

# Indium(I)-Mediated, Tandem Carbonyl Addition-Oxy-Cope Rearrangement of $\gamma$ -Pentadienyl Anions to Cyclohexenones and Conjugated Aromatic Ketones

Nidia P. Villalva-Servín, A. Melekov, Alex G. Fallis\*

Centre for Research in Biopharmaceuticals, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5

Fax +1(613)5625170 ; E-mail: afallis@science.uottawa.ca

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**Abstract:** Treatment of 5-bromopenta-1,3-diene with indium metal in the presence of  $\alpha,\beta$ -unsaturated ketones results in initial  $\gamma$ -pentadienylation to generate the hydroxy-1,4-diene. In the case of aromatic conjugated ketones or cyclohexenones the indium alkoxide undergoes spontaneous oxy-Cope rearrangement to afford the 1,4-addition product. The second double bond is required for this [3,3] sigmatropic rearrangement as allyl groups fail to undergo this in situ rearrangement. This behavior is consistent with an indium(I) pentadiene species and appears to be the first example of an indium-mediated oxy-Cope rearrangement.

**Key words:** indium, oxy-Cope, [3,3] sigmatropic rearrangement,  $\gamma$ -pentadienyl, conjugate addition

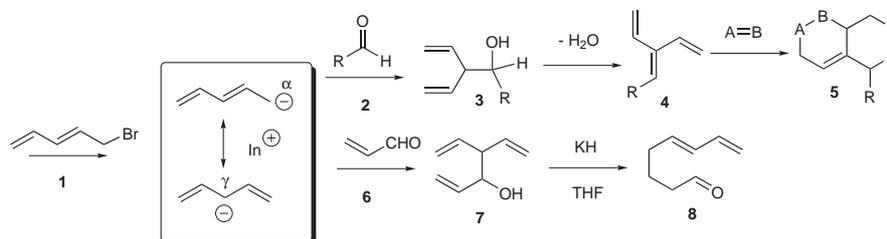
Previously we have established that treatment of 5-bromopenta-1,3-diene (**1**) with indium metal, in DMF, DMSO, or water, in the presence of carbonyl compounds **2** or **6** resulted in  $\gamma$ -pentadienylation to generate the 1,4-diene alcohol **3** or **7** exclusively (Scheme 1).<sup>1</sup> This behaviour is in contrast to many other cases of organometallic pentadienyl anions in which the reactions are not regioselective, and the delocalized anion may react at either the  $\alpha$  or  $\gamma$  position depending upon the metal counter ion selected. In addition, magnesium metallopentadienyl systems also afford dimerization products.<sup>2</sup> Elimination of water from the dienols **3** afforded trienes of type **4** which we have employed to prepare multicyclic systems represented by **5** via a tandem diene transmissive strategy.<sup>1a,3</sup> Recently Schreiber and co-workers have extended our in situ domino tetra-cycloaddition protocol to diversity oriented syntheses for the preparation of more than 29,000 multicyclic compounds.<sup>4</sup>

Conjugate addition to unsaturated aldehydes is often troublesome, but this pentadienylindium anion reacted only at the carbonyl group of **6**. Subsequent anionic oxy-Cope rearrangement (reagent: KH) provided direct access to the conjugate addition product **8** for further manipulation to hydrindanes after installation of a chiral dienophile.<sup>5</sup>

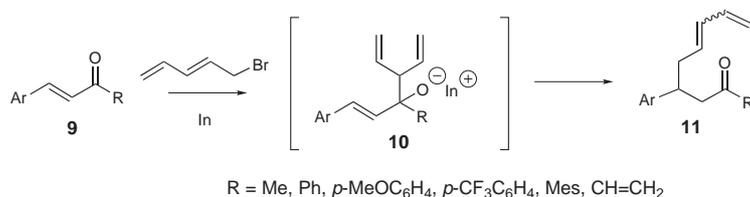
In order to extend the utility of this reagent we have investigated a series of unsaturated ketones as partially summarized in Scheme 2 and tabulated in Tables 1 and 2. Unexpectedly, the reactivity pattern was not uniform and initially rather perplexing as it appeared that in some cases the 1,2-addition compound dominated while other substrates appeared to generate the 1,4-addition product from the direct conjugate addition of the  $\alpha$ -pentadienyl anion.

Mesityl oxide (**12**) reacted sluggishly to afford the 1,2-addition product **13** in (30% yield, 72 h). In contrast the phenyl substituted unsaturated methylketone **14** gave only the conjugated system **15** in 55% yield (Table 1, entry 2). <sup>1</sup>H NMR analysis revealed the geometry of the double bond to be exclusively *cis* ( $J = 10.9$  Hz), a result that differed from the exclusively *trans* orientation we observed previously with the unsaturated aldehydes after potassium anionic oxy-Cope rearrangement.<sup>5</sup> The *trans* stereochemistry has also been reported for the rearrangement of zinc alkoxides related to **7**.<sup>6</sup> Unexpectedly, the related diphenyl ketone **16** was less selective. However, the *cis* isomer was still the dominant product as determined from the 1.7:1 ratio of the *cis/trans* isomers **17**.

The mixed stereochemistry observed in Table 1, entry 3 suggested there was either a competition between the direct carbonyl and conjugate addition pathways or else a



**Scheme 1** Summary of previous  $\gamma$ -pentadienylindium reactions with carbonyl compounds



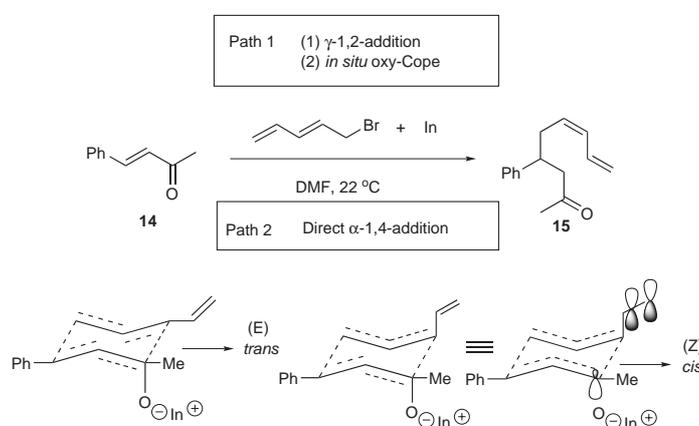
**Scheme 2** Possible In(I)-mediated oxy-Cope sequence to conjugate addition product

**Table 1** Addition of  $\gamma$ -Pentadienylindium to Unsaturated Ketones

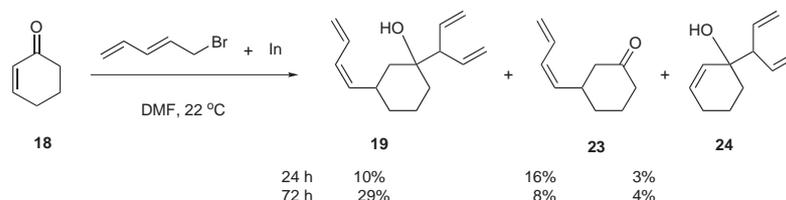
Entry	Conjugated Ketone	Product	Yield (%)
1			30
2			55
3			27
4			29
5			37
6		no reaction	0

more subtle 1,2-carbonyl addition was followed by a very rapid indium-mediated oxy-Cope rearrangement under these mild conditions (Scheme 2, Path 1, Scheme 3). If Path 1 was preferred then the stereochemical divergence was likely a consequence of competing transition states. The chair transition state is usually favored for Cope rearrangements in which the non-bonded interactions are minimized.<sup>7</sup> The fact that the *cis*-olefin dominates implies the chair conformation with an axial vinyl group is preferred (Scheme 3). We have established below that allylindium species do not rearrange spontaneously and thus a second alkenyl group is required for this in situ [3,3] sigmatropic reaction. Consequently, there may also be a favorable dipole and orbital interaction with the oxygen anion and the adjacent axial olefin substituent that overrides the normal preference for an equatorial vinyl group en route to the *trans* product. Additional support for this contention is provided by the established influence of vinyl substituents on the rate of rearrangement. Theoretical studies assumed that only the *trans* product was formed and concluded that a 3-vinyl substituent decreased the activation enthalpy by ca. 5 kcal/mol.<sup>8</sup> Conjugated phenyl groups also lowered the enthalpy of activation for chair transition states leading to increased allyl radical-like features in the transition region that have been termed 'chameleonic' based on calculations with phenyl substituents.<sup>9</sup>

However, differentially substituted unsaturated aromatic ketones with 1,3-diene anions have not received systematic scrutiny and to draw unambiguous conclusions further examples were investigated. The pentadienyl reagent displayed homogenous reactivity when it was heated at



**Scheme 3** Possible competitive pathways and oxy-Cope transition states



**Scheme 4**  $\gamma$ -Pentadienyl addition to cyclohexenone (**18**)

60–80 °C for two hours before quenching with cinnamaldehyde and only the expected alcohol from  $\gamma$ -addition was produced. In addition, a sample of the unsaturated alcohol **3** (Scheme 1) was heated at 80 °C in the absence of base and no rearrangement was observed.

In an attempt to clarify these results, a reaction with cyclohexenone (**18**, Table 1, entry 4) was examined at different time intervals in order to determine the product reactivity profile. In addition to the new major product **23** after 24 hours, lesser quantities of the expected product **19** and **24** were also observed (Scheme 4). The most abundant new product **23** contained a substitution pattern in which the pentadiene moiety was attached to the alkene while the minor product **24** was consistent with ‘Grignard type’ addition to the carbonyl. This result could have involved competitive 1,2- and 1,4-additions, although the formation of the *cis*-diene implicated the intervention of the sigmatropic rearrangement from the minor isomer. Two days later the ratio had changed and **19** was the major product as observed previously, although some of the carbonyl adduct **24** still remained. These results clearly imply that these reactions proceed by an initial carbonyl addition followed by an indium-mediated oxy-Cope rearrangement as illustrated in Scheme 2 and summarized in Path 1 of Scheme 3.

In principle, the conjugate addition to 4,4-dimethylcyclohexenone (**20**) should be impeded relative to reaction at the carbonyl center. Therefore, the isolation of **21** was also consistent with the initial formation of the 1,2-product followed by room temperature (22 °C) [3,3] sigmatropic rearrangement (Table 1, entry 5). In a parallel manner to cyclohexenone (**18**), the newly generated ketone was then attacked by a second molecule of the reagent. It was anticipated that the bulky *tert*-butyl vinyl ketone (**21**) would inhibit the carbonyl addition in favor of conjugate addition, but experimentally it was completely inert providing circumstantial evidence that carbonyl addition was preferred when feasible and conjugate addition were disfavored (Table 1, entry 6).

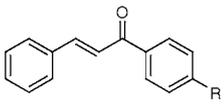
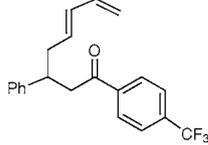
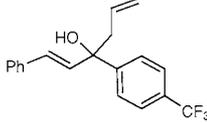
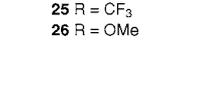
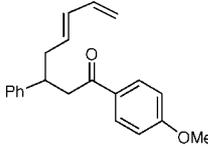
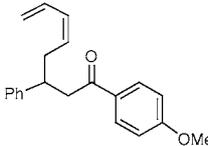
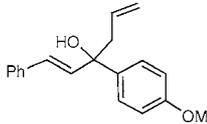
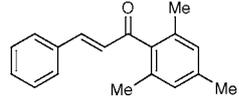
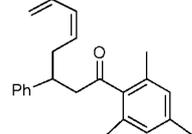
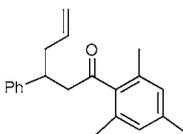
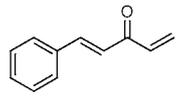
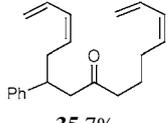
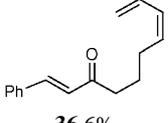
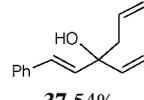
The fact that **14** gave a single isomer but **16** gave an isomeric mixture suggested a difference in the transition states (above) or possibly an electronic influence at the carbonyl center as a consequence of phenyl substitution, which may influence the preferred transition state. In order to access whether different electronic and steric parameters were important modulators of the product distribution for phenyl ketones a second series with different functional groups in the aryl ring was selected plus an

example in which the competition between a phenyl vinyl ketone versus a vinyl ketone could be compared.

Four representative phenyl vinyl ketones **25**–**28** were prepared by Grignard addition to cinnamyl aldehyde followed by benzylic oxidation with manganese dioxide. The ketones were examined under controlled conditions (DMF, 22 °C, 4 h)<sup>10</sup> to establish the initial product mixture rather than to seek high yields. In this manner, the yield variation could be attributed to the nature of reactants and not the reaction conditions. It appeared, as mentioned above, that a second double bond might be a prerequisite for facile [3,3] rearrangement and to establish if this was the case, the allylindium reagent was also added to these ketones under identical conditions for comparison (Table 2).

Selective carbonyl addition to **25** and **26** produced the allyl products **30** and **32** (Table 2, entries 1 and 2). In contrast, the steric bulk of the mesitylene system **27** appeared to inhibit 1,2-addition and reluctantly afforded a small amount of the conjugate addition product **34** (Table 2, entry 3). Further evidence for the preference of the allyl group towards 1,2-addition was provided from the results with **28**, which afforded **37** in yield 54%. Again there was no rearrangement product in spite of the presence of the unsubstituted double bond. These results confirmed that the indium-mediated oxy-Cope rearrangement required a second double bond and were only observed with the pentadienyl reagent. The electron-withdrawing influence of the trifluoromethyl group in **25** favored the *trans* [3,3] sigmatropic rearrangement product **29** while for **26** a mixture of the *cis* and *trans* products **31a/31b** (1:1) were generated (Table 2, entry 2). This implied that these products arose from different transition states. In the case of the sterically hindered mesitylenyl ketone **27** the carbonyl addition was clearly inhibited but the *cis* rearrangement product **33** was formed in low yield (Table 2, entry 3). The pentadienyl reagent is more sterically demanding than the allyl system and the product distribution from compound **28** should provide a definitive conclusion of the importance of the competitive pathways. The *cis*-olefin product mixture consisting of **35** and **36** indicated the conjugate addition was not operative. Instead, the dominant 1,2-addition route was followed by the preferred, spontaneous rearrangement to the unsubstituted olefin to give **36** followed by sequential formation of **35**. In contrast, as mentioned above, the reaction with the allyl reagent terminated at the carbonyl addition stage to generate **37** and failed to undergo further rearrangement (Table 2, entry 4).

**Table 2** Addition of  $\gamma$ -Pentadienyl- and Allylindium to Conjugated Aromatic Ketones<sup>10</sup>

Reactant		Product(s)		
Entry	Conjugated Ketone	Product(s)	Yield	
1	 <b>25</b> R = CF <sub>3</sub> <b>26</b> R = OMe	 <b>29</b> 20%	 <b>30</b> 37%	
2	 <b>26</b> R = OMe	 <b>31a</b> 17%	 <b>31b</b>	 <b>32</b> 31%
3	 <b>27</b>	 <b>33</b> 6%	 <b>34</b> 8%	
4	 <b>28</b>	 <b>35</b> 7%	 <b>36</b> 6%	 <b>37</b> 54%

Chan and Yang<sup>11</sup> have established that the reaction of allyl bromide with indium metal in either DMF or water generated an allylindium(I) species [CH<sub>2</sub>=CHCH<sub>2</sub>-In(I)] that could be detected by its transient <sup>1</sup>H NMR signal. This observation, coupled with the results above, is consistent with a similar conclusion for the structure of the indium(I) pentadienyl anion {CH<sub>2</sub>=CHCH[In(I)]-CH=CH<sub>2</sub>} generated from the reaction of indium metal with the 5-bromopenta-1,3-diene. The monovalent species is also favored by the relatively low first ionization potential of indium metal compared to the second and third ionization values. The conjugate addition products are thus a consequence of an indium(I)-mediated oxy-Cope reaction preceded by the generation of the alkoxide from the initial carbonyl addition of the In(I)  $\gamma$ -pentadienyl anion.

In conclusion, we have established that the addition of  $\gamma$ -pentadienylindium(I) to unsaturated ketones afforded the conjugate addition product preferentially, via a tandem carbonyl addition In(I) oxy-Cope rearrangement pathway. This discovery augments the catalogue of subtle effects that influence these [3,3] sigmatropic rearrangements such as the enone-accelerated carbocyclic Cope reaction

we observed recently,<sup>12</sup> and the fact that allylic ethers retard oxy-Cope rearrangements.<sup>13</sup>

#### Addition of $\gamma$ -Pentadienyl- and Allylindium to Conjugated Aromatic Ketones; 3-Phenyl-1-(4-trifluoromethylphenyl)octa-5,7-dien-1-one (**29**); Typical Procedure (Table 2)<sup>10</sup>

5-Bromopenta-1,3-diene (0.21 g, 1.44 mmol, 3.98 equiv) was added to a solution of 3-phenyl-1-(4-trifluoromethylphenyl)prop-2-en-1-one (**25**; 0.10 g, 0.36 mmol, 1.0 equiv) in DMF-H<sub>2</sub>O, (2:1, 1 mL). The suspension was cooled to 0 °C and HCl (10  $\mu$ L) was added followed by the addition of indium metal powder (0.083 g, 0.72 mmol, 2.0 equiv) in portions. The reaction mixture was warmed to 60 °C and stirred for 4 h. After cooling to 22 °C, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and poured into Et<sub>2</sub>O (25 mL). The suspension was filtered through a silica gel pad, washed thoroughly with Et<sub>2</sub>O (2  $\times$  10 mL) and purified by flash column chromatography [petroleum ether (bp 40–60 °C)-Et<sub>2</sub>O, 98:2] to afford **29** as a colorless oil (66%).

IR (neat): 3086–2839, 1693 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>/TMS, 500 MHz):  $\delta$  = 7.96 (d, *J* = 8.1 Hz, 2 H), 7.67 (d, *J* = 8.2 Hz, 2 H), 7.24 (m, 5 H), 6.24 (ddd, *J* = 16.9, 10.3, 10.3 Hz, 1 H) 6.05 (dd, *J* = 15.2, 10.5 Hz, 1 H), 5.58 (ddd, *J* = 15.0, 7.5, 7.5 Hz, 1 H), 5.07 (dd, *J* = 16.9, 1.3 Hz, 1 H), 5.02 (dd, *J* = 10.2,

1.3 Hz, 1 H), 3.52–3.46 (m, 1 H), 3.31 (d,  $J = 7.0$  Hz, 2 H), 2.51 (t,  $J = 7.3$  Hz, 2 H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3/\text{TMS}$ ):  $\delta = 197.94, 143.92, 136.78, 133.27, 129.37, 128.53, 127.45, 127.43, 126.56, 125.59, 125.56, 125.53, 125.50, 44.73, 41.11, 39.44, 34.25$ .

ESI  $^+\text{NH}_4$ :  $m/z = 362$  [344 + 18].

#### 1-Phenyl-3-(4-trifluoromethylphenyl)hexa-1,5-dien-3-ol (30)

Allyl bromide (0.28 mL, 2.88 mmol, 3.98 equiv) was added to a solution of 3-phenyl-1-(4-trifluoromethylphenyl)propenone (**25**; 0.20 g, 0.725 mmol, 1.0 equiv) in DMF– $\text{H}_2\text{O}$ , (2:1, 2 mL). The suspension was cooled to 0 °C and indium metal powder (0.17 g, 1.45 mmol, 2.0 equiv) was added in portions. The reaction mixture was warmed to 60 °C and stirred for 4 h. After cooling to 22 °C, the mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (10 mL) and poured into  $\text{Et}_2\text{O}$  (50 mL). The suspension was filtered through a silica gel pad, washed thoroughly with  $\text{Et}_2\text{O}$  ( $2 \times 20$  mL) and purified by flash column chromatography [petroleum ether (bp 40–60 °C)– $\text{Et}_2\text{O}$ , 95:5] to afford **30** as a colorless oil (96%).

IR (neat): 3553, 3463, 3081–2855  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3/\text{TMS}$ , 500 MHz):  $\delta = 7.65$ – $7.60$  (m, 4 H), 7.37 (d,  $J = 7.5$  Hz, 2 H), 7.31 (t,  $J = 7.5$  Hz, 2 H), 7.24 (t,  $J = 7.3$  Hz, 1 H), 6.66 (d,  $J = 16.0$  Hz, 1 H), 6.50 (d,  $J = 16.0$  Hz, 1 H), 5.70 (dddd,  $J = 17.2, 10.2, 7.2, 7.2$  Hz, 1 H), 5.25 (d,  $J = 10.3$  Hz, 1 H), 5.20 (d,  $J = 17.9$  Hz, 1 H), 2.80 (d,  $J = 7.3$  Hz, 2 H), 2.39 (s, 1 H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3/\text{TMS}$ ):  $\delta = 149.32, 136.36, 134.29, 132.38, 129.16, 128.58, 127.83, 126.56, 125.87, 125.26, 125.23, 125.20, 120.74, 75.50, 47.07$ .

HRMS (EI):  $m/z$  calcd for  $\text{C}_{19}\text{H}_{17}\text{F}_3\text{O}$  ( $\text{M}^+$ ), 318.1231; found [ $\text{M}^+ - \text{H}_2\text{O}$ ], 300.1130.

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- (10) General Procedure: 5-Bromopenta-1,3-diene (7.21 mmol) and the ketone (1.81 mmol) were dissolved in DMF (1.3 mL) at 0 °C. Indium(powder) was added and the reaction was stirred at 21 °C for 4 h. The reaction was diluted with  $\text{CH}_2\text{Cl}_2$  (5 mL) and  $\text{Et}_2\text{O}$  (15 mL) and filtered through a silica pad and purified by flash chromatography.
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