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High Stereocontrol in the Preparation of Silyl-Protected γ-Substituted Enoldiazoacetates

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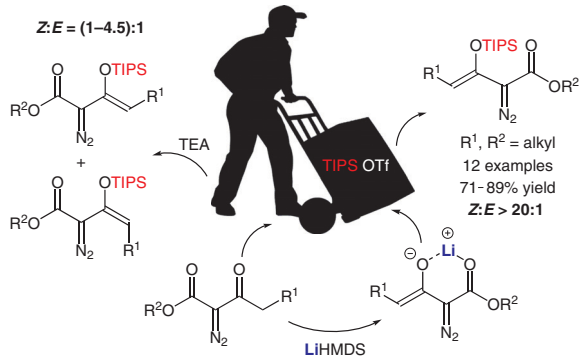

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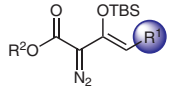
Abstract A robust and efficient synthesis of triisopropylsilyl (TIPS)-protected γ-substituted enoldiazoacetates with excellent *Z* stereocontrol by using lithium bis(trimethylsilyl)azanide (LiHMDS) as a base and TIPSOTf as a silyl transfer reagent is reported. Despite their increased size compared to previously *tert*-butyldimethylsilyl (TBS)-protected γ-unsubstituted enoldiazoacetates, a high product yield with exceptional stereocontrol has been achieved in copper-catalyzed [3+3] cycloaddition reaction with nitrones by using a chiral indeno bisoxazoline ligand.

Key words enoldiazoacetates, *Z* selectivity, cycloaddition, copper catalysis, nitrones, bisoxazolines

Silyl-protected enoldiazo compounds are becoming reagents of choice for [3+*n*] cycloaddition reactions through which their three-carbon dipolar metal carbene intermediates are able to combine with *n* atoms to form carbo- and heterocyclic products in high yields and stereoselectivities. In pursuing these transformations, 3-(*tert*-butyldimethylsilyloxy)-2-diazo-3-butenoates (**1a**) were the reactants,[1,2] and only two structural analogues (**1b**,**c** with R = Me and Ph) were reported as alternatives (Figure 1).[3]



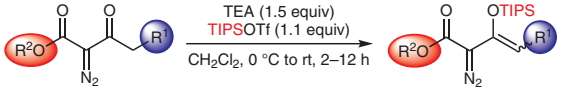
a R^1 = H; R^2 = alkyl
b R^1 = Me; R^2 = alkyl
c R^1 = Ph; R^2 = alkyl

1

Figure 1 Reported enoladiazoacetates **1** used in [3+*n*] cycloaddition reactions

These structural analogues were prepared by the standard procedure that converted the corresponding β-keto-α-diazoester to its silyl enol ether by using TBSOTf as the silyl transfer agent and triethylamine as the base.[4] This methodology proved to be satisfactory for the production of **1b**,**c** that were formed in high yields with exclusive *Z* geometry.[3,5] However, with use of triisopropylsilyl triflate (TIPSOTf) as the silyl transfer agent and triethylamine as the base, product yields were high (74–93%), but stereochemical control of the product geometry was low (Table 1).

Table 1 Scope of TIPS-Protected Enoldiazoacetates Obtained by Using Triethylamine as the Base[a]



2 **3**

Entry	R^1	R^2	Ratio (*Z*/*E*)[b]	Yield of **3** (%)[c]
1	Et	Me	3:1	**3a**, 91
2	Me	Me	3:1	**3b**, 84
3	Bn	Me	1:1	**3c**, 90
4	*i*-Pr	Me	1:1	**3d**, 74
5	*n*-C_8H_{17}	Me	(2.3):1	**3e**, 93
6	Et	*i*-Pr	(2.3):1	**3f**, 85
7	Et	Bn	(2.2):1	**3g**, 87
8	Et	4-BrBn	2:1	**3h**, 90
9	Et	4-OMeBn	(4.5):1	**3i**, 88
10	Et	3,4,5-triOMeBn	2:1	**3j**, 82
11	Et	4-CF_3Bn	2:1	**3k**, 78
12	Me	4-OMeBn	(4.5):1	**3l**, 85

[a] Reaction conditions: To **2** (2.0 mmol) in dry CH_2Cl_2 (10 mL) was added Et_3N (0.42 mL, 3.0 mmol) in one portion at 0 °C, followed by a dropwise addition of TIPSOTf (0.55 mL, 2.05 mmol); and the reaction solution was stirred at r.t. for 2–12 h.
[b] The *Z*/*E* ratios were determined by ^1H NMR analysis.
[c] Isolated yields of the combined *Z*+*E* isomers after flash-chromatography.

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Enoldiazoacetates with relatively small substituents at the 4-position (Me, **3b** and Et, **3a**) were obtained with moderate *Z*/*E* ratios of 3:1. Increasing the size of the substituent at the 4-position (*n*-C_8H_{17}, **3e**) diminished the ratio of *Z*/*E* to (2.3):1 and even to 1:1 when sterically encumbered substituents (Bn, **3c** or *i*-Pr, **3d**) were introduced. To investigate the effect of the carboxylate group on stereoselectivity, we also prepared a series of 4-ethyl-substituted alkyl enoldiazoacetates **3f–3k**. Isopropyl-, benzyl-, and 4-substituted benzyl-diazoacetates in most cases (entries 6–8, 10–11) did not show an improvement in stereoselectivity (*Z*/*E* near 2:1). Surprisingly, 4-methoxybenzyl enoldiazoacetates **3i** and **3l** were obtained with a higher *Z*/*E* ratio of (4.5):1.

Desiring to produce these enoldiazoacetates as one stereoisomer, we considered other methodologies used in the production of silyl enol ethers.[6] However, the diazo functionality places limitations on acceptable methodologies, especially the need to avoid acids. Simple alternative strategies, such as use of lower temperatures or different leaving groups and bases did not offer advantages. Our investigation was carried out with β-keto-α-diazoester **2a** and triisopropylsilyl trifluoromethanesulfonate as model substrates in dichloromethane (CH_2Cl_2) at 0 °C (Table 2). As part of our previous work on enoldiazoacetates, triethylamine (Et_3N) was used as the base, and the desired product **3a** was formed in excellent yield (91%) but with low stereoselectivity (entry 1, *Z*/*E* = 3:1). Several amine bases were screened in this transformation (entries 2–7), but none of them gave any advantage in terms of both the yield and selectivity. Most of the starting material (**2a**) was recovered because of the competing facile TIPS transfer to the nitrogen atom of those bases (entries 2–4, 6–7). Attempted optimization by changing the concentration of Et_3N did not show an improvement (ratios *Z*/*E* were lower at either lower or higher concentration, entries 8, 9). The use of other solvents either lowered the *Z*/*E* ratio (entry 10) or the yield of **3a** (entries 11, 12). Temperature screening provided a higher ratio of *Z*/*E* when the reaction was carried out at –78 °C by using *N*,*N*-diisopropylethylamine (DIPEA) as the base (entry 14, *Z*/*E* = 6:1). All of the results obtained with the use of amines are consistent with initial silicon attachment to the ketone-carbonyl group of the diazoacetoacetate followed by proton transfer enolization of the silyl-activated α-diazo-β-ketoacetate (Lewis acid-initiated enolization).[7] The TIPS group is sufficiently large to change the conformational preference of torms the *Z* isomer.he silyl-activated α-diazo-β-ketoacetate (Figure 2) inhibiting product formation from the conformation that preferentially forms the *Z* isomer.

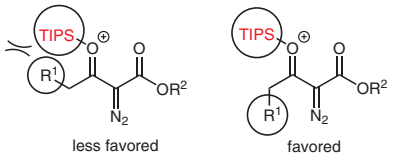
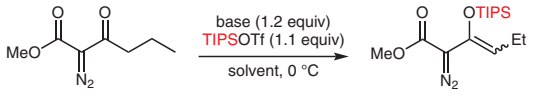


Figure 2 Preferential formation of *E* isomer in Lewis acid-initiated enolization of β-keto-α-diazoesters

As a consequence of these results, we considered employing the enolate alternative: the use of a strong base with a lithium cation that activates the ketone through presumed bidentate lithium ion coordination with both carbonyl oxygens of the ketoester that enforces proton abstraction by the base on the conformation that favors formation of the *Z* lithium enolate. Subsequent nucleophilic attack of TIPS-OTf by the enolate would produce the desired silyl enoldiazoacetate with high stereocontrol.[8] A strong base, lithium diisopropylamide (LDA), was initially used in the model reaction (Table 2, entry 15), and enoldiazoacetate **3a** was formed in good yield (74%) but with only a modest *Z*/*E* ratio of (5.5):1. In contrast, the more sterically encumbered lithium salt, lithium bis(trimethylsilyl)azanide (LiHMDS), showed a much better result to afford **3a** in 88% yield with

Table 2 Synthesis of TIPS-Protected Enoldiazoacetate **3a**: Reaction Optimization[a]



2a **3a**

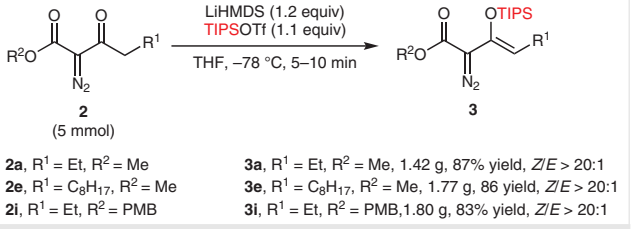
Entry	Base	Solvent	Ratio (*Z*/*E*)[b]	Yield of **3a** (%)[c]
1	Et_3N	CH_2Cl_2	3:1	91
2	DIPEA	CH_2Cl_2	4:1	51
3[d]	*i*-Pr_2NH	CH_2Cl_2	(1.3):1	37
4[d]	pyridine	CH_2Cl_2	(1.5):1	21
5	DABCO	CH_2Cl_2	1:1	82
6[d]	pyrrolidine	CH_2Cl_2	1:(1.8)	15
7[d]	piperidine	CH_2Cl_2	1:(1.5)	23
8[e]	Et_3N	CH_2Cl_2	(2.8):1	88
9[f]	Et_3N	CH_2Cl_2	(1.1):1	89
10	Et_3N	chloroform	(1.8):1	82
11[d]	Et_3N	toluene	(2.4):1	20
12	Et_3N	THF	(2.3):1	41
13[g]	Et_3N	CH_2Cl_2	(2.4):1	91
14[g]	DIPEA	CH_2Cl_2	6:1	71
15[g]	LDA	THF	(5.5):1	74
16[g]	LiHMDS	THF	>20:1	88
17[g,h]	LiHMDS	THF	–	n.d.

[a] Reaction conditions: To **1a** (85 mg, 0.50 mmol) and base (0.60 mmol) in solvent (2.0 mL) was added TIPSOTf (169 mg, 0.55 mmol) under an argon atmosphere at 0 °C.
[b] *Z*/*E* ratios were determined by ^{1}H NMR analysis,
[c] Isolated yields after flash-chromatography.
[d] Most of material **2a** was recovered.
[e] The reaction was carried out at the conc. of 0.1 M.
[f] The reaction was carried out at the conc. of 0.5 M.
[g] The reaction was carried at –78 °C.
[h] TIPSCl was used; n.d. = no product was detected.

an *Z*/*E* ratio of >20:1 (entry 16). In addition to the remarkable level of *Z* selectivity of the enolization, this procedure also gives complete reaction in just five minutes. The use of chloride instead of triflate as the leaving group in the silyl transfer agent did not lead to the desired product **3a** (entry 17); only starting material **2a** was recovered.

Having the optimized conditions in hand, we converted a variety of substrates **2** to the corresponding enoldiazoacetates **3** effectively with exclusive *Z* stereoselectivity (*Z*/*E* > 20:1) (Table 3). β-Keto-α-diazoesters **2** with small substituents R^1 = Et, Me underwent a smooth conversion to enoldiazoacetates **3a**,**b** in good yields (71–88%) (entries 1, 2). More sterically hindered alkyl groups such as Bn (**2c**) and *i*-Pr (**2d**) also worked well and afforded the desired products **3c**,**d** in high yields (85–87%). The long chain *n*-octyl group (**2e**) was also tolerated in this process to produce enoldiazoacetate **3e** in high yield (81%). Furthermore, we explored the substituent variations in the ester group, and the nature of the substituents at the 4-position (R^1) of β-keto-α-diazoester **2** (Me or Et) did not affect the reaction outcome. The isopropyl ester (**2f**) and a series of benzyl β-keto-α-diazoesters **2** bearing electron-neutral (**2g**), -donating (**2h**–**1j** and **2l**), or -withdrawing (**2k**) substituents on the aromatic ring smoothly underwent the enolization with TIPSOTf to afford the corresponding enoldiazoacetates **3** in high yields (76–89%) with excellent *Z* stereoselectivity (*Z*/*E* >20:1).

Our ultimate goal is to use the obtained γ-substituted enoldiazoacetates **3** as the reactants in [3+*n*] cycloaddition reactions. Therefore, to demonstrate the practicality and synthetic utility of the current method, 5 mmol scale reactions were carried out (Scheme 1). On this scale the desired γ-substituted enoldiazoacetates **3** were obtained in comparable high yields and excellent stereocontrol.

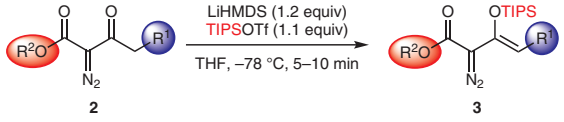


Scheme 1 Examples of the 5 mmol scale syntheses of γ-substituted enoldiazoacetates with high *Z* stereocontrol

In a previous study of the enantioselective [3+3] cycloaddition of TBS-protected (*Z*)-4-phenyl-substituted enoldiazoacetates, we reported that dirhodium catalysts were unable to effect [3+3] cycloaddition with nitrones but that silver/*t*-BuBOX [BOX: bis(oxazoline)] catalysis was effective.[3d] There is no other example of a [3+3] cycloaddition reaction of a γ-substituted enoldiazoacetate with a nitrone, and we anticipated that there could be a significant barrier to cycloaddition with the bulkier TIPS-protected γ-substituted enoldiazoacetates. However, we have found that the representative substrate, TIPS-protected (*Z*)-4-octyl-substituted enoldiazoacetate **3e**, undergoes cycloaddition with nitrone **4** using copper(I)/InBOX catalysis (Scheme 2). Chiral oxazine **5** was obtained as a single diastereomer in high yield (93%) and enantioselectivity (93% ee), and its absolute configuration was determined by comparison of the sign of optical rotation with those of previously reported [3+3] cycloaddition products to be (3*S*,6*R*).[3d] Notably, the same transformation under silver/*t*-BuBOX catalysis resulted in a high yield (81%) of oxazine **5** but negligible enantioselectivity (Scheme 2), which indicates the substantial effect of ligand and metal catalyst to stereocontrol of this process. In addition, two other combinations of metal–ligand [$Cu(MeCN)_4PF_6$/(*S*)-*t*-BuBOX and $AgSbF_6$/**L1**] did not provide an improvement in enantioselectivity (30 and 38% ee, respectively, Scheme 2), although the yields of oxazine **5** were high (83–88%). As anticipated, other examples of γ-substituted enoldiazoacetates **3** also gave high yields and selectivities in [3+3] cycloaddition with nitrone **4** with use of the Cu(I)/**L1** catalyst.

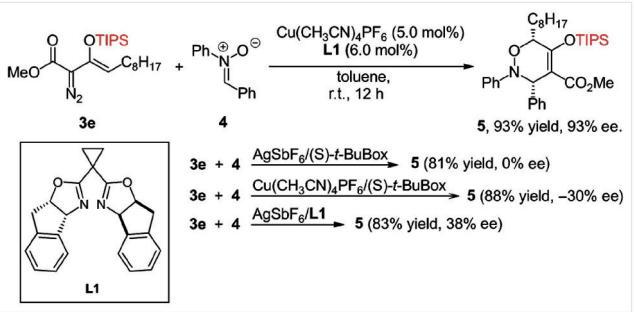
A motivation for the use of the TIPS-protected γ-substituted enoldiazoacetates is our discovery that [3+1] cycloaddition of enoldiazoesters[3a] did not occur with TBS-protect-

Table 3 Scope of TIPS-Protected Enoldiazoacetates Obtained by Using LiHMDS as the Base[9,a]



Entry	R^1	R^2	Ratio (*Z*/*E*)[b]	Yield of **3** (%)[c]
1	Et	Me	>20:1	**3a**, 88
2	Me	Me	>20:1	**3b**, 71
3	Bn	Me	>20:1	**3c**, 85
4	*i*-Pr	Me	>20:1	**3d**, 87
5	*n*-C_8H_{17}	Me	>20:1	**3e**, 81
6	Et	*i*-Pr	>20:1	**3f**, 88
7	Et	Bn	>20:1	**3g**, 81
8	Et	4-BrBn	>20:1	**3h**, 83
9	Et	4-OMeBn	>20:1	**3i**, 82
10	Et	3,4,5-triOMeBn	>20:1	**3j**, 77
11	Et	4-CF_3Bn	>20:1	**3k**, 89
12	Me	4-OMeBn	>20:1	**3l**, 76

[a] Reaction conditions: to **1** (0.50 mmol) in THF (2.0 mL) LiHMDS (0.60 mL, 0.60 mmol, 1.0 M in hexane) followed by TIPSOTf (169 mg, 0.55 mmol) were added dropwise under N_2 atmosphere at –78 °C.
[b] *Z*/*E* ratios were determined by ^{1}H NMR analysis.
[c] Isolated yields after flash chromatography.



Scheme 2 An example of a highly enantioselective copper(I)-catalyzed [3+3] cycloaddition of silyl-protected γ-substituted enoldiazoacetate **3e** with nitrone **4**

ed γ-substituted enoldiazoacetates. To exemplify the process, treatment of TIPS-protected (*Z*)-4-ethyl-substituted enoldiazoacetate **3a** with sulfur ylide **6** by using a copper(I)/SaBOX catalyst (Scheme 3) gave chiral cyclobutene **7** in high yield (74%) and enantioselectivity (90% ee) as a single diastereomer.

Another example of the utility of this methodology is found in reactions with 1-methylindole **8**. In contrast to prior reports of [3+2] cycloaddition with enoldiazoacetates,[10] the TIPS-protected γ-substituted enoldiazoacetate **3a** (*Z*/*E* > 20:1) gave the product from formal C–H functionalization (**9**) exclusively (88% isolated yield) in reactions catalyzed by rhodium acetate (Scheme 4). In contrast, the same reaction over the same reaction time with **3a** (*Z*/*E* = 1:1) gave a low yield of **9** and produced the donor–acceptor cyclopropene **10** in only 51% combined yield.

In summary, we have demonstrated the robust synthesis of TIPS-protected γ-substituted enoldiazoacetates with excellent *Z* stereoselectivity. Products were obtained in high yields from common β-keto-α-diazoesters by using LiHMDS as a base and TIPSOTf as a silyl transfer reagent. Besides high stereocontrol, another great advantage of this method is the possibility to prepare γ-substituted enoldiazoacetates in just five minutes. In addition, the first example of highly enantioselective copper-catalyzed [3+3] cycloaddition of silyl-protected (*Z*)-4-alkyl-substituted enoldiazoacetate with nitrone is reported. Future studies that focus on the application of solely the *Z* stereoisomer of enoldiazoacetates in [3+*n*] cycloaddition reactions with stable dipoles are underway in our laboratory.

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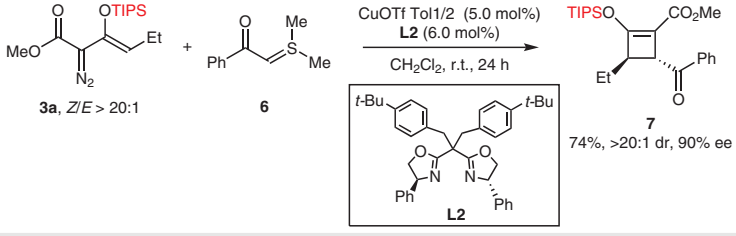
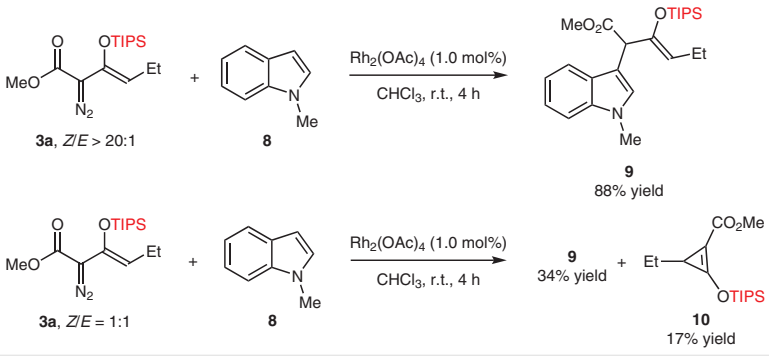
Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611865.



Scheme 3 An example of copper(I)-catalyzed [3+1] cycloaddition of silyl-protected γ-substituted enoldiazoacetate **3a** with sulfur ylide **6**



Scheme 4 An example of rhodium(II)-catalyzed reaction of silyl-protected γ-substituted enoldiazoacetate **3a** with 1-methylindole **8**

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(9) **General Procedure for the Preparation of (*Z*)-Enoldiazoacetates 3**: A 10 mL oven-dried vial equipped with a magnetic stirring bar was charged with diazoacetate **2** (0.50 mmol) and the system was filled with nitrogen. THF (2.0 mL) was then added, and the reaction solution was cooled to –78 °C (dry ice/acetone bath). LiHMDS (0.60 mL, 1.0 M in the hexanes) was introduced dropwise in 2 min, followed by the addition of TIPSOTf (168.5 mg, 0.55 mmol) at –78 °C. The resulting solution was stirred at –78 °C until the reaction was complete (monitored by TLC, about 5–15 min). THF was then removed under reduced pressure, and the residue was purified by column chromatography on silica gel which was pretreated with triethylamine (5 vol.%)/hexanes (eluent: pure hexanes) to give the desired products **3** in high yields and excellent stereoselectivity.

Methyl (Z)-2-Diazo-3-[(triisopropylsilyl)oxy]hex-3-enoate (3a): Orange oil; Yield: 138 mg (88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.07 (t, *J* = 7.2 Hz, 1 H), 3.80 (s, 3 H), 2.15–2.22 (comp, 2 H), 1.24–1.16 (comp, 3 H), 1.12 (d, *J* = 6.6 Hz, 18 H), 1.01 (t, *J* = 7.4 Hz, 3 H), ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8, 133.4, 116.3, 52.1, 19.7, 18.0, 14.1, 13.5; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_{31}N_2O_3Si$: 327.2098; found: 327.2093.

Methyl (Z)-2-Diazo-3-[(triisopropylsilyl)oxy]pent-3-enoate (3b): Orange oil; Yield: 111 mg (71%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.13 (q, *J* = 7.0 Hz, 1 H), 3.77 (s, 3 H), 1.70 (d, *J* = 7.0 Hz, 3 H), 1.20–1.13 (comp, 3 H), 1.10 (d, *J* = 6.7 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8, 134.7, 108.7, 52.1, 18.0, 13.5, 11.9; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{29}N_2O_3Si$: 313.1942; found: 313.1935.

Methyl (Z)-2-Diazo-5-phenyl-3-[(triisopropylsilyl)oxy]pent-3-enoate (3c): Orange oil, Yield 165 mg (85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (t, *J* = 7.5 Hz, 2 H), 7.23 (d, *J* = 7.1 Hz, 2 H), 7.19 (t, *J* = 7.2 Hz, 1 H), 5.31 (t, *J* = 7.4 Hz, 1 H), 3.78 (s, 3 H), 3.54 (d, *J* = 7.4 Hz, 2 H), 1.26–1.18 (comp, 3 H), 1.13 (d, *J* = 6.9 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.6, 141.0, 134.6, 128.5, 128.5, 126.1, 112.6, 52.1, 32.5, 18.0, 13.5; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{21}H_{33}N_2O_3Si$: 389.2255; found: 389.2251.

For more examples, see the Supporting Information.

(10) Jing, C.; Cheng, Q.-Q.; Deng, Y.; Arman, H.; Doyle, M. P. *Org. Lett.* **2016**, *18*, 4550.