JOC The Journal of Organic Chemistry Cite This: J. Org. Chem. XXXX, XXX, XXX−XXX

Article

pubs.acs.org/joc

Chiral Brønsted Acid-Catalyzed Metal-Free Asymmetric Direct Reductive Amination Using 1-Hydrosilatrane

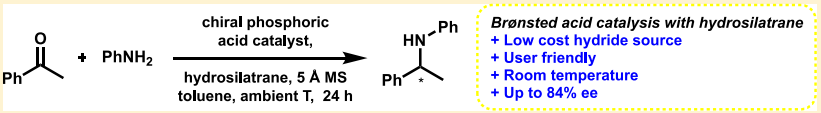
Vladislav Skrypai,[†] Sami E. Varjosaari,[†,‡] Fawwaz Azam,[§] Thomas M. Gilbert,[†] and Marc J. Adler*[,†,§]

[†]Department of Chemistry & Biochemistry, Northern Illinois University, 1425 W. Lincoln Hwy., DeKalb, Illinois 60115, United States

[‡]Department of Science & Mathematics, Coker College, 300 E. College Ave., Hartsville, South Carolina 29550, United States

[§]Department of Chemistry & Biology, Ryerson University, 350 Victoria St., Toronto, Ontario M5B 2K3, Canada

Supporting Information



ABSTRACT: The asymmetric direct reductive amination of prochiral ketones with aryl amines using 1-hydrosilatrane with a chiral Brønsted acid catalyst is reported. This is the first known example of chiral Brønsted acid-catalyzed asymmetric reductive amination using a silane as the hydride source. The reaction features a highly practical reducing reagent and proceeds efficiently at room temperature without a specialized reaction setup or equipment to exclude air or moisture. This method provides high conversion and enantiomeric excess up to 84% of the desired chiral secondary amines with minimal side products.

INTRODUCTION

Direct reductive amination (DRA) is the most practical method for synthesizing secondary and tertiary amines, molecules that are highly desired for pharmaceutical, agricultural, and fine chemical reagent applications.[1] Many of these important amines are chiral, and the development of new and improved methods for the synthesis of optically active amines has long been a thriving field in organic chemistry.[2]

Current methods can be split into two major categories: transition metal-catalyzed and metal-free organocatalyzed reactions. Transition metal-catalyzed reactions usually use hydrogen gas and an iridium, platinum, or palladium catalyst;[3−5] these metal reagents are expensive, toxic, and not always easy to work with. The organocatalyzed variations typically utilize either a Hantzsch ester[6] or trichlorosilane as the hydride source (noteworthy examples in Figure 1);[7] Hantzsch esters are expensive to purchase and have poor atom economy in synthesis and use, and trichlorosilane is both difficult to work with and produces a large amount of halogenated waste. Researchers have explored boutique hydride reagents (such as benzothiazolines[8] and indolines[9]), but the lack of ready availability of these reagents hampers their widespread adoption. In short, while excellent methods to access valuable enantioenriched amines have been developed, there is significant opportunity to optimize the balance of user-friendliness, cost-effectiveness, safety, and toxicity of such a transformation.

1-Hydrosilatrane (**1**) was first synthesized by Frye et al. in 1961,[10] but despite possessing many attributes that enable efficient hydride transfer, it had been overlooked as a reducing reagent until recently.[11−13] **1** contains a silicon with an expanded octet due to the lone pair on the nitrogen interacting with the caged silicon;[14] hypercoordination of a silane increases electron density on silane-bonded atoms making, in this case, the hydride more hydridic.[15] Despite this embedded reactivity, **1** is air- and moisture-stable, nontoxic, and can be synthesized economically in high purity and yield.

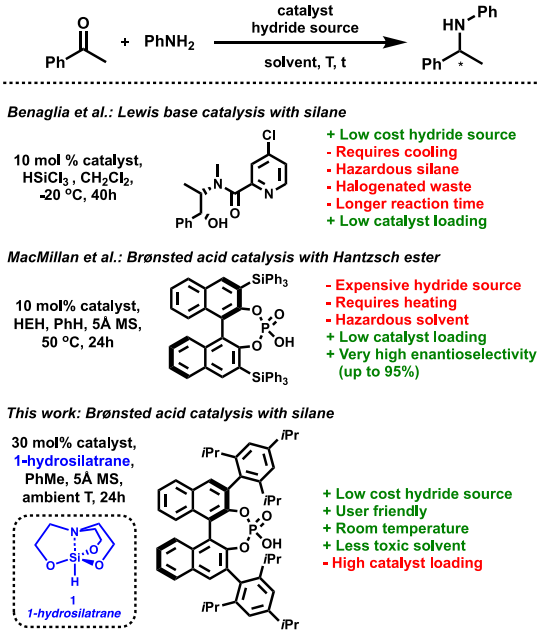


Figure 1. Metal-free asymmetric DRA.

Received: November 30, 2018
Published: April 11, 2019

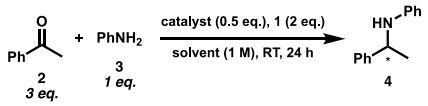
DOI: 10.1021/acs.joc.8b03073
J. Org. Chem. XXXX, XXX, XXX−XXX

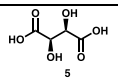
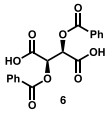
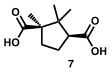
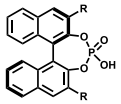
Previously, our lab has developed efficient and user-friendly methods using 1-hydrosilatrane (**1**) in the reduction of aldehydes[11] and ketones,[12] and in DRA of these carbonyl-containing compounds.[13] Aldehydes and ketones undergo rapid reduction by **1** in the presence of a Brønsted base activator, while DRA of aldehydes and ketones with secondary amines are solvent- and activator-free. To effect DRA of ketones/aldehydes with primary amines, the reaction must be performed in the presence of a Brønsted acid, specifically acetic acid in the original report.[13] The dependence of reactivity on the addition of this activator provided an opportunity to impart enantioselectivity to the reaction while utilizing the same convenient stoichiometric reductant; with this in mind, we sought to use chiral Brønsted acids to induce enantioselectivity in the DRA of ketones with primary amines. Here, we describe this novel method using 1-hydrosilatrane and a chiral phosphoric acid catalyst for DRA with high yields and good enantiomeric excess (ee).

RESULTS AND DISCUSSION

The investigation began by optimizing conditions for the reaction between acetophenone (**2**) and aniline (**3**) to yield **4** (Table 1). As the achiral reaction was activated by acetic acid,

Table 1. Catalyst Screening



entry	catalyst	ee[a]	conversion[b]
1[c]	 5	0	25
2[c]	 6	0	25
3[d]	 7	0	50
4[d]	R = H 8	4	80
5[e]	 catalysts 8-11 R =  9	9	60
6[e]	R = $SiPh_3$ 10	12	50
7[e]	R =  11	68	95

[a]ee determined by chiral GCMS. [b]Conversion determined by GC-FID. [c]Reaction run in acetonitrile. [d]Reaction run in ethyl acetate. [e]Reaction run in benzene.

chiral carboxylic acids were tested first. Tartaric acid (**5**) and its derivatives **6** and **7** (entry 1−3) were tested in polar solvents to maximize dissolution, but only gave relatively low conversions of up to 50% and no optical activity was observed in the products. More commonly used BINOL-derived chiral phosphoric acids were then tested, as these molecules have become increasingly popular because of their versatility in a broad range of asymmetric reactions[16] and have demonstrated high enantioselectivities in the reduction of imines.[17,18] The parent compound **8** (entry 4) gave higher conversion but still low ee. Increasing the bulkiness of the activator **9** (entry 5) and switching the solvent to benzene increased the ee slightly but decreased the conversion. Activator **10** (entry 6), which had previously been used with Hantzsch esters,[17] was not effective, resulting in a low ee of 12% and conversion of 50%. Finally, and gratifyingly, bulky activator **11**[17b,18] (entry 7) provided a very good ee of 68% and excellent conversion (95%).

A model for selecting chiral phosphoric acids reported by Reid and Goodman in 2017 justifies the effectiveness of activator **11** in our system and predicts the enantioselectivity observed.[19] This work also allows us to propose a possible mechanism for our reactions (Figure 2). After an imine is

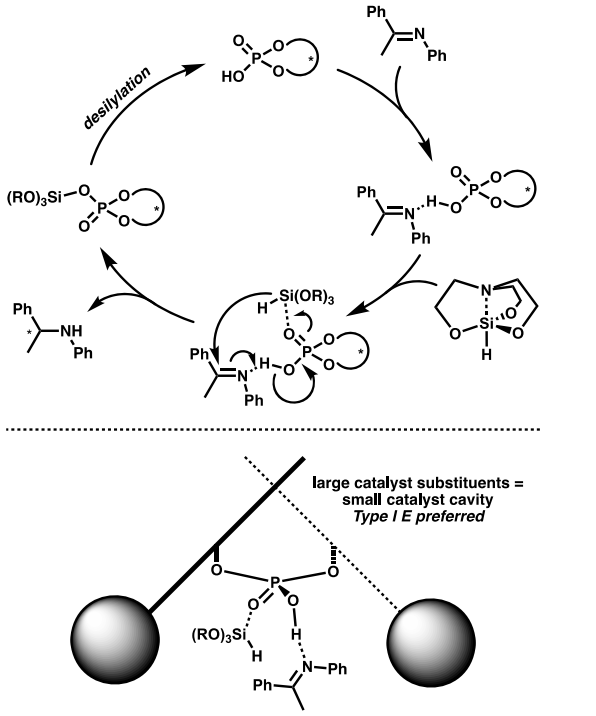


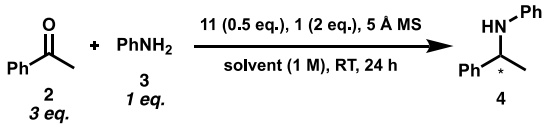
Figure 2. Catalytic cycle for asymmetric DRA (top) and transition state predicting stereoselectivity (bottom) from Reid et al.[17]

formed in situ, the chiral phosphoric acid protonates the imine. This complex then further coordinates 1-hydrosilatrane in a relatively tight pocket, allowing for enantioselective hydrogen transfer to occur. The imine is in an (*E*)-conformer as the steric hindrance is greater between the two aryl groups than with the chiral phosphoric acid. Following reduction of the protonated imine to an amine, the silatranephosphate is hydrolyzed to reform the catalyst.

The reaction solvent was optimized for activator **11** (Table 2). Benzene showed good results (entry 1) with 68% ee and almost quantitative conversions. With the intention of making the reaction more environmentally friendly, acetonitrile and ethyl acetate were tested (entry 2 and 3, respectively), but neither of these options resulted in improved ee or conversion. In fact, the enantioselectivity decreased in correlation with solvent polarity, which is not surprising given that tight hydrogen bonding between the phosphoric acid and the imine is required for stereochemical information to be transmitted

DOI: 10.1021/acs.joc.8b03073
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Solvent Optimization



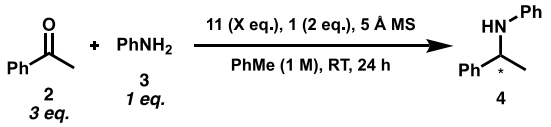
entry	solvent[a]	ee[b]	conversion[c]
1	PhH	68	95
2	MeCN	6	74
3	EtOAc	50	77
4	PhMe	70	99

[a]Anhydrous solvents. [b]ee determined by chiral GCMS. [c]Conversion determined by GC-FID.

from the catalyst to substrate. Toluene (entry 4) marginally increased the ee (to 70%) and gave quantitative conversion to the product and therefore was chosen as the solvent for future trials.

Efforts were also made to explore the impact of catalyst loading on the reaction outcome (Table 3). The yield and ee

Table 3. Catalyst Loading



entry	X (equiv of 11)[a]	ee[b]	conversion[c]
1	1	72	99
2	0.8	72	99
3	0.5	70	99
4	0.3	70	92
5	0.1	60	60

[a]Equivalents with respect to limiting reagent (aniline). [b]ee determined by chiral GCMS. [c]Conversion determined by GC-FID.

of the reaction were not significantly impacted between a stoichiometric amount and 50 mol %. A small dropoff in yield was noted when further limiting the amount of catalyst to 30 mol %, but both the yield and ee dropped dramatically at 10 mol %. After balancing results with catalyst cost and waste generation, we decided to push forward with a catalyst loading of 30 mol %.

Using the optimized conditions, a small variety of ketones were reacted with aniline and *o*-methoxyaniline to test the scope for the asymmetric DRA (Figure 3). The scope was limited to aniline and *o*-methoxyaniline because of the relatively limited ability of the gas chromatography/mass spectrometry (GC/MS) chiral column in separating the enantiomers. Reaction of aniline and acetophenone proceeded smoothly with a complete conversion to the corresponding amine (**12**) in 72% ee. Bulkier propiophenone formed **13** in excellent yield with an increased ee of 76%, while the even bulkier isobutyrophenone formed **14** with a significant decrease in conversion and lower ee of 60%. *o*-Methoxyaniline reacted with acetophenone, forming **15** with only slight decrease in conversion and ee, indicating that this method provides a relatively easy pathway to asymmetric primary amines via oxidative diarylation using methods previously reported in the literature.[20]

Electron-poor *p*-nitroacetophenone showed quantitative conversion to **16**, but the ee decreased to 56%, while

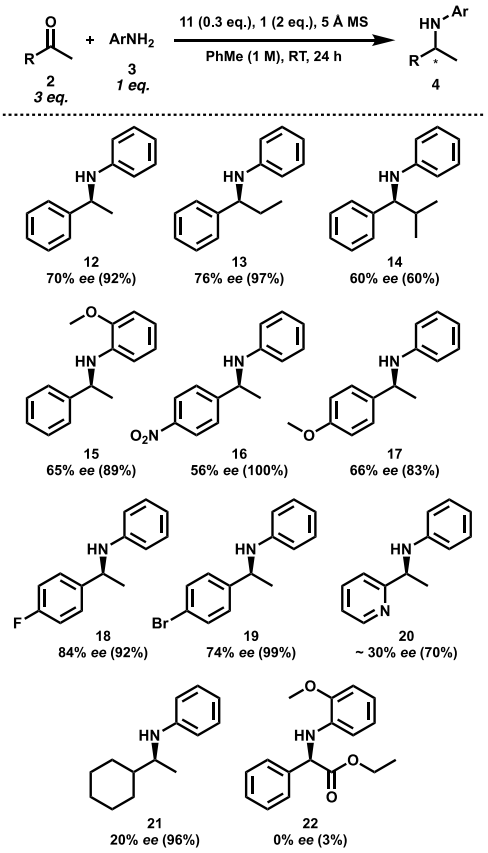


Figure 3. Reaction scope and limitations.

electron-rich *p*-methoxyacetophenone reacted with aniline in excellent conversion to give **17** with 66% ee. Reaction of para-substituted halides (**18** and **19**) gave excellent conversion and ee, with *p*-fluoroacetophenone forming **19** with 84% ee. 2-Acetylpyridine reacted with aniline to form 20 in good conversion, although the ee was not determined precisely as the two enantiomers were unable to be separated effectively on the available chiral GC/MS column. An aliphatic ketone gave good conversion, although the ee was low (**21**). Finally, the method was extended to a ketoester: although the racemic reaction with acetic acid gave a relatively good conversion,[13] the chiral counterpart resulted in negligible conversion to **22** with no ee. This could be due to intramolecular hydrogen bonding that stabilizes the positive charge on the iminium ion making it less prone to hydride transfer.

We have developed a new method for enantioselective DRA using a substituted BINOL-derived-phosphoric acid and 1-hydrosilatrane. We were able to achieve excellent conversions and up to 84% ee in the case of 4-flouroacetophenone and aniline. This work demonstrates the potential of 1-hydrosilatrane to replace less user- and environmentally friendly reagents as a mild hydride source for such reactions. We anticipate that further manipulation of the identity and structure of the reagents will make this general approach for DRA viable for synthesis of pharmaceutical and industrial applications.

EXPERIMENTAL SECTION

General Information. All chemicals were obtained from commercial sources and used without further purification, unless specified. Hydrosilatrane[11a] and phosphoric acids **10**[17b] and **11**[18] were prepared using known procedures. Column chromatography was

DOI: 10.1021/acs.joc.8b03073
J. Org. Chem. XXXX, XXX, XXX−XXX

performed using silica gel from Macherey-Nagel (60 M, 0.04−0.063 mm). ^{1}H NMR, and ^{13}C NMR were recorded on either a 300, 500 MHz Bruker AVANCE III spectrometer, or a 400 MHz Bruker AV400. Chemical shifts were reported in ppm with the solvent resonance as internal standard (^{1}H NMR $CDCl_3$ δ = 7.28, ^{13}C NMR $CDCl_3$ δ = 77.01). IR spectra were acquired using an ATI Mattson Fourier transform infrared spectrophotometer on neat samples. MS data were obtained with a Shimadzu GCMS QC2010S spectrometer. Enantiomeric ratios were analyzed by a Shimadzu GCMS QC2010S spectrometer equipped with a chiral column (CP-Chirasil Dex CB 25 × 0.25 × 0.25). Helium was used as the mobile phase at a column pressure of 120 kPa and varying split flow rates specified in this Supporting Information. The injector temperature was 230 °C, and the FID temperature was 200 °C. The oven temperatures and the retention times are specified according to the substrate.

General Procedure for Synthesis of Racemic Secondary Amines. In a 5 dram vial equipped with a stir bar were combined 1-hydrosilatrane (2 mmol), ketone (3 mmol), amine (1 mmol), and 1 mL of acetic acid. The vial was capped and stirred overnight. The resulting mixture was then diluted with diethylether and extracted three times with 1 M HCl. The aqueous layers were combined and neutralized with 3 M NaOH followed by extraction with dichloromethane three times. Combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure.

General Procedure for Synthesis of Chiral Secondary Amines. In a 5 dram vial a mixture of molecular sieves (5 Å), 1-hydrosilatrane (0.035 g, 0.2 mmol) acetophenone (0.036 mL, 0.31 mmol), aniline (0.01 mL, 0.11 mmol), and chiral activator (0.037 mmol) in 1 mL of toluene were stirred at room temperature overnight. A small portion of the mixture was then tested using a chiral GC/MS for ee. The enantiomeric ratio was determined using chirasil DEX-CB GC column.

Characterization of Isolated Racemic Products. *N-(1-Phenylethyl)aniline*[21] ***(12)***. 98% (198 mg), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 7.2 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 7.23 (tt, J = 7.3, 1.5 Hz, 1H), 7.10 (dd, J = 8.7, 7.3 Hz, 2H), 6.66 (tt, J = 7.3, 1.0 Hz, 1H), 6.53 (dd, J = 8.6, 1.1 Hz, 2H), 4.50 (q, J = 6.8 Hz, 1H), 4.2 (br, 1H), 1.53 (d, J = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.2, 145.4, 129.1, 128.7, 126.9, 125.9, 117.4, 113.5, 53.6, 25.0. IR (ATR) 3408, 3022, 2972, 1599, 1502, 1317, 1257, 746, 690 cm^{-1}.

N-(1-Phenylpropyl)aniline[22] ***(13)***. 99% (212 mg), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.37 (m, 4H), 7.29−7.26 (m, 1H), 7.13 (dd, J = 7.5 Hz, 2H), 6.67 (t, J = 7.2 Hz, 1H), 6.56 (dd, J = 8.6, 1.0 Hz, 2H), 4.27 (t, J = 7.5 Hz, 1H), 4.10 (br, 1H), 1.87 (pd, J = 7, 3 Hz, 2H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 147.6, 144.0, 129.1, 128.5, 126.9, 126.5, 117.1, 113.3, 59.7, 31.69, 10.85. IR (ATR) 3407, 2964, 2929, 2873, 1600, 1504, 1452, 1317, 1180, 1105, 1027, 1004, 902, 867, 746, 692 cm^{-1}.

N-(2-Methyl-1-phenylpropyl)aniline[23] ***(14)***. 75% (171 mg), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, J = 4.2 Hz, 4H), 7.26−7.20 (m, 1H), 7.09 (dd, J = 8.4, 7.4 Hz, 2H), 6.63 (t, J = 7.5 Hz, 1H), 6.52 (dd, J = 8.4, 1 Hz, 2H), 4.15 (d, J = 6 Hz, 2H), 2.06 (oc, J = 6.3 Hz, 1H), 1.01 (d, J = 7 Hz, 3H), 0.95 (d, J = 7 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 147.7, 142.6, 129.1, 128.2, 127.2, 126.8, 117.0, 113.2, 63.8, 34.9, 19.7, 18.6. IR (ATR): 3421, 3021, 2958, 2871, 1600, 1502, 1452, 1367, 1313, 1267, 1178, 1078, 1027, 756, 690 cm^{-1}.

2-Methoxy-N-(1-phenylethyl)aniline[24] ***(15)***. 64% (145 mg), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.31 (m, 4H), 7.25−7.22 (m, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.72 (t, J = 7.7 Hz, 1H), 6.63 (t, J = 7.7 Hz, 1H), 6.36 (d, J = 7.8 Hz, 1H), 4.67 (s, 1H), 4.50 (q, J = 6.7 Hz, 1H), 3.90 (s, 3H), 1.57 (d, J = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.6, 145.6, 137.3, 128.7, 126.9, 125.9, 121.3, 116.4, 111.0, 109.3, 55.5, 53.4, 25.3. IR (ATR) 3424, 3062, 2962, 2832, 1735, 1685, 1602, 1509, 1454, 1427, 1349, 1249, 1222, 1176, 1143, 1108, 1049, 1025, 900, 759, 734, 700 cm^{-1}.

N-(1-(4-Nitrophenyl)ethyl)aniline[25] ***(16)***. 30% (70 mg), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.10 (dd, J = 8.7, 7.4 Hz, 2H), 6.70 (tt, J = 7.4, 1.0 Hz, 1H), 6.46 (dd, J = 8.7, 1.1 Hz, 1H), 4.58 (q, J = 6.9 Hz, 1H), 4.17 (s, 1H), 1.56 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.2, 147.1, 146.5, 129.3, 126.7, 124.1, 118.0, 113.3, 53.4, 24.9 IR (ATR) 3409, 3052, 2971, 2927, 1598, 1513, 1504, 1450, 1430, 1340, 1317, 1280, 1257, 1205, 1180, 1143, 1106, 1012, 854, 748, 692 cm^{-1}.

N-(1-(4-Methoxyphenyl)ethyl)aniline[26] ***(17)***. 70% (161 mg), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.4 Hz, 2H), 7.11 (dd, J = 8.7, 7.3 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.67 (tt, J = 7.3, 1.1 Hz, 1H), 6.54 (dd, J = 8.7, 1.0 Hz, 2H), 4.47 (q, J = 6.8 Hz, 1H), 4.07 (br, 1H), 3.80 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.5, 147.3, 137.2, 129.1, 126.9, 117.3, 114.0, 113.4, 55.3, 52.9, 25.0. IR (ATR): 3405, 2962, 1602, 1504, 1461, 1317, 1284, 1241, 1176, 1105, 1031, 993, 829, 748, 692, 545 cm^{-1}.

N-(1-(4-Fluorophenyl)ethyl)aniline[27] ***(18)***. 97% (235 mg) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.34 (m, 2H), 7.13 (t, J = 8 Hz, 2H), 7.03 (t, J = 8.7 Hz, 2H), 6.69 (t, J = 7.2 Hz, 1H), 6.52 (d, J = 7.8 Hz, 2H), 4.50 (q, J = 7 Hz, 1H), 4.03 (s, 1H), 1.53 (d, J = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 147.1, 140.9, 129.1, 127.3 (d, J_{CF} = 12.5 Hz), 117.4, 115.4 (d, J_{CF} = 36.25 Hz), 113.3, 52.9, 25.2. IR (ATR) 3411, 3050, 2969, 1600, 1504, 1429, 1373, 1315, 1257, 1218, 1155, 1139, 1093, 1014, 833, 748, 690 cm^{-1}.

N-(1-(4-Bromophenyl)ethyl)aniline[21] ***(19)***. 96% (282 mg), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 2H), 7.13 (dd, J = 8.5, 7.4 Hz, 2H), 6.69 (t, 7.3 Hz, 1H), 6.50 (dd, J = 8.5, 1.2 Hz, 2H), 4.47 (q, J = 6.6 Hz, 1H), 4.03 (s, 1H), 1.52 (d, J = 7 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 147.0, 144.4, 131.8, 129.2, 127.7, 120.5, 117.6, 113.3, 53.1, 25.1. IR (ATR) 3415, 2966, 1600, 1502, 1429, 1402, 1317, 1255, 1180, 1139, 1070, 1008, 908, 821, 748, 690 cm^{-1}.

N-(1-(Pyridin-2-yl)ethyl)aniline[28] ***(20)***. 79% (172 mg), ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (d, J = 4.1 Hz, 1H), 7.63 (td, J = 7.65, 1.2 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.14 (m, 3H), 6.68 (t, J = 7.2 Hz, 1H), 6.58 (d, J = 8.4 Hz, 2H), 4.64 (q, J = 6.6 Hz, 1H), 4.47 (s, 1H), 1.57 (d, J = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 163.9, 149.3, 147.1, 136.8, 129.2, 122.0, 120.3, 117.4, 113.4, 54.8, 23.2. IR (ATR) 3403, 2969, 1600, 1502, 1471, 1432, 1317, 1259, 1180, 1153, 1025, 993, 869, 784, 746, 692 cm^{-1}.

N-(1-Cyclohexylethyl)aniline[27] ***(21)***. 72% (146 mg), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (dd, J = 8.5, 7.3 Hz, 2H), 6.68 (tt, J = 7.3, 1.0 Hz, 1H), 6.60 (dd, J = 8.8, 1.1 Hz, 2H), 3.50 (s, 1H), 3.35 (p, J = 6.5 Hz, 1H), 1.89−1.70 (m, 5H), 1.53−1.44 (m, 1H), 1.34−1.19 (m, 3H), 1.15 (d, J = 6.5 Hz, 3H), 1.10−1.06 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.0, 129.3, 116.5, 113.0, 53.0, 43.0, 29.8, 28.4, 26.7, 26.5, 26.4, 17.5. IR (ATR) 3413, 2921, 2850, 1600, 1504, 1448, 1429, 1373, 1317, 1253, 1155, 1074, 991, 863, 744, 690 cm^{-1}.

Ethyl 2-((2-Methoxyphenyl)amino)-2-phenylacetate[29] ***(22)***. 61% (155 mg), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (dd, J = 8.0, 1.5 2H), 7.39−7.31 (m, 3H), 6.82−6.66 (m, 3H), 6.37 (dd, J = 7.5, 1.5 Hz, 1H), 5.50 (d, J = 6 Hz, 1H), 5.08 (d, J = 6.3, 1H), 4.313−4.10 (m, 2H), 3.91 (s, 3H), 1.23 (t, J = 7.2 Hz), 3H. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 171.8, 147.1, 137.8, 136.0, 128.8, 128.1, 127.2, 121.0, 117.3, 110.7, 109.6, 61.7, 60.8, 55.5, 14.1. IR (ATR) 3423, 2937, 1733, 1602, 1511, 1456, 1429, 1315, 1247, 1222, 1178, 1139, 1025, 730, 696 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b03073.

Synthetic details and NMR characterization for select catalysts and full range of products, and chiral GCMS data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: marcjadler@ryerson.ca.

ORCID

Thomas M. Gilbert: 0000-0003-2053-9655

DOI: 10.1021/acs.joc.8b03073
J. Org. Chem. XXXX, XXX, XXX−XXX

Marc J. Adler: 0000-0002-1049-509X

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful for financial support provided by Northern Illinois University and Ryerson University.

■ REFERENCES

(1) (a) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; Wiley: Chichester, 2002; p. 315. (b) Bentley, K. W. β-Phenylethylamines and the isoquinoline alkaloids. *Nat. Prod. Rep.* **2006**, *23*, 444−463.

(2) (a) Tang, W.; Zhang, X. New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. *Chem. Rev.* **2003**, *103*, 3029−3070. (b) *Handbook of Homogeneous Hydrogenation*; Ojima, I., Eds; Wiley-VCH: Hoboken, 2010 (c) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. Transition metal-catalyzed enantioselective hydrogenation of enamines and imines. *Chem. Rev.* **2011**, *111*, 1713−1760. (d) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. Asymmetric hydrogenation of heteroarenes and arenes. *Chem. Rev.* **2012**, *112*, 2557−2590.

(3) Huang, H.; Liu, X.; Zhou, L.; Chang, M.; Zhang, X. Direct Asymmetric Reductive Amination for the Synthesis of Chiral β-Arylamines. *Angew. Chem., Int. Ed.* **2016**, *55*, 5309−5312.

(4) Huang, H.; Zhao, Y.; Yang, Y.; Zhou, L.; Chang, M. Direct Catalytic Asymmetric Reductive Amination of Aliphatic Ketones Utilizing Diphenylmethanamine as Coupling Partner. *Org. Lett.* **2017**, *19*, 1942−1945.

(5) Song, B.; Yu, C.-B.; Ji, Y.; Chen, M.-W.; Zhou, Y.-G. Synthesis of chiral sultams via palladium-catalyzed intramolecular asymmetric reductive amination. *Chem. Commun.* **2017**, *53*, 1704−1707.

(6) (a) Kim, K.-H.; Lee, C.-Y.; Cheon, C.-H. Enantioselective Synthesis of β-Arylamines via Chiral Phosphoric Acid-Catalyzed Asymmetric Reductive Amination. *J. Org. Chem.* **2015**, *80*, 6367−6374. (b) Sharma, M.; Mangas-Sanchez, J.; Turner, N. J.; Grogan, G. NAD(P)H-Dependent Dehydrogenases for the Asymmetric Reductive Amination of Ketones: Structure, Mechanism, Evolution and Application. *Adv. Synth. Catal.* **2017**, *359*, 2011−2025.

(7) (a) Malkov, A. V.; Stončius, S.; Kočovský, P. Enantioselective Synthesis of 1,2-Diarylaziridines by the Organocatalytic Reductive Amination of α-Chloroketones. *Angew. Chem., Int. Ed.* **2007**, *46*, 3722−3724. (b) Guizzetti, S.; Benaglia, M.; Cozzi, F.; Annunziata, R. Chiral Lewis base promoted trichlorosilane reduction of ketimines. An enantioselective organocatalytic synthesis of chiral amines. *Tetrahedron* **2009**, *65*, 6354−6363. (c) Guizzetti, S.; Benaglia, M. Trichlorosilane-Mediated Stereoselective Reduction of C=N Bonds. *Eur. J. Org. Chem.* **2010**, *2010*, 5529−5541. (d) Gautier, F.-M.; Jones, S.; Li, X.; Martin, S. J. Scope of the organocatalysed asymmetric reductive amination of ketones with trichlorosilane. *Org. Biomol. Chem.* **2011**, *9*, 7860−7868. (e) Jones, S.; Warner, C. J. A. Trichlorosilane mediated asymmetric reductions of the C=N bond. *Org. Biomol. Chem.* **2012**, *10*, 2189−2200.

(8) (a) Henseler, A.; Kato, M.; Mori, K.; Akiyama, T. Chiral Phosphoric Acid Catalyzed Transfer Hydrogenation: Facile Synthetic Access to Highly Optically Active Trifluoromethylated Amines. *Angew. Chem., Int. Ed.* **2011**, *50*, 8180−8183. (b) Saito, K.; Akiyama, T. Enantioselective organocatalytic reductive amination of aliphatic ketones by benzothiazoline as hydrogen donor. *Chem. Commun.* **2012**, *48*, 4573−4575.

(9) Saito, K.; Miyashita, H.; Akiyama, T. Asymmetric transfer hydrogenation of ketimines by indoline as recyclable hydrogen donor. *Org. Lett.* **2014**, *16*, 5312−5315.

(10) Frye, C. L.; Vogel, G. E.; Hall, J. A. Triptych-siloxazolidines: pentacoordinate bridgehead silanes resulting from transannular interaction of nitrogen and silicon. *J. Am. Chem. Soc.* **1961**, *83*, 996−997.

(11) (a) Skrypai, V.; Hurley, J. J. M.; Adler, M. J. Silatrane as a Practical and Selective Reagent for the Reduction of Aryl Aldehydes to Benzylic Alcohols. *Eur. J. Org. Chem.* **2016**, *2016*, 2207−2211. (b) Adler, M.; James, R.; Herlugson, S.; Varjosaari, S.; Skrypai, V.; Shakeel, Z.; Gilbert, T. M. One-Pot Reductive Acetylation of Aldehydes using 1-Hydrosilatrane in Acetic Acid. *SynOpen* **2019**, *3*, 1−3.

(12) (a) Varjosaari, S. E.; Skrypai, V.; Suating, P.; Hurley, J. J. M.; Gilbert, T. M.; Adler, M. J. 1-Hydrosilatrane: a Locomotive for Efficient Ketone Reductions. *Eur. J. Org. Chem.* **2017**, *2017*, 229−232. (b) Varjosaari, S. E.; Skrypai, V.; Herlugson, S. M.; Gilbert, T. M.; Adler, M. J. Enantioselective Metal-Free Reduction of Ketones by a User-Friendly Silane with a Reusable Chiral Additive. *Tetrahedron Lett.* **2018**, *59*, 2839−2843.

(13) Varjosaari, S. E.; Skrypai, V.; Suating, P.; Hurley, J. J. M.; De Lio, A. M.; Gilbert, T. M.; Adler, M. J. Simple Metal-Free Direct Reductive Amination Using Hydrosilatrane to Form Secondary and Tertiary Amines. *Adv. Synth. Catal.* **2017**, *359*, 1872−1878.

(14) Frye, C. L.; Vincent, G. A.; Finzel, W. A. Pentacoordinate silicon compounds. V. Novel silatrane chemistry. *J. Am. Chem. Soc.* **1971**, *93*, 6805−6811.

(15) (a) Brook, M. A. *Silicon in Organic, Organometallic and Polymer Chemistry*; Wiley: New York, 2000. (b) Holmes, R. R. Comparison of Phosphorus and Silicon: Hypervalency, Stereochemistry, and Reactivity. *Chem. Rev.* **1996**, *96*, 927−950. (c) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. Reactivity of penta- and hexacoordinate silicon compounds and their role as reaction intermediates. *Chem. Rev.* **1993**, *93*, 1371−1448.

(16) (a) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047−9153. (b) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Addition and Correction to Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2017**, *117*, 10608−10620.

(17) (a) Hoffmann, S.; Seayad, A. M.; List, B. A Powerful Brønsted Acid Catalyst for the Organocatalytic Asymmetric Transfer Hydrogenation of Imines. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424−7427. (b) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. Enantioselective Organocatalytic Reductive Amination. *J. Am. Chem. Soc.* **2006**, *128*, 84−86.

(18) Klussmann, M.; List, B.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R. Synthesis of TRIP and analysis of phosphate salt impurities. *Synlett* **2010**, *2010*, 2189−2192.

(19) Reid, J. P.; Goodman, J. M. Selecting Chiral BINOL-Derived Phosphoric Acid Catalysts: General Model To Identify Steric Features Essential for Enantioselectivity. *Chem.—Eur. J.* **2017**, *23*, 14248−14260.

(20) Fu, P.; Snapper, M. L.; Hoveyda, A. H. Catalytic Asymmetric Alkylations of Ketoimines. Enantioselective Synthesis ofN-Substituted Quaternary Carbon Stereogenic Centers by Zr-Catalyzed Additions of Dialkylzinc Reagents to Aryl-, Alkyl-, and Trifluoroalkyl-Substituted Ketoimines. *J. Am. Chem. Soc.* **2008**, *130*, 5530−5541.

(21) Wallach, D. R.; Stege, P. C.; Shah, J. P.; Chisholm, J. D. Brønsted Acid Catalyzed Monoalkylation of Anilines with Trichloroacetimidates. *J. Org. Chem.* **2015**, *80*, 1993−2000.

(22) Duan, H.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. Triazole−Au(I) Complexes: A New Class of Catalysts with Improved Thermal Stability and Reactivity for Intermolecular Alkyne Hydroamination. *J. Am. Chem. Soc.* **2009**, *131*, 12100−12102.

(23) Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. Zinc(II)-Catalyzed Addition of Grignard Reagents to Ketones. *J. Org. Chem.* **2010**, *75*, 5008−5016.

DOI: 10.1021/acs.joc.8b03073
J. Org. Chem. XXXX, XXX, XXX−XXX

(24) Brand, J. P.; Waser, J. Para-Selective Gold-Catalyzed Direct Alkynylation of Anilines. *Org. Lett.* **2012**, *14*, 744−747.
(25) Ruhland, T.; Nielsen, S. D.; Holm, P.; Christensen, C. H. Nanoporous magnesium aluminometasilicate tablets for precise, controlled, and continuous dosing of chemical reagents and catalysts: applications in parallel solution-phase synthesis. *J. Comb. Chem.* **2007**, *9*, 301−305.
(26) Chelouan, A.; Recio, R.; Borrego, L. G.; Álvarez, E.; Khiar, N.; Fernández, I. Sulfinamide Phosphinates as Chiral Catalysts for the Enantioselective Organocatalytic Reduction of Imines. *Org. Lett.* **2016**, *18*, 3258−3261.
(27) Sun, Q.; Wang, Y.; Yuan, D.; Yao, Y.; Shen, Q. Synthesis of Group 4 Metal Complexes Stabilized by an Amine-Bridged Bis(phenolato) Ligand and Their Catalytic Behavior in Intermolecular Hydroamination Reactions. *Organometallics* **2014**, *33*, 994−1001.
(28) Uenishi, J.; Hamada, M.; Aburatani, S.; Matsui, K.; Yonemitsu, O.; Tsukube, H. Synthesis of Chiral Nonracemic 1-(2-Pyridinyl)-ethylamines: Stereospecific Introduction of Amino Function onto the 2-Pyridinylmethyl Carbon Center. *J. Org. Chem.* **2004**, *69*, 6781−6789.
(29) Enders, D.; Rembiak, A.; Stöckel, B. A. Chemo- and Enantioselective Brønsted Acid-Catalyzed Reduction of α-Imino Esters with Catecholborane. *Adv. Synth. Catal.* **2013**, *355*, 1937−1942.

DOI: 10.1021/acs.joc.8b03073
J. Org. Chem. XXXX, XXX, XXX−XXX