

PtCl₂-Promoted cyclopropane opening in [4+2+2] homo Diels–Alder cycloadducts

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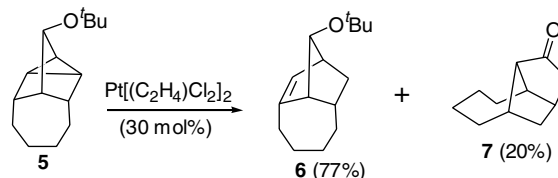
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Abstract—A new and readily available catalytic system has been developed to open the cyclopropane ring in [4+2+2] homo Diels–Alder cycloadducts formed by reaction of norbornadienes and 1,3-butadiene. The cobalt-mediated homo Diels–Alder reaction followed by this PtCl₂-promoted isomerization is a key step in the efficient route to bicyclo[5.3.0]decanes, core of numerous natural products.

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The cobalt-catalyzed [4+2+2] cycloaddition of substituted norbornadienes **1** and 1,3-butadiene is efficient chemistry that leads to highly caged olefinic cycloadducts **2**.^{1,2} As we have shown in previous studies,^{3–7} these cycloadducts can be opened to yield perhydroazulenes **3** (Fig. 1)^{6,8} or bicyclo[4.2.1]nonanes **4**,⁷ core structures of numerous natural products. The key feature in both these routes was a Pt(II)-promoted cyclopropane opening of adduct **2**.^{6,9,10} While the cobalt-mediated homo Diels–Alder reaction tolerates a wide range of functionalities with a relatively small catalyst load (5%),^{1c,2} the Pt-catalyzed cyclopropane opening using Zeise's dimer was more problematic, especially for the formation of bicyclo[5.3.0]decanes **3**. A minimum 30% of Zeise's dimer^{6,8} was usually needed in order to



Scheme 1.

achieve acceptable yields. At this level of catalyst load, the reaction is near stoichiometric in platinum. Decreasing the amount of Zeise's dimer led to very long reaction times and lower yields. Furthermore, by-products with the structure core **7** were often formed (Scheme 1).⁶ For these reasons, a more efficient and less expensive (Zeise's dimer, 1 g = \$140) catalytic system was needed to open the cyclopropane ring.

Different metals were screened to accomplish the cyclopropane opening (Table 1). In addition to Pt complexes, which have been successful to date, Pd-catalysts were examined since they are well known to open cyclopropanes during hydrogenation,¹¹ while Au-catalysts were also selected since there is a report of the formation of aurocyclobutanes from Au(III),¹² though not by insertion into a cyclopropane ring. In addition, earlier unreported work in our group¹³ had already screened rhodium ([Rh(CO)₂Cl]₂)¹⁴ and iridium (IrCl(CO)(PPh₃)₂)¹⁵ complexes, both reported to insert into cyclopropanes, as catalysts to open **5**, but with only limited success, so these metals were not further examined.

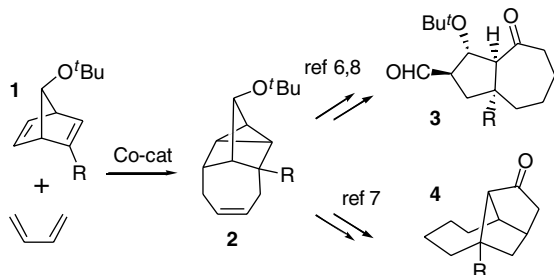


Figure 1. [4+2+2] Cycloaddition strategy toward bicyclo[5.3.0]decanes and bicyclo[4.2.1]nonanes.

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Table 1. Use of different metals for the cyclopropane opening of cycloadduct **5** to alkene **6** (Scheme 1)

Entry	Metal ^a	Yield/% (SM/%) ^b
1	PtCl ₂	39 (61)
2	PdCl ₂	28 (72)
3	[C ₃ H ₅ PdCl] ₂	13 (87)
4	PdCl ₂ (CH ₃ CN) ₂	41 (28)
5	PdCl ₂ (PPh ₃) ₂	0 (100)
6	AuI	0 (47)
7	AuBr ₃	0 (63)

^a Reactions performed in refluxing benzene for 8 h with 30% metal relative to **5**.

^b Determined by ¹H NMR.

We were pleased to see that the desired alkene **6** was obtained with palladium and platinum catalysts: PtCl₂, PtBr₂, PdCl₂, [C₃H₅PdCl]₂, and PdCl₂(CH₃CN)₂. Among them, PtCl₂ and PdCl₂ seemed very promising since the by-product **7** was not observed. The gold catalysts, however, led only to decomposition and considerable recovered starting material (entries 6 and 7); no desired alkene **6** was detected in these reactions. Given these results, PtCl₂ was then chosen to optimize the reaction conditions (Table 2). High boiling point, π-donor solvents were found to be the best for this isomerization (Table 2, compare entries 1 and 6), while ethereal solvents gave poor conversions (entries 2–4). Bromobenzene (entry 5) led to an intractable mixture containing some starting material. In refluxing *o*-xylene with 30% PtCl₂, **5** was converted to the olefinic product **6** in quantitative yield (Table 2, entry 6). Moreover, by simply

switching to mesitylene, at the same temperature, the amount of catalyst could be decreased to 20%, which represents a major improvement compared to Zeise's dimer, not only because of the smaller catalyst load (20% vs 30% of Zeise's dimer, which corresponds to 60% platinum) but also because the by-product **7** was not produced. The same conditions were applied to PdCl₂ and PdCl₂(CH₃CN)₂ (entries 8 and 9) but the yields were not as high as with PtCl₂ in promoting isomerization to olefin **6**.

When decreasing the catalyst loading to 10% (entry 10), the reaction became very sluggish and precipitate formation, presumably of the platinum catalyst, occurred after 10–12 h. Since this precipitation halts the reaction, we next focused on the use of different additives that would stabilize the catalyst but would still allow for sufficient reactivity for insertion into the cyclopropane. The first trials were based on the use of alkenes as additives since platinum is known to coordinate with olefins to form stabilized complexes.^{9b} Therefore, three different olefins (1-methylcyclohexene, 1,5-cyclooctadiene, and 1,4-cyclohexadiene) were added to the reaction (Table 3, entries 1–3). Unfortunately, no improvement in the reactivity of the catalyst was observed.

Following the work of Fürstner and co-workers, who used PtCl₂ under a stabilizing CO atmosphere to form cyclobutenes via enyne cycloisomerization,¹⁶ the reaction was next performed under similar conditions. Unfortunately, the reaction failed to proceed with 10%

Table 2. Optimization of the reaction conditions in the opening of cycloadduct **5** to alkene **6** (Scheme 1)

Entry	Metal/% ^a	Solvent, temp, time	Yield/% (SM/%) ^b
1	PtCl ₂ (30)	Benzene, reflux, 12 h	39 (61)
2	PtCl ₂ (30)	Ether, rt, 12 h	0 (100)
3	PtCl ₂ (30)	THF, reflux, 12 h	13 (87)
4	PtCl ₂ (30)	Diglyme, 140 °C, 12 h	0 (31)
5	PtCl ₂ (30)	Bromobenzene, 140 °C, 12 h	0 (26)
6	PtCl ₂ (30)	<i>o</i> -Xylene, 140 °C, 3 h	100 (0)
7	PtCl ₂ (20)	Mesitylene, 140 °C, 7 h	100 (0)
8	PdCl ₂ (30)	<i>o</i> -Xylene, 140 °C, 5 h	47 (45)
9	PdCl ₂ (CH ₃ CN) ₂ (30)	<i>o</i> -Xylene, 140 °C, 5 h	51 (24)
10	PtCl ₂ (10)	Mesitylene, 140 °C, 12 h	71 (28)

^a Percent metal relative to **5**.

^b Determined by ¹H NMR.

Table 3. Use of additives to lower the catalyst loading in the opening of cycloadduct **5** to alkene **6** (Scheme 1)



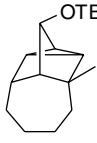
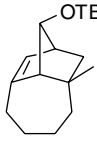


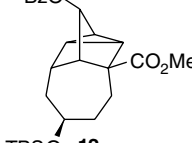
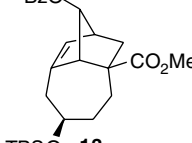
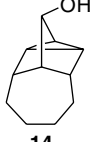
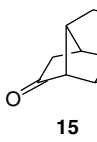
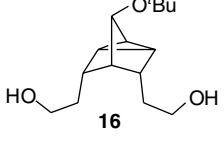
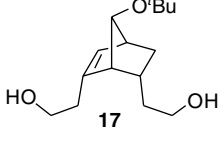
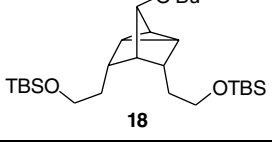
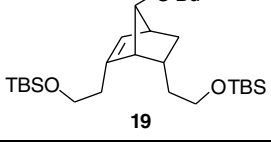
Entry	Metal/% ^a	Additive/%	Yield ^b /%(SM ^b /%)
1	PtCl ₂ (10)	1-Methylcyclohexene (10)	66 (34)
2	PtCl ₂ (10)	1,5-Cyclooctadiene (10)	55 (45)
3	PtCl ₂ (10)	1,4-Cyclohexadiene (10)	60 (35)
4	PtCl ₂ (10)	CO	0 (100)
5	PtCl ₂ (10)	PPh ₃ (20)	97 ^c (0)
6	PtCl ₂ (5)	PPh ₃ (10)	56 (44)
7	PtCl ₂ (5)	P(<i>p</i> -C ₆ H ₄ F) ₃ (10)	61 (30)
8	PtCl ₂ (5)	P(C ₆ F ₅) ₃ (10)	86 ^c (10)

^a Reactions were performed in mesitylene at 140 °C; percent metal relative to **5** (in parentheses).

^b Determined by ¹H NMR.

^c Isolated yield.

Table 4. Cyclopropane opening of different [4+2+2] cycloadducts^a

Entry	Starting material	Product	Yield ^b
1	 5	 6	86
2	 8	 9	89
3	 10	 11	86
4	 12	 13	91
5	 14	 15	79
6	 16	 17	33 ^c
7	 18	 19	69 ^c

^a All reactions were performed in mesitylene at 140 °C, 5 mol % PtCl₂, 10 mol % tris(pentafluorophenyl)phosphine as described in the typical procedure.¹⁸

^b Isolated yield.

^c 10% catalyst was used.

PtCl₂ leaving only unreacted starting material (Table 3, entry 4).

Phosphine ligands were finally studied. Widenhoefer has recently shown that the addition of 2 eq. of P(*p*-CF₃C₆H₄)₃ to Zeise's dimer gave a very efficient catalyst for the hydroamination of vinyl arenes with carboxamides, also in mesitylene at 140 °C.¹⁷ This work indicated that even if the platinum center was rendered less electrophilic (by phosphine complexation), the phosphine ligand was labile enough to still allow for

good reactivity while stabilizing the catalyst. In the event, PPh₃ (2 equiv compared to PtCl₂) was added to the reaction mixture. Under these conditions, only 10% PtCl₂ was necessary and after 15 h at 140 °C in mesitylene, the desired olefin **6** was obtained in 97% isolated yield (Table 3, entry 5). In an effort to further decrease the catalyst load, two more weakly donating phosphines were evaluated: tris(*p*-fluorophenyl)phosphine (entry 7) and tris(pentafluorophenyl)phosphine (entry 8). The latter showed significant improvement compared to PPh₃: in an optimized procedure, the

isomerization of cycloadduct **5** catalyzed by a 1:2 mixture of PtCl_2 (5%) with $\text{P}(\text{C}_6\text{F}_5)_3$ (10%) led to **6** in 86% isolated yield.¹⁸

Using the optimized catalytic system and reaction conditions, several cyclopropanes derived from different [4+2+2] cycloadducts were then opened (Table 4). From this study a few points can be highlighted. First, more highly caged structures **5**, **8**, **10**, **12**, and **14** give higher yields of cyclopropane-opened product (entries 1–5) compared to less strained tricyclanes **16** and **18** (entries 6 and 7). This may be explained by a faster formation of the platinumacyclobutane via insertion of the Pt(II) into the more strained cyclopropane.⁹ Second, a free alcohol can play a determining role in directing the platinum insertion. Thus, ketone **15** is obtained in good yield due to the hydroxyl-directed Pt(II)-insertion into the top face of the cyclopropane.⁷ In a further indication of coordination of Pt(II) with hydroxyl groups, diol olefin **17** forms in 33% yield only, while **19** is produced in 69% yield with the protected alcohols (compare entries 6 and 7). The lower yield obtained in the former case is probably due to the coordination of the platinum by the two hydroxyl groups in **16** away from the cyclopropane. These latter two reactions required 10 mol % Pt to optimize the yield.

In summary, a new, readily available catalyst $\text{PtCl}_2/\text{P}(\text{C}_6\text{F}_5)_3$ (1:2) has been demonstrated to open the cyclopropane ring of [4+2+2] homo Diels–Alder cycloadducts. The cobalt-mediated homo Diels–Alder reaction followed by this platinum-promoted isomerization is an efficient methodology leading to the core of numerous natural products. Further applications of this methodology are under study and will be reported in due time.

Acknowledgments

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- Typical procedure: To a mixture of PtCl_2 (3 mg, 0.0113 mmol) in mesitylene (1 mL) was added tris(pentafluorophenyl)phosphine (12 mg, 0.0227 mmol), then cycloadduct **5** (50 mg, 0.227 mmol) under argon. The reaction was stirred at 140 °C for 12 h then allowed to cool to rt. The solution was passed through a short plug of silica gel, eluting with CH_2Cl_2 (3 × 1 mL), then the filtrate was concentrated in vacuo. The crude material was purified by flash chromatography (hexanes/EtOAc, 10/1) to give olefin **6** as a colorless liquid (43 mg, 86%).