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Tetraarylphosphonium-Supported Carbodiimide Reagents: Synthesis, Structure Optimization and Applications

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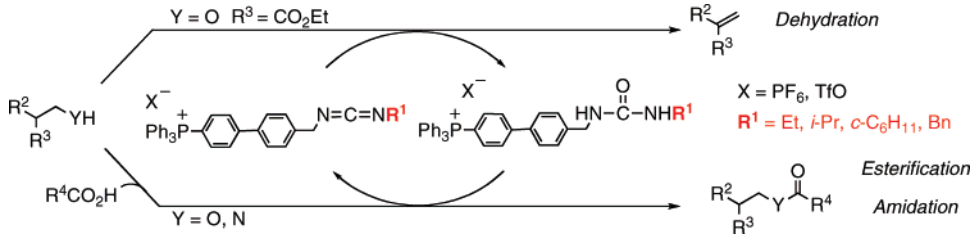

New tetraarylphosphonium (TAP)-supported alkyl- and arylcarbodiimides were synthesized and used as coupling reagents for esterification reactions, amidation reactions and dehydration reactions of hydroxyesters. Taking advantage of the solubility properties imparted by the tetraarylphosphonium unit, a simple precipitation and filtration allowed complete separation of the urea by-products. This paper describes the structure optimization study of the various TAP-supported carbodiimide reagents to obtain the desired reactivity and solubility profile. Furthermore, we have demonstrated that the diimide reagent can be regenerated from the urea to recycle the reagents.

Introduction

Carbodiimides are versatile reagents that are widely used in organic synthesis and bioorganic chemistry. These compounds are capable of a variety of transformations including peptide coupling,[1] amide bond formation,[2] esterification,[3] anhydride formation,[4] oxidation[5] and dehydrating reactions of β-hydroxycarbonyl derivatives.[6] While there are many carbodiimides available for these reactions, dicyclohexylcarbodiimide (DCC) is the reagent most commonly used. However, the major limitation of using DCC and its analogues is the formation of the toxic *N*-alkylurea byproduct that may require demanding purification steps for its complete removal.

In recent years, various approaches have been developed in carbodiimide-mediated reactions to separate the desired product from the urea byproduct. One method consists of using water-soluble derivatives such as 1-(3-(dimethylamino)-propyl-3-ethylcarbodiimide hydrochloride (EDCI),[7] which generates basic urea byproducts that can be easily removed by an acidic aqueous workup. Another process involves the use of polymer-bound carbodiimide reagents, since removal of the resulting supported urea byproducts can be achieved by filtration.[8] This method reduces the need for difficult work-ups and remove cumbersome purification procedures. Furthermore, these reagents display lower toxicity than DCC. The most popular supported carbodiimide reagents are generally synthesized on cross-linked polystyrene beads, macroporous ion exchange resins or inorganic supports.[9] They include isopropylcarbodiimide (PS-DIC),[10]

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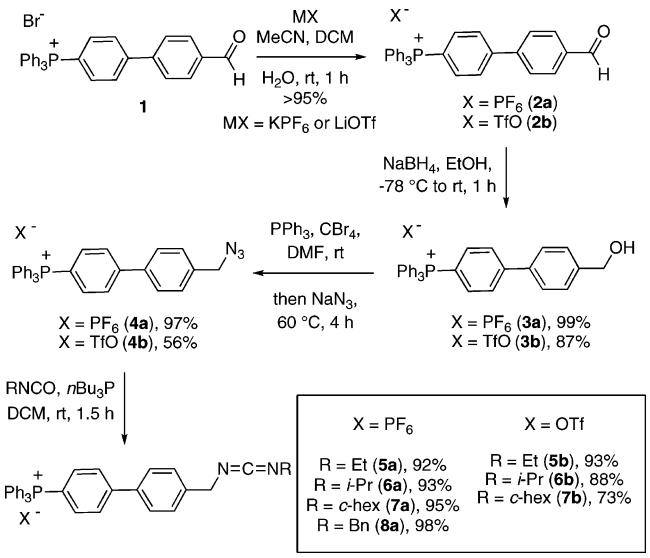
SCHEME 1



N-benzyl-*N*′-cyclohexyl-carbodiimide (PS-BDDC)[11] and polymer-tethered-EDC.[12] Although the use of these reagents is a considerable improvement with regards to purification compared to DCC, there still exist several limitations, including reaction-scale restriction (quantity and loading capacity of the solid supported reagent) and low reaction rates. Consequently, soluble polymers have been developed that can combine advantages of solid-phase and solution-phase reactions. For instance, reaction progress can be easily monitored by standard techniques (LCMS, TLC, HPLC, or NMR) and, as the reaction is carried out under homogeneous conditions, the use of a large excess of reagents is not necessary. To our knowledge, only Hanson and co-workers have described the design of a high-load soluble oligomeric variant of DCC ($^{2G}OACC_n)_{18}$ via a ROM polymerization step.[13]

Recently, our group has been interested in using tetraarylphosphonium (TAP) salts as new solubility control groups (SCG) for reagents.[14] We have previously shown that TAP salts are usually soluble in polar solvents (CH_2Cl_2, CH_3CN, DMSO, PhCN, DMF) and can be precipitated upon addition of less polar solvents such as hexane, Et_2O or toluene. In this context, we report herein the preparation of a series of novel and inexpensive soluble supported carbodiimides, where the carbodiimide moiety is covalently linked to the soluble TAP support. The loadings of these supported reagents are quite high when compared to their solid supported analogues. These reagents were successfully applied in esterification, amidation and dehydration reactions and their structures were optimized to facilitate the removal of byproducts by a precipitation/filtration sequence.

Results and Discussion

Several structurally related carbodiimide derivatives were prepared from readily available isocyanates via a Staudinger reaction with a TAP-supported azide (Scheme 1). The desired TAP-supported azide **4** bearing a biphenyl linker was prepared in three steps from aldehyde **1**.[15] The solubility of TAP salts is counterion-dependent; therefore, to simplify the purification procedure, the bromide counterion was exchanged to generate less soluble phosphonium salts. Subjecting **1** to potassium hexafluorophosphate or lithium trifluoromethanesulfonate in aqueous solution furnished the corresponding hexafluorophosphate **2a** ($X^- = PF_6^-$) and triflate **2b** ($X^- = TfO^-$) salts, respectively, in quantitative yields. The reduction of the aldehydes **2** to alcohols **3** was achieved using sodium borohydride in a mixture of ethanol and CH_2Cl_2 at −78 °C. It should be emphasized that analytically pure phosphonium derivatives **2** and **3** were easily obtained by a selective precipitation of the salt from a CH_2Cl_2 solution upon diethyl ether addition. Alcohols **3a** and **3b** were then converted into the corresponding primary bromides that were directly transformed into azides **4a** (97%) and **4b** (56%).

Subsequent condensation of the azides with various alkyl isocyanates gave the corresponding supported carbodiimides **5**−**8** in good yields. The salts were either used crude or quickly filtered through a pad of silica gel to remove any residual impurities from the Staudinger reaction. The solubility properties of the TAP-supported carbodiimides were consistent with those of other tetraaryphosphonium salts in that all seven salts were soluble in chlorinated solvents and could be precipitated upon diethyl ether addition. The triflate salts were not as clean as the hexafluorophosphate analogues, and all our attempts to increase their purities by crystallization or chromatography failed. Nevertheless, all seven salts were tested in the coupling and dehydration reactions.

The first reaction that was studied was the amide formation from a carboxylic acid and an amine (Table 1). The typical procedure involved combining a slight excess of a carboxylic acid (1.10 equiv) with the appropriate TAP-supported carbodiimide reagent (1.20 equiv) followed by the addition of an amine (1.00 equiv). All reactions were complete within 3 h and, after standard acidic and basic extractions to remove any remaining starting material, the crude mixture was dissolved in CH_2Cl_2. Et_2O addition induced the precipitation of the TAP-supported reagent's byproduct. A subsequent filtration led to the desired product free of the carbodimiide/urea.[16]

To determine the optimal structure of the supported carbodiimide reagent, two aspects were investigated. First, the reactivity of the TAP-supported reagents was evaluated by comparing the yields of the coupling product to that of DCC or EDCI/HOBt.[17] Second, the efficiency of the removal of the byproducts by a precipitation/filtration sequence was assessed by measuring the amount of phosphonium salt remaining in the filtrate relative to the desired coupling product following the precipitation/filtration sequence. The coupling reactions between hexanoic acid or *p*-bromophenylacetic acid and phenethylamine could be accomplished in excellent yields and purity using supported carbodiimide reagent **5a** and **6a** (Table 1, entries 1 and 3). Furthermore, the purity of the coupling product between alanine and glycine was excellent after the removal of the phosphonium-supported byproducts by precipitation/filtration (Table 1, entry 2), and no racemization was observed.[17,18] In

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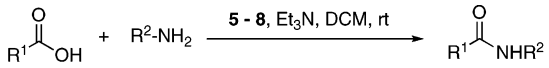
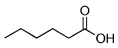
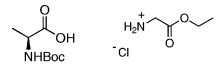
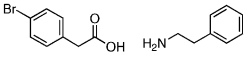
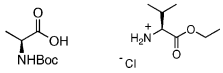
(16) See Supporting Information for typical NMR spectra of crude reaction products after the precipitation/filtration sequence.
(17) Nozaki, S.; Kimura, A.; Muramatsu, I. *Chem. Lett.* **1977**, *18*, 1057.
(18) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447.

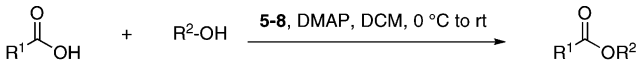
TABLE 1. TAP-Supported Carbodiimide Amidation Reactions

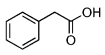
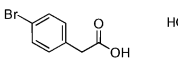
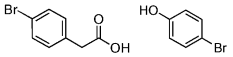
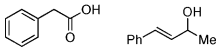


entry	carboxylic acid	nucleophile	product	DCC or EDCI/ HOBt	5a	6a	7a	8a	5b	6b	7b
					yield[a] (purity)[b]						
1			**9**	77[c]	93 (>98)	90 (>98)	81 (98)	60 (98)	60 (96)	64 (92)	56 (90)
2			**10**	79	70 (>98)	67 (>98)	61 (89)	66 (94)	62 (95)	60 (95)	60 (87)
3			**11**	85[c]	85	82	81	81	52	51	60
4			**12**	51[d]	45	-	-	-	-	-	-

[a] Isolated yield of the coupling product after precipitation and filtration of phosphonium-supported byproducts. [b] The purity is given by the [% expected coupling product] − [% remaining phosphonium salt] measured by ^{1}H NMR of the final product. [c] RCO_2H (1.0 equiv), RNH_2 (1.0 equiv), DCC (1.2 equiv), HOBt (1.0 equiv), DMAP (0.10 equiv), CH_2Cl_2, 0 °C to rt. [d] The product is contaminated with ca. 5% of *N*,*N*-dicyclohexylurea that could not be completely removed by the EtOAc precipitation.

TABLE 2. TAP-Supported Carbodiimide Esterification Reactions



entry	carboxylic acid	Nucleophile	product	DCC or EDCI/ HOBt	5a	6a	7a	8a	5b	6b	7b
					yield[a] (purity)[b]						
1			**13**	87[xx]	97 (>98)	92 (>98)	92 (ND)	91 (>98)	90 (93)	99 (95)	77 ND
2			**14**	91[c]	83 (>98)	84 (>98)	67 (ND)	75 (92)	51 (92)	52 (>98)	41 (ND)
3			**15**	89[c]	97	96	89	93	93	89	76
4			**16**	92	88	-	-	-	-	-	-

[a] The yields were measured both by NMR and isolation of pure coupling product. [b] The purity is given by the [% expected coupling product] − [% remaining phosphonium salt]. [c] Procedure B was followed, but DCC (1.2 equiv) was used instead of the phosphonium supported carbodiimide reagent.

general, the yields of the coupling products were higher when using PF_6 salts (**5a**−**8a**) than those observed with triflate salts (**5b**−**7b**). We believe that the main reason for this observation is the fact that the purity of the reagents **5a**−**8a** are higher than that of **5b**−**7b** since all the reagents should display similar reactivities. More importantly, the complete removal of the phosphonium salts by a single precipitation/filtration procedure was very effective with reagent **5a** or **6a**. This can be explained, since the carbodiimide reagents possessing the smallest R group had the most suitable solubility properties. This was expected as the less lipophilic salts are more readily precipitated from the solution by the addition of a less polar solvent. Similarly, the coupling between alanine and valine proceeded well under the same conditions when using **5a** as the carbodiimide reagent (Table 1, entry 4).[19]

Similar trends were observed for the carbodiimide-mediated esterification reactions of carboxylic acids. The typical procedure that was used involved adding the TAP-supported reagent (1.10 equiv) to a mixture of a carboxylic acid (1.00 equiv), an alcohol (1.00 equiv) or a phenol (3.00 equiv) and DMAP (0.10 equiv) at 0 °C. All reactions were complete within 3 h at room temperature, and the TAP-supported urea byproduct was removed from the desired ester by precipitation upon ether addition followed by filtration.

For the same reasons as those outlined for the amidation reactions, reagents **5a** and **6a** provided excellent yields of the corresponding esters. The reaction proceeded extremely well for the esterification of phenylacetic acid and benzyl alcohol (Table 2, entry 1) where a 97% yield of the ester was obtained with carbodiimide **5a**. Most supported carbodiimide reagents were effective for this reaction and the byproducts formed with almost all of the reagents could be removed by a single precipitation/filtration sequence. The esterification using the more sterically hindered isopropanol was almost as efficient as when DCC was used (Table 2, entry 2). As before, supported carbodiimide reagents **5a** and **6a** provided the highest yields and the highest ester purity after the removal of the byproducts. It was also possible to use the supported reagents to generate

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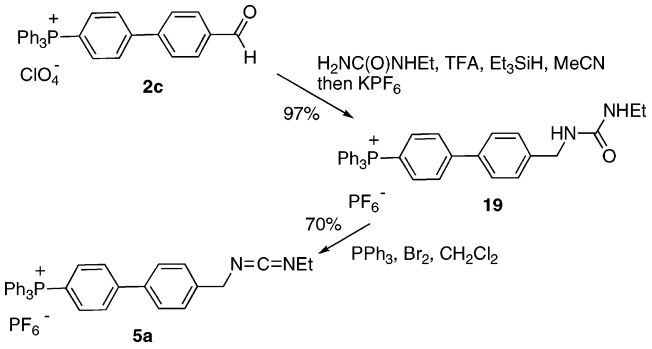
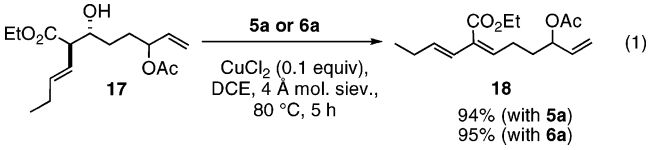
(20) Barbayianni, E.; Fotakopoulou, I.; Schmidt, M.; Constantinou-Kokotou, V.; Bornsheuer, U. T.; Kokotos, G. *J. Org. Chem.* **2005**, *70*, 8730.

SCHEME 2



the phenol ester in high yield (Table 2, entry 3). The coupling reaction between phenylacetic acid and a more sensitive alcohol was accomplished successfully and in high yield (Table 2, entry 4).

We have also tested the TAP-supported carbodiimide reagents in the dehydration reaction of a β-hydroxyester (eq 1).[21] The $CuCl_2$-catalyzed dehydration of alcohol **17** with carbodiimide **5a** or **6a** was carried out in refluxing DCE and resulted in the formation of diene **18** in a better yield than that obtained using the parent unsupported reagents (86%).[22] As above, the complete removal of the urea byproduct was achieved by a single precipitation/filtration sequence.



The effectiveness of reagent **5a** in many reactions prompted us to improve its synthesis and recycling procedure (Scheme 2). Treatment of aldehyde **2c**[23] with *N*-ethylurea under Dubé's conditions[24] led to the phosphonium-supported urea **19**. This compound, which is usually the byproduct of the phosphonium-supported carbodiimide **5a**, can be efficiently dehydrated into **5a** upon treatment with triphenylphosphine/Br_2/Et_3N.

Conclusion

In summary, new soluble TAP-supported carbodiimide reagents have been prepared and shown to be excellent coupling reagents for the preparation of amides and esters and for the dehydration of β-hydroxy-esters. The urea byproducts were easily removed following simple workup procedures involving a precipitation/filtration sequence. Among the various SCG-carbodiimides that were prepared, the hexafluorophosphate tetraarylphosphonium salts **5a** and **6a** are the best supported reagents in terms of efficiency, and their byproducts are less soluble and more easily removed. Finally, the high reagent loadings (1.42−1.55 mmol/g), high reactivity and the possibility of recycling make them attractive alternatives to non-supported carbodiimide reagents.

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(22) Moreau, B.; Ginisty, M.; Alberico, D.; Charette, A. B. *J. Org. Chem.* **2007**, *72*, 1235.

(23) Aldehyde **2c** was prepared by washing the bromide **1** with $LiClO_4$ in acetonitrile (see ref 15 for details).

(24) Dubé, D.; Scholte, A. A. *Tetrahedron Lett.* **1999**, *40*, 2295.

Experimental Section

General Procedure for the Formation of (4′-Formyl-1,1′-biphenyl-4-yl)(triphenyl)phosphonium Salts 2a and 2b. To a solution of aldehyde **1**[15] (7.64 mmol, 1.00 equiv) in DCM (10 mL) and CH_3CN (30 mL) was added a solution of corresponding metal salt (KPF_6 or LiOTf, 1.20 equiv) in H_2O (10 mL). After 1 h of stirring, TLC analysis (DCM/MeOH = 95/5) showed that the anion had completely exchanged. The mixture was then concentrated under reduced pressure and diluted with DCM. The reaction mixture was then washed with water and the resulting aqueous layer was washed with DCM. The combined organic layers were washed twice with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was diluted with a minimum of DCM and was precipitated upon Et_2O addition (5 vol). The heterogeneous solution was decanted and the solution was reprecipitated twice using the above procedure to afford pure **2a** and **2b** as pale-yellow solid foams.

(4′-Formyl-1,1′-biphenyl-4-yl)(triphenyl)phosphonium Hexafluorophosphate (2a). Pale yellow foam; yield 100%; mp 95−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.02−7.98 (m, 4H), 7.89−7.84 (m, 5H), 7.80−7.75 (m, 7H), 7.69−7.64 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8 (s, 1C), 146.6 (s, 1C), 144.0 (s, 1C), 136.2 (s, 1C), 135.6 (s, 3C), 134.9 (d, J = 11.1 Hz, 2C), 134.2 (d, J = 10.1 Hz, 6C), 130.6 (d, J = 13.1 Hz, 6C), 130.3 (s, 2C), 129.3 (d, J = 13.1 Hz, 2C), 128.2 (s, 2C), 117.3 (d, J = 89.6 Hz, 3C), 116.8 (d, J = 90.6 Hz, 1C); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.3 (s, 1P), −144.0 (hept, J = 712.7 Hz, 1P); IR (film) 1698, 1597, 1439, 1109, 832, 724 cm^{-1}; MS (+ES) for $C_{31}H_{24}OP$: *m/z* 443.2 $[M]^+$; MS (-ES) for $^{31}PF_6$: *m/z* 145.1 $[M]^-$. Anal. Calcd for $C_{31}H_{24}F_6OP_2$: C 63.27, H 4.11. Found: C 63.24, H 3.93.

(4′-Formyl-1,1′-biphenyl-4-yl)(triphenyl)phosphonium Trifluoromethanesulfonate (2b). Pale yellow foam; yield 100%; mp 55−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.13−8.00 (m, 4H), 7.89−7.84 (m, 5H), 7.80−7.75 (m, 7H), 7.69−7.64 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8 (s, 1C), 146.5 (s, 1C), 143.9 (s, 1C), 136.1 (s, 1C), 135.6 (s, 3C), 135.0 (d, J = 11.1 Hz, 2C), 134.2 (d, J = 11.1 Hz, 6C), 130.6 (d, J = 13.1 Hz, 6C), 130.3 (s, 2C), 129.3 (d, J = 13.1 Hz, 2C), 128.1 (s, 2C), 117.2 (d, J = 90.6 Hz, 3C), 116.8 (d, J = 90.9 Hz, 1C); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.3 (s, 1P); IR (film) 1698, 1597, 1439, 1261, 1109, 1030, 724, 636 cm^{-1}; MS (+ES) for $C_{31}H_{24}OP$: *m/z* 443.2 $[M]^+$; MS (-ES) for $^{32}SO_3CF_3$: *m/z* 149.1 Anal. Calcd for $C_{32}H_{24}F_3O_4PS$: C 64.86, H 4.08, S 5.41. Found: C 64.66, H 3.94, S 5.37.

General Procedure for the Formation of {4′-(Hydroxymethyl)-1,1′-biphenyl-4-yl}(triphenyl)phosphonium Salt 3a and 3b. To a solution of aldehyde **2** (7.64 mmol, 1.00 equiv) in DCM (0.20 M) at −78 °C was added dropwise a solution of $NaBH_4$ (9.17 mmol, 1.20 equiv) in EtOH (30 mL). The solution was warmed to 0 °C for 1 h. A half-saturated NH_4Cl aqueous solution (75 mL) was carefully added. The combined organic layers were separated and the aqueous layer was washed with DCM (2 × 100 mL). The organic solution was washed with water (3 × 75 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was dissolved with DCM (10 mL) and was the phosphonium salt was precipitated upon Et_2O addition (50 mL). The ether layer was decanted and the above isolation protocol was repeated twice to afford pure alcohol **3a** and **3b**.

{4′-(Hydroxymethyl)-1,1′-biphenyl-4-yl}(triphenyl)phosphonium Hexafluorophosphate (3a). White foam; yield 99%; mp 97−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94−7.83 (m, 5H), 7.79−7.74 (m, 6H), 7.70−7.62 (m, 10H), 7.47 (d, J = 7.9 Hz, 2H), 4.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1 (s, 1C), 142.3 (s, 1C), 137.0 (s, 1C), 135.5 (d, J = 2.9 Hz, 3C), 134.8 (d, J = 11.6 Hz, 2C), 134.2 (d, J = 10.4 Hz, 6C), 130.6 (d, J = 12.8 Hz, 6C), 128.8 (d, J = 13.3 Hz, 2C), 127.6 (s, 2C), 127.4 (s, 2C), 117.9 (s, 1C), 117.0 (s, 1C), 64.3 (s, 1C); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.3 (s, 1P), −144.0 (hept, J = 712.7 Hz, 1P); IR (film)

3063, 1596, 1439, 1393, 1109, 831 cm^{-1}; MS (+ES) for $C_{31}H_{24}O_1P_1$: *m/z* 445.2 $[M]^+$; MS (-ES) for $^{31}PF_6$: *m/z* 145.1 $[M]^-$ Anal. Calcd for $C_{31}H_{26}F_6OP_2$: C 63.06, H 4.44. Found: C 63.79, H 4.37.

{4′-(Hydroxymethyl)-1,1′-biphenyl-4-yl}(triphenyl)phosphonium Trifluoromethanesulfonate (3b). White foam; yield 88%; mp 80−85 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91−7.87 (m, 4H), 7.80−7.75 (m, 6H), 7.68−7.61 (m, 9H), 7.57 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 4.69 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1 (s, 1C), 143.2 (s, 1C), 136.4 (s, 1C), 135.6 (s 3C), 134.7 (d, J = 10.6 Hz, 2C), 134.2 (d, J = 10.3 Hz, 6C), 130.6 (d, J = 12.9 Hz, 6C), 128.7 (d, J = 13.3 Hz, 2C), 127.6 (s, 2C), 127.1 (s, 2C), 117.9 (s, 1C), 117.0 (s 1C), 63.8 (s, 1C); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.3 (s, 1P); IR (film) 3062, 1595, 1438, 1392, 1262, 1154, 1111, 1030, 724, 636 cm^{-1}; HRMS (+ES) calcd for $C_{31}H_{26}O_1P_1$ $[M]^+$: 445.1716, found 445.1727; MS (-ES) for $^{32}SO_3CF_3$ $[M]^-$: *m/z* 149.1.

General Procedure for the Formation of {4′-(Azidomethyl)-1,1′-biphenyl-4-yl}(triphenyl)phosphonium Salt 4. To a solution of alcohol **3** (7.62 mmol, 1.00 equiv), PPh_3 (11.4 mmol, 1.50 equiv) and CBr_4 (11.4 mmol, 1.60 equiv) in anhydrous DMF (40 mL) was added NaN_3 (22.9 mmol, 3.00 equiv). After stirring for 10 min, the reaction was warmed to 60 °C for 4 h. The solution was then cooled to room temperature and DCM and water were added. The aqueous layer was then washed twice with DCM, and the combined organic phases were washed five times with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was diluted with DCM, precipitated upon Et_2O addition and the mixutre was decanted. The crude solid was resubmitted twice to this dissolution/precipitation sequence. Finally, the solid was dissolved in DMF (5 mL) at 85 °C and precipitated from a mixture of hexane/*i*PrOH (100 mL, 1/1) to afford the azido compound **4** with (**4b**) or without (**4a**) further purification.

{4′-(Azidomethyl)-1,1′-biphenyl-4-yl}(triphenyl)phosphonium Hexafluorophosphate (4a). For analytical data, a sample has been purified by flash chromatography (DCM = 100%). White foam; yield 97%; mp 70−75 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97−7.95 (m, 2H), 7.91−7.87 (m, 3H), 7.78−7.75 (m, 7H), 7.73−7.63 (m, 9H), 7.46 (d, J = 7.9 Hz, 2H), 4.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3 (d, J = 3.0 Hz, 1C), 137.8 (s, 1C), 136.2 (s, 1C), 135.4 (d, J = 2.0 Hz, 3C), 134.6 (d, J = 11.1 Hz, 2C), 134.0 (d, J = 10.1 Hz, 6C), 130.4 (d, J = 12.1 Hz, 6C), 128.8 (s, 2C), 128.7 (s, 4C), 127.6 (s, 2C), 117.2 (d, J = 89.6 Hz, 1C), 115.4 (d, J = 91.6 Hz, 1C), 53.9 (s, 1C); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.3 (s, 1P), −144.0 (hept, J = 712.7 Hz, 1P); IR (film) 3064, 2098, 1597, 1439, 1110, 833 cm^{-1}; HRMS (+ES) calcd for $C_{31}H_{25}N_3P_1$ $[M]^+$: 470.1781, found 470.1795; HRMS (-ES) calcd for $^{31}PF_6$ $[M]^-$: 144.9647, found 144.9650.

{4′-(Azidomethyl)-1,1′-biphenyl-4-yl}(triphenyl)phosphonium Trifluoromethanesulfonate (4b). White foam; yield 56% (flash chromatography $CHCl_3$/EtOAc/*i*PrOH = 95/4/1 to 80/15/5); mp 48−53 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97−7.94 (m, 2H), 7.90−7.86 (m, 3H), 7.79−7.74 (m, 7H), 7.72−7.61 (m, 9H), 7.44 (d, J = 7.9 Hz, 2H), 4.39 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3 (d, J = 3.0 Hz, 1C), 137.8 (s, 1C), 136.2 (s, 1C), 135.4 (d, J = 2.0 Hz, 3C), 134.6 (d, J = 11.1 Hz, 2C), 134.0 (d, J = 10.1 Hz, 6C), 130.4 (d, J = 12.1 Hz, 6C), 128.8 (s, 2C), 128.7 (s, 4C), 127.6 (s, 2C), 117.2 (d, J = 89.6 Hz, 1C), 115.4 (d, J = 91.6 Hz, 1C), 53.9 (s, 1C); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.1 (s, 1P); IR (film) 3062, 2096 1596, 1439, 1261, 1151, 1109, 1030, 725, 636 cm^{-1}; HRMS (+ES) calcd for $C_{31}H_{25}N_3P_1$ $[M]^+$: 470.1781, found 470.1795; MS (-ES) for $^{32}SO_3CF_3$ $[M]^-$: *m/z* 149.1.

General Procedure for the Formation of [4′-{((Alkylimino)-methyleneamino)methyl}biphenyl-4-yl]triphenylphosphonium Salt (5, 6). To a solution of azide **4** (1.62 mmol, 1.00 equiv) in DCM (10 mL) at room temperature was added dropwise *n*-Bu_3P (1.94 mmol, 1.50 equiv) to produce a green solution. The corresponding isocyanate (1.94 mmol, 1.50 equiv) was then slowly added and the mixture was stirred for an additional 90 min. The solution was concentrated under reduced pressure and the residue was dissolved in DCM (10 mL). Addition of ether induced the phosphonium salt precipitation. Filtration over Celite led to the solid that was further submitted to the dissolution/precipitation protocol described above three times to afford the expected carbodiimides **5** and **6**. The solid was further purified by flash chromatography in the case of hexafluorophosphate salts.

[4′-{((Ethylimino)methyleneamino)methyl}biphenyl-4-yl]-(triphenyl)phosphonium Hexafluorophosphate (5a). White foam; yield 92% (ca. 90% pure). The purity of the product could be improved by doing a flash chromatography on a small pad of silica using $CHCl_3$/EtOAc/*i*PrOH/Et_3N (97/2/1/3 to 95/4/1/3) as eluent. However, the overall recovery was low (30%) due to the carbodiimide sensitivity on silica gel; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 2.8 Hz, J = 8.4 Hz, 2H), 7.89−7.86 (m, 3H), 7.78−7.74 (m, 7H), 7.71−7.62 (m, 9H), 7.44 (d, J = 8.0 Hz, 2H), 4.42 (s, 2H), 3.20 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3 (s, 1C), 137.2 (s, 1C), 135.6 (s, 3C), 134.8 (d, J = 10.1 Hz, 2C), 134.2 (d, J = 10.1 Hz, 6C), 130.6 (d, J = 10.1 Hz, 6C), 128.9 (s, 2C), 128.8 (s, 2C), 128.2 (s, 3C), 127.6 (s, 3C), 117.9 (d, J = 89.6 Hz, 1C), 115.8 (d, J = 91.6 Hz, 1C), 49.9 (s, 1C), 41.2 (s, 1C), 16.5 (s, 1C); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.3 (s, 1P), −144.0 (hept, J = 712.5 Hz, 1P); IR (film) 3063, 2121, 1596, 1438, 1109, 829, 723, 690 cm^{-1}; HRMS (+ES) calcd for $C_{34}H_{30}N_2P_1$ $[M]^+$: 497.2141, found 497.2142; HRMS (-ES) calcd for $^{31}PF_6$ $[M]^-$: 144.9647, found 144.9650.

[4′-{((Isopropylimino)methyleneamino)methyl}biphenyl-4-yl]-(triphenyl)phosphonium Hexafluorophosphate (6a). White foam; yield 93% (ca. 90% pure). The purity of the product could be improved by doing a flash chromatography on a small pad of silica using $CHCl_3$/EtOAc/*i*PrOH/Et_3N (95/4/1/3) as eluent. However, the overall recovery was low (57%) due to the carbodiimide sensitivity on silica gel. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 3.2 Hz, J = 8.4 Hz, 2H), 7.89−7.86 (m, 3H), 7.78−7.74 (m, 7H), 7.71−7.62 (m, 9H), 7.44 (d, J = 8.0 Hz, 2H), 4.40 (s, 2H), 3.52 (hept, J = 6.4 Hz, 1H), 1.12 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7 (s, 1C), 139.8 (s, 1C), 137.7 (s, 1C), 135.6 (s, 3C), 134.8 (d, J = 11.1 Hz, 2C), 134.2 (d, J = 10.1 Hz, 6C), 130.6 (d, J = 13.1 Hz, 6C), 128.9 (s, 2C), 128.8 (s, 2C), 128.3 (s, 3C), 127.6 (s, 3C), 117.4 (d, J = 89.6 Hz, 1C), 115.4 (d, J = 91.6 Hz, 1C), 50.1 (s, 1C), 49.0 (s, 1C), 24.4 (s, 1C); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.3 (s, 1P), −144.0 (hept, J = 712.5 Hz, 1P); IR (film) 3062, 2970, 2114, 1596, 1438, 1108, 829, 723, 689 cm^{-1}; HRMS (+ES) calcd for $C_{35}H_{32}N_2P_1$ $[M]^+$: 511.2298, found 511.2302; HRMS (-ES) calcd for $^{31}PF_6$ $[M]^-$: 144.9647, found 144.9650.

Improved Synthesis of Phosphonium Supported Carbodiimide 5a. To a solution of aldehyde **2c**[15] (25.00 g, 46.04 mmol, 1.00 equiv) and *N*-ethylurea (12.17 g, 138.13 mmol, 3.00 equiv) in MeCN (230 mL, 0.20 M) at room temperature was added TFA (10.26 mL, 138.13 mmol, 3.00 equiv), followed by Et_3SiH (22.06 mL, 138.13 mmol, 3.00 equiv). The reaction mixture was stirred for 18 h. The solution was diluted with CH_2Cl_2 (500 mL) and washed with water (3 × 50 mL), 10% (w/v) aqueous K_2CO_3 (2 × 50 mL) and water (50 mL). The organic layer was transferred to a 2-L round-bottom flask and an aqueous solution of KPF_6 (12.71 g, 69.06 mmol, 1.50 equiv, 0.69 M) was added. The biphasic solution was vigorously stirred for 30 min. The layers were separated and the organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The slow addition of Et_2O (250 mL) to the resultant oil with vigorous stirring gave a solid product that was collected by filtration. The solid was washed with Et_2O (100 mL). The crude phosphonium supported urea **19** (27.44 g) was obtained as a yellow solid and was used directly in the next step. To a solution of PPh_3 (11.98 g, 45.69 mmol, 1.10 equiv) at 0 °C in CH_2Cl_2 (105 mL, 0.40 M) was slowly added Br_2 (2.55 mL, 49.84 mmol, 1.20 equiv), followed by Et_3N (14.4 mL, 103.8 mmol, 2.50 equiv). After 10 min, a solution of crude phosphonium **19** (27.44 g, 41.54 mmol, 1.00 equiv) in CH_2Cl_2 (105 mL, 0.40 M) was slowly added. The reaction mixture was warmed to room temperature and stirred for

90 min. The solution was diluted with CH_2Cl_2 (500 mL) and washed with water (2 × 75 mL), with saturated aqueous $Na_2S_2O_3$ (75 mL) and with saturated aqueous $NaHCO_3$ (75 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting oil was triturated with Et_2O (250 mL) followed by decantation. The oily crude product was then dissolved in a mixture of CH_2Cl_2/hexane/Et_3N (400 mL, 80/19.8/0.2). The solution was filtered through a 2.5 cm high/10 cm diameter pack of silica gel (prewashed with 0.2% triethylamine/hexanes) and washed with CH_2Cl_2/Et_3N (1.60 L, 99.8/0.2). The organic layer was concentrated under reduced pressure to half of its volume and washed with water (75 mL) and saturated aqueous $NaHCO_3$ (75 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The slow addition of Et_2O (250 mL) to the resultant oil with vigorous stirring gave a solid that was collected by filtration and further washed with Et_2O (100 mL). The phosphonium salt **5a** (20.57 g, 70% for two steps) was obtained as a beige solid.

General Procedure A: Amide Bond Formation. To a solution of the carboxylic acid (0.22 mmol, 1.10 equiv) in DCM (2 mL) was added at room temperature TAP-carbodiimide (0.23 mmol, 1.20 equiv) followed by the amine (0.20 mmol, 1.00 equiv). For entries 2 and 4, triethylamine (0.20−0.40 mmol, 1.00−2.00 equiv) was also added. The reaction mixture was stirred until TLC analysis indicated complete consumption of the starting materials. DCM was then added and the organic layer was washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was then dissolved in a minimum volume of DCM; Celite was added followed by Et_2O to induce the complete precipitation of the phosphonium salt (or with a mixture of Et_2O/DCM = 2.5/1 for entry 3). The mixture was filtered through a 1-cm-high micropack of silica gel and concentrated under reduced pressure to afford the expected pure coupling product.

General Procedure B: Esterification. To a stirred solution of the carboxylic acid (0.20 mmol, 1.00−1.10 equiv) in DCM at room temperature was added, DMAP (0.10−0.20 equiv) followed by the corresponding alcohol (1.00−3.00 equiv). After the reaction mixture was cooled to 0 °C, TAP-carbodiimide reagent (1.20 equiv) was added. The ice bath was then removed and the mixture was stirred at room temperature until TLC analysis indicated complete consumption of the starting materials. After dilution with DCM, the organic layer was washed successively with brine, 10% aqueous HCl, brine, saturated aqueous $NaHCO_3$, brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was then dissolved in a minimum of DCM; Celite was added followed by Et_2O (5 volumes) to induce the complete precipitation of the phosphonium salt. The mixture was filtered through a 1-cm-high micropack of silica gel and concentrated under reduced pressure to afford the expected pure coupling product. A sample was purified by flash chromatography for complete characterization.

Ethyl 6-Acetoxy-2-[(1*E*)-but-1-enyl]octa-2,7-dienoate (18). To the (*2R*,*E*)-ethyl-6-acetoxy-2-(but-1-enyl)-3*R*-hydroxyoct-7-enoate (**17**) (45 mg, 0.15 mmol, 1.00 equiv) dissolved in DCE (3 mL) were added molecular sieves 4 Å (around 250 mg), $CuCl_2$ (2 mg, 0.015 mmol, 0.10 equiv), and finally the corresponding TAP-carbodiimide **5a** (148 mg, 0.23 mmol, 1.50 equiv). The reaction was stirred at 85 °C for 6 h. After cooling to room temperature, the reaction mixture was diluted with DCM (10 mL) and filtered. The resulting organic layer was washed successively with water (20 mL), with 15% (w/v) aqueous NH_4Cl (20 mL) and with brine (20 mL). After drying over anhydrous Na_2SO_4 and concentration under reduced pressure, the crude product was diluted with DCM (5 mL) and precipitated upon Et_2O (25 mL) addition. Filtration through a 1-cm-high micropack of silicagel afforded the desired diene **18**.

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Supporting Information Available: Experimental procedures for the preparation of all reagents and compounds as well as characterization data for each reaction and detailed structural assignment. This material is available free of charge via the Internet at http://pubs.acs.org.

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