Catalytic Three-Component Synthesis of Conjugated Dienes from Alkynes via Pd^0, Pd^{II}, and Pd^{IV} Intermediates Containing 1,2-Diimine**

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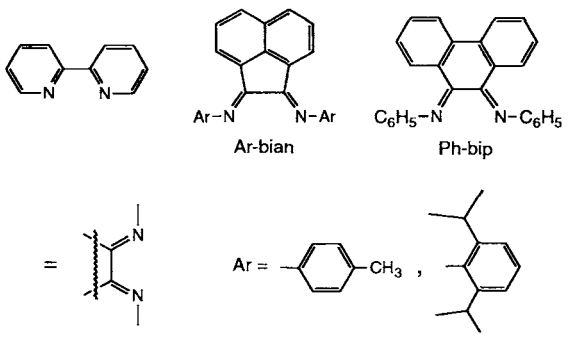
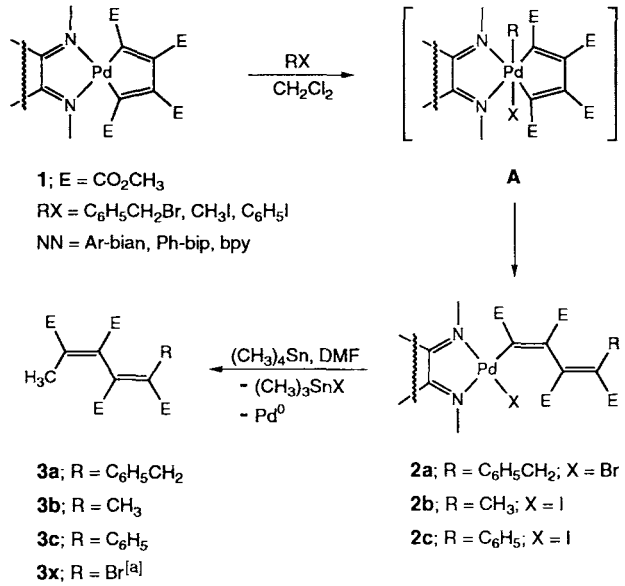
The direct synthesis of conjugated dienes from alkynes is highly desirable for forming valuable synthetic intermediates.[1] A number of methods are available for the stereoselective preparation of dienes from acetylenes,[2] but these either rely on the use of a stoichiometric amount of a reactive organometallic species (precluding the presence of sensitive substituents),[3] require more than one reaction step,[4] or start from pure stereoisomers of alkenyl compounds in cross-coupling reactions.[5] A high-yield, selective catalytic procedure for preparing conjugated "open-chain" dienes directly from acetylenes has not been described.[6]

As part of our continuing studies on carbon–carbon and carbon–heteroatom cross-coupling reactions[7] mediated by palladium compounds with ancillary, rigid, bidentate nitrogen ligands (Scheme 1), instead of the usual phosphanes, we report a new catalytic three-component synthesis of conjugated dienes by coupling of alkynes with an organic halide and tetramethyltin. Mechanistic details have been elucidated that reveal that stereospecific oxidative addition and reductive elimination at carbopalladacyclic compounds occurs, and that intermediate Pd^0, Pd^{II}, and Pd^{IV} species are involved in the catalytic cycle.



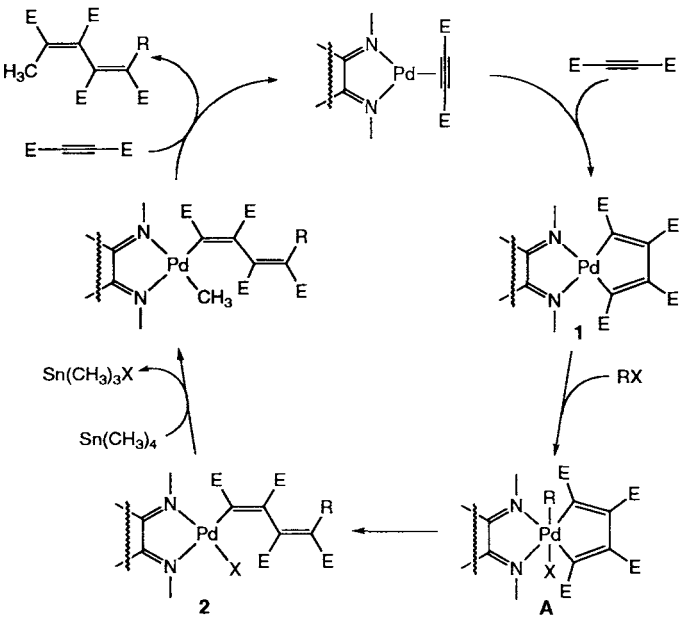
Scheme 1. Bidentate N ligands.

Palladacycles **1**[8] react with one equivalent of an organic halide (for example benzyl bromide, methyl iodide, or iodobenzene) in dichloromethane at 20 °C to give dienyl(NN-κ^2-*N*,*N*)palladium(II) halides **2**[9] (Scheme 2; NN = bis (arylimino)acenaphthene (Ar-bian), bis(phenylimino)phenanthrene (Ph-bip),[10] or 2,2′-bipyridine (bpy)). Compounds **2** are formed by a sequence of oxidative addition and reductive elimination at palladium via triorgano(NN-κ^2*N*,*N*)palladium(IV) halides **A**.[11] Reaction of **2a–c** with tetramethyltin in DMF at 60–85 °C leads to the selective formation of 2,5-difunctionalized 2,4-hexadienoates **3a–c**. Sequential addition of methyl iodide and one equivalent of Br_2 to **1** in dichloromethane results in the 2-bromo-5-methyl derivative **3x**.



Scheme 2. Stoichiometric reaction of palladacyclopentadienes **1** with organic halides and Me_4Sn. [a] With addition of Br_2 (instead of Me_4Sn) to **2b** in CH_2Cl_2 directly after its formation.

Since formation of palladacycles **1** from $[Pd(dba)_2]$ (dba = dibenzylideneacetone) and electron-poor alkynes is much faster than oxidative addition of benzyl bromide to zero-valent Pd species, and insertion of a third molecule of acetylene in **1** is slower than reaction of the organic halide with **1** to give **2**, we anticipated that a catalytic procedure for the synthesis of dienes **3** (Scheme 3), consisting of the single steps shown above, was feasible. Indeed, employing **1** as the precatalyst (or $[Pd(dba)_2]$ and an equimolar amount of Ar-bian or Ph-bip) with



Scheme 3. Proposed cycle for the three-component synthesis of conjugated dienes from alkynes, RX, and Me_4Sn catalyzed by palladium/N ligand. E = CO_2CH_3; RX = $C_6H_5CH_2Br$, CH_3I, C_6H_5I.

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[**] Rigid Bidentate Nitrogen Ligands in Organometallic Chemistry and Homogeneous Catalysis. Part 12. Part 11: R. van Asselt, C. J. Elsevier, C. Amatore, A. Jutand, *Organometallics* **1997**, *16*, 317. This work was supported in part (H. H.) by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO).

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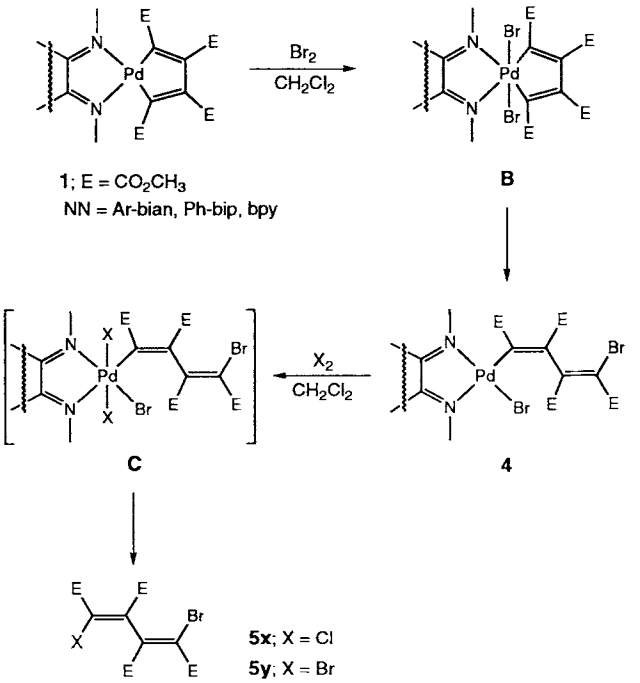
100 equivalents of dimethyl butynedioate, 50 equivalents of tetramethyltin; and 50–200 equivalents of benzyl bromide, methyl iodide; or iodobenzene in DMF at 65 °C resulted after 8–16 h in the complete conversion of the alkyne into conjugated dienes **3a–c**. DMF was selected as the solvent to obtain convenient rates, as reactions in acetonitrile and THF are sluggish, probably because transmetalation is the rate-determining step. The best results were obtained when employing [Pd(Ar-bian)] compounds as the catalyst (71–85% yields of isolated **3a–c**). 1-Dimethylamino-1,2-di(methoxycarbonyl)ethene formed as a secondary product in approximately 10% yield due to base- or palladium-catalyzed decarbonylative addition of DMF to coordinated dimethyl butynedioate.[12] This, in conjunction with the fact that the latter reaction does not occur in the absence of palladium species, points to the occurrence of zero-valent palladium species in the catalytic cycle. In the case of **3c** small amounts of the cyclotrimerization product hexamethylmellitate (4%) and 1-phenyl-1,2-di(methoxycarbonyl)-1-propene (7%)[13] formed as well. Importantly, no direct cross-coupling between the organic halide and tetramethyltin took place. We obtained palladacycles **1** containing mono- and bidentate nitrogen ligands for dimethyl butynedioate (E = CO_2Me) and hexafluoro-2-butyne (E = CF_3), but stoichiometric or catalytic reactions of methylpropynoate, phenylacetylene, and 1-octyne were unsuccessful so far.

Reactions of **1** with two equivalents of Br_2 in dichloromethane at 20 °C afforded (2*E*,4*E*)-2,5-dibromo-2,4-hexadienoates **5y** and [$PdBr_2$(NN-κ^2N,N)] (Scheme 4). Intermediate **B**, a diorganopalladium(IV) dihalide,[14] formed instantaneously and quantitatively at 200 K in CD_2Cl_2, as demonstrated by in situ ^{1}H NMR spectroscopy for NN = bis(2,6-diisopropylphenyl)bian or Ph-bip; the signals for the methoxycarbonyl groups adjacent to palladium in **B** are shifted to higher frequency by about 0.8 ppm.[15] The C_{2v} symmetry of **B** was apparent from the pair-wise equivalence of protons on the backbone of the NN ligand, the palladacyclopentadiene moiety, and the two (perpendicular) *N*-aryl groups, and from the fact that only two



Scheme 4. Stoichiometric reactions of palladacycles **1** with molecular halogen to give 1,4-dihalo-1,3-dienes via diorganopalladium(IV) dihalides **B** and organopalladium(IV) trihalides **C**.

doublets were observed for the four CH(CH_3)$_2$ groups of the bis(*N*-2,6-diisopropylphenyl)bian derivative.[16] Reductive elimination from **B** to give **4**, which could be isolated,[17] was completed in 10–15 min at 200 K.

Reaction of **4** with Br_2 gave **5y** and [$PdBr_2$(NN-κ^2N,N)], and that of **4** with PhI·Cl2 led to the chemoselective formation of 2-bromo-5-chloro-2,4-hexadienoates **5x**. The 5-chloro-2,4-hexadienylpalladium(II) chloride analogue of **4** also reacted with Br_2 to give exclusively **5x**. These results, taken together with the fact that no elimination of dibromodienes was observed from the reaction of **4** with ICl and, moreover, that such reactions could not be effected with palladium–phosphane analogues of **4**, strongly indicate the occurrence of intermediate organopalladium(IV) trihalide species **C**, from which stereospecific reductive elimination of one of the apical halogens and the dienyl moiety takes place.

Interestingly, three oxidation states of palladium are involved in the catalytic cycle. This merits further attention, especially in view of the current interest in catalytic reactions (presumably) involving palladium in high oxidation states.[11a, 14b, c, 18] Phosphane ligands are not compatible; they either react with the alkyne, or the palladium–phosphane species involved exhibit no catalytic activity whatsoever under the conditions described.

To our knowledge the procedure described here represents the first straightforward, regioselective, three-component protocol for the synthesis of conjugated dienes involving alkynes, which are themselves sensitive to nucleophilic attack. Dienes **3** and **5** obtained by this procedure may serve as building blocks, for instance in conjugate-addition, Diels–Alder, and (for **3x** and **5**) catalytic C–C coupling reactions, for example with vinyltin and boron reagents to obtain conjugated trienes and tetraenes. The drawback of the limited scope of the reaction (as far as the alkyne is concerned) may partly be overcome by modification of the substituents, including dealkoxycarbonylation.

The results obtained thus far prompt us to undertake a more detailed investigation regarding the generality and the mechanism of this convenient protocol for the catalytic synthesis of conjugated dienes from readily available starting materials.

Experimental Section

Typical procedure for the catalytic synthesis of **3**: A solution of [Pd(*p*-tolbian){C(CO_2Me)=C(CO_2Me)C(CO_2Me)=C(CO_2Me)}] (15 mg, 0.02 mmol), dimethyl butynedioate (245 μL, 2.0 mmol), Me_4Sn (180 mg, 1.0 mmol), and methyl iodide (0.6 mL, 10 mmol) in DMF (10 mL) was stirred under a nitrogen atmosphere in a closed Schlenk tube for 16 h at 65 °C. In the case of benzyl bromide or iodobenzene 1.0 mmol of the organic halide was added, and the reaction temperature kept at 85 °C. The crude reaction mixture was dissolved in dichloromethane (100 mL), washed with water (3 × 150 mL), and dried. After removal of the solvent under vacuum, a sticky solid remained, from which the organic product was extracted with diethyl ether. After chromatographic purification on silica gel (hexanes/diethyl ether 9/1) **3a** was isolated in 71%, **3b** in 85%, and **3c** in 76% yield.

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[13] Probably formed by transmetalation of the adduct resulting from phenylpalladation of $[Pd^0(NN)(MeO_2CC{\equiv}CCO_2Me)]$.
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[15] ^1H NMR data for $PdC(CO_2CH_3)$ and $PdC{=}C(CO_2CH_3)$ groups in $CDCl_3$: **B** (223 K): $\delta = 3.61$ and 3.57 (iPr_2-bian derivative), 3.72 and 3.58 (Ph-bip derivative); **1**: (223 K): $\delta = 2.66$ and 3.46 (iPr_2-bian derivative), 2.93 and 3.65 ppm (Ph-bip derivative).
[16] ^1H NMR data for the $(CH_3)_2CH$ groups of the 2,6-iPr_2-bian derivative in $CDCl_3$: **B** (200 K): $\delta = 1.26$ (d) and 0.52 (d); **1**: (200 K): $\delta = 1.32$ and 0.54; **4**: (223 K): $\delta = 1.39$ (d), 1.27 (d), 1.09 (d) and 0.60 (d; no C_s plane perpendicular to the $Pd(X)CN_2$ plane for **4**).
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Conformation Design of a Fully Flexible βII-Hairpin Analogue**

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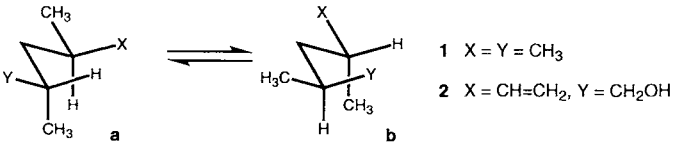
Isosteric, non-hydrolyzable analogues of secondary-structure elements of peptides are of high current interest in medicinal chemistry and serve as peptidomimetics. Such structural units yield important information on complex structure–activity relationships and are neccessary for a rational design of low molecular weight, non-peptide pharmaceutical agents.[1] Moreover, such analogues of peptide structures may be important for inducing α-helix or β-turn structures in adjacent peptide sequences.[2] Far less is known about the prerequisites for the induction of β-sheet structures, in which tertiary interactions play a decisive role. Gellman et al. pointed out that good model systems for studying the formation of β-hairpin structures are lacking.[3]

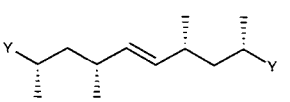
We are interested in a rational conformation design of open-chain hydrocarbon backbones that possess a strong conformational bias and yet maintain full flexibility.[4] We therefore tried to apply the principles of nature's conformation design, demonstrated in polyketide natural products, to designing new molecular backbones. We demonstrate here the value of such an approach with the design of a fully flexible β-hairpin analogue.

A β hairpin is the simplest form of an antiparallel β-sheet conformation, and is defined by a β-turn region flanked by two antiparallel peptide strands that are hydrogen bonded through the corresponding backbone CO and NH groups. Different structural types of β turns are characterized by the ϕ and ψ dihedral angles of the peptide backbone.[5] Figure 1 shows the structure of a βII-type hairpin with $\phi_1 = -60$, $\psi_1 = 120°$, $\phi_2 = 90°$, and $\psi_2 = 0°$. The requirements that a mimic must meet are 1) a reversal in the peptide-chain direction and 2) the promotion of intramolecular hydrogen-bond formation.[2] In addition, our approach allows preservation of conformational flexibilty similar to that of the natural prototype.

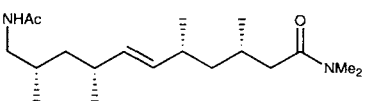
Our design is based on 2,4-dimethylpentane units such as the ones nature uses in its conformation design of polyketide natural products.[4] 2,4-Dimethylpentane (**1**) is biconformational, and equally populates, to greater than 90%, two enantiomorphous and, hence, isoenergetic low-energy conformations **1a** and **1b**.



The position of the conformer equilibrium could be biased to one side by varying the substituents X and Y. In **2a** X suffers an additional *gauche* interaction, which Y does not have, and is therefore in the sterically more encumbered position. When X in **2** is a less sterically demanding vinyl group and Y a hydroxymethyl group, conformation **2a** should be preferentially populated. In fact, an equilibrium ratio **a**:**b** of about 3.5:1 was found for **2** in $CDCl_3$ solution. Therefore, **2** represents a backbone segment with a conformational preference. It can be combined with itself or other building blocks to yield larger molecular frameworks. The combination of two segments of **2** results in structure **3**, which should have a U-shaped molecular backbone that is similar to β-turn und β-hairpin moieties of peptides.



3 Y = CH_2OH **4** Y = CH_3



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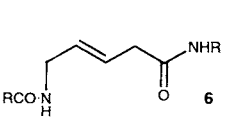

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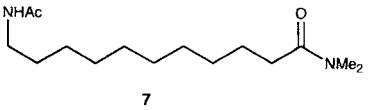

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