Heck-type reactions of allylic alcohols
Part IV: (2-Substituted)-1-indanones via 5-endo-trig cyclizations

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Received 17 July 2007; received in revised form 3 December 2007; accepted 16 December 2007

Available online 26 December 2007

Abstract

Various conditions have been tested to obtain efficiently 2-methyl-1-indanone via the Pd-catalyzed 5-endo-trig cyclization of 1-(o-bromophenyl)-2-methylprop-2-en-1-ol. High yield (97%) was obtained at 120 °C in DMF with Pd(OAc)\textsubscript{2}/cinchonine as the catalytic system and NaHCO\textsubscript{3} as the base. Use of this procedure for the synthesis of other substituted indanones led to lower yields but replacing thermal heating by microwave heating improved greatly the results.

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Keywords: Palladium; Catalysis; Heck reaction; Cyclization; Allylic alcohol; DMF; Cinchonine; Microwaves

1. Introduction

Over the last past years, we have studied the asymmetric protonation of prochiral enolic species with catalytic amounts of homochiral amino alcohols [1,2]. Since the Heck arylation of allylic alcohols can afford ketones via the formation of an enol as intermediate [3], we envisaged the synthesis of optically active ketones using this procedure. However, the Pd-catalyzed reactions of phenyl iodide with 3-methyl-3-buten-2-ol in the presence of homochiral amino alcohols led to very low ee’s whatever the experimental conditions [4,5]. In the aim to obtain, as intermediate, a single enol configuration which, furthermore, would be rigid, we have subsequently examined the 5-endo-trig cyclization of 1-(o-bromophenyl)-2-methylprop-2-en-1-ol (1a) which possesses a prochiral allylic alcohol moiety to obtain 2-methyl-1-indanone (2a). When we started these studies [4], such a Pd-catalyzed cyclization was only reported from (Z)- and (E)-1-(o-bromo-phenyl)-oct-2-en-1-ols, in the absence of a chirality source, leading to 3-pentyl-1-indanone in 48–52% yields [6].\textsuperscript{1} According to the Baldwin’s rule, the 5-endo-trig cyclization is, furthermore, a disfavored reaction [7–9]. In the course of our studies, Pan and co-workers have however synthesized 1H-inden-1-ones from the Pd-catalyzed reaction of 1-(o-bromoaryl)-prop-2-en-1-ols under an air atmosphere [10]. According to these authors, this reaction involved the intramolecular Heck-type cyclization followed by the aerial oxidation of the resulting 1H-inden-1-ols. Our results are here reported.

2. Results and discussion

Preliminary experiments have been carried out at 120 °C in DMF using the prochiral substrate 1a, Pd(OAc)\textsubscript{2} as the catalyst, NaHCO\textsubscript{3} as the base, and a catalytic amount of cinchonine or (+)-endo-2-hydroxy-endo-3-aminoborane. The expected ketone, 2a, was isolated in high yields but, unfortunately, was racemic (Table 1, runs 1 and 2). Lower reaction temperatures decrease the efficiency of the reaction without improving the optical activity. The use of (R)-BINAP instead

\textsuperscript{1} Since the submission of the present study, new examples have been reported by Ray et al. [44].
of the amino alcohol led to a mixture of 2a and 1-phenyl-2-
methylprop-2-en-1-ol (3a), 2a being once more more racemic (run 3).
With PPh3 as the ligand or in the absence of ligand, 2a was
selectively obtained when Pd(OAc)2 was the catalyst (runs 4–6),
while the Pd2(dba)3·CHCl3/PPh3 system affords 2a and 3a (run 7).
Complementary experiments using various inorganic and
organic bases have shown the absence of enantio-induction by
cinchonine, and the determining role of the base on both selectiv-
ity and efficiency of the reaction (runs 11–15). Thallium acetate
and, in particular, KF/Al2O3 afforded 3a as the main product
(runs 11 and 12). Triethylamine yielded effectively 2a (run 13)
while N,N-dicyclohexylmethylamine and the use of only cin-
chonine led to low conversions (runs 14 and 15). Under all
these conditions, we never detected the formation of 2-methyl-
1H-inden-1-one or 2-methyl-1H-inden-1-ol. Given the results
depicted in Table 1, it appears that the cinchonine/NaHCO3 mix-
ture is the most effective combination to obtain 2a. We suspect
that cinchonine can be a N,N- or N,N-bidentate ligand stabiliz-
ing palladium species [11]. Nevertheless, the oxidative addition
reaction of the substrate to the Pd0 species could occur from a
monoligated palladium complex [12].

The formation of 3a corresponds to the hydrogenolysis of the
Ar–Br bond. We have recently reported [15] that, in the presence
of an inorganic base, the hydrogenolysis is due to the decompo-
sition of DMF [16] and reaction of the resulting dimethylanine
with ArPdBr species [17] as depicted in Scheme 1. Intermediate
A, formed by insertion of Pd0 into the Ar–Br bond, reacts with
dimethylanine to yield B that suffers a β–H elimination [18].
Reductive elimination of Pd0 from the resulting ArPdH complex
(C) gives 3a. As previously observed [15], the efficiency of this
hydrogenolysis process, that uses DMF as the hydrogen source,
depends on the experimental conditions.

The obtention of racemic 2a from reactions carried out in the
presence of homochiral aminoalcohols could be due to the experi-
mental conditions, namely basic conditions and high tem-
perature, that could induce the racemisation of the optically
active ketone. Furthermore, the absence of enantioselectivity
could also be due to the mechanism of the Heck reaction. Let
us to consider the Heck-type cyclization of 2a (Scheme 2). The
formation of enolic intermediate D is admitted for such a reac-
tion [4,19]. The ketone could be obtained from D via either
free prochiral enol E (path a) or addition/elimination of HPdBr
(path b) but Smadja et al. have shown that path a is, at best, a
minor reactive pathway [20]. According to studies on the Pd-
induced domino reaction of benzyl β-ketoesters [21] carried

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### Table 1

<table>
<thead>
<tr>
<th>Run</th>
<th>Additive (0.1 equiv.)</th>
<th>Base (1.1 equiv.)</th>
<th>Time h</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cinchonine</td>
<td>NaHCO3</td>
<td>19</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>HNBOH</td>
<td>NaHCO3</td>
<td>17</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>(R)-BINAP</td>
<td>NaHCO3</td>
<td>17</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>PPh3</td>
<td>NaHCO3</td>
<td>22</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>NaHCO3</td>
<td>16</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>NaHCO3</td>
<td>22</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>PPh3</td>
<td>NaHCO3</td>
<td>22</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>Cinchonine</td>
<td>Cs2CO3</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>Cinchonine</td>
<td>Na2CO3</td>
<td>22</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>Cinchonine</td>
<td>NaOAc</td>
<td>16</td>
<td>79</td>
</tr>
<tr>
<td>11</td>
<td>Cinchonine</td>
<td>TIOAc</td>
<td>16</td>
<td>86</td>
</tr>
<tr>
<td>12</td>
<td>Cinchonine</td>
<td>KF/Al2O3</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>13</td>
<td>Cinchonine</td>
<td>NEt3</td>
<td>22</td>
<td>90</td>
</tr>
<tr>
<td>14</td>
<td>Cinchonine (1.2 equiv.)</td>
<td>Cy2NMe</td>
<td>24</td>
<td>17</td>
</tr>
</tbody>
</table>

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a HNBOH: (++)-endo-2-hydroxy-endo-3-aminobornane [13].
b Using Pd2(dba)3·CHCl3 as the catalyst.
c 500 mg/mmol; prepared as previously described [14].
d Reaction carried out at 100 °C.
out in the course of the present work, the enantioselection step leading to chiral ketones from enolic species and homochiral amino alcohols occurs at the level of the free enol. The above comments are in agreement with the formation of racemic 2a.

It seems of interest to point out that the Heck reaction is mechanistically germane to the mode of the Wacker oxidation of ethylene. Indeed, the Wacker process produces an enolic intermediate similar to D, and it has been shown that the β-H elimination product never leaves the coordination sphere of the palladium at this level, the formation of the aldehyde occurring through the addition/elimination of HPdX[22–24]. Recent calculations on the Wacker mechanism from Goddard and co-workers [25] led us to envisage a halide-mediated reductive elimination (Scheme 3, path d) rather than the usually accepted β-hydride elimination (Scheme 3, path c) for the F → 2a step of the Heck reaction.

Since we have been able to carry out the 5-endo-trig cyclization of 1a in high yields, this type of reaction was examined using other substrates under the experimental conditions of run 1, Table 1 (Eq. (1), Table 2). Changing the methyl substituent for a phenyl or an ethyl provided expected cyclized products 2b and 2c with fair yields, while the yield decreased to 42% in the absence of a substituent in this position. The cyclization of ethyl 2-((o-bromophenyl)(hydroxy)methyl)acrylate (1e) led to the concomitant cleavage of the C–CO₂Et bond to afford 2d; this is likely due to the instability of β-ketoester 2e under the experimental conditions [26]. A low yield of cyclized product 2f was isolated from 1f that has a methoxy substituent on the aromatic moiety. In the presence of two methoxy substituents or one nitro substituent on the aromatic moiety (1g and 1h respectively), some conversion of the substrate was observed but without production of the expected cyclized product.

According to the literature, Heck reactions are often improved under microwave irradiation [27,28]. The efficiency of this activation method, that has seldom been used for Heck reactions of allylic alcohols [29], has been studied from our substrates (Table 3). The reactions have then be carried out under the conditions depicted in Eq. (1) except the use of microwave heating at 100 °C with a microwave power of 300 W for 0.5 h, instead of oil-bath heating at 120 °C for 16–24 h. As exemplified by the results compiled in Table 3, this procedure increased strongly the yields from 1b, 1c, 1d, 1e and 1f. Moreover, 2g was thus isolated in 61% yield while this compound was not isolated under thermal heating conditions. Nevertheless, the formation of 2h remains precluded under these conditions.

![Scheme 2](image)

![Scheme 3](image)
Table 2
Pd-catalyzed reaction of allylic alcohols 1b–1h under the conditions depicted in Eq. (1)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>1b</th>
<th>1c</th>
<th>1d</th>
<th>1e</th>
<th>1f</th>
<th>1g</th>
<th>1h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (h)</td>
<td>16</td>
<td>24</td>
<td>24</td>
<td>21</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Product (yield %)</td>
<td>2b, 67</td>
<td>2c, 56</td>
<td>2d, 42</td>
<td>2d, 47</td>
<td>2f, 12</td>
<td>2g, 0</td>
<td>2h, 0</td>
</tr>
</tbody>
</table>

Table 3
Pd-catalyzed reaction of allylic alcohols 1b–1h under microwave irradiation

<table>
<thead>
<tr>
<th>Substrate</th>
<th>1a</th>
<th>1b</th>
<th>1c</th>
<th>1d</th>
<th>1e</th>
<th>1f</th>
<th>1g</th>
<th>1h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product (yield %)</td>
<td>2a, 92</td>
<td>2b, 90</td>
<td>2c, 93</td>
<td>2d, 86</td>
<td>2d, 86</td>
<td>2f, 84</td>
<td>2g, 61</td>
<td>2h, 0</td>
</tr>
</tbody>
</table>

Table 4
Pd-catalyzed reaction of naphthalene derivatives under thermal (Δ) and microwave (μw) conditions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>R</th>
<th>Δ (yield %)</th>
<th>μw (yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td>Me: a</td>
<td>44</td>
<td>87</td>
</tr>
<tr>
<td><img src="image2.png" alt="Image" /></td>
<td>Ph: b</td>
<td>0</td>
<td>63</td>
</tr>
<tr>
<td><img src="image3.png" alt="Image" /></td>
<td>Me: a</td>
<td>56</td>
<td>92</td>
</tr>
<tr>
<td><img src="image4.png" alt="Image" /></td>
<td>Ph: b</td>
<td>10</td>
<td>68</td>
</tr>
<tr>
<td><img src="image5.png" alt="Image" /></td>
<td>Me: a</td>
<td>24</td>
<td>74</td>
</tr>
<tr>
<td><img src="image6.png" alt="Image" /></td>
<td>Ph: b</td>
<td>0</td>
<td>23</td>
</tr>
</tbody>
</table>

4 All reactions were carried out with relative amounts of reactants as those of Table 1, run 1 by heating with an oil-bath at 120 °C for 20 h (Δ) or microwaves at 100 °C (microwave power: 300 W) for 0.5 h (μw).

These results urge us to examine the 5-endo-trig cyclization of naphthalene derivatives 4, 5 and 6 (R = Me (a) or Ph (b)) under both heating methods (Table 4). Under the thermal conditions, incomplete conversions were attained in 20 h; moderate yields of ketones 7a, 8a and 9a were obtained from substrates with the methyl substituent while, with a phenyl substituent, the expected cyclized compound was isolated only from 5b. Shifting to microwave conditions increased greatly the results, a low yield being obtained only from 6b.

3. Conclusion

The Pd-catalyzed 5-endo-trig cyclization of 1-(o-bromoaryl)-2-substituted-prop-2-en-1-ols can efficiently proceed, particularly under microwave irradiation, using cinchonine as the ligand, sodium bicarbonate as the base and DMF as the solvent. The chemical yields are nevertheless sensitive to the substitution pattern of the substrate. The absence of optical activity for the cyclized products could be due to the required experimental conditions and/or to the nature of the intermediates.

4. Experimental

Substrates 1a–1d, 1f–1h, 4a, 4b, 5a, 5b, 6a and 6b have been prepared by addition of Grignard reagents to bromoarylaldehydes following a reported procedure [30] (see Supplementary Material for yields and characterization data). The synthesis of 1e was carried out via a Baylis-Hillmann reaction as reported [31].

4.1. Cyclization procedure

To a mixture of Pd(OAc)2 (11 mg, 0.05 equiv.), cinchonine (30 mg, 0.1 equiv.) and NaHCO3 (92 mg, 1.1 equiv.) under an argon atmosphere was added a solution of the substrate (1 mmol) in DMF (2 mL). The mixture was heated either at 120 °C with an oil-bath for the time indicated in Tables, or at 100 °C for
0.5 h using a microwave apparatus (CEM-Discover, LabMate type) with a microwave power held at 300 W. After cooling to room temperature and addition of diethyl ether, the mixture was filtered over a small pad of Celite. The filtrate was successively washed with water and brine, then dried over MgSO4. After elimination of the solvent, the product was isolated by flash-chromatography.

The NMR data of 2a [32], 2b [33], 2c [34], 2d [35], 2f [36], 2g [37], 3a [38], 8a [39], 8b [40] and 9b [41] were in agreement with those of literature.

2-Methyl-1,2-dihydrocyclopenta[α]naphthalen-3-one (7a): mp 70–71 °C (literature [42] 71–72 °C). 1H NMR (250 MHz, CDCl3): (1.29 (d, 3H, J = 6.9 Hz, Hα), 2.70 (m, 1H, CH2), 2.86 (dd, 1H, J = 17.6, 3.3 Hz, CH2), 3.57 (m, 1H, CH), 7.46–7.59 (2H, Hα), 7.62 (d, 1H, J = 8.6 Hz, Hα), 7.68 (d, 1H, J = 8.6 Hz, Hα), 7.81 (d, 1H, J = 7.6 Hz, Hα), 7.90 (d, 1H, J = 7.6 Hz, Hα), 13C NMR (62.9 MHz, CDCl3): (16.7, 33.4, 34.5, 37.9, 41.1, 44.6, 119.8, 124.5, 127.1, 128.6, 130.4, 133.8, 136.7, 154.8, 209.4).

2-Phenyl-1,2-dihydrocyclopenta[α]naphthalen-3-one (7b): mp 65–67 °C. 1H NMR (250 MHz, CDCl3): (2.81 (dd, 1H, J = 14.3, 2.0 Hz, CH2), 3.43 (dd, 1H, J = 14.3, 7.5 Hz, CH2), 3.90 (dd, 1H, J = 7.5, 2.0 Hz, CH), 7.10–7.30 (5H, Hα), 7.51–7.65 (2H, Hα), 7.69 (t, 1H, J = 8.4 Hz, Hα), 7.76 (t, 1H, J = 8.4 Hz, Hα), 7.88 (d, 1H, J = 8.4 Hz, Hα), 7.98 (d, 1H, J = 7.5 Hz, Hα), 13C NMR (62.9 MHz, CDCl3): (34.5, 53.3, 120.1, 124.6, 126.1, 127.0, 127.6, 129.1, 129.5, 133.9, 136.9, 140.0, 155.2, 205.9).

2-Methyl-2,3-dihydrocyclopenta[b]naphthalen-1-one (9a): mp 88–89 °C. 1H NMR (250 MHz, CDCl3): (1.29 (d, 3H, J = 7.3 Hz, CH3), 2.74 (m, 1H, CH2), 2.82 (dd, 1H, J = 17.2, 5.0 Hz, CH2), 3.48 (m, 1H, CH), 7.35–7.54 (2H, Hα), 7.72–7.80 (2H, Hα), 7.89 (d, 1H, J = 8.0 Hz, Hα), 8.25 (s, 1H, Hα). 13C NMR (62.9 MHz, CDCl3): (14.6, 32.8, 41.1, 122.9, 124.3, 126.0, 126.7, 128.6, 130.6, 132.4, 135.5, 144.5, 208.0).

Acknowledgements

This work was supported by CNRS and the European Community (COST D12/0028/99). The French group is grateful to “Ministère de la Recherche et de la Technologie” for a Ph.D. studentship to B.G., to CNRS for a temporary position to "Ministère de la Recherche et de la Technologie" for a Ph.D. studentship to B.G., and to Engelhard Company for generous gifts of palladium salts. The Spanish group is grateful to MEC (Project CTQ2005-04968) and to the University of Girona (grant to I.G.).

Appendix A. Supplementary data


References


[7] For examples of 5-endo-trig cyclizations, see:
(a) Ref. [7];


[10] For examples of N-O- or N,N-bidentate ligands in palladium chemistry, see:


[12] Reference [1].
[27] For examples, see:
(b) A. Díaz Ortiz, P. Prieto, E. Vázquez, Synlett (1997) 269–270;
(g) D.E. Bergbreiter, S. Furyk, Green Chem. 6 (2004) 280–285;
[28] For reviews, see: