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Organocatalyzed Diastereo- and Enantioselective Conjugate Addition of Nitroalkanes to β-Silylmethylene Malonates: Direct Access to Enantioenriched Organosilanes

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Abstract *Cinchona*-alkaloid derived bifunctional thiourea catalysed conjugate addition reaction of nitroalkanes to β-silylmethylene malonates is reported for direct access of densely functionalized enantioenriched organosilanes in good yields (up to 86%) with excellent stereoselectivities (up to 98:2 dr and 90% ee). Using *pseudoenantiomeric* catalyst, both the enantiomers of the conjugate addition products were easily accessible. Preparative scale synthesis of two conjugate addition products confirmed the practical applicability of the current methods. Furthermore, synthetic potential of these organosilanes was demonstrated by employing one of the products in the formal asymmetric synthesis of nootropic drug (*R*)-oxiracetam, synthesis of sila-analogue of PAR-2 agonist AC-264613 and synthesis of (*R*)- *N*-benzyl-4-hydroxy-pyrrolidin-2-one, intermediate for the synthesis of several pharmaceuticals.

Introduction

Chiral organosilanes are valuable substrates in organic synthesis,[1] materials science,[2] and agroscience.[3] Suitably substituted silicon groups attached to carbon atom can be converted to a hydroxyl group by Tamo-Fleming oxidation.[4] Chiral organosilanes (Figure 1, A[5] and B[6]) and silicon-containing organic molecules are attractive targets owing to their impressive application in medicinal chemistry. The replacement of carbon with silicon or introduction of

silyl group in organic molecules can improve the pharmacological properties. [7] Several elegant transition metal catalysed enantioselective methods[8] have been developed for the synthesis of enantioenriched organosilanes whereas the organocatalyzed methods for their direct synthesis are limited.

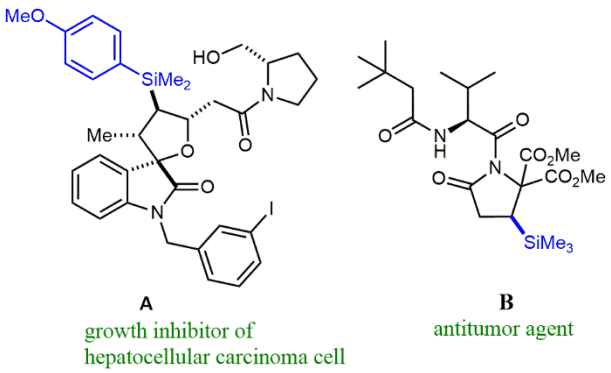

Figure 1. Selected examples of medicinally important chiral organosilanes.

In the realm of chiral organosilanes synthesis under organocatalytic conditions, Jørgensen and co-workers demonstrated an organocatalyzed Michael addition reaction of β-ketoesters with silicon-substituted α,β-unsaturated aldehydes followed by acid-catalysed decarboxylation and aldol condensation for the synthesis of 5-(trialkylsilyl)cyclohex-2-enones (Scheme 1 A).[9] Ghosh and co-workers developed asymmetric organocatalyzed direct conjugate addition of alkyl methyl ketones and aldehydes to a β-silylmethylene malonate to form β-silyl carbonyl compounds (Scheme 1 B). [10] In 2011, Hoveyda and co-workers reported a NHC catalysed silyl conjugate addition to α,β-unsaturated carbonyl compounds for the synthesis of β-silyl carbonyl compounds (Scheme 1 C). [11] More recently, Fu, Huang and co-workers developed carbene- catalysed formal [4+2] annulation of enals with β-silyl enones to form enantiopure organosilanes (Scheme 1 D). [12] As part of our recent interest on catalytic enantioselective synthesis of organic molecules bearing a silyl substituted asymmetric carbon[13] and in general development of bifunctional thio(urea) catalysed reactions,[14,15] we envisaged that organocatalyzed conjugate addition of nitroalkanes to β-silylmethylene

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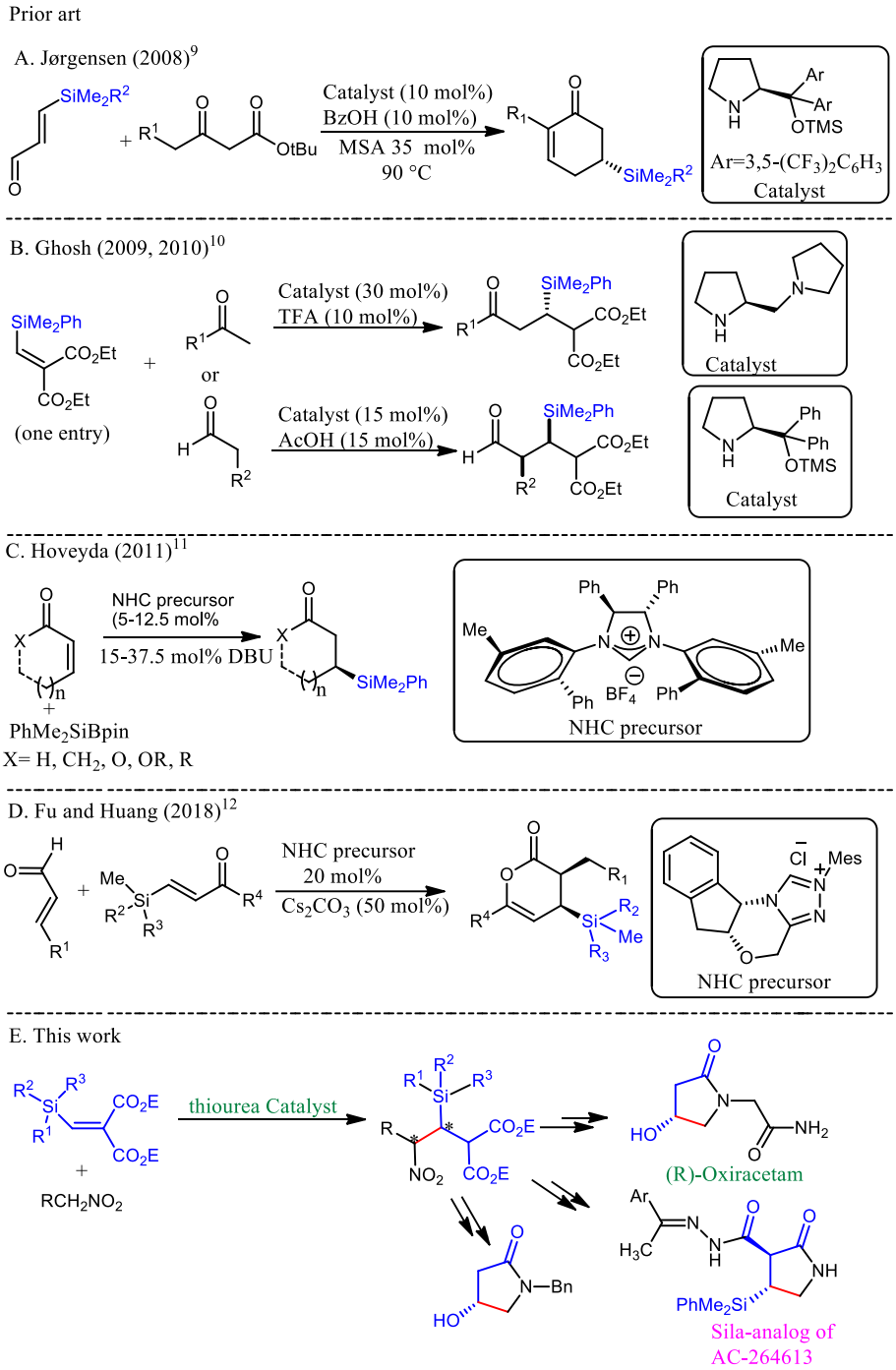
malonates would be the most straightforward approach to rapid access of enantioenriched organosilanes (Scheme 1 E).



Scheme 1. Selected state-of-the-art strategies for the synthesis of enantioenriched organosilanes under organocatalytic conditions and present work.

Literature survey reveals that there are two details studies[16,17]on organocatalyzed asymmetric conjugate addition of homologous nitroalkanes to aryl/alkylidene malonates and only one report[18] on organocatalyzed nitromethane addition to aryl/alkylidene malonates. The reported[18] conjugate addition of nitromethane to aryl/alkylidene malonates took place with moderate yields and long reaction time (3-5 days) in presence of 10 mol% catalyst and nitromethane as a solvent. In addition, bifunctional iminophosphorane catalysed Michael addition of nitroalkanes to enone diesters is also reported. [19] However, to the best of our knowledge, organocatalytic asymmetric conjugate addition reaction of nitroalkanes to β-silylmethylene malonates has not been studied so far. In this paper, we disclose the first catalytic conjugate addition of nitroalkanes including nitromethane to β-silylmethylene malonates for the diastereo- and enantioselective synthesis of organosilanes (Scheme 1 E). The important feature of these conjugate addition products is the presence of different functional groups which could be useful for downstream synthetic transformation.

RESULTS AND DISCUSSION

Initially, we started the optimization studies by screening readily available bifunctional hydrogen-bonding organocatalysts[20] **I-XII** (Figure 2) for the Michael addition reaction between β-silylmethylene malonate**1a** and nitromethane **2a** in toluene as a solvent. To our delight, quinidine derived thiourea catalyst **I** furnished the desired conjugate addition product **3a** with 82% yield and 76% ee at 30°C. Whereas the quinidine derived urea catalysts **II** delivered the product **3a** with similar enantioselectivity but with lower yield (Table 1, entry 2) due to incomplete reaction. Both the quinine and hydroquinine derived thiourea catalysts **III** and **IV** also delivered the desired product **3a**, with opposite configuration, in good yields but with slight erosion of enantioselectivity compared to quinidine derived catalysts **I** and **II (**Table1, entries 3-4). Cinchonidine derived thiourea catalyst **V** also produced the product **3a** with slightly better enantioselectivity as compared to catalysts **III** and **IV** (Table 1, entry 5).

Interestingly, quinidine derived thiourea catalyst **VI** bearing a 4-nitrophenyl group afforded the conjugated addition product **3a** with 86% ee (Table 1, entry 6) in good yield 84%. Catalyst **VII**, the *pseudoenantiomer* of catalyst **VI**, lead to product ***ent*-3a** with 79% ee (Table 1, entry 7). The quinidine derived squaramide catalyst **VIII** provided **3a** in 79% yield with 72% ee (Table 1, entry 8). On the other hand, the quinine derived squaramide catalyst **IX** furnished the desired product ***ent*-3a** in 78% yield with 60% ee (Table 1, entry 9). Squaramide catalyst **X** also yielded the product **3a** in 54% yield with 40% ee (Table 1, entry 10). Bifunctional urea catalyst **XI** derived from *trans*-1,2-diaminocyclohexane was not effective as lower ee was recorded on employment of the catalyst (Table 1, entry 11). Hydroquinine derivative $(DHQ)_2PHAL$ **XII** was also screened (not included in the Table 1) for the model reaction and found to be inefficient as 42% consumption (determined from ^1H NMR of the crude reaction mixture) of the β-silylmethylene malonate **1a** was observed in 24 h at 30°C. From the above studies, catalyst **VI** exhibited the best catalytic performance in terms of reaction rate, yield and enantioselectivity and therefore was chosen for further optimization experiments. With the optimal catalyst **VI**, subsequently, solvent screening studies were carried out. Solvent screening revealed that toluene and dichloromethane (DCM) were the choice of solvents (Table 1, entries 6 and 13). To avoid halogenated solvents, toluene was selected as the reaction medium for further studies. When the catalyst loading was changed from 10 mol% to 5 mol%, the enantioselectivity of the **3a** and yield almost remained the same (Table 1, entry 6 *vs* 15). Lowering the reaction temperature to 0 °C lead to improvement in enantioselectivity of **3a** without much affecting the chemical yield (Table 1, entry 16). When the amount of nitromethane was reduced from 20 equivalents to 10 equivalents, the chemical yield and enantioselectivity of **3a** remained the almost the same (Table 1, entry 16 *vs* 17). However, when the reaction was performed at -10°C with prolonged reaction time, erosion in yield and no improvement of ee value was observed (Table 1, entry 18). In additional attempt, at 0 °C, upon

decrease of the loading of catalyst **VI** from 5 mol% to 2.5 mol%, the product **3a** still could be obtained in high yield and enantioselectivity but drop in reaction rate was observed. (Table 1, entry 19). From the above studies, we set the optimized reaction conditions as: **1a** (0.2 mmol, 1 equiv), **2a** (2 mmol, 10 equiv), **VI** (5 mol%) in toluene (0.4 mL) at 0 °C (Table 1, entry 17).

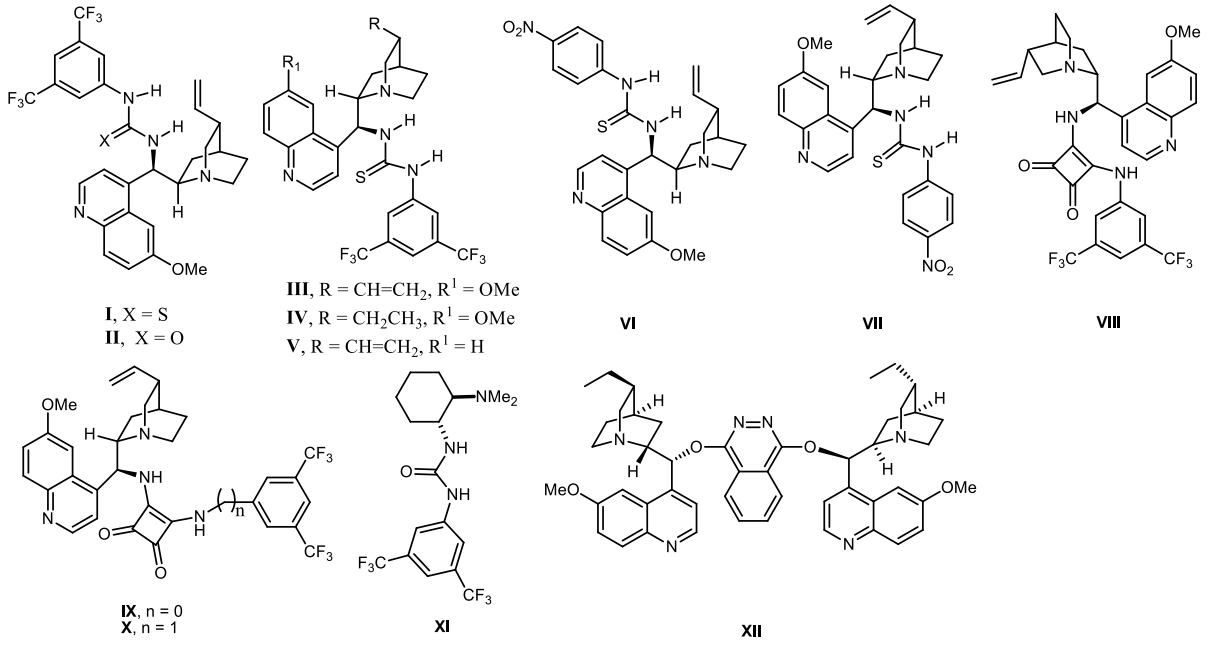
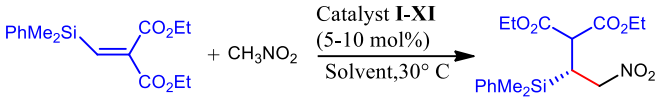


Figure 2. Structures of screened bifunctional organocatalysts.

Table 1. Catalysts Screening and Optimization of Reaction Conditions.[a]



1a **2a** **3a**

Entry	Cat. (mol%)	Solvent	Time (h)	Yield (%)[b] of **3a**	%ee[c] of **3a**
1	**I** (10)	toluene	18	82	76
2[d]	**II** (10)	toluene	48	74	76
3	**III** (10)	toluene	4	84	73[e]
4	**IV** (10)	toluene	4	82	73[e]
5	**V** (10)	toluene	6	81	76[e]

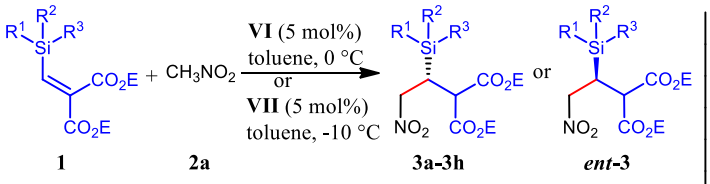
6	**VI** (10)	toluene	6	84	86
7	**VII** (10)	toluene	6	83	79[e]
8	**VIII** (10)	toluene	10	79	72
9	**IX** (10)	toluene	14	78	60[e]
10[f]	**X** (10)	toluene	17	54	40[e]
11	**XI** (10)	toluene	12	77	52[e]
12	**VI** (10)	THF	18	79	81
13	**VI** (10)	DCM	6	82	86
14	**VI** (10)	nitromethane	5	81	80
15	**VI** (5)	toluene	9	83	86
16[g]	**VI** (5)	toluene	22	83	90
17[h]	VI (5)	toluene	24	83	90
18[i]	**VI** (5)	toluene	48	80	90
19[j]	**VI** (2.5)	toluene	48	77	90

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (4 mmol), catalyst (0.02 mmol, 10 mol%) in solvent (~0.3mL) at 30 °C. [b] Isolated yield of **3a** after column chromatography. [c] Determined by HPLC using chiralpak AD-H column. [d] 90% conversion of the starting material **1a**, determined by ^{1}H NMR analysis of the crude reaction mixture. [e] Opposite enantiomer. [f] 75% conversion of the starting material **1a**, determined by ^{1}H NMR analysis of the crude reaction mixture. [g] The reaction was performed at 0°C, 20 equiv of nitromethane **2a** and 0.3 mL of toluene were used. [h] The reaction was performed at 0°C, 10 equiv of nitromethane **2a** and 0.4 mL of toluene were used. [i] The reaction was performed at -10°C, 10 equiv of nitromethane **2a** and 0.4 mL of toluene were used. [j] The reaction was performed at 0°C, 10 equiv of nitromethane **2a** and 0.4 mL of toluene were used.

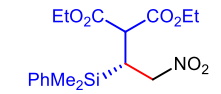
After establishing the optimized conditions, the Michael addition reactions of nitromethane **2a** with different β-silylmethylene malonates **1a**-**1h** (Table 2) were explored. The β-silylmethylene malonates **1a**-**1d** with the silyl group from dimethylphenylsilyl to methyl-diphenylsilyl groups, the conjugate addition reactions proceeded smoothly and the corresponding products **3a**-**3d** were formed with good to excellent yields (72-83%) and good enantioselectivities (80-90% ee) (Table 2). The β-silylmethylene malonate **1e** with the bulky *tert*-butyldiphenylsilyl group also participated in the conjugate addition reaction in presence of 20 mol% of catalyst **VII** at room temperature and the corresponding product **3e** was isolated in 67% yield with 65% ee. Furthermore, β-silylmethylene malonate **1f** having triphenylsilyl group also furnished the desired product **3f** in 80% yield with 85.5% ee. These results suggest that as the steric bulk of the silyl group increases the reactivity of β-silylmethylene malonates decreases. Notably, the β-silylmethylene malonates **1g** and **1h** with pentamethyldisiloxanyl group as the silyl moiety also afforded the corresponding products **3g** and **3h** with excellent yield (Table 2). In addition, dimethylphenylsilyl allylidine malonate **1i** and β-dimethylphenylsilyl-acrylate **1j** remained unreactive under the optimized reaction conditions (see the supporting information for details). Accessing both the antipode products with similar level of enantioselectivity is challenging specially the reactions catalysed by *Cinchona* alkaloids or their derivatives due to their existence as a single enantiomer. [21] When the Michael addition reaction of nitromethane **2a** with β-silylmethylene malonates **1a** was performed in the presence of 5 mol% of quinine derived catalyst **VII,** (*pseudoenantiomer* of the catalyst **VI**) under optimized conditions the enantiomeric product ***ent*-3a** was obtained in 80% yield with good enantioselectivity (81% ee). Lowering the reaction temperature offered slight improvement of enantioselectivity (83% ee) of ***ent*-3a**. Therefore, catalyst **VII** in dry toluene

at -10°C yielded ***ent*-3a**, ***ent*-3b**, ***ent*-3c** and ***ent*-3f** (Table 2) in good yields (77-83%) and enantioselectivities (76-84.5%).

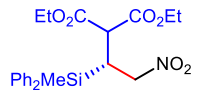
Table 2. Scope of β-Silylmethylene Malonates.[a]



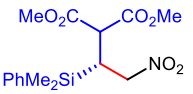
1a, R^1= Me, R^2= Me, R^3= Ph, E= Et
1b, R^1= Me, R^2= Ph, R^3= Ph, E= Et
1c, R^1= Me, R^2= Me, R^3=Ph, E= Me
1d, R^1= Me, R^2= Ph, R^3= Ph, E= Me
1e, R^1= Ph, R^2= Ph, R^3= *t*-Bu, E= Me
1f, R^1= Ph, R^2= Ph, R^3= Ph, E= Me
1g, R^1= Me, R^2= Me, R^3= OTMS, E= Et
1h, R^1= Me, R^2= Me, R^3= OTMS, E= Me



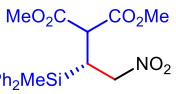
3a, 24h, 83%,[b] 90% ee[c]



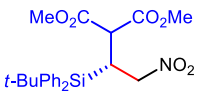
3b, 24h,72%,[b] 86.5% ee[c]



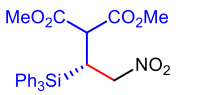
3c, 10h, 79%,[b] 81% ee[c]



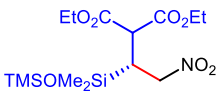
3d,16h, 77%,[b] 80% ee[c]



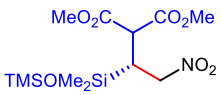
3e, 72h, 67%,[b] 65% ee[c]



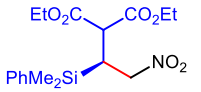
3f, 72h, 80%,[b] 85.5% ee[c]



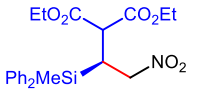
3g,[d] 14h, 86%[b]



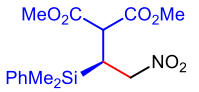
3h,[d] 6h, 77%,[b]



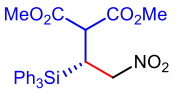
***ent*-3a**
24h, 80%,[b] 83% ee[c]



***ent*-3b**
24h,77%,[b] 84.5% ee[c]

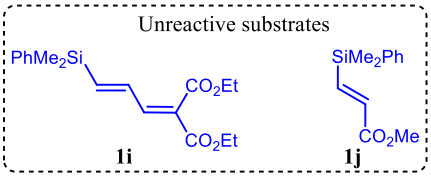


***ent*-3c**
13h, 82%,[b] 76% ee[c]



***ent*-3f**
72h, 83%,[b] 84.5% ee[c]

Unreactive substrates



1i **1j**

[a]Reaction conditions: For **3a, 3c**, **3d, 3g** and **3h**, **1** (0.2 mmol), **2a** (2 mmol), catalyst **VI** (0.01 mmol, 5 mol%) in dry toluene (0.4 mL) at 0°C. For **3b**, **1b** (0.2 mmol), **2a** (4 mmol), catalyst **VI** (0.01 mmol, 5 mol%) in dry toluene (0.3 mL) at 0°C. For ***ent*-3b**, **1b** (0.2 mmol), **2a** (4 mmol), catalyst **VII** (0.01 mmol, 5 mol%) in dry toluene (0.3 mL) at -10°C. For ***ent*-3a** and ***ent*-3c**, **1** (0.2 mmol), **2a** (2 mmol), catalyst **VII** (0.01 mmol, 5 mol%) in dry toluene (0.4 mL) at -10°C. For **3e**, **1** (0.2 mmol), **2a** (4 mmol), catalyst **VI** (0.04 mmol, 20 mol%) in dry toluene (0.3 mL) at 28-30°C. For **3f**, **1f** (0.2 mmol), **2a** (4 mmol), catalyst **VI** (0.02 mmol, 10 mol%) in dry toluene

(0.3 mL) at 0°C. For ***ent*-3f**, **1f** (0.2 mmol), **2a** (4 mmol), catalyst **VII** (0.02 mmol, 10 mol%) in dry toluene (0.3 mL) at -10°C. [b]Isolated yield of **3** after column chromatography, 1-5% substrate **1** was recovered, [c]Determined by HPLC using chiral stationary phase. [d]ee of **3g** and **3h** could not be determined.

The conjugate addition product **3f** was isolated as a white solid with ee 85.5%. The optical purity of **3f** was improved to >93% ee by single recrystallization. The absolute configuration of the stereogenic center bearing the silyl group in compound **3f** was determined to be (*R*) by single crystal X-ray crystallographic analysis (Figure 3).[22] The absolute configuration of other products **3a-3h** were assigned to be (*R*) in analogy with **3f**.

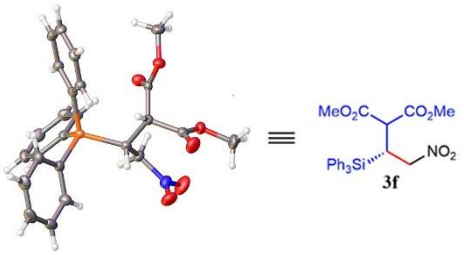
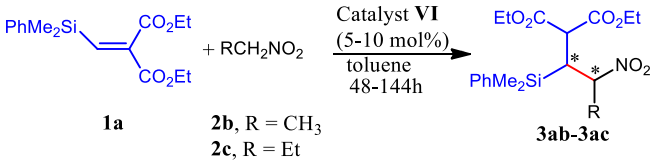


Figure 3. The ORTEP diagram of single crystal X-ray of product **3f (CCDC 1983892)**.

Next, the scope of the developed conjugate addition reaction was tested with homologous nitroalkanes. Performing the reaction between β-silylmethylene malonates **1a** and nitroethane **2b** (20 equiv) using 5 mol% of the catalyst **VI** in toluene at 0°C, the product **3ab** was isolated in 64% yield and good enantioselectivity (78%) as well as excellent diastereoselectivity[23](Table 3, entry 1). When the same reaction was carried out at low temperature (-20°C) in presence of 10 mol% of the catalyst **VI**, the product **3ab** was isolated in 70% yield with improvement of enantioselectivity (Table 3, entry 2). Under the same reaction conditions, the nitropropane addition product **3ac** was obtained in 75% yield with

excellent diastereoselectivity[23] (98:2) and with 74% ee for the major diastereoisomer **3ac** (Table 3, entry 3).

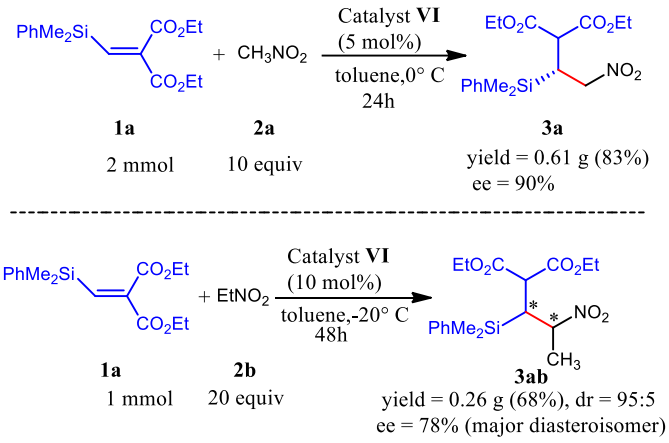
Table 3. Scope of Nitroalkanes[a]



Entry	Cat. (mol%)	Temp.	Nitroalkane	Yield (%) of **3** [b]	dr[c]	%ee[d]
1	5	0 °C	**2b**	64 (96%)[e]	96:4	78
2	10	-20 °C	**2b**	70 (>99%) [e]	96:4	80
3	10	-20 °C	**2c**	75 (>98%)[e]	98:2	74

[a]Reaction conditions: **1a** (61 mg, 0.2 mmol), **2** (4 mmol), catalyst **VI** in toluene. [b] Isolated yield of both the diastereoisomer after column chromatography. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] The ee of major diastereoisomer was determined by HPLC using a Daicel Chiralcel OD-H column. [e] Conversion of the starting material **1a** given in the parentheses, determined by ^{1}H NMR analysis of the crude reaction mixture.

To demonstrate the scalability of the above developed catalytic protocol, large scale synthesis of **3a** and **3ab** were carried out. In both the cases the product **3a** and **3ab** were obtained with similar level of stereoselectivity (Scheme 2) as compared to small scale reaction.

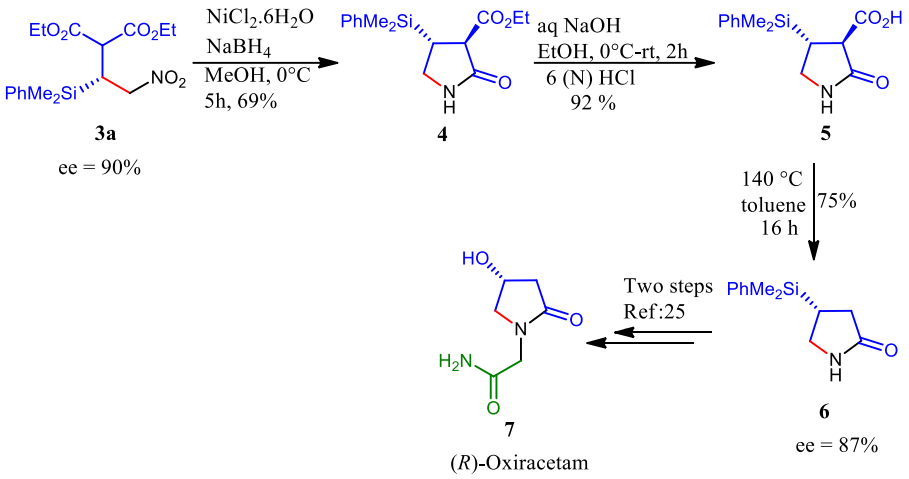


Scheme 2. Preparative Scale Synthesis of **3a** and **3ab**

The practical value of the synthesized organosilanes was exemplified in the asymmetric total formal synthesis of (*R*)-oxiracetam, a nootropic drug used in the treatment of Alzheimer's diseases,[24] synthesis of (*R*)-*N*-benzyl-4-hydroxy-pyrrolidin-2-one, versatile intermediates for the synthesis of several pharmaceuticals[25] and Sila-analogue of the PAR-2 agonist AC-264613. [26]

Asymmetric formal total Synthesis of (*R*)-oxiracetam **7** started with the sodium borohydride reduction of nitro group of conjugate addition product **3a** followed by concomitant lactamization which yielded the lactam **4** (Scheme 3). The relative *trans* configuration of the major product **4** was determined from ^{1}H,^{1}H-NOESY spectrum (details, see supporting information). Subsequent hydrolysis of the lactam **4** with sodium hydroxide followed by acidification with 6(N) HCl provided the corresponding acid **5** in 92% yield (Scheme 3). The decarboxylation of the acid **5** afforded the lactam **6** with 75% isolated yield and 87% ee (Scheme 3). The absolute stereochemistry of the chiral center at C(4) in **6** was assigned to be (*R*) by comparing the specific optical rotation value of **6** with that reported in the literature[27] ($[\alpha]_D^{25}$ = +11.4 (c =0.8; $CHCl_3$, ee = 87%), lit.[25] $[\alpha]_D^{28}$ = +17.9 (c = 1.00, $CHCl_3$). Therefore, the absolute configuration of its progenitor **3a** was also assigned to be (*R*). With the lactam **6** as the advanced intermediate in hand, (*R*)-oxiracetam **7** could be easily accessed in

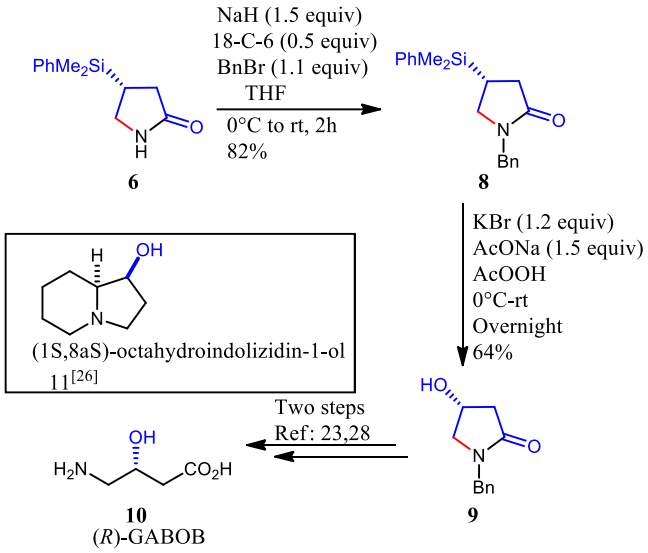
two steps using commercially available reagents following the synthetic route developed by the Procter group. [27]



Scheme 3. Asymmetric Formal Total Synthesis of (*R*)-Oxiracetam **7**.

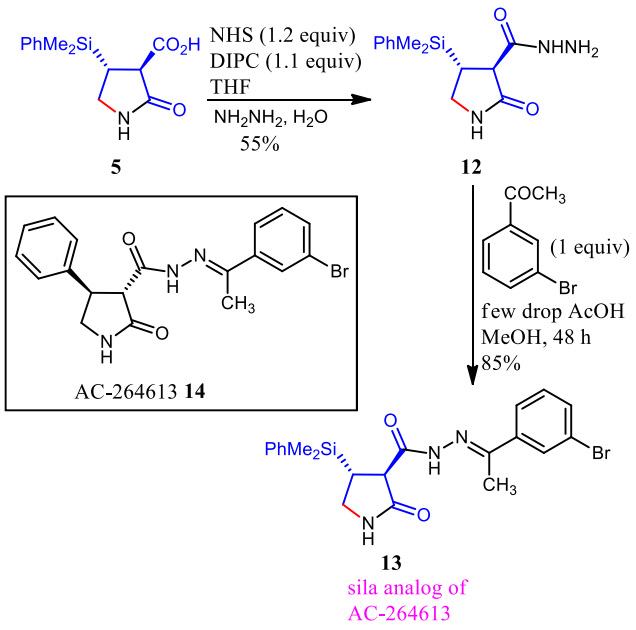
Chiral 4-hydroxy-pyrrolidin-2-one and its *N*-substituted derivatives are key intermediate for the synthesis of many pharmaceuticals[25,27] and alkaloids. [28] Lactam **6** can be easily transformed to *N*-substituted derivatives of 4-hydroxy-pyrrolidin-2-one. *N*-alkylation of lactam **6** by benzyl bromide furnished **8** with 82% yield (Scheme 4). [29] Subsequently, the dimethyl(phenyl)silyl group in **8** was converted to a hydroxy group (Scheme 4) following the Tamao–Fleming oxidation[4] with retention of configuration at C(4) chiral center and provided (*R*)- *N*-benzyl-4-hydroxy-pyrrolidin-2-one **9** which can be transformed to (*R*)-GABOB **10**.[25,30] In addition, the opposite enantiomer of **9** is the known intermediate for the preparation of alkaloid (1S,8aS)-octahydroindolizidin-1-ol **11**. [28]The ^{1}H and ^{13}C NMR and specific rotation value for **9** were in close agreement with those reported values. [30]

10.1002/ejoc.202000306



Scheme 4. Asymmetric transformation of lactam **6** to (*R*)- *N*-benzyl-4-hydroxy-pyrrolidin-2-one **9** is shown.

After accomplishing the formal synthesis of (*R*)-oxiracetam **7** and synthesis of (*R*)- *N*-benzyl-4-hydroxy-pyrrolidin-2-one **9**, next, we targeted the asymmetric synthesis of sila-analogue **13** of the proteinase-activated receptor-2 (PAR-2) agonist AC-264613 (Scheme 5). The small-molecule **14** was identified as a PAR-2 agonist by a high-throughput screening process. [26] Incorporation of silicon into drug or bio-active molecules has beneficial effect as it enhances their lipophilicity, ease membrane permeability and hence bio-availability. [7] The synthesis of sila-analogue **13** of AC264613 was achieved in two steps starting from the acid **5** (Scheme 5). The reaction of **5** with N-hydroxysuccinimide (NHS) and diisopropylcarbodiimide (DIPC) produced *in situ* NHS ester which upon reaction with hydrazine hydrate yielded hydrazide **12**. [31] Subsequent condensation of **12** with 3′-bromoacetophenone in presence of catalytic amount of acetic acid in methanol furnished the sila-analogue **13** of AC264613 (Scheme 5).



Scheme 5. Asymmetric transformation of acid **5** to a Sila-analogue **13** of AC264613 is shown.

CONCLUSION

In summary, we have developed the conjugate addition reactions of nitroalkanes to β-silylmethylene malonates for the straightforward synthesis of enantioenriched organosilanes with multiple functional handles under mild organocatalytic conditions. The chiral organosilanes were obtained in good yields and stereoselectivities. To showcase the synthetic potential of the developed methodology, one of the conjugate addition products was exploited for the asymmetric formal synthesis of medicinally important molecules such as (*R*)-Oxiracetam, synthesis of (*R*)- *N*-benzyl-4-hydroxy-pyrrolidin-2-one and Sila-analogue of the PAR-2 agonist AC-264613.

General experimental

Solvent removal was performed with a rotary evaporator that was connected to a dry ice condenser. TLC (0.5 mm) was carried out using Merck TLC plate. Column chromatography was performed on silica gel (230-400 mesh). The ^{1}H and ^{13}C NMR spectroscopic data were recorded with 500 MHz (^{1}H NMR: 500 MHz, ^{13}C NMR: 125 MHz) Varian spectrometer. The

^{1}H and ^{13}C chemical shifts are given in ppm (δ scale) and are measured relative to $CHCl_3$ (7.27 ppm) and $CDCl_3$ (77.0 ppm), respectively, as internal standards. High resolution mass spectra were recorded at 60-70 eV with a Waters Micromass Q-TOF spectrometer (ESI, Ar). Enantiomeric ratio (*er*) values were determined by HPLC analysis with a JASCO (JASCOPU-2080) instrument fitted with a Daicel Chiralpak AD-H column, Daicel Chiralcel OD-H column and Daicel Chiralpak OJ-H with UV-2075 detector (λ fixed at 254 nm or 220 nm). Melting points (mp) were measured in a Büchi B-540 apparatus. FTIR was recorded in Bruker tensor II. All the solvents were dried according to standard procedures and stored over activated molecular sieves (4 Å) before use. Nitromethane, nitroethane and nitropropane were purchased from commercial source and used without any purification or drying. The detail procedure for synthesis of β-silylmethylene malonates **1a**-**1h**, synthesis of catalysts **I**-**XI** and procedure for the preparation of racemic samples **3a**-**3ac** are available in supporting information.

General procedure

General Procedure for the preparation of enantioenriched organosilanes 3a-3d, 3g, 3h and *ent*-3a-*ent*-3c

Under Argon atmosphere, in an oven dried 5 mL round-bottom flask equipped with a magnetic stirring bar, β-Silylmethylene malonate **1** (0.2 mmol, 1 equiv) and catalyst **VI** (5 mg, 0.01mmol, 5 mol%) or catalyst **VII** (5 mg, 0.01mmol, 5 mol%) were dissolved in 0.4 mL of dry toluene and stirred at room temperature for about 5 min. The reaction mixture was cooled to 0°C (for **3a**-**3d** and **3g**, **3h**) or -10 °C (for ***ent*-3a-*ent*-3c**) and stirred for 5 min. Nitromethane (105 µl, 2 mmol, 10 equiv) was added to the reaction mixture and stirred for 6-24 h. Once the β-silylmethylene malonate **1** was consumed (monitored by TLC/^{1}HNMR), the reaction mixture was quenched by addition of saturated aqueous solution of NH_4Cl and diluted with CH_2Cl_2. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% petroleum ether/EtOAc-8%

petroleum ether/EtOAc) to afford the corresponding products **3a-3d, 3g, 3h and *ent*-3a- *ent*-3c**. [*It should be noted for* **3b** *and* ***ent*-3b,** *210 µl (4 mmol, 20 equiv) of nitromethane and 0.3 mL of dry toluene were used.*]

(*R*)-diethyl2-(1-dimethyl(phenyl)silyl)-2-nitroethyl)malonate 3a

Purified by column chromatography on silica gel (5% petroleum ether/EtOAc-8% petroleum ether/EtOAc). The above titled compound was isolated as colourless liquid (61 mg, 83%). **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.54-7.52 (m, 2 H), 7.43-7.37 (m, 3 H), 4.76 (dd, *J* = 15.0, 9.0 Hz, 1 H), 4.47 (dd, *J* = 14.7, 4.0 Hz, 1 H), 4.14-4.05 (m, 4 H), 3.54 (d, *J* = 4.5 Hz, 1 H), 2.60 (pent, *J* = 4.5 Hz, 1 H), 1.25-1.21 (m, 6 H), 0.42 (s, 3 H), 0.41 (s, 3 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: δ 168.8, 168.5, 135.4, 134.0 (2 C), 129.9, 128.0 (2 C), 74.6, 61.8, 61.7, 50.3, 25.2, 13.9 (2 C), -3.38, -3.79; The ee was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (97/3)]; flow rate 1.0 mL/min; λ = 254 nm; τ_{minor} = 8.05 min, τ_{major} = 10.77 min, $[\alpha]_D^{24}$ = -6.5 (*c* 1.56, $CHCl_3$, ee = 90%); **HRMS (ESI)** calcd for $C_{17}H_{25}NNaO_6Si$ $[M + Na]^+$: 390.1343, found: 390.1337.

(*S*)-diethyl2-(1-dimethyl(phenyl)silyl)-2-nitroethyl)malonate *ent*-3a

Purified by column chromatography on silica gel (5% petroleum ether/EtOAc-8% petroleum ether/EtOAc). The above titled compound was isolated as colourless liquid (59 mg, 80%). The ee was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (97/3)]; flow rate 1.0 mL/min; λ = 254 nm; τ_{major} = 7.89 min, τ_{minor} = 10.58 min, $[\alpha]_D^{24}$ = +8.2 (*c* 2.32, $CHCl_3$, ee = 83 %).

(*R*)-diethyl 2-(1-methyldiphenylsilyl)-2-nitroethyl)malonate 3b

Purified by column chromatography on silica gel (5% petroleum ether/EtOAc-8%petroleum ether/EtOAc). The above titled compound was isolated as colourless liquid (62 mg, 72%).**^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.61-7.56 (m, 4 H), 7.46-7.37 (m, 6 H), 4.93 (dd, *J* = 14.9, 9.6, Hz, 1 H), 4.50 (dd, *J* = 14.9, 3.2 Hz, 1 H), 4.05-3.92 (m, 4 H), 3.57 (d, *J* = 4.3 Hz, 1 H), 3.16-

3.13 (m, 1 H), 1.20 (t, *J* = 7.5 Hz, 3 H), 1.16 (t, *J* = 7.5 Hz, 3 H), 0.73 (s, 3 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: δ 168.7, 168.4, 134.9 (2 C), 134.7 (2 C), 133.3, 133.27, 130.1, 130.0, 128.2 (2 C), 128.1 (2 C), 74.4, 61.8, 61.6, 50.0, 23.5, 13.8, 13.7, -5.0; The ee was determined by HPLC using a Daicel Chiralcel OD-H [hexane/*i*-PrOH (97/3)]; flow rate 1.0 mL/min; λ = 254 nm; τ_{minor} = 8.78 min, τ_{major} = 9.46 min, $[\alpha]_D^{26}$ = -26.9 (*c* 2.38, $CHCl_3$, ee = 86.5%); **HRMS (ESI)** calcd for $C_{22}H_{27}NNaO_6Si$ $[M + Na]^+$: 452.1500, found: 452.1492.

(*S*)-diethyl 2-(1-methyldiphenylsilyl)-2-nitroethyl)malonate *ent*-3b

Purified by column chromatography on silica gel (5% petroleum ether/EtOAc-8%petroleum ether/EtOAc). The above titled compound was isolated as colourless liquid (66 mg, 77%). The ee was determined by HPLC using a Daicel Chiralcel OD-H [hexane/*i*-PrOH (97/3)]; flow rate 1.0 mL/min; λ = 254 nm; τ_{major} = 8.20 min, τ_{minor} = 9.12 min, $[\alpha]_D^{24}$ = +30.0 (*c* 2.37, $CHCl_3$, ee = 84.5%).

(*R*)-dimethyl 2-(1-dimethyl(phenyl)silyl)-2-nitroethyl)malonate 3c

Purified by column chromatography on silica gel (5% petroleum ether/EtOAc-10% petroleum ether/EtOAc). The above titled compound was isolated as colourless liquid (54 mg, 79%).**^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.53-7.51 (m, 2 H), 7.42-7.38 (m, 3 H), 4.76 (dd, *J* = 14.7, 9.2 Hz, 1 H), 4.46 (dd, *J* = 14.7, 4.0 Hz, 1 H), 3.66 (s, 3 H), 3.64 (s, 3 H), 3.58 (d, *J* = 4.5 Hz, 1 H), 2.61 (pent, 1 H), 0.42 (s, 3 H), 0.41 (s, 3 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: δ 169.2, 168.9, 135.1, 134.0 (2 C), 130.0, 128.1 (2 C), 74.5, 52.7, 52.6, 49.8, 25.4, -3.5, -3.9; The ee was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (97/3)]; flow rate 1.0 mL/min; λ = 220 nm; τ_{minor} = 9.75 min, τ_{major} = 12.32 min; $[\alpha]_D^{25}$ = -4.4 (*c* 1.23, $CHCl_3$, ee = 81%); **HRMS (ESI)** calcd for $C_{15}H_{21}NNaO_6Si$ $[M + Na]^+$: 362.1030, found: 362.1034.

(*S*)-dimethyl 2-(1-dimethyl(phenyl)silyl)-2-nitroethyl)malonate *ent*-3c

Purified by column chromatography on silica gel (5% petroleum ether/EtOAc-10% petroleum ether/EtOAc). The above titled compound was isolated as colourless liquid (56 mg, 82%). The

ee was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (97/3)]; flow rate 1.0 mL/min; λ = 220 nm; τ_{major} = 8.60 min, τ_{minor} = 10.35 min; $[\alpha]_D^{26}$ = +5.8 (*c* 1.66, $CHCl_3$, ee = 76%).

(*R*)-dimethyl 2-(1-methyldiphenylsilyl)-2-nitroethyl)malonate 3d

Purified by column chromatography on silica gel (first petroleum ether, then 8% petroleum ether/EtOAc). The above titled compound was isolated as colourless liquid (62 mg, 77 %). **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.60-7.55 (m, 4 H), 7.45-7.37 (m, 6 H), 4.94 (dd, *J* = 14.9, 9.7 Hz, 1 H), 4.50 (dd, *J* = 14.9, 3.1 Hz, 1 H), 3.62 (d, *J* = 4.4 Hz, 1 H), 3.57 (s, 3 H), 3.52 (s, 3 H), 3.16-3.12 (m, 1 H), 0.73 (s, 3 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: δ 169.0, 168.7, 134.9 (2 C), 134.7 (2 C), 133.1, 133.0, 130.2, 130.1, 128.3 (2 C), 128.2 (2 C), 74.4, 52.6, 52.5, 49.6, 23.8, -5.1; The ee was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (97/3)]; flow rate 1.0 mL/min; λ = 220 nm; τ_{minor} = 12.32 min, τ_{major} = 15.47 min; $[\alpha]_D^{25}$ = -32.7 (*c* 1.86, $CHCl_3$, ee = 80%); **HRMS (ESI)** calcd for $C_{20}H_{23}NNaO_6Si$ $[M + Na]^+$: 424.1187, found: 424.1175.

(*R*)-dimethyl 2-(1-(*tert*-butyldiphenylsilyl)-2-nitroethyl)malonate 3e

Under Argon atmosphere, in an oven dried 5 mL round-bottom flask equipped with a magnetic stirring bar, β-Silylmethylene malonate **1e** (76.5 mg, 0.2 mmol, 1 equiv) and catalyst **VI** (20 mg, 0.04 mmol, 20 mol%) were dissolved in 0.3 mL of dry toluene and stirred at 28°C for about 5 min. Nitromethane (210 µl, 4 mmol, 20 equiv) was added to the reaction mixture and stirred for 72 h at 28-30°C. The reaction mixture was subjected to column chromatography on silica gel(first petroleum ether, then 5%petroleum ether/EtOAc) to afford the corresponding product **3e** as colourless liquid (60 mg, 67%).**^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.60 (d, *J* = 6.9 Hz, 2 H), 7.56 (d, *J* = 7.0 Hz, 2 H), 7.47-7.37 (m, 6 H), 5.34 (dd, *J* = 15.3, 10.2 Hz, 1 H), 4.67 (dd, *J* = 15.3, 1.95 Hz, 1 H), 3.81 (d, *J* = 2.55 Hz, 1 H), 3.67 (s, 3 H), 3.43-3.40 (m, 1 H), 3.23 (s, 3 H), 1.19 (s, 9 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: δ 169.3, 168.1, 136.3 (2 C), 136.2 (2 C), 131.4,

131.0, 130.05, 130.03, 128.01 (2 C), 127.96 (2 C), 74.1, 52.7, 52.0, 48.9, 28.6 (3 C), 22.1, 18.9; The ee was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (97/3)]; flow rate 1.0 mL/min; λ = 254 nm; τ_{minor} = 8.52 min, τ_{major} = 9.63 min; $[\alpha]_D^{25}$ = -4.0 (*c* 2.19, $CHCl_3$, ee = 65%); **HRMS (ESI)** calcd for $C_{23}H_{29}NNaO_6Si$ $[M + Na]^+$: 466.1656, found: 466.1668.

General Procedure for the preparation of enantioenriched organosilanes 3f and ***ent*-3f**

Under Argon atmosphere, in an oven dried 5 mL round-bottom flask equipped with a magnetic stirring bar, β-Silylmethylene malonate **1f** (81 mg, 0.2 mmol, 1 equiv) and catalyst **VI** (10 mg, 0.02mmol, 10 mol%) or catalyst **VI** (10 mg, 0.02mmol, 10 mol%) were dissolved in 0.3 mL of dry toluene and stirred at room temperature for about 5 min. The reaction mixture was cooled to 0°C (for **3f**) or -10 °C (for ***ent*-3f**) and stirred for 5 min. Nitromethane (210 µl, 4 mmol, 20 equiv) was added to the reaction mixture and stirred for 72 h. Once the β-silylmethylene malonate **1f** was consumed (monitored by TLC/^{1}HNMR), the reaction mixture was quenched by addition of saturated aqueous solution of NH_4Cl and diluted with CH_2Cl_2. The reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% petroleum ether/EtOAc-9% petroleum ether/EtOAc) to afford the corresponding products as white solid.

(*R*)-dimethyl 2-(2-nitro-1-(triphenylsily)ethyl)malonate 3f

Purified by column chromatography on silica gel (5% petroleum ether/EtOAc-9% petroleum ether/EtOAc). The above titled compound was isolated as white solid (74 mg, 80%). Mp: 106-107 °C (EtOAc/petroleum ether); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.60 (d, *J* = 7.0 Hz, 6 H), 7.49-7.46 (m, 3 H), 7.44-7.41 (m, 6 H), 5.27 (dd, *J* = 15.2, 9.8 Hz, 1 H), 4.64 (dd, *J* = 15.2, 2.5 Hz, 1 H), 3.85 (d, *J* = 3.9 Hz, 1 H), 3.59 (s, 3 H), 3.53-3.50 (m, 1 H), 3.28 (s, 3 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: δ 169.1, 168.5, 136.1 (6 C), 131.2 (3 C), 130.4 (3 C), 128.3 (6 C), 74.2, 52.7, 52.2, 49.3, 23.5; The ee was determined by HPLC using a Daicel Chiralpak OD-H

[hexane/*i*-PrOH (97/3)]; flow rate 1.0 mL/min; λ = 220 nm; τ_{minor} = 10.63 min, τ_{major} = 13.07 min; $[\alpha]_D^{25}$ = -34.1 (*c* 0.99, $CHCl_3$, ee = >93.0%); After single recrystallization, the ee of **3f** improved to >93.0%; **HRMS (ESI)** calcd for $C_{25}H_{25}NNaO_6Si$ $[M + Na]^+$: 486.1343, found: 486.1336.

(*S*)-dimethyl 2-(2-nitro-1-(triphenylsily)ethyl)malonate *ent*-3f

Purified by column chromatography on silica gel (5% petroleum ether/EtOAc-9% petroleum ether/EtOAc). The above titled compound was isolated as white solid (77 mg, 83%). mp: 104-105.5 °C (IPA/n-hexane); The ee was determined by HPLC using a Daicel Chiralpak OD-H [hexane/*i*-PrOH (97/3)]; flow rate 1.0 mL/min; λ = 220 nm; τ_{major} = 9.96 min, τ_{minor} = 12.06 min; $[\alpha]_D^{20}$ = +33.8 (*c* 1.22, $CHCl_3$, ee = 90%); After single recrystallization, the ee of ***ent*-3f** improved to 90%.

(*R*)-diethyl 2-(2-nitro-1-(1,1,3,3,3-pentamethyldisiloxanyl)ethyl)malonate 3g

Purified by column chromatography on silica gel (first petroleum ether, then 4% petroleum ether/EtOAc). The above titled compound was isolated as colourless liquid (65 mg, 86%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 4.74 (dd, *J* = 14.8, 8.2 Hz, 1 H), 4.54 (dd, *J* = 14.8, 4.7 Hz, 1 H), 4.23-4.12 (m, 4 H), 3.63 (d, *J* = 5.0 Hz, 1 H), 2.30 (dt, *J* = 8.1, 4.9 Hz, 1 H), 1.27 (td, *J* = 7.1, 2.6 Hz, 6 H), 0.19 (s, 3 H), 0.17 (s, 3 H), 0.07 (s, 9 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: δ 169.0, 168.7, 74.2, 61.8, 61.6, 49.9, 26.8, 13.93, 13.91, 1.7 (3 C), 0.34, 0.21; $[\alpha]_D^{25}$ = +2.48 (*c* 1.21, $CHCl_3$); **HRMS (ESI)** calcd for $C_{14}H_{29}NNaO_7Si_2$ $[M + Na]^+$: 402.1375, found: 402.1378.

(*R*)-dimethyl 2-(2-nitro-1-(1,1,3,3,3-pentamethyldisiloxanyl)ethyl)malonate 3h

Purified by column chromatography on silica gel (first petroleum ether, then 7% petroleum ether/EtOAc). The above titled compound was isolated as colourless liquid (54 mg, 77%).**^{1}H NMR (500 MHz, $CDCl_3$)**: δ 4.74 (dd, *J* = 14.8, 8.4 Hz, 1 H), 4.54 (dd, *J* = 14.8, 4.6 Hz, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.69 (d, *J* = 4.95 Hz, 1 H), 2.32 (pent, *J* = 4.8 Hz, 1 H), 0.19 (s, 3 H), 0.18 (s, 3 H), 0.08 (s, 9 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: δ 169.4, 169.1, 74.2, 52.7, 52.6,

49.5, 27.0, 1.7 (3 C), 0.20, 0.198; $[\alpha]_D^{25}$ = +5.75 (*c* 1.4, $CHCl_3$); **HRMS (ESI)** calcd for $C_{12}H_{25}NNaO_7Si_2$ $[M + Na]^+$: 374.1062, found: 374.1068.

***Asymmetric synthesis of* 3ab**

Under Argon atmosphere, in an oven dried 5 mL round-bottom flask equipped with a magnetic stirring bar, β-Silylmethylene malonate **1a** (61 mg, 0.2 mmol, 1 equiv) and catalyst **VI** (10 mg, 0.02mmol, 10 mol%) were dissolved in 220 µl of dry toluene and stirred at room temperature for about 5 min. The reaction mixture was cooled to -20 °C and stirred for 5 min. Nitroethane (285 µl, 4 mmol, 20 equiv) was added to the reaction mixture and stirred for 48 h at -20 °C. Once the β-silylmethylene malonate **1a** was consumed (monitored by ^{1}HNMR), the reaction mixture was quenched by addition of saturated aqueous solution of NH_4Cl and diluted with CH_2Cl_2. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was analysed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio (*by integration of ^{1}H-NMR signal: δmajor 0.53 ppm.* s*, δminor 0.49 ppm.* s), then the residue was purified by column chromatography on silica gel (first petroleum ether, then 3% petroleum ether/EtOAc) to afford **3ab** (almost as a single diastereomer) in 70% (53 mg) yield, colourless liquid. **Data of major diastereomer**: **^{1}H NMR (500 MHz, $CDCl_3$)**: *δ* 7.64-7.62 (m, 2 H), 7.38-7.37 (m, 3 H), 4.79-4.72 (m, 1 H), 4.27-4.20 (m, 2 H), 4.18-4.08 (m, 2 H), 3.38 (d, *J* = 3.6 Hz, 1 H), 2.56 (dd, *J* = 11.0, 3.6 Hz, 1 H), 1.41 (d, *J* = 6.6 Hz, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 0.53 (s, 3 H), 0.34 (s, 3 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: *δ* 169.0, 168.7, 138.5, 134.0 (2 C), 129.3, 128.0 (2 C), 85.3, 62.0, 61.7, 51.5, 31.9, 20.4, 14.0, 13.9, -0.7, -3.1; The ee of major diastereomer was determined by HPLC using a Daicel Chiralcel OD-H [hexane/*i*-PrOH (97/3)]; flow rate 0.5 mL/min; λ = 220 nm; τ_{minor} = 10.18 min, τ_{major} = 21.68 min; $[\alpha]_D^{25}$ = -39.0 (*c* 2.67, $CHCl_3$, ee = 80%); **HRMS (ESI)** calcd for $C_{18}H_{27}NNaO_6Si$ $[M + Na]^+$: 404.1500, found: 404.1509.

Asymmetric synthesis of 3ac

Under Argon atmosphere, in an oven dried 5 mL round-bottom flask equipped with a magnetic stirring bar, β-Silylmethylene malonate **1a** (61 mg, 0.2 mmol, 1 equiv) and catalyst **VI** (10 mg, 0.02mmol, 10 mol%) were dissolved in 140 µl of dry toluene and stirred at room temperature for about 5 min. The reaction mixture was cooled to -20 °C and stirred for 5 min. Nitropropane (356 µl, 4 mmol, 20 equiv) was added to the reaction mixture and stirred for 144 h. Once the β-silylmethylene malonate **1a** was consumed (monitored by ^{1}HNMR), the reaction mixture was quenched by addition of saturated aqueous solution of NH_4Cl and diluted with CH_2Cl_2. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was analysed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio (*by integration of ^{1}H-NMR signal: δmajor 0.51 ppm.* s*, δminor 0.48 ppm.* s and *δmajor 0.32 ppm.* s*, δminor 0.41 ppm.* s), and % of conversion of **1a** (> 99% conversion of **1a** after 144h as measured by ^{1}HNMR of the crude reaction mixture). The reaction mixture was subjected to column chromatography on silica gel (first petroleum ether, then 3% petroleum ether/EtOAc) to afford the corresponding product (almost as a single diastereomer) **3ac**, colourless liquid **3ac** (59 mg, 75 %). **Data of major diastereomer**: **^{1}H NMR (500 MHz, $CDCl_3$)**: *δ* 7.64-7.63 (m, 2 H), 7.38-7.37 (m, 3 H), 4.51 (td, *J* = 10.7, 3.0 Hz, 1 H), 4.32-4.22 (m, 2 H), 4.20-4.08 (m, 2 H), 3.39 (d, *J* = 3.3 Hz, 1 H), 2.51 (dd, *J* = 11.0, 3.3 Hz, 1 H), 1.77-1.64 (m, 2 H), 1.32 (t, *J* = 7.1 Hz, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 0.76 (t, *J* = 7.3 Hz, 3 H), 0.51 (s, 3 H), 0.32 (s, 3 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: *δ* 169.1, 168.8, 138.8, 134.0 (2 C), 129.2, 127.9 (2 C), 92.4, 62.0, 61.7, 51.4, 30.9, 27.4, 14.0, 13.9, 10.7, -0.5, -3.5; The ee of major diastereomer was determined by HPLC using a Daicel Chiralcel OD-H [hexane/*i*-PrOH (97/3)]; flow rate 1.0 mL/min; λ = 220 nm; τ_{minor} = 4.50 min, τ_{major} = 10.47 min; $[\alpha]_D^{24}$ = -34.0 (*c* 1.93, $CHCl_3$, ee =74%); **HRMS (ESI)** calcd for $C_{19}H_{29}NO_6SiK$ $[M + K]^+$: 434.1401, found: 434.1413.

Preparative Scale Synthesis of 3a

Under Argon atmosphere, in an oven dried 25 mL round-bottom flask equipped with a magnetic stirring bar, β-Silylmethylene malonate **1a** (612 mg, 2 mmol, 1 equiv) and catalyst **VI** (50 mg, ~0.10 mmol, 5 mol%) were dissolved in 4 mL of dry toluene and stirred at room temperature for about 5 min. Then, the reaction mixture was cooled to 0°C and stirred for 5 min. Then nitromethane **2a** (1.1 mL, 20 mmol, 10 equiv) was added to the reaction mixture and stirred for 24 h. the reaction mixture was quenched by addition of saturated aqueous solution of NH_4Cl and diluted with CH_2Cl_2. The reaction mixture was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% petroleum ether/EtOAc-8% petroleum ether/EtOAc) to afford the corresponding products **3a** in 0.61 g (83% yield).

***Preparative Scale Synthesis of* 3ab**

Under Argon atmosphere, in an oven dried 25 mL round-bottom flask equipped with a magnetic stirring bar, β-Silylmethylene malonate **1a** (306 mg, 1.0 mmol, 1 equiv) and catalyst **VI** (50 mg, 0.1mmol, 10 mol%) were dissolved in 1.1mL of dry toluene and stirred at room temperature for about 10 min. The reaction mixture was cooled to -20 °C and stirred for 5 min. Nitroethane (1.4 mL, ~20 mmol, 20 equiv) was added to the reaction mixture and stirred for 48 h at -20 °C. Once the β-silylmethylene malonate **1a** was consumed (monitored by ^{1}HNMR), the reaction mixture was quenched by addition of saturated aqueous solution of NH_4Cl and diluted with CH_2Cl_2. The reaction mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was analysed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio (*by integration of ^{1}H-NMR signal: δmajor 0.53 ppm.* s*, δminor 0.49 ppm.* s), then the residue was purified by column chromatography on silica gel (first petroleum ether,

then 3% petroleum ether/EtOAc) to afford **3ab** (almost as a single diastereomer) in 68% (260 mg) yield, colourless liquid.

(*3R,4R*)-ethyl 4-(dimethyl(phenyl)silyl)-2-oxopyrrolidine-3 carboxylate 4

Under Argon atmosphere, to a suspension of **3a** (632 mg, 1.72 mmol) and $NiCl_2$•$6H_2O$ (450 mg, 1.89 mmol) in MeOH (8.0 mL) was added $NaBH_4$ (780 mg, 20.6 mmol) carefully at 0 °C. The reaction mixture was stirred at 0 °C for 5 h. The reaction mixture was passed through a pad of Celite and silica gel and flushing with 150 mL of 5% MeOH/CH_2Cl_2. The solvent was removed under reduced pressure and the residue was directly subjected to column chromatography on silica gel (first CH_2Cl_2 then 3% MeOH/ CH_2Cl_2) to afford **4** as a red liquid (346 mg, 69%). *It should be noted that diastereomer ratio of the crude could not be determined but after column chromatography the product **4** was isolated as a single diastereomer.* **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.48-7.46 (m, 2 H), 7.39-7.36 (m, 3 H), 6.74 (bs, 1 H), 4.15-4.10 (m, 2 H), 3.43 (t, J = 9.5 Hz, 1 H), 3.22-3.17 (m, 2 H), 2.40 (q, J = 9.5 Hz, 1 H), 1.23 (t, J =7.2 Hz, 3 H), 0.33 (s, 6 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: δ 174.5, 170.3, 135.2, 133.8 (2 C), 129.7, 128.1 (2 C), 61.6, 49.9, 42.5, 26.0, 14.0, -5.0, -5.2; $[\alpha]_D^{27}$ = +30.9 (*c* 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{15}H_{22}NO_3Si$ $[M + H]^+$: 292.1369; found: 292.1371

(*3R,4R*)-4-(dimethyl(phenyl)silyl)-2-oxopyrrolidine-3 carboxylic acid 5

To a stirred solution of **4** (330 mg, 1.13 mmol) in EtOH (5.0 mL) was added aq. NaOH 1N (1.5 mL, 1.32 equiv) dropwise at 0 °C. After completion of addition, the cold bath was removed. The reaction mixture was stirred at room temperature for 90 min. The reaction mixture concentrated, acidified with HCl (6N) and extracted with EtOAc (4 x 20 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The acid **5** was isolated as a light-brown solid (272 mg, 92% yield). **^{1}H NMR (500 MHz, CD_3OD)**: δ 7.54-7.52 (m, 2 H), 7.38-7.37 (m, 3 H), 4.89 (bs, 2 H), 3.43 (t, J = 9.6 Hz, 1

H), 3.22 (t, *J* = 9.7 Hz, 1 H), 3.18 (d, *J* = 10.5 Hz, 1 H), 2.34 (q, *J* = 10.2 Hz, 1 H), 0.36 (s, 3 H), 0.35 (s, 3 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: δ 176.7, 173.8, 136.8, 135.0 (2 C), 130.7, 129.1(2 C), 51.6, 43.7, 27.4, -4.7, -5.2; **IR (ATR)**: 3280, 1719, 1663,1285, 1251, 1110, 852, 829 cm^{-1}; **HRMS (ESI)** calcd for $C_{13}H_{17}NO_3Si$ $[M - H]^-$: 262.0898; found: 262.0898.

(*R*)-4-(dimethyl(phenyl)silyl)pyrrolidine-2-one 6

The acid **5** (263 mg, 1.0 mmol), without any further purification, was dissolved in toluene (10 mL) and refluxed for 16h. The reaction mixture was brought to room temperature and then concentrated under reduced pressure. The residue was directly subjected to column chromatography on silica gel (first 50% EtOAc/petroleum ether then EtOAc) to afford **6** as a white solid (165 mg, 75%). Mp: 89-90 °C (EtOAc/petroleum ether); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.48-7.47 (m, 2 H), 7.39-7.36 (m, 3 H), 6.61 (bs, 1 H), 3.41 (t, *J* = 9.3 Hz, 1 H), 3.27 (t, *J* = 9.6 Hz, 1 H), 2.35 (dd, *J* = 16.9, 9.8 Hz, 1 H), 2.18 (dd, *J* = 16.9, 11.0 Hz, 1 H), 1.93 (pent, , *J* = 9.5 Hz, 1 H), 0.33 (s, 3 H), 0.32 (s, 3 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: δ 179.7, 136.2, 133.7 (2 C), 129.5, 128.0 (2 C), 44.1, 32.0, 21.2, -4.9, -5.2; $[\alpha]_D^{25}$ = +11.4 (*c* 0.8, $CHCl_3$, ee = 87%) lit.[27] $[\alpha]_D^{28}$ = +17.9 (c = 1.00, $CHCl_3$); The ee of was determined by HPLC using a Daicel Chiralcel OD-H [hexane/*i*-PrOH (80/20)]; flow rate 1.0 mL/min; λ = 220 nm; τ_{major} = 8.51 min, τ_{minor} = 10.63 min; **HRMS (ESI)** calcd for $C_{12}H_{18}NOSi$ $[M + H]^+$: 220.1152, found: 220.1152.

***(R)-1-benzyl-4-(dimethyl(phenyl)silyl)pyrrolidine-2-one* 8**

Under Argon atmosphere, in an oven dried 25 mL round-bottom flask equipped with a magnetic stirring bar, sodium hydride (52 mg, 50% in oil, 1.1 mmol, 1.5 equiv.) was made oil free by washing with dry hexane and then 2 mL of dry THF was added. To this stirred suspension of sodium hydride solution sequentially, a solution of 18-crown-6 in 0.5 mL of dry THF, lactam **6** (160 mg, 0.73 mmol, 1 equiv) in 2.0 mL of dry THF and benzyl bromide (96

µl, 0.80 mmol, 1.1 equiv) in 1.0 mL of dry THF were added at 0 °C. After the addition, the cold bath was removed and then the reaction mixture was stirred at 32 °C for 2h. The reaction mixture was quenched with water (8 mL) and extracted with $CHCl_3$ (3× 15 mL). The combined extract was washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The residue was directly subjected to column chromatography on silica gel (10% EtOAc/petroleum ether to 25% EtOAc/petroleum ether) to afford **8** (185 mg, 82%) as a colorless liquid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.44-7.43 (m, 2 H), 7.40-7.26 (m, 6 H), 7.19 (d, *J* = 7.2 Hz, 2 H), 4.56 (d, *J* = 14.8 Hz, 1 H), 4.25 (d, *J* = 14.8 Hz, 1 H), 3.31 (t, *J* = 9.5 Hz, 1 H), 3.15 (t, *J* = 9.4 Hz, 1 H), 2.55 (dd, *J* = 17.0, 10.0 Hz, 1 H), 2.34 (dd, *J* = 16.9, 10.6 Hz, 1 H), 1.76 (pent, *J* = 9.8 Hz, 1 H), 0.29 (3 H), 0.28 (3 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: δ 175.1, 136.5, 136.1, 133.6 (2 C), 129.5, 128.6 (2 C), 128.0 (2 C), 127.9 (2 C), 127.4, 48.4, 46.6, 39.9, 17.7, -4.9, -5.3; $[\alpha]_D^{25}$= -4.3 (c = 3.1, $CHCl_3$); **HRMS (ESI)** calcd for $C_{19}H_{24}NOSi$ $[M + H]^+$: 310.1633, found: 310.1627.

***(R)-1-benzyl-4-hydroxypyrrolidine-2-one* 9**

Potassium bromide (32 mg, 0.32 mmol, 1.2 equiv), sodium acetate (33 mg, 0.41 mmol, 1.5 equiv) and lactam **8** (84 mg, 0.27 mmol, 1 equiv) were stirred at 0 °C. To this mixture was dropwise added peracetic acid (~32% solution in acetic acid, 3 mL). The reaction mixture was warmed slowly to room temperature and stir for overnight. Sodium thiosulphate (solid) was added to the reaction mixture and stirred until (approx. 10 min) the clear solution became turbid. Solvent was removed under reduced pressure and the residue was dissolved in dichloromethane and passed through a pad of Na_2SO_4. The organic solvent was evaporated under reduced pressure. The residue was directly subjected to column chromatography on silica gel (EtOAc) to afford **9** (33 mg, 64%) as a white solid. mp: 103-104°C; lit.[30] for (*S*)-enatiomer, 107.5–109°C; **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.33-7.30 (m, 2 H), 7.28-7.25 (m, 1 H), 7.22 (d, *J* = 7.3 Hz, 2 H), 4.48 (d, *J* = 14.8 Hz, 1H), 4.45-4.42 (m, 1 H), 4.40 (d, *J* = 14.8 Hz, 1H),

3.48 (dd, *J* = 10.9, 5.6 Hz, 1H), 3.36 (bs, 1 H), 3.19 (d, *J* = 10.9 Hz, 1H), 2.70 (dd, *J* = 17.4, 6.6 Hz, 1H), 2.43 (dd, *J* = 17.4, 1.7 Hz, 1H), **13C{1H} NMR (125 MHz, $CDCl_3$)**: δ 173.2, 135.9, 128.7 (2 C), 127.9 (2 C), 127.6, 64.1, 55.7, 46.3, 41.1; $[\alpha]_D^{25}$= +38.0 (c = 1.22, $CHCl_3$), lit.[30] for (*S*)-enatiomer $[\alpha]_D^{20}$ = -35.2 (c = 1.30, $CHCl_3$); **IR (ATR)**: 3287, 1651, 1482, 1442, 1422, 1406, 1285, 1212, 1084, 974, 737 cm^{-1}; **HRMS (ESI)** calcd for $C_{11}H_{14}NO_2$ $[M + H]^+$: 192.1026, found: 192.1025.

(*3R,4R*)-4-(dimethyl(phenyl)silyl)-2-oxopyrrolidine-3-carbohydrazide 12

The solution of DIPC (124 µl, 0.79 mmol, 1 equiv) in dry THF (2mL) was added dropwise to a stirred solution of the acid **5** (208 mg, 0.79 mmol) and N-hydroxysuccinimide (109 mg, 0.95 mmol, 1.2 equiv) in dry THF (6.0 mL) at 0 °C under Argon atmosphere. The reaction mixture was slowly brought to room temperature and stirred for overnight. The suspension was filtered and residue was washed with diethyl ether (2 x 0.5 mL). The filtrate was added dropwise at 0°C to a solution of hydrazine hydrate (130 µl) in THF (0.5 mL) and the mixture was stirred for 2 h at 5°C. The reaction mixture was filtered and residue was washed with diethyl ether (2 × 0.5 mL). The solvent was removed under reduced pressure and the residue was directly subjected to column chromatography on silica gel (CH_2Cl_2 to 7% MeOH/ CH_2Cl_2) to afford **12** (120 mg, 55%) as thick liquid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 8.36 (bs, 1 H), 7.48-7.47 (m, 2 H), 7.36-7.35 (m, 3 H), 6.71-6.67 (m, 1 H), 3.40 (t, *J* = 9.7 Hz, 1 H), 3.17 (t, *J* = 9.4 Hz, 1 H), 2.99 (d, *J* = 10.5 Hz, 1 H), 2.48 (q, *J* = 9.5 Hz, 1 H), 0.35 (s, 3 H), 0.34 (s, 3 H); **13C{1H} NMR (125 MHz, $CDCl_3$)**: δ 175.8, 169.2, 135.7, 133.9 (2 C), 129.7, 128.1 (2 C), 48.3, 42.7, 23.0, -4.5, -5.0; **IR (ATR)**: 3232, 1691, 1654, 1424, 1253, 1112, 882, 735 cm^{-1}; **HRMS (ESI)** calcd for $C_{13}H_{19}N_3NaO_2Si$ $[M + Na]^+$: 300.1147, found: 300.1147.

***(3R, 4R, E)-N′-(1-(3-bromophenyl)ethylidene)-4-(dimethyl(phenyl)silyl)-2oxopyrrolidine-3-carbohydrazide* 13**

3′-bromoacetophenone (49 µl, 0.37 mmol, 1 equiv) was added drop wise to a stirred solution of **12** (103 mg, 0. 37 mmol, 1 equiv) and acetic acid (2 drops) in 2 mL dry ethanol. The reaction mixture was stirred at 30 °C for 48h. The solvent was removed under reduced pressure and the residue was directly subjected to column chromatography on silica gel (CH_2Cl_2 to 3% MeOH/ CH_2Cl_2) to afford **13** (144 mg, 85%) as a white solid. [*The product **13** exists as a E/Z mixture*[31]*and could not be separated in column chromatography or by crystallization*]. (The product was contaminated with small amount of inseparable unidentified impurities which could be separated by single recrystallization). Mp: 174-175 °C (EtOAc/petroleum ether); **^{1}H NMR (500 MHz, $CDCl_3$, *E*/*Z* mixture)**: δ 10.8 (s, 1H, major), 9.0 (bs, 1 H, minor), 7.97 (s, 1 H, major), 7.85 (s, minor), 7.73 (d, *J* = 8.0 Hz, 1 H, major), 7.59 (d, *J* = 7.8 Hz, 1 H, minor), 7.54-7.51 (m, 2 H, major), 7.48 (d, *J* = 7.8 Hz, 1 H, major), 7.43 (d, *J* = 7.0 Hz, 1 H, major), 7.38-7.36 (m, 3 H, major), 7.38-7.36 (m, 1 H, minor), 7.28-7.21 (m, 6 H, minor), 6.37 (bs, 1 H, minor), 6.23 (bs, 1 H, minor), 4.48 (d, *J* = 11.7 Hz, 1 H, minor), 3.49 (t, *J* = 9.2 Hz, 1 H, minor), 3.39 (t, *J* = 10.0 Hz, 1 H, major), 3.30 (t, *J* = 9.9 Hz, 1 H, minor), 3.25-3.20 (m, 2 H, major), 2.59 (q, *J* = 10.4 Hz, 1 H, minor), 2.51 (q, *J* = 9.9 Hz, 1 H, major), 2.26 (s, 3 H, major), 2.16 (s, 3 H, minor), 0.48 (s, 3 H, major), 0.44 (s, 3 H, major), 0.34 (s, 3 H, minor), 0.33(s, 3 H, minor); **13C{1H} NMR (125 MHz, $CDCl_3$, *E*/*Z* mixture)**: 176.3 (major), 175.7 (minor), 172.7 (minor), 164.3 (major), 150.7 (major), 146.7 (minor), 139.83 (major), 139.78 (minor), 135.8 (major), 135.4 (minor), 134.0 (2 C, major), 133.9 (2 C, minor), 132.3 (major), 132.2 (minor), 129.9 (minor), 129.7 (major), 129.5 (2 C, major), 129.2 (minor), 128.0 (2 C, major), 127.9 (2C, minor), 125.2 (major), 124.9 (minor), 122.6 (minor), 122.5 (major), 48.2 (major), 46.2 (minor), 42.7 (major), 26.3 (minor), 22.4 (major), 13.6 (major), 13.0 (minor), -3.9 (major), -4.7 (major), -4.8 (minor), -5.0 (minor); $[\alpha]_D^{22}$= +120.0 (c = 2.7, $CHCl_3$, after single

crystallization); **IR (ATR)**: 3270, 2947, 2887, 1711, 1662, 1546, 1423, 1293, 1253, 1156, 1108, 772 cm^{-1}; **HRMS (ESI)** calcd for $C_{21}H_{24}BrN_3NaO_2Si$ $[M + Na]^+$: 480.0713, found: 480.0707.

Keywords: Enantioenriched organosilanes, Organocatalysis, (*R*)-oxiracetam, 4-hydroxy-pyrrolidin-2-one

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