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Facile Preparation and Functionalization of Chiral Stabilized Ylides from Common Chiral Auxiliaries Using Triphenylphosphoranylideneketene (the Bestmann Ylide) and Their Use in Wittig Reactions

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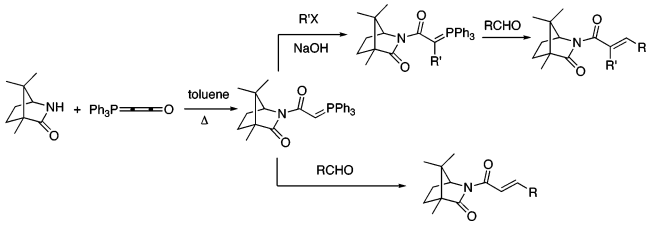


Camphor-derived lactams and other related chiral controllers have been found to react with the Bestmann ylide (triphenylphosphoranylideneketene) upon heating in toluene. The resulting parent ylides provide convenient access to a structurally diverse set of chiral stabilized ylides via functionalization. The utility of these chiral ylides for Wittig reactions has been briefly investigated and the effects of α-substitution noted.

Phosphorus ylides stabilized by a variety electron-withdrawing groups (EWG) have found wide use in the Wittig reaction.[1,2] Isolated examples of the preparation of such ylides bearing a removable oxazolidinone or camphor sultam auxiliaries have appeared.[3,4] Their utility for complex molecule synthesis is increasingly well established as additional examples of their use and the use of the related chiral Horner−Wadsworth−Emmons (HWE) phosphonates are reported.[5,6] We required a convenient route to sizable quantities of chiral stabilized ylides such as **1**−**4** (Chart 1). Convenient access to the parent ylides should afford

CHART 1

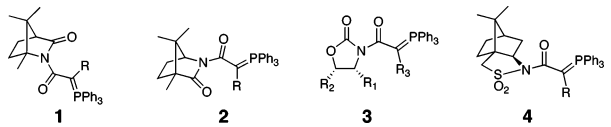
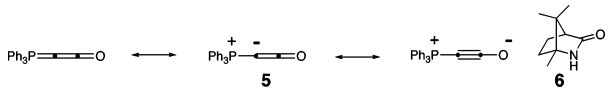


CHART 2



access to their more functionalized counterparts via well-established alkylation and acylation chemistry.[7]

We identified triphenylphosporanylideneketene (**5**), the Bestmann ylide, as a likely starting point as it is readily available in multigram quantities in one step from commercial starting materials (Chart 2).[8,9] Our first attempts involving conversion of camphor lactam **6** to the Li or K salts with *n*BuLi or KH followed by addition of **5** were not promising. Complex mixtures containing high molecular weight materials were observed. This seemed surprising because **5** was well known to react with a variety of electrophiles and nucleophiles, including amines, alcohols, and thiols, and chiral alcohols that afford chiral ester stabilized ylides.[10,11] Consideration of the electronic structure of **5** suggested that the use of the amide anion was counterproductive. In actuality, ylide **5** reacts smoothly with relatively acidic neutral nucleophiles because proton transfer and not nucleophilic addition is likely the rate-determining step. Although α amino esters,[12] acidic NH heterocycles,[10a,13] vinylogous amides and thioamides,[13] and sulfonamides[10a] have been observed to react, generally nucleophiles with a pK_a > ∼18 (apparent upper limit of the basicity of **5**) such as NH-carboxamides and lactams have not been employed previously in reactions with **5**.

We were gratified that simply heating a mixture of **5** and lactam **6** in toluene at reflux smoothly afforded the desired stabilized imide ylide **7** in 90% yield (Table 1). The estimated pK_a of lactam **6** is 20−25. Thus, the apparent upper limit of the basicity of **5** can now be regarded as in that range. We found that the reaction was general for other camphor-derived lactams such as **8** and **9**, as well as other prototypical chiral auxiliaries such as Evan's oxizolidinones **10**[14] and the Oppolzer sultam **11**,[15]

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(10) (a) Bestmann, H. J.; Schmid, G.; Sandmeier, D. *Chem. Ber.* **1980**, *113*, 912−918. (b) Bestmann, H. J.; Schobert, R. *Angew. Chem.* **1985**, *97*, 783−784. (c) Schobert, R.; Siegfried, S.; Gordon, G. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2393−2397.

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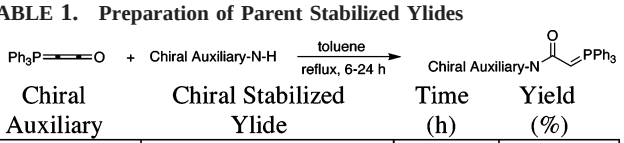
TABLE 1. Preparation of Parent Stabilized Ylides



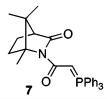
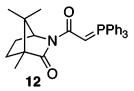
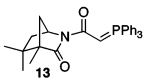
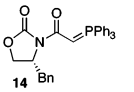
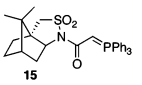
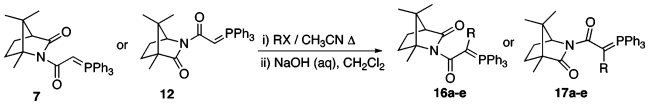
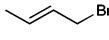
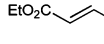
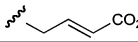
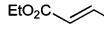
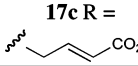
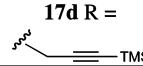
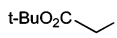
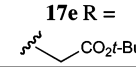
Chiral Auxiliary	Chiral Stabilized Ylide	Time (h)	Yield (%)
		~24	90%
		26	88%
		~24	82%
		~24	85%
		6	75%

TABLE 2. Alkylation and Acylation of Ylides 7 and 12

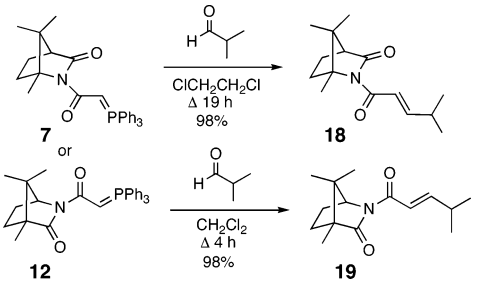


Ylide	Halide	Time (h)	Product	Yield
7	CH_3-I	2	**16a** R = CH_3	98%
12	CH_3-I	2	**17a** R = CH_3	98%
7	$CH_3(CH_2)_5$-I	24	**16b** R= *n*Hexyl	98%
12	CH_2=$CHCH_2$Br	1	**17b** R = allyl	93%
7		1	**16c** R = (*E*)-crotyl	85%
7		2	**16d** R = 	88%
12		2	**17c** R = 	85%
12		2	**17d** R = 	95%
12		19	**17e** R = 	91%
7	*i*PrCOCl	0.5	**16e** R = C(O)*i*Pr	98%

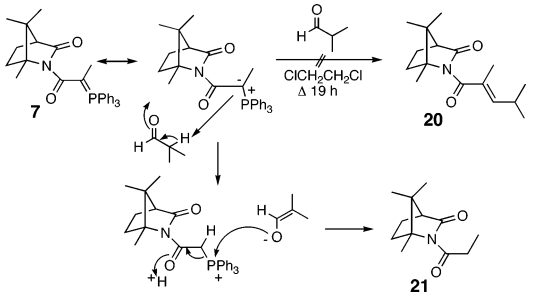
affording the imide or sulfonyl amide stabilized ylides **12**,**13** and **14**,[3c]**15**[4] in excellent yields (Table 1).

Further functionalization of these ylides occurred smoothly as expected. Alkylation or acylation of the parent ylides **7** or **12** with a variety of alkyl and acyl halides followed by treatment with NaOH afforded the expected substituted ylides **16a**−**e** and **17a**−**e** in excellent yields (Table 2).[16,17]

SCHEME 1. Wittig Reactions of Ylides 7 and 12



SCHEME 2. Attempted Wittig Reaction: Reduction of Ylide 7



The parent ylides **7** and **12** react smoothly with simple aldehydes, affording the expected (*E*)-α,*β*-unsaturated imides. Exposure of either ylide **7** or **12** to isobutyraldehyde in hot dichloromethane or dichloroethane afforded exclusively the expected (*E*)-α,*β*-unsaturated imides **18** and **19** in excellent yields (both 98%) as for the parent ylides **14** and **15** (Scheme 1).[3,4]

Somewhat surprisingly, more functionalized analogues of **7** and **12**−**15** have not been previously reported, and nothing was known of their behavior (e.g., **16** and **17**) upon exposure to aldehydes. Ylides **16** and **17** should behave analogously to the parent ylides **7** and **12**. Surprisingly, the reactivity of these materials differs markedly from the parent ylides.

Thus, upon exposure of **16a** to isobutyraldehyde in refluxing dichloroethane, none of the expected (*E*)-trisubstituted α,*β*-unsaturated imide **20** was observed. Instead, a complex mixture was obtained containing unreacted aldehyde, aldol condensation products of isobutyaldehyde, and the propionimide **21**,[18] resulting from effective reduction of the ylide.

The precise origin of imide **21** is still uncertain. A plausible mechanism would involve enolization of the aldehyde by the ylide **16a** followed by collapse of the enolate-phosphonium salt ion pair by attack at phosphorus affording the enolate, and, subsequently upon protonation, the propionimide **21** (Scheme 2). Similar results were obtained using the ylide **17a** with isobutyraldehyde. No olefination occurred, and the analogous propionimide **22**[18] was observed (Chart 3).

To examine the role of steric hindrance in the aldehyde, we reacted **16a** with the unbranched butyraldehyde in dichloroethane (80 °C, 18 h), resulting in slow conversion to the expected trisubstituted α,*β*-unsaturated imide **23** in 31% yield (Chart 3). Because competing formation of imide **21** was noted, the scope

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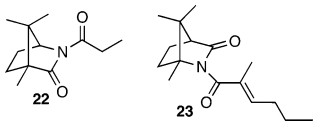
CHART 3



SCHEME 3. Olefination of Ylide 17a

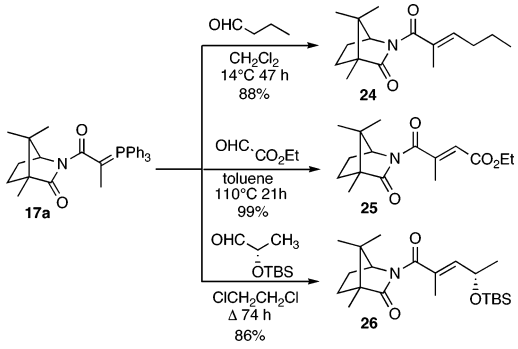
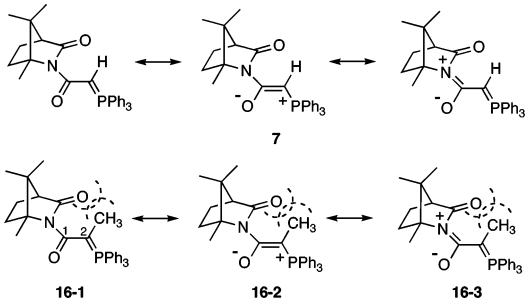


CHART 4



of reactivity of ylide class **16** seems limited. Thus, we examined reaction of the less congested ylide **17a** with several reactive, unbranched and α-heteroatom branched aldehydes. Reactions with **17a** proceed smoothly in excellent yield (conditions unoptimized) to afford exclusively the expected (*E*)-α,*β*-unsaturated imides **24**−**26**. However, the reactivity of ylide **17a** is also much lower than the parent ylide **12** (Scheme 3). Use of lower temperatures and longer reaction times was necessary to achieve complete conversion of **17a** and avoid formation of the byproduct imide **22**. The chiral lactaldehyde affords imide **26** as a single diastereomer with no observable epimerization of the chiral center.

At first, the low reactivity and apparently higher basicity of these chiral ylides seemed anomalous. However, it can be seen that these properties have their origin in the structure and conformational requirements of the substituted ylides **16** and **17**. Strain imparted by delocalization of the nitrogen lone pair onto the endocyclic carbonyl group of imides derived from bicyclic lactams such as **6**−**8** raises the energy of this resonance contributor as shown by the participation of the exocyclic carbonyl group in anchimeric assistance.[19]

The major contributors to that stabilization are those depicted for **7** (Chart 4). Strong dipole forces orient the carbonyl groups anti in the absence of a chelating metal ion. That places the hydrogen or alkyl substituent in **7** and the related ylides in a very congested environment because the delocalization requires coplanarity of the *N*-acyl substituent and the endocyclic carbonyl group. It has previously been seen that reactivity and enantioselectivity of reactions of α-substituted enones bearing typical chiral controller units were significantly diminished because of unfavorable allylic strain derived from interactions between the chiral controller moiety and the α substituent.[20,21]

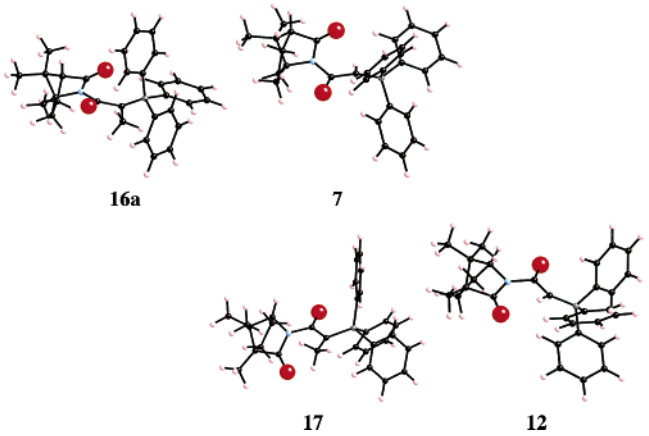


FIGURE 1. Model (HF 3-21G* Spartan 2004) of ylides **16a**, **7**, **17a**, and **12**.

We wished to probe the origin of the apparently higher basicity and relatively low reactivity of the α-substituted ylides **16a** and **17a**, which could arise from steric inhibition of delocalization of the negative charge of the ylide moiety by the α substituent. Thus, resonance form **16-1** (Chart 4) is rendered the major contributor due to twisting about the $N-C_1$ and/or the C_1-C_2 side chain bonds, reducing the stabilization and increasing the basicity of **16a** and **17a**.

Examination of a computational model (HF 3-21G* Spartan 2004) of ylide **16a** (Figure 1) lends some support to this argument. A relatively small (absolute value of the OC_1C_2P dihedral angle: 23°) twist occurs about the C_1-C_2 bond. The parent ylide **7** is only slightly twisted (absolute value of the OC_1C_2P dihedral angle: 2°), so substantial delocalization should be possible for both. However, the ylide carbon in **16a** is effectively buried within the molecular framework, shielded on both faces by a combination of the bridgehead methyl, endocyclic carbonyl, and two P-phenyl groups. It is actually quite remarkable that any reactivity is seen at all. Tortional strain about the C_1-C_2 bond is reduced in ylides **17a** and **12** as is evident from the observed OC_1C_2P dihedral angles 4° and 1° as shown in Figure 1. Thus, some combination of resonance stabilization and reduction steric shielding appears to be responsible for the more normal reactivity and basicity observed for ylide **17a**. As can be seen, the lower face of ylide **17a** appears more accessible (from the bottom as depicted in Figure 1), that is partially shielded by two P-phenyl moieties.

Facile introduction of a chiral controller unit by olefination enables diastereoselective conjugate addition,[22] reduction,[23] and alkylation,[24] making these attractive reagents for stereoselective

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functionalization of acyclic systems. An application of such chiral ylides to complex molecule synthesis has been recently reported.[25]

Experimental Section[26]

General Procedure for the Preparation of Chiral Ylides 7, 12−15. A mixture of triphenylphosphoranylideneketene (the Bestmann ylide) **5**[8] (1.0−1.5 equiv) and 1.0 equiv of the chiral auxiliary (**6**, **8**−**11**) in toluene (1−2 M) was heated to reflux (6−26 h) until no starting material was detected (monitored by ^{1}H NMR). The reaction mixture was concentrated in vacuo, and the residue was isolated and purified by chromatography on SiO_2 and/or recrystallization to provide the stabilized ylides as a solid (**7**, **12**−**15**).

(1*R*,4*S*)-1,7,7-Trimethyl-2-[2-(triphenylphosphanylidene)-acetyl]-2-aza-bicyclo[2.2.1] heptan-3-one (7). According to the general procedure above, ketene **5**[8] (18.8 g, 0.062 mol, 1.5 equiv) and lactam **6** (6.3 g, 0.041 mol) were dissolved in 21 mL of toluene, and the resulting mixture was heated until no more **6** could be detected by ^{1}H NMR (∼24 h). The solvent was removed in vacuo, and the residue was recrystallized from ethyl acetate at −20 °C, affording 17.0 g (90%) of ylide **7** as a tan solid having mp 182−184 °C, $[\alpha]_D^{20}$ −55.9° (*c* 3.1, CH_2Cl_2), and spectral characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) 7.71−7.66 (m, 6H), 7.56−7.53 (m, 3H), 7.47−7.44 (m, 6H), 4.22 (d, J = 25 Hz, 1H), 2.31 (d, J = 4 Hz, 1H), 2.17−2.13 (m, 1H), 2.00−1.94 (m, 1H), 1.80−1.77 (m, 1H), 1.69−1.66 (m, 1H), 1.46 (s, 3H), 1.06 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 177.8, 167.4, 133.2, 131.9, 128.8, 127.5 (d, J_{C-P} = 91 Hz), 71.9, 56.1, 48.2, 43.6 (d, J_{C-P} = 116 Hz), 33.0, 23.8, 18.7, 17.8, 13.4; ^{31}P NMR (160 MHz, $CDCl_3$) 14.5; IR (film) 2966, 1708, 1567, 1431 cm^{-1}. HRMS (EI). Calcd for $C_{29}H_{31}NO_2P$ $(M + H)^+$: 456.2092. Found: 456.2091.

(1*S*,4*R*)-4,7,7-Trimethyl-2-[2-(triphenylphosphanylidene)-acetyl]-2-aza-bicyclo[2.2.1]heptan-3-one (12). According to the general procedure above, ketene **5** (9.07 g, 0.03 mol, 1.5 equiv) and lactam **8** (3.07 g, 0.041 mol) were disolved in 10 mL of anhydrous toluene, and the resulting mixture was heated until no more **8** could be detected by ^{1}H NMR (26 h). The solvent was removed in vacuo, and the residue was purified by chromatography on SiO_2 with elution by 20−50% ethyl acetate in hexane, followed by recrystallization from ethyl acetate at −20 °C, affording 7.98 g of ylide **12** (88%) as a pale yellow solid having mp 222−224 °C, $[\alpha]_D^{20}$ +45.5° (*c* 2.67, CH_2Cl_2), and spectral characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) 7.77−7.65 (m, 6H), 7.55−7.52 (m, 3H), 7.47−7.42 (m, 6H), 4.84 (d, J = 25 Hz, 1H), 4.36 (s, 1H), 1.94−1.90 (m, 1H), 1.76−1.1.56 (m, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 178.7, 165.7, 133.3, 131.9, 129.1, 127.5 (d, J_{C-P} = 91 Hz), 63.1, 56.5, 47.9, 39.8 (d, J_{C-P} = 119 Hz), 30.3, 27.3, 18.6, 18.0, 9.77; ^{31}P NMR (160 MHz, $CDCl_3$) 14.4; IR (film) 2955, 1708, 1561, 1478, 1431 cm^{-1}. HRMS (EI). Calcd for $C_{29}H_{31}NO_2P$ $(M + H)^+$: 456.2092. Found: 456.2097.

General Procedure: Alkylation of Ylides 7 and 12. A mixture of ylide **7** (1.0 equiv) and alkyl bromide or iodide, or acyl chloride (2.0 equiv), in anhydrous acetonitrile (0.5 M) was heated to reflux. The resulting homogeneous mixture was kept at reflux for the time period as specified (0.5−24 h). The reaction mixture was concentrated in vacuo, and the residue was redissolved in dichloromethane (0.25 M). A 1 M solution of aqueous NaOH (2.0 equiv) was added, and the mixture was stirred vigorously at room temperature for 2 h. The phases were separated, the aqueous phase was extracted with twice the volume of dichloromethane, and the combined organic phases were dried over magnesium sulfate and concentrated in vacuo to give a solid residue. This solid residue was purified by chromatography on SiO_2 with elution with 50−100% ethyl acetate in hexane to provide the alkylated ylides **16a**−**d**, **17a**−**e** mainly as white solids in 85−98% yield.

General Procedure for Condensation of Ylides 7, 12, 16a, and 17a with Aldehydes. A solution of the ylide **7**, **12**, **16a**, or **17a** (1.5 equiv) and the aldehyde (1.0 equiv) in anhydrous CH_2Cl_2, $(CH_2Cl)_2$, or toluene was heated at 40−100 °C in a sealed tube until no aldehyde could be detected by TLC analysis (4−74 h). The reaction mixture was cooled to room temperature and concentrated in vacuo to provide crude oily products. The oily residue was purified by chromatography on SiO_2 with elution by 5% ethyl acetate in hexane to provide the unsaturated carbonyl compounds as a colorless oil in 31−99% yields.

(1*R*,4*S*)-1,7,7-Trimethyl-2-[(2*E*)-4-methyl-pent-2-enoyl)]-2-aza-bicyclo[2.2.1]heptan-3-one (18). A solution of 91.1 mg (0.2 mmol, 1.5 equiv) of ylide **7** and isobutyraldehyde (12.2 μL, 9.62 mg, 0.13 mmol) in anhydrous $ClCH_2CH_2Cl$ was heated at ∼83 °C in a sealed tube until no aldehyde could be detected by TLC analysis (19 h). The reaction mixture was cooled to room temperature and concentrated in vacuo to provide crude oily products. The oily residue was purified by chromatography on SiO_2 with elution by 5% ethyl acetate in hexane to provide 44.5 mg (89%) of unsaturated imide **18** as a colorless oil having the spectral characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) 6.94 (dd, J_1 = 15 Hz, J_2 = 6 Hz, 1H), 6.86 (d, J = 16 Hz, 1H), 2.50−2.49 (m, 1H), 2.34 (d, J = 4 Hz, 1H), 2.04−2.00 (m, 2H), 1.84−1.81 (m, 1H), 1.61−1.60 (m, 1H), 1.48 (s, 3H), 1.07 (d, J = 7 Hz, 6H), 1.03 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 178.5, 167.3, 154.8, 121.9, 72.9, 55.4, 47.5, 32.1, 23.7, 21.4, 21.3, 18.6, 17.5, 13.3; IR (film) 2965, 1746, 1679, 1634, 1456 cm^{-1}. HRMS (EI). Calcd for $C_{15}H_{24}NO_2$ $(M + H)^+$: 250.1807. Found: 250.1804.

(1*S*,4*R*)-4,7,7-Trimethyl-2-[(2*E*,4*S*)-2-methyl-4-*tert*-butyldimethylsilyloxy-pent-2-enoyl]-2-aza-bicyclo[2.2.1]heptan-3-one (26). A solution of 704.4 mg (1.5 mmol, 1.5 equiv) of ylide **17a** and 188.3 mg of TBS protected (*S*)-lactaldehyde (1.0 mmol) in anhydrous $ClCH_2CH_2Cl$ was heated at ∼83 °C in a sealed tube until no aldehyde could be detected by TLC analysis (74 h). The reaction mixture was cooled to room temperature and concentrated in vacuo to provide crude oily products. The oily residue was purified by chromatography on SiO_2 with elution by 5% ethyl acetate in hexane to provide 0.353 g (86%) of unsaturated imide **26** as a colorless oil having the spectral characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) 5.81 (d, J = 8 Hz, 1H), 4.62−4.55 (m, 1H), 4.11 (d, J = 2 Hz, 1H), 2.01−1.93 (m, 1H), 1.82 (d, J = 1 Hz, 3H), 1.81−1.67 (m, 2H), 1.57−1.50 (m, 1H), 1.25 (d, J = 6 Hz, 3H), 1.03 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 177.2, 171.0, 141.5, 129.3, 65.8, 64.8, 56.3, 47.2, 30.8, 26.6, 25.8, 23.2, 18.7, 18.1, 17.7, 13.5, 9.6, −4.6, −4.9; IR (film) 2959, 2939, 2857, 2360, 1752, 1672, 1473 cm^{-1}. HRMS (EI). Calcd for $C_{21}H_{37}NNaO_3Si$ $(M + Na)^+$: 402.2440. Found: 402.2463

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Supporting Information Available: A description of general experimental methods, additional detailed experimental procedures, analytical data, and the ^{1}H NMR and selected ^{13}C, ^{31}P, and IR spectra for **7**, **12**−**15**, **16a**−**e**, **17a**−**e**, **18**, **19**, and **24**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) General experimental methods section and additional experimental procedures and characterization data may be found in the Supporting Information.