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Indium-Mediated γ-Pentadienylation of Aldehydes and Ketones: Cross-Conjugated Trienes for Diene-Transmissive Cycloadditions

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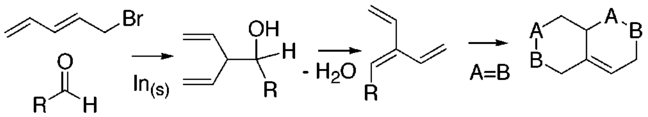
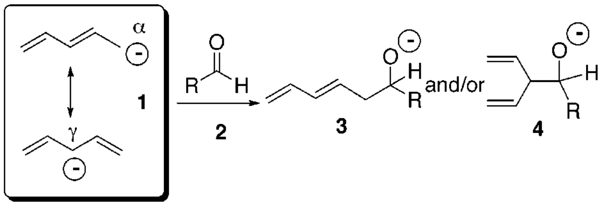
ABSTRACT



Treatment of 5-bromo-1,3-pentadiene with indium metal in the presence of carbonyl compounds results in γ-pentadienylation to generate the 1,4-diene. Elimination of the resulting alcohol affords cross-conjugated triene systems which rapidly react with appropriate dienophiles to give tandem intermolecular Diels–Alder adducts.

Metal allyl reagents are among the most studied systems for the addition of a three-carbon unit to carbonyl groups under a variety of conditions. Similarly, the corresponding pentadienyl moiety **1** is known to condense with both aldehydes and ketones (Scheme 1). However, in many circumstances the reaction is not regioselective, and the delocalized anion may react at either the α or γ position. This usually results in a mixture of the conjugated diene **3** and the skipped diene system **4**. Clearly, for synthetic applications, it is important to control this product distribution.

Scheme 1. Pentadienyl Anion Condensations



Previous investigations have reported varying levels of selectivity. Examples include organolithium,[1] zinc,[1] borane,[2] magnesium,[3] beryllium,[4], tin,[5] and silicon[6] reagents of various types.

Our synthetic interests required the introduction of diene and triene units under mild conditions in highly functionalized, sensitive molecules. Chan and colleagues[7] have demonstrated the utility of allyl indium species in water for the allylation of carbonyl compounds bearing labile dimethyl acetals where the tin and zinc reagents failed.[7a] They also established that allyl indium reagents react at the γ position[8] and are compatible with free hydroxyl groups.[9] We have been pleased to discover that the reagent generated from 5-bromo-1,3-pentadiene[10] and indium metal also adds in a regioselective manner to give nonconjugated compounds of type

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(1) (a) Gerard, F.; Miginiac, P. *Bull. Soc. Chim. Fr.* **1974**, 1924. (b) Gerard, F.; Miginiac, P. *Bull. Soc. Chim. Fr.* **1974**, 2527. (c) Ghosez, L.; Marko, I.; Hesbain-Frisque, A.-M. *Tetrahedron Lett.* **1986**, *27*, 5211. (d) Chen, L.; Ghosez, L. *Tetrahedron Asym.* **1991**, *2*, 1181. (e) Jung, M. E.; Nichols, C. J. *Tetrahedron Lett.* **1996**, *37*, 7667.

(2) (a) Fujita, K.; Schlosser, M. *Helv. Chim. Acta* **1982**, *65*, 1258. (b) Suginome, M.; Yamamoto, Y.; Fujii, K.; Ito, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9608.

(3) Yasuda, H.; Yamauchi, M.; Nakamura, A.; Sei, T.; Kai, Y.; Yasuoka, N.; Kasai, N. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1089.

(4) Yasuda, H.; Ohnuma, Y.; Nakamura, A.; Kai, Y.; Yasuoka, N.; Kasai, N. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1101.

(5) Nishigaichi, Y.; Fujimoto, M.; Takuwa, A. *Synlett* **1994**, 731.

(6) Kobayashi, S.; Nishio, K. *Chem. Lett.* **1994**, 1773.

(7) For organoindium reviews, see: (a) Chan, T. H.; Li, C. J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181. (b) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (c) Cintas, P. *Synlett* **1995**, 1087.

(8) Isaac, M. B.; Chan, T. H. *Tetrahedron Lett.* **1995**, *36*, 8957.

(9) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017.

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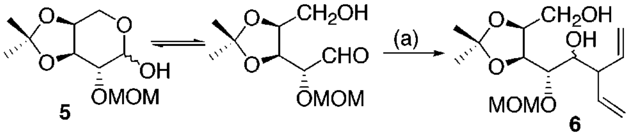
4 even with sensitive substrates. For example, as illustrated in Scheme 2, the lactol **5** reacted slowly, but cleanly, in DMF at 21 °C to give the secondary diol-diene **6** in 96% yield (1:1 ratio of diastereomers). In contrast, the diastereoselectivity increased to 12:1 when THF was used as the solvent. During these investigations Araki and co-workers[11] reported related studies with substituted penta-2,4-dienyl indiums, including an example of a pentadienyl indium condensation with benzaldehyde.

Scheme 2. Pentadienyl Anion Condensation with Lactol **5**

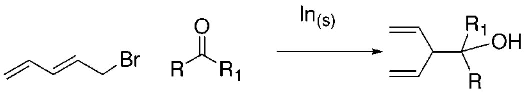


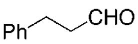
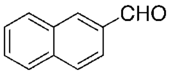
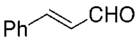
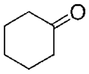
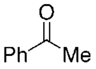
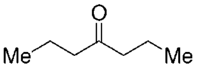
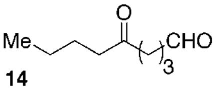
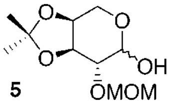
(a) $In_{(s)}$, $BrCH_2CH{=}CHCH{=}CH_2$, DMF, 21 °C, 165 h, 96%

Table 1 summarizes the results of experiments with several substrates.[12] In all cases the only addition product detected from reactions in water or DMF was the γ-substituted isomer. The α,β-unsaturated aldehyde (entry 4) afforded the 1,2-addition product preferentially rather than the product from Michael addition. The yields in the ketone condensations are lower, probably due to a combination of reduced electrophilicity and greater steric bulk compared to the aldehydes (entries 5 and 6). Consistent with this analysis, 4-heptanone (entry 7) was unreactive possibly due to the increased steric encumbrance from the freely rotating alkyl substituents compared to cyclohexanone (entry 5). This result implied that selective addition to an aldehyde should occur in the presence of a ketone. Entry 8 confirmed that this was the case and that selective addition should prove useful in complex systems.

It is of interest that the reactivity of the pentadienyl indium reagent differed from the 1-bromo-2,4-hexadiene−indium system studied by Araki and co-workers[11] in two important aspects. Their reactions were sluggish and gave reduced yields in water compared to DMF, and the reagent was unreactive toward ketones. The reasons for these subtle differences are not clear at present. Recently Chan and Yang[13] have established that allyl indium additions to ketones proceed via the formation of an indium(I) species rather than indium(III). A parallel process involving metal surface mediated allyl radical anions is also possible. In view of the close structural similarity between pentadienyl and allylindium species, the mechanisms are likely closely related.

Table 1. Pentadienylindium Condensations with Aldehydes and Ketones



Entry	Substrate	Solvent	Time	Yield
1	$C_9H_{19}CHO$ **7**	DMF	19 h	65%
2	 **8**	H_2O	16 h	65%
3	 **9**	DMF	17 h	72%
4	 **10**	DMF	20 h	72%
5	 **11**	DMF	21 h	55%
6	 **12**	H_2O	18 h	50%[a]
7	 **13**	DMF or H_2O	67 h	0%
8	 **14**	DMF	7 h	58%[b]
9	 **5**	DMF	165 h	96%[c]

[a] Yield was 89% based on recovered starting material; [b] Addition selective for aldehyde; [c] 1:1 diastereomeric mixture, (12:1 diastereomeric mixture in THF)

Dehydration of these diene products under Mitsunobu type conditions (Ph_3P, DEAD, C_6H_6, 80 °C) generated the corresponding cross-conjugated trienes. For example, the alcohol **15**, derived from **8**, was converted to the triene **16** which is appropriately functionalized for diene transmissive tandem Diels−Alder reactions[14] upon exposure to various dienophiles (Scheme 3). The reaction of **16** with *N*-phenylmaleimide (**17**) afforded **18** in situ which reacted spontaneously with a second mole of the dienophile to give **19** (81%). In a similar manner benzoquinone (**20**) added to

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(10) Prevost, C.; Miginiac, P.; Miginiac-Groizeleau, L. *Bull. Soc. Chim. Fr.* **1964**, 2485.

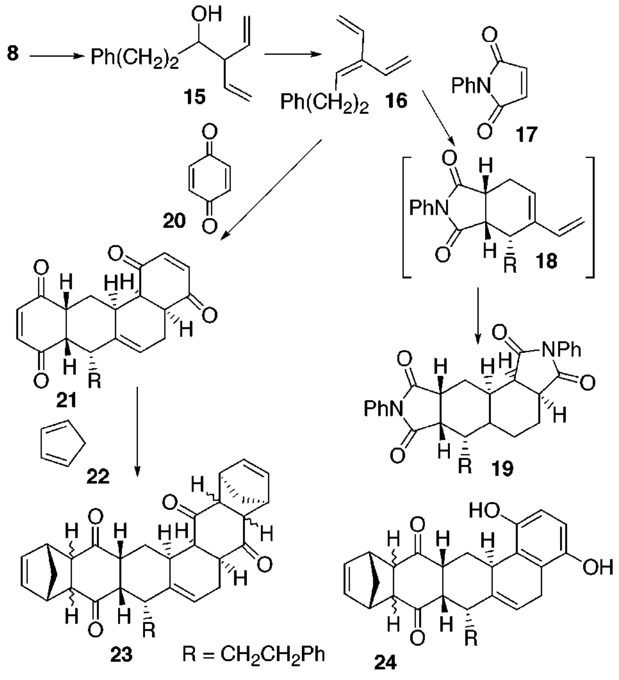
(11) Hirashita, T.; Inoue, S.; Yamamura, H.; Kawai, M.; Araki, S. *J. Organomet. Chem.* **1997**, *549*, 305.

(12) **General Procedure for the Preparation of Diene−Alcohols.** Indium powder (100 mesh, 0.223 g, 1.94 mmol) was added in portions to a mixture of 5-bromo-1,3-pentadiene (0.504 g, 3.43 mmol) and the carbonyl compound (1.48 mmol) in either water or DMF (0.3 mL). The reaction is exothermic, and thus it is important to adjust the rate of indium addition to control the rate of temperature increase. The reaction mixture was stirred for the allotted time. The aqueous reactions were diluted with water (1 mL) and extracted with ether (3×), and the organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The reactions in DMF were diluted with CH_2Cl_2 (2 mL) and then added to ether (25 mL). The resulting mixture was filtered through a pad of silica gel. The silica was washed with additional solvent, and the filtrate was concentrated. The products were purified by flash chromatography.

(13) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228.

(14) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167.

Scheme 3. Diene-Transmissive Cycloadditions



16 at 21 °C to afford the tetracyclic skeleton **21**. The stereochemistry of **21** was established by X-ray analysis. Further reaction of the bis-quinone adduct **21** with excess cyclopentadiene (**22**) at 21 °C afforded the octacyclic skeleton **23** as a mixture of diastereomers. This tetracycloaddition sequence may be run stepwise or in one reaction vessel (16 h, 48 h, 21 °C) to give **23** in 71% yield accompanied by 9% of **24**. These examples illustrate the ease with which multicyclic ring systems may be constructed directly from repetitive cycloadditions in a facile manner.

In conclusion, we have established that the organoindium reagent derived from 5-bromo-1,3-pentadiene and indium metal reacts with excellent regioselectivity with a variety of aldehydes and ketones to afford the nonconjugated, (γ-pentadienylation) diene products in respectable yields. These are straightforward reactions that do not require inert atmospheres nor anhydrous solvents. In addition, the trienes derived from dehydration of the condensation products afford rapid entry to complex multicyclic skeletons from tandem [4 + 2] cycloadditions. Synthetic applications of this condensation−elimination−cycloaddition strategy are currently under investigation, as are Cope rearrangement combinations.

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