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Metal-Catalyzed [4 + 2 + 2] Cycloadditions: Cycloadducts of Substituted Norbornadienes and Their Opening with Zeise's Dimer

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The homo Diels−Alder (HDA) reactions of norbornadiene (**1**) result in caged structures with the generation of multiple stereogenic centers.[1] First reported as [2 + 2 + 2] cycloadditions, both thermal and transition-metal-catalyzed reactions were investigated throughout the 1960s and 1970s, particularly as researchers probed the transition-metal-catalyzed dimerization of **1**.[2] The transition-metal-catalyzed [4 + 2 + 2] reactions of **1** with butadiene were first reported using Fe(acac)$_3$/DPPE/Et$_2$AlCl[3] and Co(acac)$_2$/Et$_3$Al[4] catalytic systems. Lyons later optimized the cobalt system to produce adducts in yields up to 90%.[5] More recently, Lautens has achieved good levels of enantioselectivity in this [4 + 2 + 2] chemistry,[6] thereby extending previous work on the related enantioselective [2 + 2 + 2] reactions.[7]

We became interested in the HDA reactions of **1** as a route to cis-fused bicyclic systems (Scheme 1), and recently reported opening both [2 + 2 + 2]- and [4 + 2 + 2]-adducts to cis-fused bicycles using Nickon's acid catalyzed opening of deltacyclanes[8] with subsequent Baeyer-Villager chemistry.[9] Others have also noted the potential of opening the [2 + 2 + 2]-adducts[8,10] or the tricyclic brendanes[11] and brexanes[12] to biquinanes, and Lautens has recently reported the use of Hg(II) to cleave the deltacyclanes to brendanes, ultimately opening to biquinanes.[13] To expand the utility of this chemistry, we examined the [4 + 2 + 2] reactions with three specific goals in mind: (1) optimize the catalytic system for the cycloadditions, (2) determine the regioselectivity using 2-substituted norbornadienes, and (3) establish a protocol for opening the cycloadducts to bicyclo[5.3.0]-decanes.

Scheme 1

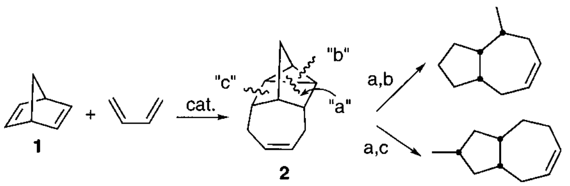

Table 1. [4 + 2 + 2] Cycloadditions of Norbornadiene (1) with 1,3-Butadiene To Give 2

Item	Catalyst/Conditions[a]	Time (h)	Yield (%)[b]
1	Co$_2$(CO)$_8$ (1 - 10 mol%)/DPPE or PPh$_3$ (2 eq)[c]	4- 22	0
2	Ni(COD)$_2$ (5 mol%)/PPh$_3$ (2 eq)/ClCH$_2$CH$_2$Cl	18	0
3	Ni(acac)$_2$ (1 mol%)/DPPE (1.5 eq)/Et$_2$AlCl (10 eq)/tol	5	0
4	Fe(acac)$_3$ (1 mol%)/DPPE (1.5 eq)/Et$_2$AlCl (10 eq)/tol	8	79
5	Co(acac)$_2$ (1 mol%)/DPPE (1.5 eq)/Et$_2$AlCl (10 eq)/tol	4	79
6	Co(acac)$_2$ (1 mol%)/PPh$_3$ (1.5 eq)/Et$_2$AlCl (10 eq)/tol	22	0
7	CoI$_2$ (2.5 mol%)/DPPE (1 eq)/Zn (10 eq)/CH$_2$Cl$_2$	4	85
8	CoI$_2$ (2.5 mol%)/PPh$_3$ (2 eq)/Zn (10 eq)/CH$_2$Cl$_2$	4	28
9	CoI$_2$ (2.5 mol%)/DPPE (2 eq)/Zn (10 eq)/ClCH$_2$CH$_2$Cl	4	83
10	CoI$_2$ (2.5 mol%)/DPPE (2 eq)/ZnI$_2$ (5 eq)/CH$_2$Cl$_2$	4	81
11	Co$_2$(CO)$_8$ (2.5 mol%)/DPPE (2 eq)/ZnI$_2$ (5 eq)/CH$_2$Cl$_2$	4	30

(a) All reactions at 60 °C; mol% of metal is relative to **1**, no. of ligand mol. eq. is relative to transition metal. Reactions in toluene: 0.5 M in **1**, reactions in CH$_2$Cl$_2$ and ClCH$_2$CH$_2$Cl: 1.6 M in **1**. (b) Isolated yields. (c) Reactions run in toluene, CH$_2$Cl$_2$, and ClCH$_2$CH$_2$Cl.

As originally reported, both cobalt[5,6] and iron[3] salts in the presence of reducing agents successfully catalyzed the reaction (Table 1, items 4 and 5), though similar chemistry with nickel, an excellent catalyst for the [2 + 2 + 2] reaction,[1,14,15] failed (Table 1, items 2 and 3). It has been accepted that zero- or low-valent metal complexes are the active catalysts, so it was surprising that Co$_2$(CO)$_8$ did not produce adduct **2** (Table 1, item 1). This lack of reactivity of zero-valent cobalt raised the possibility that a multimetal center might be the true catalyst, as suggested by Schrauzer in explaining norbornadiene dimerization to produce Binor-S.[15a,16] Indeed, we know of no reports of a [4 + 2 + 2] reaction of **1** that did not employ a multimetal catalytic system. In support of this, when ZnI$_2$ was added to Co$_2$(CO)$_8$, **2** was produced, in 30% yield (Table 1, item 11). Recently, Binger has employed a CoI$_2$/PPh$_3$/ZnI$_2$ catalytic system to produce [2 + 2 + 2] adducts of norbornadiene, demonstrating that cobalt in a zero- or low-valent state is not necessary.[17] The same conclusion appears to hold true for the [4 + 2 + 2] reaction as an 81% yield of **2** was produced using a similar Binger catalyst (Table 1, item 10), though neither CoI$_2$ nor ZnI$_2$ alone catalyzed the reaction. Finally, reactions employing DPPE as the ligand produced cycloadducts in good to excellent yields, but the use of PPh$_3$ was either unsuccessful or produced **2** in only low yield (Table 1, items 6 and 8). The most successful catalytic systems that emerged from these studies were the modified Lyons catalyst,[5,6] (Table 1, item 5), the Duan catalyst[18] (Table 1, item 7), and the Binger catalyst[17] (Table 1, item 10).

Our next objective was to examine the [4 + 2 + 2] reactions of substituted norbornadienes (Scheme 2, Table 2). 7-*tert*-Butoxynorbornadiene[19] (**3a**) gave excellent yields

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Scheme 2

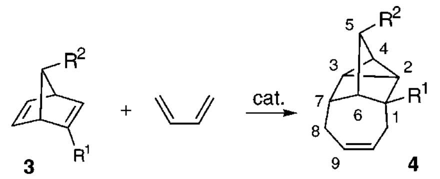
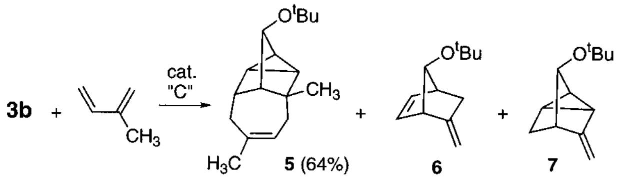


Table 2. [4 + 2 + 2] Cycloadditions of 3

Item: 3	R^1	R^2	Cat.[a]	Temp (°C)	Time (h)	4:Yield (%)[b]
1:**3a**	H	^{t}BuO	A	50	13	**4a**:84
2:**3b**	Me	^{t}BuO	A	60	9	**4b**:82
3:**3c**	Me	H	A	60	8	**4c**:82
4:**3d**	CH_2OMe	H	A[c]	90	24	**4d**:15
5:**3d**	"	"	B	90	24	**4d**:44
6:**3d**	"	"	C	90	5	**4d**:59
7:**3e**	CO_2Me	H	A, B	rt, 60	12	0[d]
8:**3e**	"	"	C	80	31	**4e**:76
9:**3f**	TMS	H	A, C	50, 90	18, 28	0[e]

(a) Catalyst "A": $Co(acac)_2/DPPE/Et_2AlCl$ (1/1.5/10), 1 mol% based on Co relative to **3**, in toluene; Catalyst "B": $CoI_2/DPPE/Zn$ (1/2/10), 2.5 mol% based on Co relative to **3**, in CH_2Cl_2; Catalyst "C": $CoI_2/DPPE/Zn$ (1/2/10), 2.5 mol% based on Co relative to **3**, in $ClCH_2CH_2Cl$. (b) Isolated yields. (c) 2.5 mol% catalyst based on Co relative to **3d**. (d) With catalyst A, the [4+2] Diels-Alder adduct was produced; with catalyst B, only (**3e**) was recovered. (e) Starting material (**3f**) was recovered.

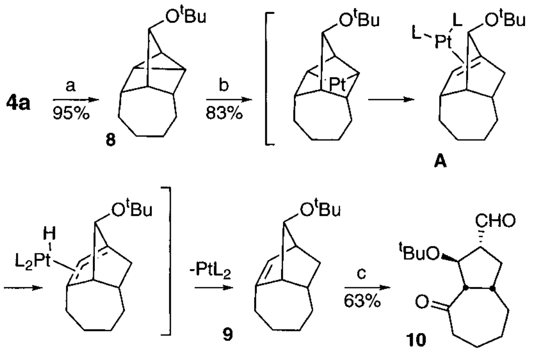
Scheme 3



of cycloadduct **4a**, in parallel with results for the analogous [2 + 2 + 2] reactions of **3a**.[20,21] The most striking discovery was the regioselectivity observed in the adducts produced from the 2-substituted norbornadienes **3b**−**e**:[22] in all cases, regioisomer **4** with the original norbornadienyl 2-substituent located at C1 of the adduct was the sole [4 + 2 + 2] product detected irrespective of the electron demands of the substituent. For the methoxymethyl and methyl ester derivatives **3d** and **3e**, use of the CoI_2/DPPE/Zn catalyst in 1,2-dichloroethane was essential. Attempts to employ the iron-based catalyst (Table 1, item 4) with **3c** invariably gave a lower yield of adduct. No reactions were observed with 2-(trimethylsilyl)norbornadiene (**3f**).[23] This exclusive regioselectivity in the [4 + 2 + 2] reactions of **3b**−**e** stands in contrast to the variable regioselectivity observed in the [2 + 2 + 2] reactions of 2-substituted norbornadienes, which were very sensitive to the nature of the substituent.[6,15b]

Even more remarkable was the regioselectivity observed in the reaction of **3b** with isoprene to produce **5** as the sole [4 + 2 + 2] adduct detected (64%, Scheme 3). Byproducts **6** (22%) and **7** (6%) were also produced. This excellent regiocontrol translates into a potentially useful route to substituted cis-fused bicyclo[5.3.0]decanes with an angular carbon-based substituent at a ring fusion center, as found in the pseudoguaianolide sesquiterpenes,[24] if the desired ring opening can be achieved.

Scheme 4[a]



[a] Key: (a) H_2, Pd−C, THF, rt, 5 h; (b) $[Pt(C_2H_4)Cl_2]_2$ (50 mol %), Et_2O ($\uparrow\downarrow$), 9 h; (c) O_3, then Me_2S, CH_2Cl_2.

Attempts to apply the acid-catalyzed cyclopropane opening previously used on **2**[9] to the [4 + 2 + 2] adduct **3a** failed, leading only to loss of the *tert*-butyl group. Zeise's dimer $[Pt(C_2H_4)Cl_2]_2$ has been shown to insert into cyclopropanes to produce stable platinacyclobutanes,[25] while catalytic opening of cyclopropanes with rearrangement to olefins by transition metals,[26] including Zeise's dimer,[27] has also been demonstrated. Hydrogenation of **4a** followed by treatment with Zeise's dimer led directly to olefin **9**, which provided bicyclo[5.3.0]decanone **10** following ozonolysis (Scheme 4). Presumably, platinum insertion into the cyclopropane ring of **8** followed by a sequence of platinum-mediated hydride shifts leads to exclusive formation of anti regioisomer **9** with no syn isomer (*tert*-butoxyl group *syn* to olefin) detected, the bulky *tert*-butoxyl group apparently preventing migration of the platinum to the syn face. This proposed mechanism passes through the platinum complex of anti-Bredt intermediate **A**. Such transition-metal complexes of strained bridgehead olefins are known,[28] and the transient occurrence of 1-norbornene is also strongly supported.[29]

In conclusion, cobalt-catalyzed [4 + 2 + 2] cycloadditions of **1** proceed readily when a bimetal system is employed. A zero- or low-valent cobalt species is not essential, but the presence of the second metal apparently is required. With 2-substituted norbornadienes, excellent regioselectivity is shown, producing the C1-substituted adducts.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C spectra for all compounds (32 pages).

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