imine **3d** (5.00 g, 12.9 mmol) in CH_2Cl_2 (10 mL) was added by syringe to the catalyst solution at 0 °C. Stirring the mixture for 10 min gave an orange solution to which was rapidly added ethyl diazoacetate (1.484 mL, 14.2 mmol) by syringe. Some bubbling was noted after the addition. The reaction was allowed to proceed for 6 h at 0 °C and then for 14 h at room temperature (22 °C). The reaction mixture was transferred to a 500-mL flask, diluted with hexanes (250 mL), and then the volatiles were removed under vacuum to give the crude aziridine **3d** as an off-white solid. The ^{1}H NMR spectrum of this material revealed **3d** with *cis*:*trans* ≥ 50:1 and indicated that < 1 % of **4d** and **5d** were formed. Purification of **3d** by column chromatography on silica gel with a mixture of ethyl acetate:hexanes (3:7) gave aziridine **3d** (5.20 g, 11 mmol) as a white solid in 85 % yield. The optical purity of this material was determined to be 96 % *ee* by HPLC analysis (OD-H column). Crystallization from hexanes:CH_2Cl_2 (10:1, 300 mL) gave **3d** (4.43 g) with 99 % *ee*. A second crop was taken but found to be only 90 % *ee*. Spectral data for **3d**: m.p. 141 – 143 °C (hexanes:CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.99$ (t, $J = 7$ Hz, 3H), 2.24 (s, 3H), 2.25 (s, 3H), 2.68 (d, $J = 7$ Hz, 1H), 3.18 (d, $J = 7$ Hz, 1H), 3.95 (s, 1H), 3.95 (m, 2H), 7.07 (d, $J = 9$ Hz, 1H), 7.19 (m, 1H), 7.28 (m, 7H), 7.45 (d, $J = 7$ Hz, 2H), 7.81 (d, $J = 7$ Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 13.84$, 20.64, 46.57, 47.03, 60.89, 77.49, 122.75, 122.78, 126.05, 127.18, 127.30, 127.45, 127.61, 128.55, 128.65, 133.97, 141.35, 141.57, 142.21, 167.45 168.07, 168.24; IR (thin film) 3030 (w), 2980 (w), 1770 (s), 1731 (s), 1600 cm^{-1} (m); MS (EI): *m*/*z* (relative intensity): 474 (21) [*M*+1], 306 (12), 195 (10), 167 (100); *m*/*z* calcd for $C_{28}H_{27}NO_6$: 474.1903, found 474.1903. Elemental analysis calcd for $C_{28}H_{27}NO_6$: C 71.02, H 5.75, N 2.96; found: C 71.23, H 5.88, N 2.94. $[\alpha]_D^{23} = -17.3°$, ($C = 1$ from CH_2Cl_2) taken on 99 % *ee* material (HPLC). Further experimental details can be found in the Supporting Information.

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[5] The VANOL ligand was prepared according to the same procedure that has been reported for the VAPOL ligand.[4c]

[6] A second crop was taken but had only approximately 90 % *ee*.

[7] The optical rotation of an authentic sample of L-DOPA was found to be $[\alpha]_D = -8.2°$.

Stereoselective Synthesis of R_P- and S_P-Dithymidine Phosphorothioates via Chiral Indolooxazaphosphorine Intermediates Derived from Tryptophan**

Yixin Lu and George Just*

The use of phosphorothioates as DNA analogues useful in antisense-based therapy is well established[1] and led to the development of Vitravene as the first antisense drug.[2] Several other phosphorothioate oligonucleotides (PS-Oligos) are in clinical trials. Although Stec et al. described an elegant oxathiaphospholane-based approach[3]for preparing diastereomerically pure phosphorothioates, it has not been used for large-scale production of PS-Oligos, which are still used as a mixture of about 10^6 diastereomers. The use of cyclic *N*-acylphosphoramidites as promising monomers for the stereocontrolled synthesis of phosphorothioates was recently reported by Beaucage et al.[4]

Previously, we developed cyclic phosphoramidites[5]such as sugar-derived oxazaphosphorinanes,[5b,c] indolooxazaphosphorines (**a**),[5e, f] and indoleimidazoles[5i] for the stereoselective synthesis of PS-Oligos. Here we report on the use of promising indolooxazaphosphorine precursors derived from tryptophan which do not require a difficult chromatographic separation and may form the basis of a practical process.

As demonstrated in the indolooxazaphosphorine approach,[5f] chiral auxiliary **a** led to the stereoselective synthesis of phosphorothioate in solution. When it was applied to solid-phase synthesis, a β-elimination caused rearrangement to give

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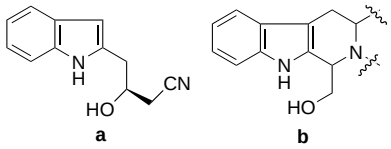
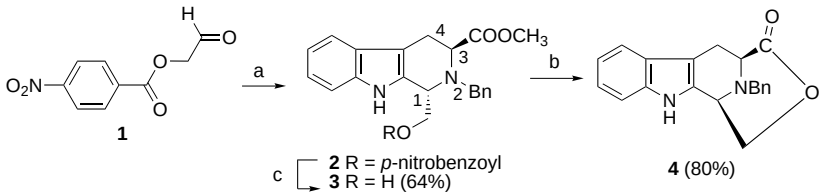
Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

a cyanoethyl phosphonate.[5g] We therefore decided to synthesize a chiral auxiliary of type **b**, which can be derived from tryptophan. Removal of the chiral auxiliary could then be

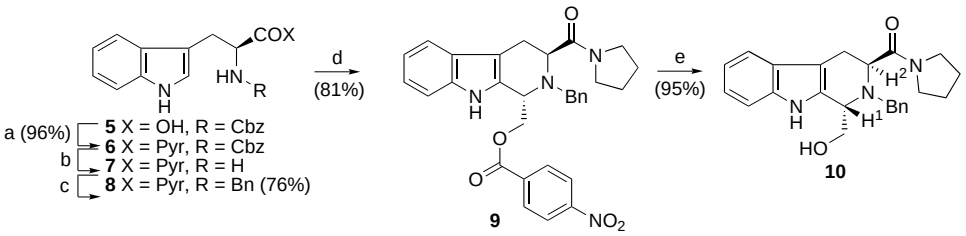


effected by direct displacement of the primary alcohol group or by neighboring-group participation of an appropriately positioned functionality. When benzyl serves as a protecting group for N_b of tryptophan, a Pictet–Spengler reaction tends to yield a single diastereomer.[6] This could well solve the chirality problem of the new chiral auxiliary. Furthermore, the chiral auxiliary can be derived from natural chiral tryptophan, making the method very attractive and inexpensive.

The synthesis of the chiral auxiliary is illustrated in Scheme 1. Dimethylallyl alcohol was transformed into its *p*-nitrobenzoate, ozonolysis of which then gave aldehyde **1**. Pictet–Spengler reaction between **1** and N_b-benzyl tryptophan methyl ester[6] in toluene without acid catalyst afforded the desired condensed product **2**. Ester **2** was then methanolyzed by reaction with sodium methoxide in methanol. To our surprise, lactone **4** or its enantiomer was obtained as the product.



Scheme 1. a) N_b-Benzyl tryptophan methyl ester, toluene, reflux, Dean–Stark trap; b) NaOMe, MeOH; c) iPrNH$_2$, 80 °C.

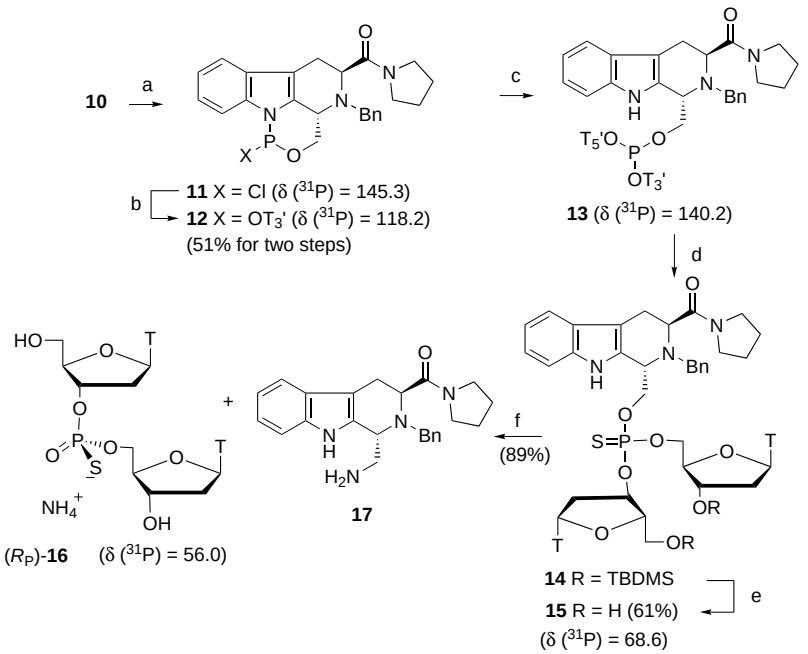


Scheme 2. a) Pyrrolidine, Et_3N, HBTU, CH_3CN, RT; b) H_2, Pd/C, ethyl acetate/H_2O/AcOH; c) PhCHO, $NaCNBH_3$, MeOH, pH 6; d) **1**, toluene, reflux, Dean–Stark trap; e) NaOH, H_2O/THF, 55 °C. Cbz = carboxybenzyl, HBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, Pyr = 1-pyrrolidyl.

Cook et al. showed that Pictet–Spengler reactions between N_b-benzyl tryptophan methyl ester and bulky aldehydes led to stereospecific formation of the *trans* diastereomer.[6a] Since our product was a single isomer, it follows that epimerization occurs readily at C1 or C3. These facile epimerizations are precedented.[6b] Participation of the neighboring amide group has been reported.[5d, 7] We therefore considered synthesizing a chiral auxiliary with an amide group. Removal of the chiral auxiliary by neighboring-group participation can be expected at the end of the synthesis should facile epimerization occur during removal.

Chiral auxiliary **10** with a neighboring pyrrolidine amide (Pyr) group was easily prepared (Scheme 2). Commercially available N_b-Cbz-L-tryptophan (**5**) was coupled with pyrrolidine to yield amide **6**. The Cbz protecting group was then removed to give **7**, which upon reductive amination with benzaldehyde was transformed into **8**. Pictet–Spengler condensation of **8** with aldehyde **1** afforded **9** as a single diastereomer, which was then hydrolyzed to furnish **10** as a single isomer. The absence of cross-peaks between the H^1 and H^2 protons in the NOESY spectra of **10** means the expected *trans* configuration is very likely.[6a]

The application of chiral auxiliary **10** to the stereoselective synthesis of phosphorothioates is outlined in Scheme 3. A solution of **10** and triethylamine in dichloromethane was added slowly to phosphorus trichloride at 0 °C. Initially, several ^{31}P NMR signals were observed. After heating at 50 °C for one day to equilibrate, a single peak at around $\delta = 145$ was observed, corresponding to **11**. When intermediate **11** was further treated with 5′-*O*-TBDMS-thymidine ($T_{3'}OH$) in the



Scheme 3. a) PCl_3, Et_3N, CH_2Cl_2; b) $T_{3'}OH$, Et_3N, CH_2Cl_2; c) $T_{5'}OH$, DBU, THF; d) Beaucage's reagent; e) TBAF; f) conc. ammonia/EtOH, 55 °C. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, T = thymine residue, TBAF = tetrabutylammonium fluoride, TBDMS = *tert*-butyldimethylsilyl, $T_{3'}OH$ = 5′-*O*-TBDMS-thymidine, $T_{5'}OH$ = 3′-*O*-TBDMS-thymidine.

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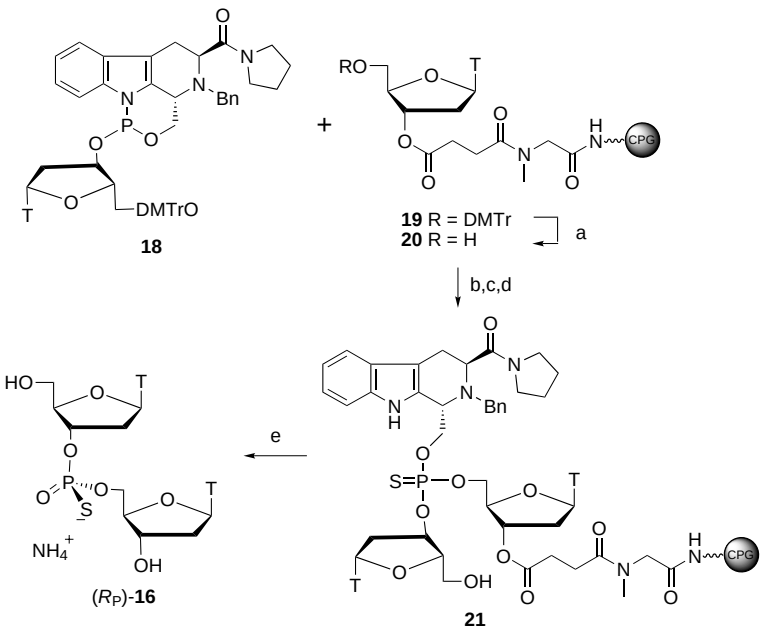
presence of triethylamine in dichloromethane, the reaction went to completion in 10 min to yield a single isomer of phosphoramidite **12** with a ^{31}P NMR signal at $\delta = 118.2$. Cyclic phosphoramidite **12** was stable enough to be easily purified by column chromatography on silica gel. When purified **12** was treated with 3′-*O*-TBDMS-thymidine ($T_{3'}OH$) in the presence of five equivalents of DBU, the displacement was completed within 20 min at room temperature, as established by the formation of a characteristic major ^{31}P NMR peak at $\delta = 140$ corresponding to phosphite triester **13**. The DBU was removed by filtration through a short column, and sulfurization with Beaucage's reagent[8] afforded phosphorothioate **14** with a major ^{31}P NMR signal at around $\delta = 68$. Removal of silyl protecting groups gave dithymidine phosphorothioate **15**.

We next attempted to remove the chiral auxiliary. The solution of **15** in water/THF was first heated at 55 °C. No reaction had occurred after one day. We then treated **15** with concentrated ammonia/ethanol (3/1) at 55 °C for 16 h. To our delight, phosphorothioates **16** were obtained, as indicated by the presence of two peaks at $\delta = 56.1$ and 56.0 in a ratio of 1 to 40 in the ^{31}P NMR spectrum. The configurations of minor and major isomers were assigned as S_P and R_P, respectively, on the basis of their ^{31}P NMR chemical shifts.[5h] The chiral auxiliary we recovered had structure **17**, and this means direct attack by ammonia was responsible for its removal. Should the chiral auxiliary epimerize to give a *cis* configuration, neighboring-group participation would be expected to yield lactone **4** or its hydrolyzed product after deprotection.



Scheme 4. a) Cl_3CCOOH; b) DBU, then **18**; c) Beaucage's reagent; d) Cl_3CCOOH; e) conc. ammonia/EtOH, 55 °C. DMTr = 4,4′-dimethoxytrityl.

The methyl ester chiral auxiliary **3** was used for the stereoselective synthesis of phosphorothioates in a similar manner, and the same results were obtained.

To demonstrate that our methodology is compatible with solid-phase synthesis of oligonucleotides, we synthesized R_P- and S_P-dithymidine phosphorothioates on a solid phase. The solid-phase syntheses of dithymidine phosphorothioates were performed manually (Scheme 4). 5′-*O*-DMTr-thymidine (**19**), obtained by immobilizing thymidine on controlled pore glass (CPG) with a DBU-resistant sarcosinyl-succinoyl linker,[9] was detritylated and treated with excess DBU followed by the addition of L-tryptophan-derived monomer **18**. After 20 min at room temperature, the solid support was washed with acetonitrile and sulfurized with Beaucage's reagent, followed by detritylation to furnish phosphorothioate **21**. The solid support was heated in concentrated ammonia at 55 °C for 16 h to cleave the dimer and remove the chiral auxiliary to furnish (R_P)-dithymidine phosphorothioate **16**.

The configuration at the phosphorus center of **16** was established by comparison of reverse-phase HPLC (RP-HPLC) chromatograms of **16** and thymidine dimers synthesized by a nonstereoselective method. It is documented in the literature[10] that the R_P isomer of the dinucleotide eluted faster than S_P isomer in RP-HPLC. The configuration of **16** was accordingly assigned as R_P. The identity of **16** was also proved by HPLC-MS, which showed the peak of the dithymidine phosphorothioate anion. Similarly, the monomer derived from D-tryptophan led to the formation of the S_P dimer, which was also confirmed by HPLC comparison and HPLC-MS analysis.

In summary, chiral indolooxazaphosphorine auxiliaries can be easily prepared from L- and D-tryptophans. When applied in solution and solid-phase syntheses of dithymidine phosphorothioates, the L-tryptophan-derived chiral auxiliary led to the formation of the R_P isomer, and the D-tryptophan-derived precursor to the S_P isomer. The adaptation of the methodology to routine solid-phase synthesis of oligonucleotides is underway.

Experimental Section

10: Amide **8** (0.35 g, 1 mmol) and aldehyde **1** (0.23 g, 1.1 mmol) in toluene were heated to reflux with removal of water. After 4 h, evaporation to a small volume provided a light yellow crystalline product **9** (0.32 g, 60 %). The mother liquid was purified by chromatography to give more **9** (0.11 g, 21 %; HRMS (FAB): calcd for $C_{31}H_{31}N_4O_5$: 539.2294; found: 539.2293). A solution of **9** (110 mg, 0.2 mmol) in 2 N aqueous NaOH (3 mL) and THF (3 mL) was warmed to 55 °C for 1 h. Extraction with ethyl acetate provided **13** as a white solid (74 mg, 95 %). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.05$ (br, 1H), 7.56 (d, 1H, $J = 7.5$ Hz), 7.10 – 7.30 (m, 8H), 4.10 (m, 2H), 4.01 – 4.03 (m, 2H), 3.90 – 3.96 (m, 1H), 3.72 – 3.80 (m, 2H), 3.40 – 3.58 (m, 4H), 2.72 – 2.76 (dd, 1H, $J = 4.0$, 16.5 Hz), 1.87 – 2.03 (m, 4H); ^{13}C NMR (125.7 MHz, CD_3COCD_3): $\delta = 169.79$, 139.32, 136.17, 130.35, 128.58, 128.42, 127.12, 126.83, 121.83, 119.40, 118.27, 110.73, 108.66, 63.71, 57.75, 56.86, 52.75, 46.17, 26.30, 23.99, 19.04, 14.02; HRMS (EI) calcd for $C_{24}H_{27}N_3O_2$: 389.2103; found: 389.2099.

12: A solution of **10** (39 mg, 0.1 mmol) in CH_2Cl_2 containing Et_3N (30.7 μL, 0.22 mmol) was added slowly to a solution of PCl_3 (8.7 μL, 0.1 mmol) in CH_2Cl_2 (0.25 mL) at 0 °C. The NMR tube was then sealed. After heating at 50 °C for 24 h, a solution of 5′-*O*-TBDMS-thymidine (39 mg, 0.11 mmol) and Et_3N (15.4 μL, 0.11 mmol) was added to the solution of **11**, and the NMR tube was resealed. When ^{31}P NMR spectroscopy showed the disappearance of the signal at $\delta = 144$ and the formation of new signal at around $\delta = 118$, the solvent was removed in vacuo. Purification by flash chromatography afforded **12** as a white solid (39 mg, 51 %). ^{31}P NMR

(202.3 MHz, $CDCl_3$): $\delta = 116.96$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.48$ (br, 1H), 7.54 (d, 1H, $J_{4,5} = 7.5$ Hz), 7.51 (d, 1H, $J_{6,7} = 7.5$ Hz), 7.45 (s, 1H), 7.19–7.35 (m, 7H), 6.12 (m, 1H), 4.90 (m, 1H), 4.36 (m, 1H), 3.45–4.00 (m, 8H), 3.50 (m, 3H), 3.26 (m, 1H), 3.13 (m, 1H), 2.96 (m, 1H), 2.23 (m, 1H), 2.01–2.06 (m, 1H), 1.82–1.95 (m, 7H), 0.91 (s, 9H), 0.08 (2s); HRMS (FAB): calcd for $C_{40}H_{53}N_5O_7PSi$: 774.3452; found: 774.3455.

15: DBU (37 μL, 0.25 mmol) was added to a stirred solution of **12** (38.6 mg, 0.05 mmol) and 3′-*O*-TBDMS-thymidine (35.6 mg, 0.1 mmol) in dry THF (2 mL) at room temperature. After 20 min, the ^{31}P NMR spectrum of the reaction mixture showed a single signal at around $\delta = 140$. The mixture was then loaded onto a short column to filter off DBU. After evaporation of the solvent, the residue was dissolved in dry CH_2Cl_2, and Beaucage's reagent (10 mg, 0.05 mmol) was added at room temperature. After stirring for 5 min, ^{31}P NMR spectroscopy revealed a single peak at around $\delta = 68$. The solvent was removed, the residue was dissolved in THF, and TBAF was added. After 2 h, the solvent was removed in vacuo. CH_2Cl_2 was added to the residue, and the extract was washed with water and brine and dried over magnesium sulfate. Purification by column chromatography afforded **15** as a white solid (28 mg, 61%).

16 and **17**: Phosphorothioate **15** (28 mg, 0.026 mmol) was dissolved in concentrated ammonia/ethanol (3/1, 5 mL). The mixture was heated at 55 °C for 16 h. The ^{31}P NMR signal shifted quantitatively from $\delta = 68$ to 56. The reaction mixture was extracted with chloroform several times. The combined organic extracts were washed with brine and dried over magnesium sulfate. The solvent was removed to provide **17** (9.2 mg, 91%) as a light yellow solid. The aqueous crude product was purified by flash chromatography to give **16** (15 mg, 89%).

17: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.41$ (d, 1H, $J = 8.0$ Hz), 7.23–7.35 (m, 6H), 7.13 (m, 1H), 7.02 (m, 1H), 4.71 (br, 1H), 4.04–4.14 (m, 2H), 3.94 (m, 2H), 3.68–3.86 (m, 2H), 3.11–3.23 (m, 4H), 2.97 (m, 1H), 2.82 (m, 1H), 1.55–1.82 (m, 5H); HRMS (FAB): calcd for $C_{24}H_{29}N_4O$: 389.2341 $[(M+1)]^+$; found: 389.2343.

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Early Transition Metal α-Diazoalkane Complexes**

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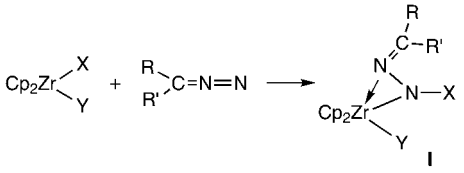
The reaction of diazoalkanes with transition metals results either in coordination through the nitrogen atoms or in formation of a carbon–metal bond. Many N-bonded substituted transition metal diazoalkanes have been studied,[1] but only four series of C-bonded late transition metal compounds have been isolated.[2] α-Metalated diazoalkanes $L_nM{-}C(N_2)R$ containing an early transition metal have not yet been reported. Treatment of zirconocene Zr^{IV} complexes with diazoalkanes results in insertion into Zr–C,[3] Zr–H,[3c] Zr–P,[4] and zirconium–metal bonds[5] to give the corresponding hydrazonato ligands **I** [Eq. (1)].



(1)

We have shown that 1-aza-zirconacyclopentene complexes **1a** and **1b**[6] (see Scheme 1) contain a strongly electrophilic metal center (mostly because of the inductive electron-withdrawing properties of the σ-bonded nitrogen atom) and a rather nucleophilic imido group that does not share its lone-pair electron density with the adjacent metal center because of the strain in the metallacycle.[7] Indeed phosphanes **1a** and **1b** activate C–H bonds in relatively acidic carbonic acids, such as acetylenes and methylene compounds.[8] Although electrophilic, metal-mediated, aliphatic C–H bond cleavage is precedented,[9] its application to the functionalization of complex substrates is very rare. The present report deals with a novel electrophilic sp^2-C–H bond activation and its application for the preparation of α-diazomethylzirconium complexes, which are the first C-metalated diazoalkanes $L_nMC(N_2)R$ with an early transition metal.

Treatment of **1a** and **1b** with ethyl diazoacetate (**2**) in THF at room temperature gave the light yellow, thermally stable solids **4a** and **4b** (Scheme 1) in excellent yields (>88%). The ^{31}P NMR spectra of **4a** and **4b** display a singlet at $\delta = 49.4$ and 58.5, respectively. The total disappearance of the sp^2-CH

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