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Note

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Synthesis of Diphenylhexatriene by the Pd-Catalyzed Dimerization of Cinnamyl Acetate

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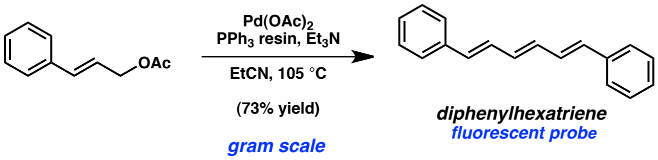
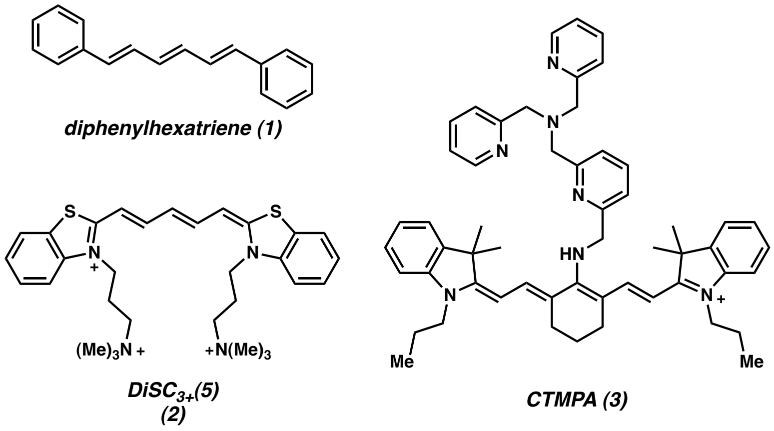
Abstract



A mild and operationally-simple method to synthesize diphenylhexatriene (DPH) is reported. The method relies on the Pd-catalyzed dimerization of cinnamyl acetate and provides efficient access to DPH in a single step.

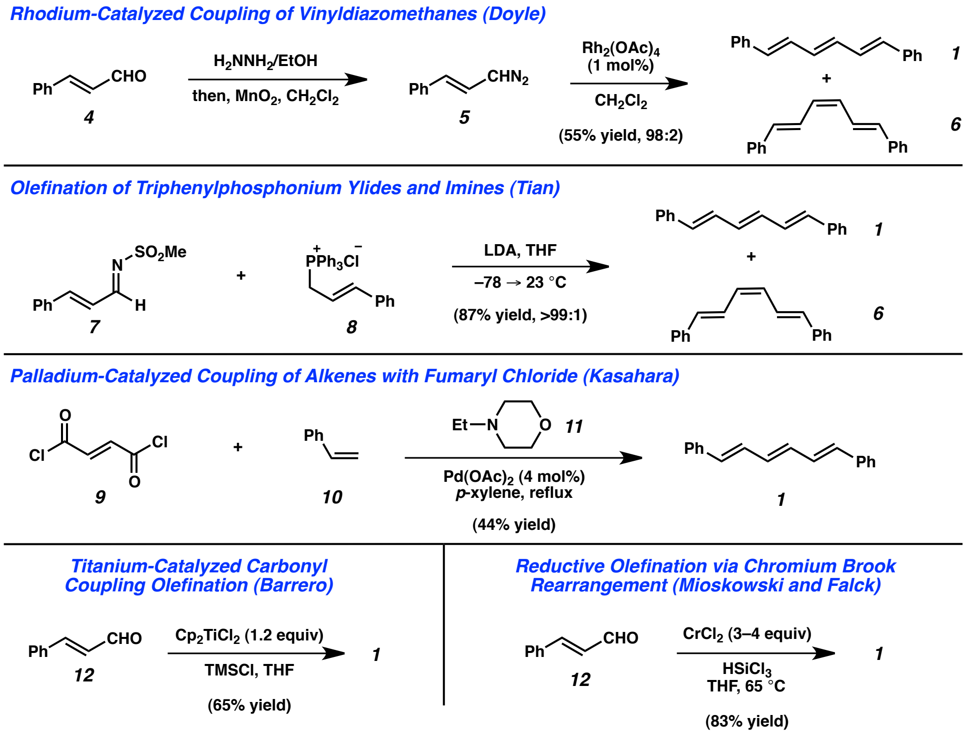
The synthesis of conjugated hydrocarbons that display interesting fluorescence properties remains an important area of research. For example, compounds such as diphenylhexatriene (DPH, **1**), DiSC$_{3+}$(5) (**2**), and CTMPA (**3**) (Figure 1), play key roles as fluorescent probes in biological studies.[1] Of these, DPH is exceptionally noteworthy as it can be utilized in an array of applications, such as serving as a lipid membrane fluorescent probe for cancer studies,[2] performing as a biological sensor for detecting fatty acyl chains,[2] and monitoring protein aggregation to identify both amorphous and fibrillar aggregates.[1c]

Figure 1. Conjugated Hydrocarbons as Fluorescent Probes.



Several reported methods for the synthesis of diphenylhexatriene (**1**) are summarized in Figure 2. Doyle and Yan disclosed a method to arrive at diphenylhexatriene (**1**) and its isomer **6** in 55% yield (98:2 mixture of isomers). Their approach first involved conversion of cinnamaldehyde (**4**) to diazo compound **5**. Subsequent rhodium-catalyzed dimerization of **5** provided DPH (**1**).[3] The Tian group reported a stereoselective olefination of triphenylphosphonium ylide **8** with *N*-sulfonyl imine **7** to arrive at **1** in 87% yield.[4] Kasahara and coworkers discovered the palladium-catalyzed coupling of fumaryl chloride (**9**) with styrene (**10**) to provide **1** in 44% yield.[5] Two methods to directly convert cinnamaldehyde (**12**) to DPH (**1**) in good yields have also been reported. A titanium-catalyzed dimerization furnished DPH (**1**) in 65% yield, as recently shown by the Barrero group.[6] Finally, Mioskowski and Falck have disclosed a reductive olefination of cinnamaldehyde (**12**) via a chromium Brook rearrangement to yield diphenylhexatriene (**1**) in 83% yield.[7]

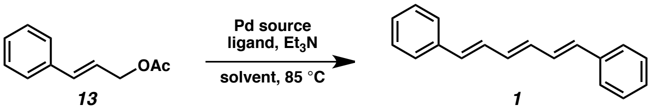
Figure 2. Various Approaches to Diphenylhexatriene (**1**).



While investigating unrelated transformations involving π-allyl Pd intermediates, we unexpectedly found that cinnamyl acetate (**13**) may be readily converted to diphenylhexatriene (**1**) using Pd catalysis. As shown in Table 1, we initially observed that exposure of cinnamyl acetate to $Pd(OAc)_2$, PPh_3, and triethylamine in DMSO gave **1** in 48% yield (entry 1). We also investigated the dimerization in toluene, 1,2-dichloroethane, and tetrahydrofuran (entries 2–4), but **1** was not observed when these solvents were employed.[8] Gratifyingly, the use of acetonitrile as solvent furnished **1** in 92% yield (entry

5). After identifying acetonitrile as the optimal solvent, we examined the influence of ligands. Several phosphorous-based ligands were tested, namely, triphenyl phosphite, tricyclohexylphosphine, and tri-*ortho*-tolylphosphine, but DPH (**1**) formation was not observed (entries 6–8).[8] However, dimerization in the presence of dppf as the ligand yielded 77% of the desired triene **1** (entry 9). We also investigated the use of Pd/C without ligand additives, but the reaction shut down completely (entry 10). With these results in hand the conditions described in entry were selected for further optimization studies. In order to ease the purification process, the use of a triphenylphosphine resin was examined. To our delight, replacement of PPh_3 with a solid-supported variant gave **1** in quantitative yield (entry 11).[9] It was also found that propionitrile could be substituted for acetonitrile to give **1** in comparable yields (entry 12). The use of propionitrile was beneficial in that it allowed for reactions to be conducted at higher temperatures and led to more consistent results in larger-scale experiments.

Table 1. Optimization of Reaction Conditions.[a]

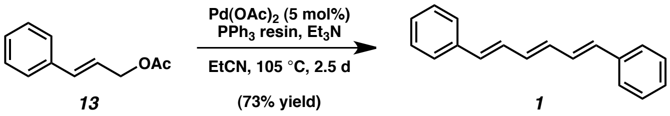


entry	Pd source	ligand	solvent	yield[b]
1	$Pd(OAc)_2$	PPh_3	DMSO	48%
2	$Pd(OAc)_2$	PPh_3	toluene	0%
3	$Pd(OAc)_2$	PPh_3	1,2-dichloroethane	0%
4	$Pd(OAc)_2$	PPh_3	tetrahydrofuran	0%
5	$Pd(OAc)_2$	PPh_3	acetonitrile	92%
6	$Pd(OAc)_2$	$P(OPh)_3$	acetonitrile	0%
7	$Pd(OAc)_2$	PCy_3	acetonitrile	0%
8	$Pd(OAc)_2$	P(*o*-tolyl)$_3$	acetonitrile	0%
9	$Pd(OAc)_2$	dppf	acetonitrile	77%
10	Pd/C	--	acetonitrile	0%
11	$Pd(OAc)_2$	PPh_3 resin	acetonitrile	100%
12	$Pd(OAc)_2$	PPh_3 resin	propionitrile	96%[c]

[a] Conditions unless otherwise stated: Pd source (5 mol%), ligand (15 mol%), cinnamyl acetate **13** (1 equiv), Et_3N (3 equiv) in solvent (0.2 M) at 85 ºC for 24 h. [b] Yield determined by ^1H NMR analysis of the crude reaction mixture using hexamethylbenzene as an internal standard. [c] Reaction performed at 105 ºC.

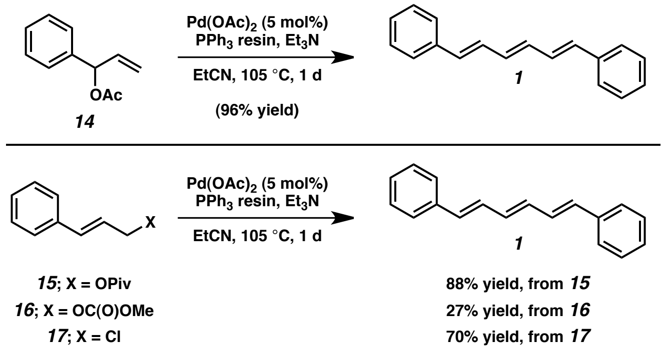
With suitable reaction conditions in hand for the efficient synthesis of **1**, we tested the scalability of our procedure (Figure 3). Performing the coupling using >10 mmol of cinnamyl acetate (**13**) under our optimized reaction conditions ($Pd(OAc)_2$, PPh_3 resin, and triethylamine in propionitrile at 105 ºC) gave diphenylhexatriene (**1**) in 73% isolated yield after flash column chromatography.[10] This result underscores the effectiveness of our method for preparing the fluorescent probe DPH (**1**).

Figure 3. Synthesis of Diphenylhexatriene (**1**).



We also tested the viability of accessing **1** using substrates other than cinnamyl acetate (Figure 4). Initially, we examined the branched isomer of cinnamyl acetate, **14**,[11] and subjected it to our coupling conditions. DPH (**1**) was formed in 96% yield, which is comparable to the results obtained using cinnamyl acetate (**13**).[12] Other linear derivatives of cinnamyl alcohol were also probed under our optimized dimerization conditions. Cinnamyl pivalate **15**[13] underwent smooth coupling to furnish **1** in 88% yield, whereas the corresponding carbonate **16**[14] yielded only 27% of the desired product. In the latter case, the remainder of the mass consisted of unreacted starting material and cinnamyl alcohol. Finally, commercially available cinnamyl chloride **17** was converted to **1** in 70% yield using our standard conditions.

Figure 4. Testing Substrate Variation for the Synthesis of Diphenylhexatriene (**1**).



In summary, we have developed an efficient means to synthesize the important fluorescent probe diphenylhexatriene. The method relies on the unusual palladium-catalyzed dimerization of cinnamyl acetate to furnish DPH (**1**) in good yield. Our method is scalable and provides access to gram quantities of the desired conjugated triene. The use of alternate electrophilic derivatives, other than cinnamyl acetate, can also be used to efficiently access **1**.

Experimental Section

Representative Procedure for Optimization Studies (Table 1, entry 1 is used as an example). Diphenylhexatriene (1). A flame-dried 4-mL vial equipped with a magnetic stir bar was charged with hexamethylbenzene (6.5 mg, 0.04 mmol, 10 mol%), $Pd(OAc)_2$ (4.6 mg, 0.02 mmol, 5 mol%), and PPh_3 (15.7 mg, 0.06 mmol, 15 mol%) while purging with N_2. Subsequently, DMSO (2.0 mL), Et_3N (167 μL, 1.2 mmol, 3 equiv) and cinnamyl acetate (67 μL, 0.4 mmol, 1 equiv) were added to the reaction vial. The solvent was sparged with N_2 for 20 minutes and the vial was capped with a Teflon-lined screw cap. The reaction was heated at 85 °C for 24 h. The reaction was allowed to cool to room temperature and was then diluted with benzene:Et_2O (1:1, 5 mL). The solution was filtered by passage over a short plug of silica plug (x 2), and eluted with additional benzene:Et_2O (1:1, 5 mL). The yield was determined by ^1H NMR analysis with hexamethylbenzene as an internal standard.

Diphenylhexatriene (**1**): To a flame-dried pressure tube equipped with a stir bar was added $Pd(OAc)_2$ (0.129 g, 0.568 mmol) and PPh_3 resin (1.42 g, 1.70 mmol), while purging with N_2. The vent needle was removed and EtCN (19 mL), triethylamine (4.74 mL, 34.0 mmol) and cinnamyl acetate (1.91 mL, 11.4 mmol) were added. The solvent was sparged with N_2 and the resulting mixture was stirred vigorously for 45 min. The pressure tube was capped and the reaction was heated at 105 °C. After 2.5 d, the reaction mixture was allowed to cool to 23 °C. The mixture was then diluted with benzene:Et_2O (1:1, 20 mL), filtered by passage over silica gel (x 2), and eluted with additional benzene:Et_2O (1:1, 20 mL). The solvent was removed under reduced pressure. Purification by flash chromatography (95:5 hexanes:EtOAc) afforded diphenylhexatriene (**1**) as a yellow solid (0.96 g, 73% yield). R_f 0.4 (95:5 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, J = 7.5, 4H), 7.32 (t, J = 7.5, 4H); 7.24 (t, J = 7.5, 2H), 6.89 (dddd, J = 15.0, 7.5, 7.5, 3.0, 2H), 6.60 (d, J = 15.0, 2H), 6.52 (dd, J = 7.5, 3.0, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.4, 133.6, 132.7, 129.1, 128.7, 127.6, 126.4; IR (film): 3058, 3013, 1594, 1490, 1447, 1178, 1072 cm^{-1}; HRMS-CI (*m/z*) $[M]^+$ calcd for $C_{18}H_{16}$, 232.1252; found, 232.1253; m.p. 193–195 °C. Spectral data match those previously reported.[4]

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Commercially available PPh_3 resin (CAS# 39319-11-4) was employed.

[10] Purification of diphenylhexatriene by silica gel chromatography is accompanied by some mass loss, which is attributed to the compound's propensity to precipitate out of solution.

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