proposed for thiourea[62−64] catalysts, and Lewis acid activation[65] of electrophiles is well-known. In order to further understand the observed binding of the catalyst to the nitro acceptor, we performed a series of mass spectrometry experiments with various pyrrolidine species and also a thiourea to compare with previous reports (Figure 2). Donor and acceptor pairs were combined in a 1:1 ratio in methanol, allowed to sit for 10 min, and then further diluted into methanol just prior to injection for ESI-MS analysis (positive mode). Evidence for adduct formation was observed for the thiourea and all NH pyrrolidines, including a binding of catalyst (*S*)-**2c** to 4-chloronitrostyrene (**11**) where the withdrawing nature of the Cl was expected to diminish the interaction. Only the *N*-protected pyrrolidine (*S*)-**1b** did not show any adduct formation by MS. This result suggests that silyl pyrrolidine catalyst (*S*)-**2c** can activate nitro-olefin acceptors through hydrogen-bonding between the catalyst N−H and the nitro group, rather than an interaction between the Lewis basic oxygen of the nitro group with the electropositive silicon.[66] While previous reports from Okino et al.[63] and Li et al.[62] have demonstrated hydrogen bonding between nitro groups and thiourea organocatalysts using ^{1}H NMR titration studies, this is the first evidence for pyrrolidine activation of a nitro acceptor through hydrogen-bonding interactions supported by ESI-MS. Therefore, this suggests evidence for a transition-state model involving two pyrrolidine catalyst molecules: one pyrrolidine activating the carbonyl donor through enamine formation and a second pyrrolidine activating the nitro-olefin acceptor through hydrogen-bonding.

It can also be considered that the conjugate addition of a pyrrolidine catalyst to the nitroacceptor provides an alternate explanation for the adduct observed at *m*/*z* 459. While this conjugate addition may be facilitated under MS conditions, experiments performed using ^{1}H NMR spectroscopy do not detect formation of the conjugate addition product. When ^{1}H NMR spectroscopy is used to monitor a mixture of catalyst (*S*)-**2a** with nitrostyrene in a 1:1 mixture in deuterated chloroform, no new signals are observed. Based on previous reports, diagnostic signals for the formation of a conjugate addition product would appear as two signals near 4.4 and 4.9 ppm, corresponding to two protons α to the nitro group.[67] If the conjugate addition product is formed, then the concentration is too low to be detected using NMR methods. The similar adduct formation observed for both thiourea and pyrrolidine experiments would also indicate a common opportunity for the formation of a hydrogen-bonding adduct rather than the covalent conjugate addition product.

■ CONCLUSIONS

In conclusion, we have demonstrated an efficient synthesis of silylated pyrrolidine catalysts using the enhanced reactivity of silyl fluoride electrophiles to improve yield and enantioselectivity. While the increased reaction rates for silyl fluoride reagents compared to silyl chloride reagents has been previously reported, this is the first case that demonstrates the use of silyl fluoride reagents as a strategy to enhance enantioselectivity for C−Si bond formation in a substitution reaction.[21] Thus, this may provide a general strategy for enantioselective silylation. Here, this method allows the preparation of several sterically demanding silylated pyrrolidines that are difficult to synthesize or not otherwise attainable. We have demonstrated the activity and enantioselectivity of the new (*S*)-*tert*-butyldiphenylsilyl pyrrolidine catalyst (*S*)-**2c** for various asymmetric Michael reactions at 5 mol % catalyst loading and specifically highlighted the utility of this catalyst for the more challenging reactions with acetaldehyde. We provide further insight into the mechanism of pyrrolidine-based catalysts by demonstrating the first example of ESI-MS evidence for activation of a nitro acceptor by formation of a hydrogen-bonding adduct with the catalyst amine. Incorporating silicon as a functional group into existing and future catalyst structures may be useful to enhance catalytic properties for improved enantio- and diastereoselectivity, and lower the necessary catalyst loading. Exploration of new enantioselective catalyst structures based on the properties of silicon are currently underway in our laboratory.

■ EXPERIMENTAL SECTION

General Information. Commercially available reagents were obtained from commercial sources and used without further purification unless otherwise indicated, particularly to be noted for propionaldehyde, which was freshly distilled for some reactions. The following abbreviations are used throughout: ethyl acetate (EtOAc), acetonitrile (MeCN), dichloromethane (DCM), isopropanol (IPA), methanol (MeOH), enantiomeric excess (ee), triethylamine (Et_3N). All Michael addition reactions were performed in glass vials with Teflon caps and exposure to atmospheric conditions. All ^{1}H and ^{13}C spectra were recorded at ambient temperature at 300, 400, and 600 MHz or 75, 100, and 150 MHz, respectively. ^{29}Si NMR spectra were recorded at ambient temperature at 119 MHz. The ^{1}H spectral data are reported as follows: chemical shift in parts per million downfield from tetramethylsilane on

the δ scale, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; s, septet; m, multiplet; dd, doublet of doublets, and b, broadened), coupling constant (Hz), and integration. Carbon NMR chemical shifts are reported in ppm from tetramethylsilane with the solvent reference employed as the internal standard (deuterochloroform ($CDCl_3$)) at 77.16 ppm.

Unless otherwise indicated, all chiral stationary phase HPLC analyses were performed with a Daicel CHIRALCEL OD-H column (4.6 × 250 mm, 5 μm), CHIRALPAK AD-H column (4.6 × 250 mm, 5 μm), or CHIRALPAK AS-H column (4.6 × 250 mm, 5 μm), with corresponding guard columns, with a flow rate of 1.0 mL/min (2-propanol/hexanes isocratic system) using a photodiode array detector and 40 °C column oven temperature. Compounds were analyzed by HRMS on an orbitrap spectrometer using electrospray ionization in the positive ion mode at >60000 resolution and using typical ESI source values. These settings result in mass accuracies <5 ppm. Some compounds were analyzed by LRMS in the positive ion mode on a Qtrap spectrometer. Source parameters were 5 kV spray voltage, with a curtain plate temperature of 275 °C and sheath gas setting of 15. Samples were analyzed via flow injection analysis by injecting 20 μL samples into a stream of 80% MeOH/20% aqueous solution with 0.1% formic acid, flowing at 300 μL/min. Optical rotations were obtained on a polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0 dm cell. Specific rotations are reported in degrees per decimeter at 23 °C, and the concentrations are given in grams per 100 mL of solvent. Solvents used for optical rotations were MeOH (reagent grade) and $CHCl_3$ (stabilized with 0.5−1% EtOH, and filtered through basic alumina).

When indicated, the progress of reactions was monitored by analytical thin-layer chromatography using glass plates precoated with silica gel 60 F254 and visualized with UV light. Flash chromatography was performed either on silica gel 60 Å (0.035−0.070 mm) or silica gel 150 Å grade 62 (60−200 mesh).

General Procedure for the Conversion of Silyl Chloride Reagents to Silyl Fluoride Reagents. A solution of *tert*-butyldiphenylchlorosilane (5.0 g, 18.19 mmol, 1.0 equiv) in anhydrous dimethoxyethane (120 mL) was placed in an oven-dried, Ar-purged 250 mL round-bottom flask with a stir bar. Hexafluoroammonium silicate (6.481 g, 36.38 mmol, 2.0 equiv) was added to the flask, and a reflux condenser with positive Ar pressure was connected to the flask. The reaction was refluxed for 5 days, allowed to cool to room temperature, and poured over saturated aqueous ammonium chloride, the layers were separated, and the aqueous layer was extracted 3 × 15 mL with DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give a brown oil. The crude product was purified through vacuum distillation (bp 87 °C at 4.5×10^{-4} Torr) to give 3.83 g (81%) of *tert*-butyldiphenylfluorosilane as a light yellow oil.

General Procedure for the Synthesis of *N*-Boc-Protected Catalysts (*S*)-1a−c. A solution of *N*-Boc-pyrrolidine (0.30 g, 1.75 mmol, 1.0 equiv) in anhydrous diethyl ether (8.8 mL) was placed in an oven-dried, argon-purged 25 mL round-bottom flask with a stir bar, septum, and positive argon pressure. (−)-Sparteine (0.52 mL, 2.28 mmol, 1.3 equiv) was added through the septum, and the reaction was cooled to −78 °C in a dry ice/acetone bath. Freshly titrated *sec*-butyl lithium (2.28 mmol, 1.3 equiv) was added dropwise, and the reaction was allowed to stir at −78 °C. After 5.5 h, the fluorosilane (2.63 mmol, 1.5 equiv) was added dropwise, and the mixture was allowed to stir at −78 °C for 15 min and then allowed to warm to room temperature for 15 min. The reaction was quenched by the addition of deionized water (20 mL), the aqueous and organic layers were separated, and the aqueous layer was extracted with 3 × 15 mL of EtOAc. The combined organic layers were washed with 100 mL of 5% aqueous phosphoric acid and then with brine, dried over Na_2SO_4, filtered, and then concentrated to give a light yellow oil. The crude product was purified on a flash silica gel column (100% hexanes to 90:10 hexanes/EtOAc) to give (*S*)-**1a**−**c** as a clear oil.

*Data for (S)-**1a**.* Product is a clear oil, 0.586 g, 91% yield: ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotomers, major peaks provided) δ 7.64−7.48 (m, 4H), 7.39−7.27 (m, 6H), 4.02−3.80 (m, 1H), 3.61−3.29 (m, 1H), 3.18−2.95 (m, 1H), 2.17−1.90 (m, 1H), 1.89−1.76 (m, 1H), 1.71−1.59 (m, 1H), 1.51−1.41 (m, 1H), 1.27 (s, 9H), 0.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 154.4, 136.7, 135.5, 134.9, 134.7, 129.2, 127.6, 79.2, 78.4, 46.6, 28.6, 28.3, 25.7, 24.5, −3.5, −4.3; LRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{30}NO_2Si$ 368.2, found 368.4.

*Data for (S)-**1b**.* The triphenylfluorosilane was predissolved in a minimum of Et_2O (∼1.5 mL) prior to addition to the organolithium reaction mixture. Product is a white solid, 0.700 g, 93% yield: ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotomers, major peaks provided) δ 7.65−7.51 (m, 6H), 7.42−7.29 (m, 9H), 4.39−4.16 (m, 1H), 3.62−3.32 (m, 1H), 3.29−3.03 (m, 1H), 2.13−1.86 (m, 2H), 1.76−1.58 (m, 1H), 1.30−1.21 (m, 1H) 1.05 (s, 9H, and minor rotomer peak at 1.17); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 136.3, 134.5, 133.7, 129.4, 127.7, 79.4, 78.6, 46.7, 46.1, 29.4, 28.2, 26.0, 24.5; LRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{32}NO_2Si$ 430.2, found 430.5.

*Data for (S)-**1c**.* Product is a clear oil, 0.646 g, 90% yield. $[\alpha]^{22}_D$ = 42.3 (*c* 0.299, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80−7.54 (m, 4H), 7.43−7.28 (m, 6H), 4.51−4.43 (m, 1H), 3.61−3.29 (m, 1H), 2.77−2.61 (m, 1H), 2.12−1.71 (m, 2H), 1.47 (s, 9H), 1.13 (s, 9H), 1.10−1.05 (m, 1H), 0.95−0.83 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.5, 136.8, 134.9, 134.50, 134.48, 130.3, 129.3, 129.2, 128.0, 127.7, 127.5, 79.0, 47.0, 44.8, 28.7, 28.0, 26.7, 26.1, 24.5, 18.8; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{36}NO_2Si$ 410.2510, found 410.2509.

General Procedure for the Synthesis of Catalysts (*S*)-2a−c·HBr. A solution of (*S*)-**1** (1.46 mmol, 1.0 equiv) in 15 mL of anhydrous DCM was placed in a 100 mL round-bottom flask with a stir bar and septum. Zinc bromide (1.65 g, 7.31 mmol, 5 equiv) was added to the flask, and the reaction was allowed to stir for 15 h. Deionized water (20 mL) was added to the reaction and stirring continued for 1 h. The aqueous and organic layers were separated, and the aqueous layer was extracted with 3 × 15 mL of DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give a tan solid. The catalyst was purified and enantioenriched upon trituration. The crude product was dissolved in a minimal amount of DCM (∼5−15 mL) ignoring small amounts of solid that do not completely dissolve. Hexanes was added (20 to 50 mL), and the mixture was swirled to mix the solvents, where the purified catalyst (*S*)-**2**·HBr precipitated out as a white solid that was isolated by suction filtration, rinsing with hexanes. The product obtained was determined to be 99% ee on the basis of chiral stationary phase HPLC analysis after *N*-protection. In one out of seven cases for (*S*)-**2c**·HBr, trituration afforded the catalyst with 96% ee instead of the expected 99% ee.

*Data for (S)-**2a**·HBr.* Product is a white solid, 0.396 g 84% yield: mp 163−165 °C dec; $[\alpha]^{22}_D$ = +1.9 (*c* 0.316, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (bs, 2H), 7.76 − 7.63 (m, 2H), 7.63 − 7.50 (m, 2H), 7.49 − 7.30 (m, 6H), 3.29 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.09 − 2.81 (m, 2H), 2.17 − 2.00 (m, 1H), 1.93 − 1.65 (m, 3H), 0.90 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.3, 135.1, 132.4, 132.1, 130.4, 128.5, 128.4, 47.3, 46.8, 28.3, 25.0, −5.5; ^{29}Si NMR (119 MHz, $CDCl_3$) δ −8.61; HRMS (ESI) *m*/*z* $[M - Br]^+$ calcd for $C_{17}H_{22}NSi$ 268.1516, found 268.1507. Slow recrystallization from DCM and hexanes afforded single crystals, and the absolute configuration was determined to be *S* by X-ray analysis. The catalyst was derivatized to the *N*-benzoyl structure for chiral stationary phase HPLC analysis: 99.5% ee, see (*S*)-**15a** below.

*Data for (S)-**2b**·HBr.* Product is a white solid, 0.496 g, 74% yield: mp = 277−279 °C dec; $[\alpha]^{22}_D$ = +16.7 (*c* 0.318, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (bs, 2H), 7.73 − 7.63 (m, 5H), 7.50 − 7.37 (m, 10H), 3.73 (dd, *J* = 9.0, 9.0 Hz, 1H), 3.02 (ddd, *J* = 15.4, 5.7, 5.7 Hz, 1H), 2.88 − 2.66 (m, 1H), 2.44 − 2.21 (m, 1H), 1.95 − 1.67 (m, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 137.1, 132.0, 131.7, 129.7, 48.7, 48.3, 29.5, 26.2; HRMS (ESI) *m*/*z* $[M - Br]^+$ calcd for $C_{22}H_{24}NSi$ 330.1672,

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found 330.1676. Slow recrystallization from DCM and hexanes afforded single crystals, and the absolute configuration was determined to be (*S*) by X-ray analysis. The catalyst was derivatized to the *N*-benzoyl structure for chiral stationary-phase HPLC analysis: 99.6% ee, see (*S*)-**15b** below.

*Data for (S)-**2c**·HBr.* Product is a white solid, 0.432 g, 76% yield: mp = 187−189 °C dec; $[\alpha]^{23}_{D}$ = +28.5 (*c* 0.302, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.56 (bs, 2H), 7.78 (dd, *J* = 6.4, 2.9 Hz, 2H), 7.69 (dd, *J* = 7.4, 1.6 Hz, 2H), 7.51 − 7.38 (m, 6H), 3.61 (dd, *J* = 9.1, 9.1 Hz, 1H), 3.24 (ddd, *J* = 11.1, 7.1, 4.1 Hz, 1H), 2.81 − 2.59 (m, 1H), 2.34 − 2.15 (m, 1H), 1.90 − 1.58 (m, 3H), 1.17 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.2, 136.7, 130.6, 130.42, 130.38, 129.2, 128.6, 128.4, 48.0, 44.5, 29.2, 28.3, 25.0, 18.3; ^{29}Si NMR (119 MHz, $CDCl_3$) δ −3.44; HRMS (ESI) *m*/*z* $[M - Br]^+$ calcd for $C_{20}H_{28}NSi$ 310.1985, found 310.1991. Slow recrystallization from DCM and hexanes afforded single crystals, and the absolute configuration was determined to be *S* by X-ray analysis. The catalyst was derivatized to the *N*-tosylated structure for chiral stationary-phase HPLC analysis: 99.7% ee, see (*S*)-**15c** below.

General Procedure for the Generation of Free Amine Catalysts (*S*)-2a−c. To a solution of catalyst (*S*)-**2**·HBr (0.861 mmol) in DCM (10 mL) in a 25 mL round-bottom flask was added Amberlyst-A21 basic resin (2.5 g). The mixture was allowed to stir for 1 h and then filtered to remove the Amberlyst. The resulting solution was concentrated in vacuo, redissolved in a minimum of DCM (∼1 mL), and then filtered through a silica gel plug using 90:10 DCM/MeOH to remove any remaining Amberlyst residue. The solution was then concentrated in vacuo to give (*S*)-**2a−c** as a lightly colored oil that was used without further purification.

*Data for (S)-**2a**.* Prepared from 0.300 g of (*S*)-**2a**·HBr according to the general procedure to afford 0.228 g of (*S*)-**2a** as a lightly colored oil in 99% yield: $[\alpha]^{23}_{D}$ = +0.7 (*c* 0.924, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70−7.51 (m, 4H), 7.48−7.23 (m, 6H), 2.97 (dddd, *J* = 11.6, 11.6, 5.8, 5.8 Hz, 1H), 2.85−2.67 (m, 2H), 2.60 (bs, 1H), 1.93 (ddd, *J* = 11.4, 7.4, 4.6 Hz, 1H), 1.69 (ddd, *J* = 13.2, 8.5, 5.0 Hz, 1H), 1.63−1.45 (m, 2H), 0.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 135.2, 135.0, 134.9, 129.43, 129.42, 127.90, 127.87, 48.7, 47.2, 28.6, 26.4, −6.1; ^{29}Si NMR (119 MHz, $CDCl_3$) δ −8.3; LRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{22}NSi$ 268.2, found 268.5.

*Data for (S)-**2b**.* Prepared from 0.353 g of (*S*)-**2b**·HBr according to the general procedure to afford 0.278 g of (*S*)-**2b** as a white solid in 98% yield: mp = 105−107 °C; $[\alpha]^{22}_{D}$ = +7.7 (*c* 0.662, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63−7.57 (m, 5H), 7.45−7.30 (m, 10H), 3.13 (dd, *J* = 10.1, 7.7 Hz, 1H), 2.97 (ddd, *J* = 11.7, 7.3, 4.7 Hz, 1H), 2.77 (ddd, *J* = 10.7, 7.4, 7.4 Hz, 1H), 2.07 (ddd, *J* = 15.4, 9.6, 5.8 Hz, 1H), 1.81−1.60 (m, 2H), 1.60−1.46 (m, 1H), N−H peak not observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 133.8, 129.8, 128.1, 49.2, 46.6, 29.2, 26.8; ^{29}Si NMR (119 MHz, $CDCl_3$) δ −11.9. LRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{24}NSi$ 329.2, found 329.4.

*Data for (S)-**2c**.* Prepared from 0.336 g of (*S*)-**2c**·HBr according to the general procedure to afford 0.264 g of (*S*)-**2c** as a lightly colored semisolid in 99% isolated yield: $[\alpha]^{23}_{D}$ = +35.8 (*c* 0.884, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75−7.60 (m, 4H), 7.45−7.27 (m, 6H), 3.03 (dd, *J* = 10.6, 7.6 Hz, 1H), 2.88 (ddd, *J* = 12.2, 7.2, 5.1 Hz, 1H), 2.73 (ddd, *J* = 10.4, 7.5 Hz, 1H), 2.02 (dddd, *J* = 16.0, 12.1, 7.8, 4.6 Hz, 1H), 1.69 (dddd, *J* = 20.1, 15.5, 7.5, 4.5 Hz, 1H), 1.56 (dddd, *J* = 10.6, 10.6, 9.2, 9.2 Hz, 1H), 1.43 (dddd, *J* = 19.5, 16.7, 7.4, 4.1, 1H), 1.12 (s, 9H), N−H peak not observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.6, 136.5, 133.6, 133.2, 129.40, 129.35, 127.8, 127.7, 48.8, 45.1, 29.4, 28.5, 26.6, 18.5; ^{29}Si NMR (119 MHz, $CDCl_3$) δ −3.5. HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{28}NSi$ 310.1985, found 310.1981.

General Procedure A for the Asymmetric Michael Addition of Aldehydes to Nitroolefins. Triethylamine (0.0187 mmol, 0.05 equiv) was added to a stirred solution of catalyst (*S*)-**2c**·HBr (0.0073 g, 0.0187 mmol, 0.05 equiv) and nitroolefin (0.374 mmol, 1.0 equiv) in 9:1 hexane/THF (0.4 mL) at 0 °Cand allowed to stir for 5 min. Aldehyde (3.74 mmol, 10 equiv) was then added, and the reaction was allowed to stir until complete as judged by TLC (100% $CHCl_3$) and then quenched by the addition of 1.0 N HCl (5 mL). The organic layer was separated, and the aqueous layer extracted with 3 × 10 mL of EtOAc. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated to give a colored oil. The crude product was purified on a flash silica-gel column (hexanes/DCM). The purity of propionaldehyde was shown to affect the reaction rate and diastereoselectivity, although the enantioselectivity was not affected. See the Supporting Information for a full table comparing selectivity for reactions performed with undistilled vs distilled propionaldehyde and the effect of adding 5−100 mol % propionic acid.

*(2S,3R)-2-Methyl-4-nitro-3-phenylbutanal (**5aa**).* Prepared from 0.0558 g of *trans*-β-nitrostyrene and propanal according to general procedure A to afford 0.0674 g of **5aa** in 87% yield after 1 h. HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 40 °C, t_R (syn, major) = 15.9 min; t_R (syn, minor) = 21.7 min; t_R (anti, major) = 18.9 min; t_R (anti, minor) = 25.4 min. 99.4% ee. dr = 92:8 based on ^{1}H NMR analysis of unpurified reaction. Spectral data are consistent with literature values.[68]

*(2S,3R)-2-Butyl-4-nitro-3-phenylbutanal (**5ca**).* Prepared from 0.0558 g of *trans*-β-nitrostyrene and hexanal according to general procedure A to afford 0.0867 g of **5ca** in 93% yield after 2 h. HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 40 °C, t_R (syn, major) = 14.6 min; t_R (syn, minor) = 18.8 min; t_R (anti, major) = 15.8 min; t_R (anti, minor) = 25.6 min. 96.8% ee. dr = 93:7 based on ^{1}H NMR analysis of unpurified reaction. Spectral data are consistent with literature values.[69]

*(2S,3R)-4-Nitro-2-(1-phenylmethyl)-3-phenylbutanal (**5da**).* Prepared from 0.0670 g of *trans*-β-nitrostyrene and 0.0502 g hydrocinnamaldehyde, modifying general procedure A by using one equiv of aldehyde and 1.2 equiv of nitrostyrene with $CHCl_3$ as solvent to afford 0.0943 g of **5da** in 89% yield after 5 h. HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 40 °C, t_R (syn, major) = 41.5 min; t_R (syn, minor) = 45.8 min; t_R (anti, major) = 59.1 min; t_R (anti, minor) = 68.2 min. 92.6% ee. dr =94:6 based on ^{1}H NMR analysis of unpurified reaction. Spectral data are consistent with literature values.[70]

*(2S,3R)-2-(Benzyloxy)-4-nitro-3-phenylbutanal (**5ea**).* Prepared from 0.0558 g of *trans*-β-nitrostyrene and 0.0842 g benzyloxyacetaldehyde, modifying general procedure A by omitting Et_3N, using 0.0116 g of the free amine catalyst (*S*)-**2c** (10 mol %), and using 1.5 equiv of aldehyde to afford 0.0851 g of **5ea** in 76% yield after 8 h. HPLC-analysis: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 97:3, 0.5 mL/min, 40 °C, t_R (syn, major) = 60.6 min; t_R (syn, minor) = 65.1 min; t_R (anti, major) = 87.6 min; t_R (anti, minor) = 73.0 min. 95.2% ee. dr =61:39 based on ^{1}H NMR analysis of unpurified reaction. Spectral data are consistent with literature values.[49]

*(3R)-2,2-Dimethyl-4-nitro-3-phenylbutanal (**5fa**).* Prepared from 0.0558 g of *trans*-β-nitrostyrene and isobutyraldehyde, modifying general procedure A by using 20 mol % catalyst loading, to afford 0.0248 g of **5fa** in 30% yield after 7 days. HPLC analysis: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 40 °C, t_R (major) = 6.6 min; t_R (minor) = 7.2 min. 55.6% ee. Spectral data are consistent with literature values.[52]

*(2S,3R)-2-(1-Methylethyl)-4-nitro-3-phenylbutanal (**5ga**).* Prepared from 0.0558 g of *trans*-β-nitrostyrene and isovaleraldehyde, modifying general procedure A by using 20 mol % of catalyst (0.0292 g) and 0.0076 g of Et_3N (20 mol %) to afford 0.0525 g of **5ga** in 81% yield after 4 days. HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 40 °C, t_R (syn, major) = 12.8 min; t_R (syn, minor) = 13.8 min. 91.9% ee. Due to a slight overlap in the separation, the reported enantiomeric excess of 90% ee was calculated based on an average of two different HPLC methods as described in the Supporting Information. dr = 83:17 based on ^{1}H NMR analysis of the unpurified reaction. Spectral data are consistent with literature values.[68]

*(2S,3R)-3-(4-Chlorophenyl)-2-methyl-4-nitrobutanal (**5ab**).* Prepared from 0.0687 g of *trans*-4-chloro-β-nitrostyrene and propanal according to general procedure A to afford 0.0795 g of **5ab** in 88% yield after 30 min. HPLC analysis: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 95:5, 0.5 mL/min, 30 °C, t_R (syn, major) = 33.5 min; t_R (syn, minor) = 25.3 min; t_R (anti, major) = 29.2 min; t_R (anti, minor) = 31.1 min. 97.9% ee. dr = 88:12 based on ^{1}H NMR analysis of unpurified reaction. Spectral data are consistent with literature values.[71]

*(2S,3R)-3-(2-Fluorophenyl)-2-methyl-4-nitrobutanal (**5ac**).* Prepared from 0.0625 g of *trans*-2-fluoro-β-nitrostyrene and propanal according to general procedure A to afford 0.0791 g of **5ac** in 94% yield after 30 min. Enantiomeric excess was determined after cyclization and *N*-protection to structure **5ac′** using the procedure below. 97.1% ee. dr = 90:10 based on ^{1}H NMR analysis of unpurified reaction. Spectral data are consistent with literature values.[19]

*(3R,4S)-3-(2-Fluorophenyl)-1-(4-methoxybenzoyl)-4-methylpyrrolidine (**5ac′**).* In a 50 mL flask was dissolved 0.070 g of nitroaldehyde **5ac** in MeOH (10 mL), and 20 wt % $Pd(OH)_2$ on carbon (0.044 g, 0.062 mmol, 0.2 equiv) was added. The reaction flask was purged with hydrogen, a hydrogen balloon was put in place, and the reaction was allowed to stir, refilling the hydrogen balloon as needed, for 48 h. The reaction was filtered over Celite to remove $Pd(OH)_2$ then concentrated in vacuo to give a lightly colored oil. The crude pyrrolidine was redissolved in DCM (10 mL), then Et_3N (0.11 mL, 0.777 mmol, 2.5 equiv) was added, and finally 4-methoxybenzoyl chloride (0.063 mL, 0.466 mmol, 1.5 equiv) was added and the mixture allowed to stir for 30 min. The crude product was purified on a flash silica gel column (80:20 hexanes/EtOAc to 50:50 hexanes/EtOAc) to give 0.0818 g (84%) of **5ac′** as a clear oil. HPLC-analysis: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 90:10, 0.7 mL/min, 33 °C, t_R (syn, major) = 22.4 min; t_R (syn, minor) = 26.9 min; t_R (anti, major) = 24.3 min; t_R (anti, minor) = 37.7 min. 97.1% ee. dr = 90:10 based on ^{1}H NMR of unpurified reaction for structure **5ac**: ^{1}H NMR (600 MHz, $CDCl_3$, reported as a 1:1 mixture of rotomers) δ 7.57−7.52 (m, 2H, 1:1 mixture of rotomers), 7.29−7.22 (m, 2H), 7.12 (q, J = 7.8 Hz, 1H), 7.07−7.00 (m, 1H, 1:1 mixture of rotomers), 6.93−6.87 (m, 2H), 4.08−4.01 (m, 1H), 3.86−3.74 (m, 4H, 1:1 mixture of rotomers), 3.60 (t, J = 10.2 Hz, 1H), 3.39−3.14, (m, 2H, 1:1 mixture of rotomers), 2.60−2.32 (m, 1H, 1:1 mixture of rotomers), 1.06−1.95 (m, 3H, 1:1 mixture of rotomers); ^{13}C NMR (150 MHz, $CDCl_3$, reported as a 1:1 mixture of rotomers) δ 169.4, 161.1, 161.6 (J^1_{CF} = 255 Hz), 132.1, 129.4, 128.8 (J^2_{CF} = 15.0 Hz), 128.7 (J^3_{CF} = 8.6 Hz), 128.5 (J^3_{CF} = 8.0 Hz) 128.3 (J^4_{CF} = 4.4 Hz), 128.1 (J^4_{CF} = 4.2 Hz), 128.0, (J^2_{CF} = 23.7 Hz), 127.8 (J^2_{CF} = 24.0 Hz), 126.7 (J^3_{CF} = 14.0 Hz), 125.9 (J^3_{CF} = 14.0 Hz), 124.5 (J^4_{CF} = 3.3 Hz), 115.8 (J^3_{CF} = 10.4 Hz), 115.7 (J^3_{CF} = 10.4 Hz), 113.6, 56.0, 55.7, 55.4, 52.3, 45.7, 43.5, 40.4, 37.7, 15.8, 15.4; LRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{21}FNO_2$ 314.2, found 314.2.

*(2S,3R)-3-(4-Methoxyphenyl)-2-methyl-4-nitrobutanal (**5ad**).* Prepared from 0.0670 g of *trans*-4-methoxy-β-nitrostyrene and propanal according to general procedure A to afford 0.0772 g of **5ad** in 87% yield after 30 min. Due to the difficulty in separating the stereoisomers of this substrate, the reported enantiomeric excess is an average of two different methods of calculation as described in the Supporting Information. Average ee = 96.1%. dr =90:10 based on ^{1}H NMR analysis of unpurified reaction. Spectral data are consistent with literature values.[72]

*(2S,3S)-3-(Furan-2-yl)-2-methyl-4-nitrobutanal (**5ae**).* Prepared from 0.0520 g of (*E*)-2-(2-nitroethenyl)furan and propanal according to general procedure A to afford 0.0568 g of **5ae** in 77% yield after 30 min. HPLC analysis: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 98:2, 0.8 mL/min, 30 °C, t_R (syn, major) = 18.7 min; t_R (syn, minor) = 20.8 min; t_R (anti, major) = 22.1 min; t_R (anti, minor) = 24.9 min. 96.5% ee. dr = 87:13 based on ^{1}H NMR of unpurified reaction. Spectral data are consistent with literature values.[12]

General Procedure B for the Asymmetric Michael Addition of Acetaldehyde to Nitroolefins. Acetaldehyde (0.16 mL 3.74 mmol, 10 equiv) was added to a stirred solution of catalyst (*S*)-**2c** (0.0232 g, 0.0748 mmol, 0.2 equiv) and nitroolefin (0.374 mmol, 1.0 equiv) in 9:1 hexane/THF (0.4 mL) at 0 °C and then allowed to warm to room temperature. The reaction was allowed to stir for 3−48 h until complete as judged by TLC (100% $CHCl_3$) and then quenched by the addition of 1.0 N HCl (5 mL). The organic layer was separated and the aqueous layer extracted with 3 × 10 mL of EtOAc. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated to give a colored oil. The crude product was purified on a flash silica gel column (hexanes/DCM).

*(3R)-4-Nitro-3-phenylbutanal (**5ba**).* Prepared from 0.0558 g of *trans*-β-nitrostyrene and acetaldehyde according to general procedure B to afford 0.0542 g of **5ba** in 75% yield after 3 h. Product **5ba** was reduced to the corresponding alcohol using $NaBH_4$ for HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 40 °C, t_R (major) = 28.9 min; t_R (minor) = 35.6 min. 94.8% ee. Spectral data are consistent with literature values.[13]

*(3R)-3-(4-Chlorophenyl)-4-nitrobutanal (**5bb**).* Prepared from 0.0687 g of *trans*-4-chloro-β-nitrostyrene and acetaldehyde according to general procedure B to afford 0.0656 g of **5bb** in 77% yield after 3 h. Product **5bb** was reduced to the corresponding alcohol using $NaBH_4$ for HPLC analysis: Chiralcel OD-H column, gradient: *n*-hexane/*i*-PrOH = 98:2, 0.7 mL/min, 30 °C for 60 min, then *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 30 °C for 30 min, t_R (major) = 61.6 min; t_R (minor) = 63.2 min. 92.1% ee. Spectral data are consistent with literature values.[13]

*(3R)-3-(2-Fluorophenyl)-4-nitrobutanal (**5bc**).* Prepared from 0.0625 g of *trans*-2-fluoro-β-nitrostyrene and acetaldehyde according to general procedure B to afford 0.0600 g of **5bc** in 76% yield after 3 h. Product **5bc** was reduced to the corresponding alcohol using $NaBH_4$ for HPLC-analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 96:4, 0.8 mL/min, 40 °C, t_R (major) = 35.4 min; t_R (minor) = 39.0 min. 96.4% ee: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.35−7.20 (m, 2H), 7.17−7.02 (m, 2H), 4.72 (dd, J = 7.3, 1.1 Hz, 2H), 4.27 (p, J = 7.2 Hz, 1H), 3.03 (d, J = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 160.9 (d, J^1_{CF} = 246.2 Hz), 130.04 (d, J^4_{CF} = 1.7 Hz), 129.95 (d, J^3_{CF} = 2.2 Hz), 125.1 (d, J^2_{CF} = 13.2 Hz), 124.9 (d, J^3_{CF} = 3.5 Hz), 116.3 (d, J^2_{CF} = 21.8 Hz), 77.8 (d, J^4_{CF} = 2.7 Hz), 45.2 (d, J^3_{CF} = 2.0 Hz), 33.5 (s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −117.1 (m).

*(3R)-3-(4-Methoxyphenyl)-4-nitrobutanal (**5bd**).* Prepared from 0.0670 g of *trans*-4-methoxy-β-nitrostyrene and acetaldehyde according to general procedure B to afford 0.0518 g of **5bd** in 62% yield after 48 h. Product **5bd** was reduced to the corresponding alcohol using $NaBH_4$ for HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 40 °C, t_R (major) = 39.2 min; t_R (minor) = 43.1 min. 91.9% ee. Spectral data are consistent with literature values.[13]

*(3S)-3-(2-Furyl)-4-nitrobutanal (**5be**).* Prepared from 0.520 g of (*E*)-2-(2-nitroethenyl)furan and acetaldehyde according to general procedure B to afford 0.0432 g of **5be** in 63% yield after 48 h. Product **5be** was reduced to the corresponding alcohol using $NaBH_4$ for HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 96:4, 0.8 mL/min, 40 °C, t_R (major) = 31.8 min; t_R (minor) = 34.0 min. 90.0% ee. Spectral data are consistent with literature values.[13]

General Procedure C for the *N*-Protection of 2-Silylpyrrolidine Catalysts to (*S*)-15a−c for HPLC Analysis. To a mixture of (*S*)-**2**·HBr (0.049 mmol, 1.05 equiv) in DCM (2.5 mL) were added triethylamine (0.016 mL, 0.116 mmol, 2.5 equiv) and then the acid chloride of the corresponding protecting group (0.046 mmol, 1.0 equiv). The reaction was allowed to stir at room temperature for 1 h and then was directly purified using preparatory TLC to prepare an HPLC standard.

*Data for (S)-**15a**.* Prepared according to general procedure C using (*S*)-**2a**·HBr with benzoyl chloride for HPLC analysis. Purified by preparative TLC (80:20 hexanes/EtOAc). HPLC analysis: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 40 °C, t_R (major) = 14.6 min; t_R (minor) = 10.8 min. 99.5% ee. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.76−7.69 (m, 2H), 7.66−7.59 (m, 2H), 7.46−7.16 (m, 11H), 4.30 (dd, J = 8.7, 8.7 Hz, 1H), 3.34 (ddd, J = 10.5, 6.8, 3.9 Hz, 1H), 3.02 (ddd, J = 9.6, 6.9, 6.9 Hz, 1H), 2.21−2.04 (m, 1H), 2.00−1.80 (m, 1H), 1.78−1.55 (m, 2H), 0.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 137.3, 136.5, 135.3, 135.0, 129.8, 129.5, 129.3, 128.2, 127.9, 127.2, 50.8, 47.1, 28.6, 26.9, −2.9; LRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{26}NOSi$ 372.2, found 372.2.

*Data for (S)-**15b***. Prepared according to general procedure C using (*S*)-**2b**·HBr with 4-methoxybenzoyl chloride for HPLC analysis. Purified by preparative TLC (90:10 DCM/EtOAc). HPLC analysis: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 40 °C, t_R (major) = 41.2 min; t_R (minor) = 23.4 min. 99.6% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.65 (m, 5H), 7.49−7.26 (m, 10H), 7.05 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 4.68 (dd, J = 8.7, 8.7 Hz, 1H), 3.76 (s, 3H), 3.50−3.35 (m, 1H), 3.09 (ddd, J = 18.2, 8.4, 8.4 Hz, 1H), 2.20 (dddd, J = 8.6, 5.9, 5.7, 5.7 Hz, 1H), 2.06−1.89 (m, 1H), 1.77−1.61 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 160.7, 136.4, 134.5, 129.4, 129.3, 129.2, 127.8, 113.2, 55.3, 51.0, 45.9, 29.5, 27.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{30}H_{30}NO_2Si$ 464.2046, found 464.2041.

*Data for (S)-**15c***. Prepared according to general procedure C using (*S*)-**2c**·HBr with *p*-toluenesulfonyl chloride for HPLC analysis. Purified by preparative TLC (60:40 DCM/hexane). HPLC analysis: Chiralpak AD-H column, *n*-heptane/*i*-PrOH = 99:1, 0.70 mL/min, 25 °C, t_R (major) = 51.0 min; t_R (minor) = 36.7 min. 99.7% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, J = 7.7, 1.6 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.57 (dd, J = 7.7, 1.6 Hz, 2H), 7.46−7.27 (m, 8H), 4.47 (dd, J = 10.0, 3.3 Hz, 1H), 3.34 (ddd, J = 12.8, 8.7, 3.9 Hz, 1H), 2.52−2.35 (m, 1H), 2.42 (s, 3H), 1.70−1.57 (m, 1H), 1.56−1.43 (m, 1H), 1.24 (s, 9H), 0.96−0.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 137.0, 136.8, 136.0, 133.9, 133.2, 129.9, 129.8, 129.4, 127.9, 127.8, 127.6, 49.2, 48.0, 28.1, 27.3, 23.6, 21.7, 19.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{34}NO_2SSi$ 464.2074, found 464.2071.

ESI−Mass Spectrometry Detection of Intermediates and Hydrogen-Bond Adducts. Reaction mixtures and samples were prepared and analyzed using ESI-MS in the positive ion mode on a Qtrap spectrometer. Source parameters were 5 kV spray voltage, with a curtain plate temperature of 275 °C and sheath gas setting of 15. Samples were analyzed via flow injection analysis by injecting 20 μL samples into a stream of 80:20 MeOH/aqueous 0.1% formic acid, flowing at 300 μL/min. All raw ESI−MS data files were analyzed using Applied Biosystems Analyst Software v.1.4.2, build 1228. Spectra were processed for publication figures using Systat Software Inc. SigmaPlot software v.11.0, build 11.0.0.77.

Sample Preparation for ESI−MS Detection of Reaction Intermediates in Figure 1. *Spectrum A.* Catalyst (*S*)-**2c** (0.005 g, 0.016 mmol, 0.05 equiv) was combined with propionaldehyde (0.048 g, 0.323 mmol, 1.0 equiv) in 0.3 mL of 9:1 hexane/THF and the mixture allowed to stir for 10 min. A 10 μL aliquot of this mixture was diluted into 2 mL of methanol and directly injected for ESI−MS analysis in positive mode.

Spectrum B. Catalyst (*S*)-**2c** (0.005 g, 0.016 mmol, 0.05 equiv) was combined with *trans*-β-nitrostyrene (0.048 g, 0.323 mmol, 1.0 equiv) in 0.3 mL of 9:1 hexane/THF and allowed to stir for 1 h. A 10 μL aliquot of this mixture was diluted into 2 mL of methanol and directly injected for ESI−MS analysis in positive mode.

Spectrum C. After analysis of the reaction mixture described above to generate graph B, propionaldehyde (0.24 mL, 3.230 mmol, 10.0 equiv) was added. Immediately after addition of the aldehyde, a 10 μL aliquot of the reaction mixture was diluted into 2 mL of methanol and directly injected for ESI−MS analysis in positive mode.

Sample Preparation for ESI−MS Detection of Nitrostyrene Binding to Amines (Figure 2). A mixture of *trans*-β-nitrostyrene (0.010 g, 0.070 mmol, 1.0 equiv) and hydrogen bond donor (0.070 mmol, 1.0 equiv) in 0.1 mL of methanol was allowed to stir for 10 min. A 10 μL aliquot of this mixture was diluted into 2 mL of methanol and directly injected for ESI−MS analysis in positive mode.

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra, HPLC chromatograms, computational details, and X-ray crystal structures for (*S*)-**2a**·HBr, (*S*)-**2b**·HBr, (*S*)-**2c**·HBr, and (*R*)-**7**·HBr (as the protonated tetrabromozincate (II) salt monohydrate). This material is available free of charge via the Internet at http://pubs.acs.org.

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