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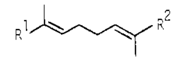
Palladium-Catalyzed Cross-Coupling Reaction of Homoallylic or Homopropargylic Organozincs with Alkenyl Halides as a New Selective Route to 1,5-Dienes and 1,5-Enynes

Sir:

The construction of 1,5-diene units present in various natural products of terpenoid origin,[1] such as **1** and **2**, via cross-coupling has been achieved in most cases by the Biellmann and related allyl–allyl coupling reactions.[2] While these reactions appear well suited for synthesizing 1,5-dienes represented by **1**, their application to the synthesis of **2** is often complicated by regiochemical scrambling and other side reactions.[3] Our recent development of a highly stereoselective method for converting terminal acetylenes into various (*E*)-β-methyl-1-alkenyl derivatives[4] prompted us to synthesize 1,5-dienes, especially those represented by **2**, via alkenyl-homoallyl or alkenyl-homopropargyl coupling. As the reaction of alkenyllithiums or the corresponding Grignand reagents with homoallylic halides leads mainly to the β-elimination of the halides,[5] the possibility of applying the palladium-catalyzed cross-coupling[6] to the synthesis of 1,5-dienes was explored. If the palladium-catalyzed cross-coupling reaction of alkenyl halides with alkyl metals containing β-carbon-bound hydrogen atoms should proceed via oxidative addition–transmetalation–reductive elimination sequence,[7] it could be competed by the well-known β-elimination reaction[8] of the hypothetical diorganopalladium intermediate **3** (Scheme I). It was therefore of interest to find out what factors affect the relative extents to which the two competing elimination processes, i.e., paths A and B, occur.



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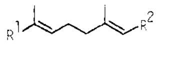


2

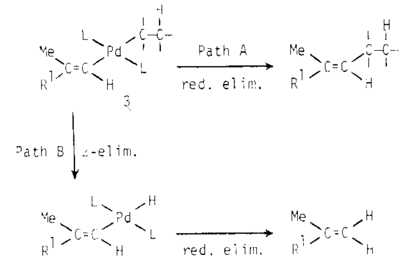
We first examined the reaction of (*E*)-1-iodo-2-methyl-1-hexene (**4**) with *n*-, *sec*, and *tert*-butylzinc chlorides and the corresponding magnesium derivatives and found that, while the *tert*-butyl metals react nearly exclusively (>90%) via β-elimination (path B), both *n*- and *sec*-butylzinc chlorides can undergo predominantly the cross-coupling reaction[9] (Table I). Far more exciting, however, were the results obtained in the corresponding reactions of homoallylzinc chloride and the trimethylsilyl derivative of homopropargylzinc chloride with **4** which proceeded at least as well as that of *n*-butylzinc chloride. Despite the presence of allylic or propargylic β-hydrogen atoms, the extent of β-elimination as judged by the amount of the deiodinated alkene was less than 1–2% (Table I). In light of the widely known β-elimination of alkylpalladium species,[8] these results are unexpected. Should these reactions proceed as shown in Scheme I, the observed results then indicate that *reductive elimination can proceed far faster than β-elimination even in cases where the latter process involves removal of an allylic or propargylic hydrogen atom.*

Table I. Pd-Catalyzed Reaction of (*E*)-1-Iodo-2-methyl-1-hexene with Alkylzinc and Alkylmagnesium Reagents[a]

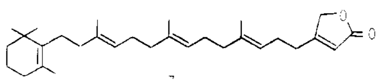
organometallic reagent[b]	time, h	product yield,[c] % cross-coupled	deiodo	homo-coupled[d]
n-BuZnCl	2	76	2	8
n-BuMgBr	2	25	51	8
sec-BuZnCl	16	68[e]	15	5
sec-BuMgBr	16	40[f]	35	1
$CH_2{=}CH(CH_2)_2ZnCl$	16	81	trace	8
$CH_2{=}CH(CH_2)_2MgBr$	16	21	37	11
$Me_3SiC{\equiv}C(CH_2)_2ZnCl$	2	91	trace	5

[a] All reactions were carried out in THF–ether at 20–25 °C under an atmosphere of nitrogen. [b] The organozinc reagents were prepared by treating the corresponding Grignard reagents with anhydrons $ZnCl_2$. [c] Yields were obtained by GLC (SE-30). [d] The homo-coupled product refers to 5,8-dimethyl-5,7-dodecadiene. [e] A 60:40 mixture of the *sec*-butyl and isomerized *n*-butyl derivatives. [f] A 40:60 mixture of the *sec*-butyl and *n*-butyl derivatives.

Scheme I



The cross-coupling procedure described above provides an expeditious and selective route to 1,5-dienes of terpenoid origin. To demonstrate its synthetic utility, we chose to synthesize (*E,E*)-farnesol (**5**) and a tetraenol, **6**, which has recently been synthesized and converted into mokupalide (**7**) by Sum and Weiler.[10]



7

2-Methylhept-2-en-6-yne (**8**) was obtained in 71% yield from 6-methyl-5-hepten-2-one by a procedure developed by us recently,[11] which consists of sequential treatment of the methyl ketone with lithium 2,2,6,6-tetramethylpiperidide (LTMP) (1.05 equiv, −78 °C, 1 h), $ClPO(OEt)_2$ (1.15 equiv, −78 °C to room temperature), LTMP (2.25 equiv, −78 °C to room temperature), and aqueous NH_4Cl (excess). The enyne **8** was converted into **9** (bp 54–55 °C, 0.55 mmHg) in 75% yield by a procedure which was developed by us recently[12] (procedure i, Scheme II). The trimethylsilyl derivative of homopropargylzinc chloride **10** was prepared by trimethylsil-

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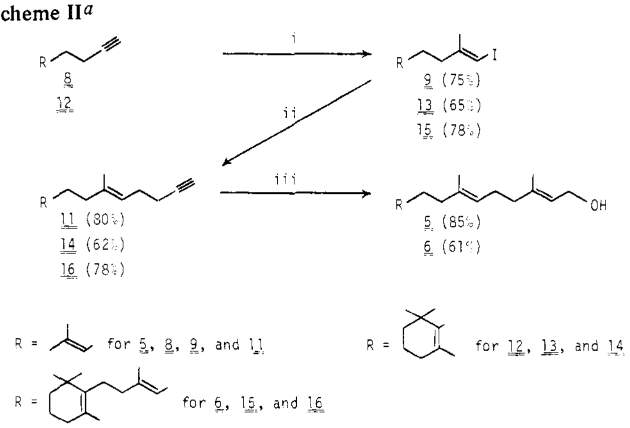
Scheme II[a]



[a] (i) Me_3Al (2 equiv)–Cl_2ZrCp_2 (0.2 equiv) in $(CH_2Cl)_2$, room temperature and then I_2 (1.2 equiv) in THF, 0 °C; (ii) $Me_3SiC{\equiv}CCH_2CH_2ZnCl$ (1 equiv), $Pd(PPh_3)_4$ (0.05 equiv) in THF, room temperature, 3–6 h and then $KF{\cdot}2H_2O$ (3 equiv) in DMF; (iii) Me_3Al (2 equiv)–Cl_2ZrCp_2 (0.2 equiv) in $(CH_2Cl)_2$, room temperature, evaporation, *n*-BuLi (1 equiv) and then $(CH_2O)_n$ in THF.

ylation of 4-bromo-1-butyne (*n*-BuLi and Me_3SiCl) followed by treatment with a mixture of Mg (1.5 equiv) and anhydrous $ZnCl_2$ (1 equiv) in refluxing THF (3–4 h).[13] The organozinc reagent **10** and **9** were mixed with $Pd(PPh_3)_4$ (0.05 equiv) to give the desired cross-coupled product in 90% GLC yield. Significantly, no other peaks were present in any more than trace amounts. The crude cross-coupled product was treated with $KF{\cdot}2H_2O$ (three times), dissolved in DMF[14] at room temperature to give **11**, bp 57–58 °C (0.5 mmHg), in 80% yield from **9** (procedure ii). The stereoisomeric purity of **11** was ≥98% based on its GLC and NMR examination, and its overall purity was >95%. Without further purification **11** was subjected to the second carbometalation followed by ate complexation and treatment with paraformaldehyde, as previously described[15] (procedure iii). Examination of the crude product by GLC (Carbowax 20M) and ^1H NMR indicated the formation of ~95% pure (*E,E*)-farnesol (**5**) in 91% yield (85% isolated). Purification by column chromatography (Florisil, 20:1 benzene–AcOEt) gave **5** which was both stereochemically and regiochemically ≥98% pure.

One distinctly attractive feature of the methodology herein reported is that the two-step cycle consisting of procedures i and ii can readily be repeated for the construction of long-chain 1,5-diene skeletons. Thus no major difficulty was encountered in synthesizing **6** by applying twice the two-step cycle consisting of procedures i and ii. Here again the overall process is estimated to be ≥98% stereoselective. Minor apparently regioisomeric byproducts (<5–10%) in crude **16** (Scheme II) were readily separated by column chromatography (Florisil, hexane). The tetraenol **6** was obtained from **16** via procedure iii (80% by NMR). After simple column chromatography (Florisil, 20:1 hexane–AcOEt) **6** was isolated in 61% yield as an essentially pure single isomer (^1H and ^{13}C NMR and TLC).

Acknowledgments. We thank the National Science Foundation, the National Institutes of Health, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also thank Matthey Bishop, Inc., for a generous loan of palladium compounds.

Supplementary Material Available: Experimental data for compounds **5**, **6**, **9**, **11**, and **13–16** (1 page). Ordering information is given on any current masthead page.

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Unprecedented Regiospecificity and Stereospecificity in Reactions of $Ph_3C^+PF_6^-$ with Rhenium Alkyls of the Formula $(\eta\text{-}C_5H_5)Re(NO)(PPh_3)(CH_2R)$

Sir:

With a single exception,[1] the abstraction or elimination of α-hydrides from transition metal alkyls has been observed only when β-hydrides are absent.[2] In this communication, we report that the rhenium alkyls $(\eta\text{-}C_5H_5)Re(NO)(PPh_3)(CH_2C_6H_5)$ (**1**), $(\eta\text{-}C_5H_5)Re(NO)(PPh_3)(CH_2CH_3)$ (**2**), and $(\eta\text{-}C_5H_5)Re(NO)(PPh_3)(CH_2CH_2CH_3)$ (**3**) each react with $Ph_3C^+PF_6^-$ to afford isolable cationic alkylidene complexes $[(\eta\text{-}C_5H_5)Re(NO)(PPh_3)({=}CHR)]^+PF_6^-$ in high yields, despite the presence of β-hydrides in **2** and **3**. Furthermore, a novel addition–elimination cycle is utilized to demonstrate that $Ph_3C^+PF_6^-$ stereospecifically abstracts one diastereotopic α-hydride over the other.

Alkyls **1–3** were isolated in 60–80% yields from the reactions of C_6H_5Li, CH_3Li, and CH_3CH_2MgCl, respectively, with the previously described[3] methylidene complex $[(\eta\text{-}C_5H_5)Re(NO)(PPh_3)(CH_2)]^+PF_6^-$ (**4**).[4] Treatment of **1** in CD_2Cl_2 with 1.1 equiv of $Ph_3C^+PF_6^-$ at −70 °C resulted in the immediate formation of benzylidene complex **5k** (eq i), as evidenced by ^1H NMR resonances at δ 16.08 (s, 1 H) and 5.89 (s, 5 H). When the solution was warmed to 10–20 °C, **5k** began to disappear as a new benzylidene complex, **5t**, formed. After solvent removal, **5t** could be isolated in 70–80% yield by crystallization from $CHCl_3$–petroleum ether (30–60 °C).[6] In the solid state, **5t** proved stable to 215 °C.