Stereoselective [2 + 2 + 2] cocyclotrimerization of oxa- and azabenzonorbornadienes† with alkynes catalyzed by nickel complexes: first transition metal-mediated synthesis of isobenzofuran and isoindole precursors

Thota Sambaiah, Daw-Jen Huang and Chien-Hong Cheng*

Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan 30043

Received (in Cambridge, UK) 22nd September 1999, Accepted 29th October 1999

Oxabenzonorbornadiene (**1a**) reacted with various alkynes in the presence of $Ni(PPh_3)_2Cl_2$, PPh_3 and zinc powder in toluene to give two common products **2a** and **2b** regardless of the alkyne used. The formation of **2a** and **2b** are proposed to be from the Diels–Alder reaction of **1a** and isobenzofuran. The latter is generated from the retro Diels–Alder reaction of [2 + 2 + 2] cycloadducts of **1a** and alkynes catalyzed by the nickel system. A series of nickel-catalyzed [2 + 2 + 2] cycloadducts (**4a**–**j** and **5a**–**d**) of oxa- and azabenzonorbornadienes (**1a**–**d**) with terminal alkynes were isolated at temperatures −5–18 °C. Similarly, hepta-1,6-diyne and octa-1,7-diyne reacted with **1a** and **1d** to give novel pentacyclic [2 + 2 + 2] cycloadducts **6a**–**d** in 62–75% yields. These products are convenient isobenzofuran and isoindole precursors that react with various dienophiles to afford the corresponding Diels–Alder adducts. In addition, the [2 + 2 + 2] cycloadducts may be used as precursors for the synthesis of aromatic compounds. For example, the reaction of **1a** with methyl but-2-ynoate catalyzed by the nickel system provided aromatic compound **3** in 94% yield. In this reaction, **1a** is a 'masked acetylene' providing an acetylene moiety to **3**.

Introduction

Isobenzofuran and its derivatives have attracted considerable attention in recent years in organic synthesis. They have been widely used as dienes in the Diels–Alder reactions[1] to provide substituted 7-oxabicyclo[2.2.1]heptanes, which are key intermediates in natural products synthesis.[2] Recently, Padwa and co-workers have synthesised the Erythrinane alkaloid skeleton[3] and a variety of 1-hydroxy-4-aminonaphthalene derivatives[4] using isobenzofuran derivatives as key intermediates. In addition, isobenzofurans and isoindoles are important building blocks for the syntheses of a variety of fascinating polycyclic unnatural products.[5,6] However, isobenzofurans and isoindoles are generally highly reactive undergoing polymerization even at low temperature. Several precursors for isobenzofurans[7] and isoindoles[8] have been developed, but most are very unstable and difficult to handle. The search for new and viable precursors to conveniently generate isobenzofurans and isoindoles continues.

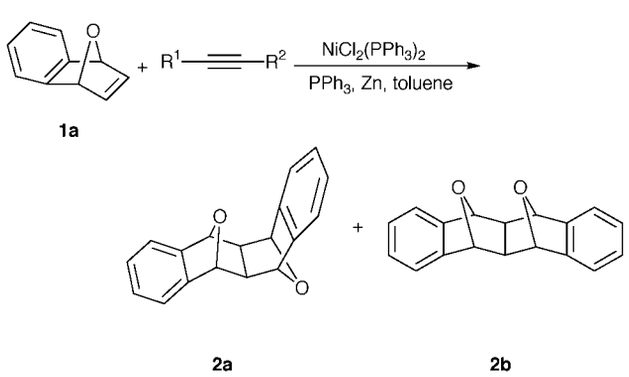
Transition metal-catalyzed [2 + 2 + 2] cocyclotrimerization is a powerful method for the construction of cyclic compounds in a chemo- and regioselective manner.[9,10] Cocyclotrimerization of three acetylenes has been extensively studied by using different metal catalysts with different unsaturated compounds.[11] The [2 + 2 + 2] cycloaddition of two acetylenes and an alkene has been less well explored.[12] In general, this cocyclotrimerization requires a high ratio of alkene to alkyne in order to suppress the competing trimerization of alkynes.[13] Recently, we reported a novel one step synthesis of cyclohexadiene derivatives of C_{60} *via* a nickel-catalyzed cycloaddition of C_{60} with diynes.[14] In addition, we[15] and Ikeda *et al.*[16] independently reported the [2 + 2 + 2] cocyclotrimerization of α,β-unsaturated carbonyl compounds with mono alkynes and diynes mediated by nickel complexes. In the pursuit for new active alkenes for [2 + 2 + 2] cocyclotrimerization, we observed the cocyclotrimerization of oxa- and azabenzonorbornadienes with alkynes. The cocyclotrimerization products may be used as convenient new precursors for isobenzofurans and isoindoles and for substituted aromatic compounds. Moreover, the reaction is an excellent method for constructing multiple fused rings by the cycloaddition of oxa- and azabenzonorbornadienes with diynes. Herein we report a detailed study of this nickel-catalyzed cocyclotrimerization reaction. Preliminary results of these studies have appeared in a communication.[17]

† The IUPAC name for benzonorbornadiene is 1,4-dihydro-1,4-methanonaphthalene.

Results and discussion

Reaction of oxabenzonorbornadiene (1a) with alkynes

Compound **1a** reacted with various alkynes (see Table 1) at 25–90 °C in the presence of $Ni(PPh_3)_2Cl_2$ (5 mol%), PPh_3 and zinc powder in toluene to give two common products **2a** and **2b** (Scheme 1) regardless of the alkyne used. These two unusual



Scheme 1

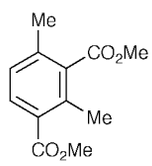
stereoisomers are readily distinguished in the ^1H and ^{13}C NMR spectra (see the Experimental section). A key difference between these two compounds is that **2a** exhibits a pair of resonances at 4.69 and 5.32 ppm for the four bridgehead protons, while **2b** shows only one resonance at 5.46 ppm for bridgehead protons. The symmetries of these two structures are

Table 1 Formation of products **2a** and **2b** from oxabenzonorbornadiene (**1a**) and various alkynes catalyzed by $NiCl_2(PPh_3)_2$–PPh_3–Zn[a]

Entry	[**1a**]/M	[Acetylene]/M	[$NiCl_2(PPh_3)_2$–PPh_3]/M	Temp/°C	Product yield (%)[b] (**2a**)	(**2b**)
1	0.40	$HC{\equiv}C(CH_2)_4CH_3$ (0.40)	0.020/0.32	80	46	25
2	0.40	HC≡CPh (0.80)	0.020/0.32	25	58	40
3	0.50	MeCH≡CHCOOMe (0.60)	0.025/0.40	30	65	31
4	0.50	TMSCH≡CHCOOEt (0.60)	0.025/0.40	30	25	36
5	0.50	$HC{\equiv}C(CH_2)_4C{\equiv}CH$ (0.50)	0.025/0.0	90	52	26
6	0.5	$N(H_2CC{\equiv}CH)_3$ (0.50)	0.025/0.40	70	43	26

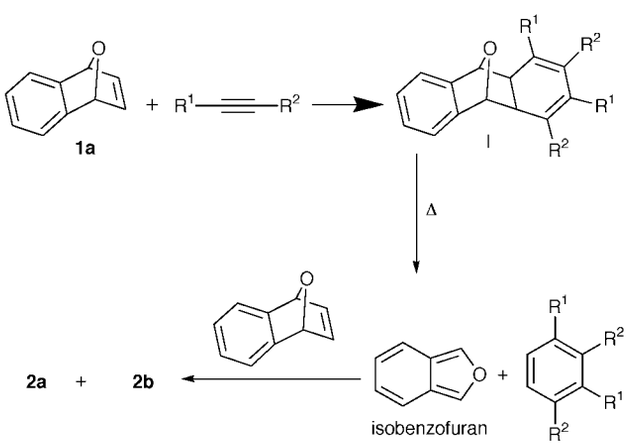
[a] Each reaction was carried out in toluene solution (2.0 ml) in the presence of the reagents shown in Table 1 and Zn metal (2.75 mmol) at the temperature specified for 24 h. [b] The yields of **2a** and **2b** were determined by ^{1}H NMR integration using norbornene as internal standard.

primarily responsible for the number of NMR peaks observed. Although common products **2a** and **2b** were observed, the yields of these two species are different with different alkynes used. The results of these reactions are shown in Table 1. In addition to the common products, aromatic compounds were also observed in the reaction mixtures of **1a** and alkynes. As an example, the reaction of **1a** and methyl but-2-ynoate at 30 °C (entry 3) gave aromatic compound **3** in 92% yield in addition to products **2a** and **2b**.



3

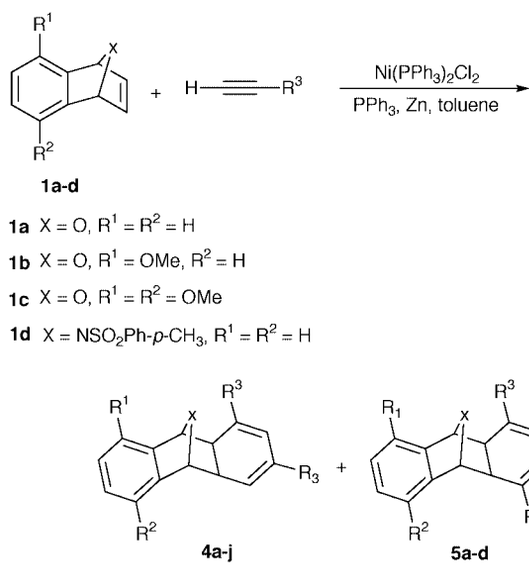
The formation of **2a**, **2b** and aromatic compounds may be explained in terms of a nickel-catalyzed [2 + 2 + 2] cocyclotrimerization of **1a** and alkyne to give intermediate **I**. This cyclohexadiene intermediate is thermally unstable and readily undergoes retro Diels–Alder cycloaddition to give an aromatic product and isobenzofuran. Diels–Alder reaction of isobenzofuran with **1a** affords the observed products **2a** and **2b**. A summary of the reaction pathway is shown in Scheme 2. The driving force for the retro Diels–Alder reaction of intermediate **I** is the formation of a low energy aromatic product.



Scheme 2

Isolation of [2 + 2 + 2] cocyclotrimerization adducts

To support the pathway proposed in Scheme 2, an attempt was made to isolate the [2 + 2 + 2] cocyclotrimerization intermediates. In view of the fact that no such products were isolated at temperatures between 40–90 °C, the reactions of **1a** and alkynes were carried out at lower temperatures. Thus, treatment of **1a** with pent-1-yne in the presence of $Ni(PPh_3)_2Cl_2$ (5 mol%), PPh_3 and zinc powder in toluene at 18 °C for 24 h gave a mixture of two cyclohexadiene derivatives **4a** and **5a** in 91% combined yield (Scheme 3). Mass spectral data show that these two

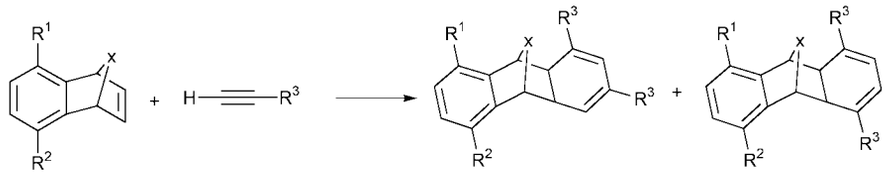


Scheme 3

products are isomers having the same molecular weight. The structures of these two regioisomers are assigned based on the ^{1}H NMR coupling patterns. The individual yields of **4a** and **5a** were determined from the ^{1}H NMR spectrum of the mixture as 22% and 69% respectively. Control reactions revealed that no desired product was formed in the absence of either $Ni(PPh_3)_2Cl_2$ or zinc metal. Additional PPh_3 was essential to stabilize Ni(0) and to achieve higher yields of products. Similarly, hex-1-yne and hept-1-yne reacted with **1a** to give **4b** and **5b** (1 : 2.1), and **4c** and **5c** (1 : 8.7) in 91 and 68% combined yields, respectively. In contrast, the reaction of phenylacetylene and ethyn-1-ylcyclohex-1-ene with **1a** afforded only 1,3-isomers **4e** and **4g**, in high yields, respectively (Table 2). It should be noted that temperature control is important for the success of isolation of cocyclotrimerization products. The reactions of pent-1-yne, hex-1-yne, hept-1-yne and ethyn-1-ylcyclohex-1-ene with **1a** were controlled at 18 °C, while the reaction of phenylacetylene with **1a** was performed at −5 °C.

In the same manner, methoxy substituted oxabenzonor-

Table 2 Cocyclotrimerization of oxa- and azabenzonorbornadienes with terminal alkynes



1a–d **4a–j** **5a–d**

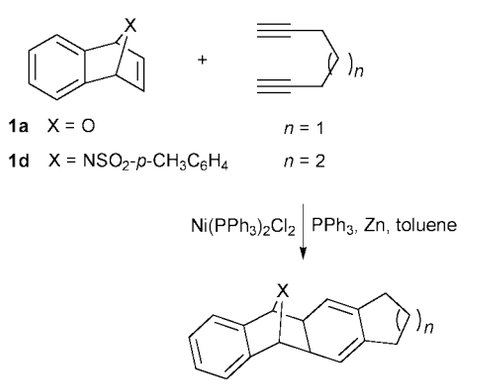
a X = O, $R^1 = R^2$ = H, $R^3 = (CH_2)_2CH_3$
b X = O, $R^1 = R^2$ = H, $R^3 = (CH_2)_3CH_3$
c X = O, $R^1 = R^2$ = H, $R^3 = (CH_2)_4CH_3$
d X = NSO_2-*p*-$C_6H_4CH_3$, $R^1 = R^2$ = H, $R^3 = (CH_2)_2CH_3$
e X = O, $R^1 = R^2$ = H, R^3 = Ph
f X = NSO_2-*p*-$C_6H_4CH_3$, $R^1 = R^2$ = H, R^3 = Ph
g X = O, $R^1 = R^2$ = H, $R^3 = -C_6H_9-$
h X = NSO_2-*p*-$C_6H_4CH_3$, $R^1 = R^2$ = H, $R^3 = -C_6H_9-$
i X = O, $R^1 = OCH_3$, R^2 = H, R^3 = Ph
i′ X = O, R^1 = H, $R^2 = OCH_3$, R^3 = Ph
j X = O, $R^1 = R^2 = OCH_3$, R^3 = Ph

Entry	Alkene	Temp/°C	$R^3C{\equiv}CH$ (R^3)	Product yield (%)[a]
1	**1a**	18	$CH_3(CH_2)_2$	**4a** (22) + **5a** (69)
2	**1a**	18	$CH_3(CH_2)_3$	**4b** (29) + **5b** (62)
3	**1a**	18	$CH_3(CH_2)_4$	**4c** (7) + **5c** (61)
4	**1d**	18	$CH_3(CH_2)_2$	**4d** (26) + **5d** (64)
5	**1a**	−5	Ph	**4e** (95)
6	**1d**	10	Ph	**4f** (93)
7	**1a**	18	$-C_6H_9-$	**4g** (95)
8	**1d**	10	$-C_6H_9-$	**4h** (90)
9	**1b**	0	Ph	**4i** + **4i′** (72)
10	**1c**	0	Ph	**4j** (74)

[a] Yields are measured by ^{1}H NMR integration method using norbornene as internal standard.

bornadienes (**1b**, **c**) undergo cocyclotrimerization with alkynes in the presence of $Ni(PPh_3)_2Cl_2$, PPh_3, and zinc powder. The reaction of **1b** with phenylacetylene afforded two regio products **4i** and **4i′** in 72% combined yields, while treatment of **1c** with phenylacetylene gave **4j** in 74% yield. Similar to substrate **1a**–**c**, azabenzonorbornadiene (**1d**) reacted with terminal alkynes hex-1-yne, phenylacetylene and ethyn-1-ylcyclohex-1-ene under similar reaction conditions to afford cocyclotrimerization products **4d** and **5d**, **4f** and **4h** in fair to excellent yields (Table 2).

The nickel-catalyzed [2 + 2 + 2] cocyclotrimerization is successfully extended to bisalkynes. Thus, hepta-1,6-diyne and octa-1,7-diyne reacted with **1a** and **1d** to give novel pentacyclic adducts **6a**–**d** in 62–75% yields (Scheme 4). The facile formation



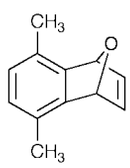
1a X = O n = 1
1d X = NSO_2-*p*-$CH_3C_6H_4$ n = 2

$Ni(PPh_3)_2Cl_2$ | PPh_3, Zn, toluene

6a X = O, n = 1 62 %
6b X = O, n = 2 70 %
6c X = NSO_2-*p*-$CH_3C_6H_4$, n = 1 71 %
6d X = NSO_2-*p*-$CH_3C_6H_4$, n = 2 75 %

Scheme 4

of products **6a**–**d** demonstrates that the present [2 + 2 + 2] cocyclotrimerization is a powerful method for the construction of multiple rings. Although methyl but-2-ynoate also undergoes cocyclotrimerization with **1a** and **1e**, the [2 + 2 + 2] cycloaddition adducts cannot be isolated at temperatures above −10 °C due to thermal instability of these adducts (*vide infra*). Attempts to isolate tetrasubstituted [2 + 2 + 2] adducts from **1a** and disubstituted alkynes such as diphenylacetylene and methyl 3-phenylpropiolate did not succeed either.



1e

In the present [2 + 2 + 2] cocyclotrimerization, the nickel system selectively catalyzes the cotrimerization of an oxa- or azabenzonorbornadiene and two alkyne moieties. Only a trace of the trimerization product of alkyne was observed in each reaction. The replacement of **1** by a less reactive olefin such as hex-1-ene, 2,3-dihydro-2*H*-pyran or cyclohexene did not give the expected [2 + 2 + 2] cotrimerization product.

All of the [2 + 2 + 2] cocyclotrimerization products of **1a**–**d** with terminal alkynes and bisalkynes are completely stereoselective giving only *exo* cyclohexadiene products. No corresponding *endo* products were observed in all of these reactions. The *exo* stereochemistry was established on the basis of the coupling constant of bridgehead proton and *endo* cyclohexadiene proton. It is well known that for norbornene and its derivatives, the coupling constant between an *endo* and a bridgehead proton is nearly zero, while the value between an *exo* and bridgehead proton is *ca.* 3 Hz and can be clearly observed.[18] In the present cyclohexadiene derivatives, all bridgehead protons appeared as singlets in the ^{1}H NMR spectra indicating these derivatives have *exo* stereochemistry.

As proposed in Scheme 2, the [2 + 2 + 2] cocyclotrimerization products **4**–**6** are thermally unstable and undergo retro Diels–Alder reaction to give isobenzofurans or isoindoles and aromatic compounds. The stability of the [2 + 2 + 2] cocyclotrimerization products depends greatly on the substituents

Table 3 Effect of nickel catalysts on the [2+2+2] cocyclotrimerization of oxabenzonorbornadiene with phenylacetylene[a]

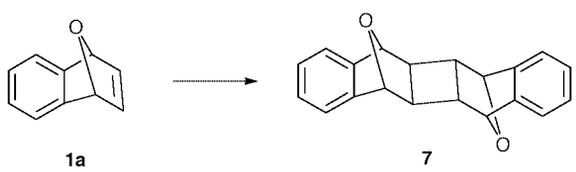
Entry	Ni catalyst/mmol	Products yield (%)[b] 4e	2a	2b	7
1	$NiBr_2$ (0.10), Zn (3.0)	—	—	—	41
2	$Ni(COD)_2$ (0.10)	—	—	—	14
3	$Ni(PPh_3)_4$ (0.050)	—	58	40	—
4	$NiCl_2(PPh_3)_2$ (0.05), PPh_3 (0.8), Zn (3.0)	18	44	26	—
5	$NiCl_2(P^nBu_3)_2$ (0.05), Zn (3.0)	—	—	—	—

[a] Reaction conditions: oxabenzonorbornadiene (0.50 mmol), phenylacetylene (1.0 mmol) and nickel catalyst (see Table 3) in toluene (1.25 ml) at ambient temperature. [b] Yields are based on oxabenzonorbornadiene.

present on the *exo* cyclohexadiene ring. The products with alkyl substituents on the *exo* cyclohexadiene ring are most stable and can be stored at room temperature for a few days in solution and in the solid state for a long time. Compounds **4g** and **4h** with a cyclohex-1-enyl substituent are stable in solution for only a few hours at room temperature. The products with phenyl substituents **4e** and **4f** can be observed only at temperatures below −5 °C. On the other hand, no [2 + 2 + 2] adduct was observed from methyl but-2-ynoate at −5–30 °C.

Effect of ligand on cocyclotrimerization

The [2 + 2 + 2] cocyclotrimerization depends greatly on the phosphine ligand[19] used (Table 3). $Ni(PPh_3)_2Cl_2$–PPh_3–Zn and $Ni(PPh_3)_4$ were found to be the catalysts of choice for the present [2 + 2 + 2] cocyclotrimerization (Table 3, entries 3, 4). The highly basic ligand *n*-Bu_3P strongly retards the reaction (entry 5). The replacement of $Ni(PPh_3)_2Cl_2$ and $Ni(PPh_3)_4$ by $Ni(COD)_2$ and $NiBr_2$–Zn (entries 1 and 2) led to no reaction between **1a** and phenylacetylene, but instead gave homo [2 + 2] dimerization of oxabenzonorbornadiene (**1a**) to yield **7** (Scheme 5).[20]



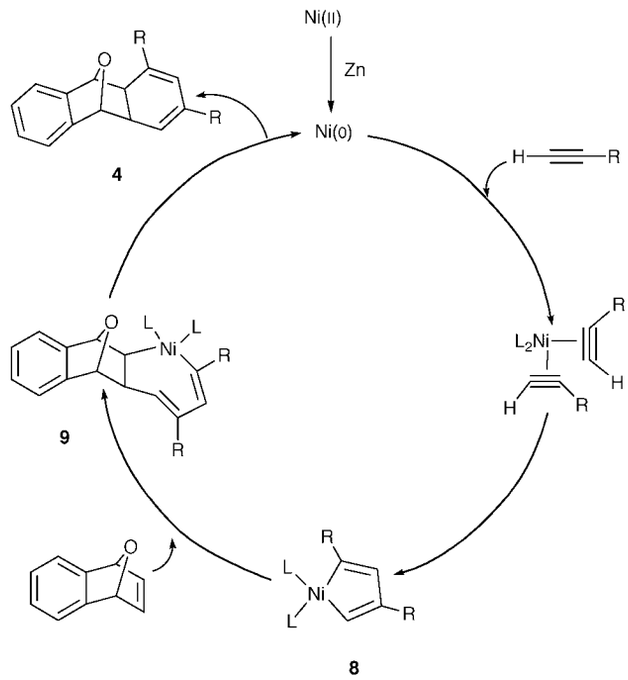
1a **7**

Scheme 5

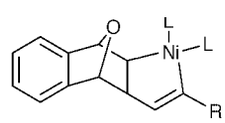
Mechanism of [2 + 2 + 2] cocyclotrimerization

Based on the well established organometallic chemistry of nickel complexes and observed regio- and stereoselectivity of cotrimerization products, a reasonable reaction mechanism for the Ni(0)-catalyzed [2 + 2 + 2] cocyclotrimerization of an oxabenzonorbornadiene and two alkynes is depicted in Scheme 6. The reduction of Ni(II) species to Ni(0) species is followed by coordination of two molecules of alkynes and oxidative cyclometallation to yield a nickelacyclopentadiene intermediate **8**.[21,22] Coordination of an oxabenzonorbornadiene (**1a**) and subsequent insertion into a Ni(II)–carbon bond produces nickelacycloheptadiene intermediate **9**. Reductive elimination of **9** affording product **4** and regenerating Ni(0) completes the catalytic cycle. Alternatively, a mechanism which involves the coordination of an oxa- or azabenzonorbornadiene and an alkyne to Ni(0) to produce a nickelacyclopentene intermediate[23] **8′** followed by insertion of another alkyne into the nickel–carbon bond to give nickelacycloheptadiene intermediate **9** can not be excluded.

It is clear from Scheme 6 that the stereochemistry of [2 + 2 + 2] cycloadducts is determined completely by the coordination of oxa- and azabenzonorbornadienes to the nickel center. The observation of only *exo* [2 + 2 + 2] cycloadducts



Scheme 6

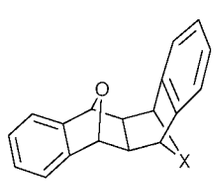


8′

indicates that coordination of the carbon–carbon double bond of oxa- or azabenzonorbornadienes to the nickel center is exclusively *via* the *exo* face. *Exo* selectivity has been observed for palladium or nickel-catalyzed addition of aryl groups to oxa- and azabenzonorbornadienes.[24] The regioselectivity of the diene moiety of [2 + 2 + 2] cycloadducts is determined at the formation of metallacycle **8** and is clearly affected by the substituent of the terminal alkynes used. Alkynes with a linear alkyl group favor the formation of 1,4-substituted metallacycle and thus 1,4-substituted cycloadducts, whereas for alkynes with a bulkier aryl or a cyclohexenyl substituent, 1,3-substituted metallacycle and cycloadducts predominate. The unfavorable formation of 1,4-substituted metallacycle for alkynes with an aryl or a cyclohexenyl substituent is likely due to steric congestion arising from these bulkier substituents with the nickel moiety.

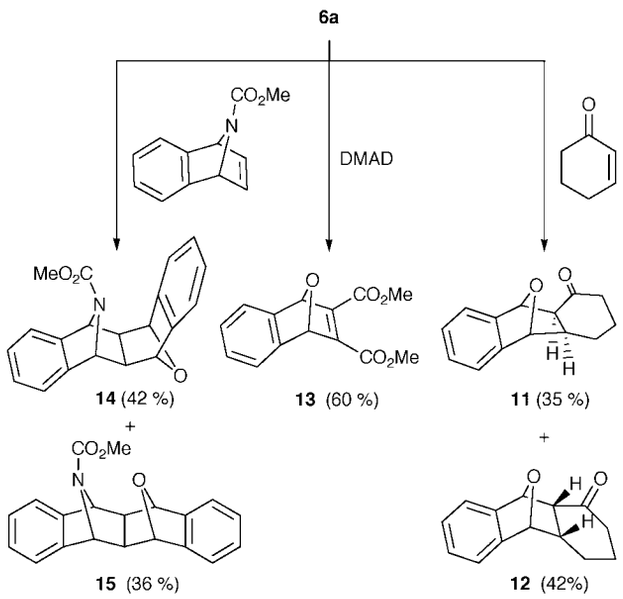
Synthetic application of the [2 + 2 + 2] cycloadducts

In addition to an efficient method for constructing multiple fused rings (Scheme 4), the present [2 + 2 + 2] cycloaddition has two other synthetic applications. First, these products are convenient isobenzofuran and isoindole precursors. For example, heating **6c** and **6d** with **1a** led to the isolation of the Diels–Alder cycloadduct of isoindole **10** in 70% yield. Treatment of **6a** with cyclohex-2-en-1-one, dimethyl acetylenedicarboxylate and *N*-methoxycarbonyl-7-azabenzonorbornadiene, respectively, in toluene at 60 °C afforded the corresponding



10 X = NSO_2-*p*-$CH_3C_6H_4$ (70 %)

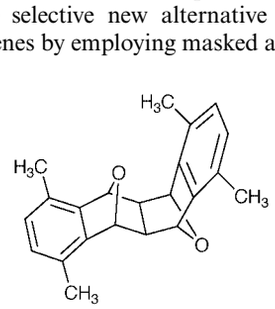
Diels–Alder cycloadducts **11** and **12** (*ca.* 1:1), **13**, and **14** and **15** (*ca.* 1:1) in 77, 60 and 68% combined yields respectively (Scheme 7). Second, the present [2 + 2 + 2] cycloaddition can



Scheme 7

be employed to synthesize aromatic compounds. The cycloaddition of **1a** and **1e** with methyl but-2-ynoate in the presence of the nickel catalyst demonstrates both applications. The reaction of **1a** with methyl but-2-ynoate produced aromatic compound **3** regioselectively and the Diels–Alder cycloadducts **2a** and **2b**. Whereas, the reaction of **1e** with methyl but-2-ynoate provided **3** and exclusively **16** in 94 and 72% yields, respectively. Compounds **1a** and **1e**, which provide an acetylene moiety to each aromatic compound, serve as 'masked acetylene' in the reactions. All new products were characterized by the ^{1}H, ^{13}C NMR, and low and high resolution mass spectral data (see the Experimental section).

In most of the regioselective cotrimerization of alkynes to arenes catalyzed by cobalt complexes, a diyne was used as one component and bistrimethylsilyl acetylene as the other. This generally led to the formation of a mixture of isomers when sterically less-hindered monoalkynes were used.[25] The present [2 + 2 + 2] cycloaddition reactions provide a highly regioselective, and *exo* selective new alternative method for the construction of arenes by employing masked acetylenes.



16

Conclusion

We have observed unusual nickel-catalyzed reactions of oxa- and azabenzonorbornadiene with various alkynes to give common products **2a**, **2b**, and aromatic compounds. These results may be rationalized based on a [2 + 2 + 2] cocyclotrimerization of two alkyne and one oxabenzonorbornadiene molecules. The [2 + 2 + 2] cycloadducts undergo retro Diels–Alder reaction to give aromatic products and isobenzofuran. The latter is then trapped by oxabenzonorbornadiene to give products **2a**, **2b**. We have isolated various [2 + 2 + 2] cycloadducts at low temperatures and have demonstrated that these nickel-catalyzed [2 + 2 + 2] cycloaddition reactions are very useful in the construction of multiple rings, synthesis of precursors of isobenzofurans and isoindoles and regioselective synthesis of substituted aromatic compounds.

Experimental

All reactions were conducted under a nitrogen atmosphere on a dual-manifold Schlenck line by using purified deoxygenated solvents and standard inert atmosphere techniques, unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Me_4Si as internal standard. Alkyl- and aryl-substituted alkynes were used as purchased without further purification. $NiCl_2(PPh_3)_2$,[26] oxabenzonorbornadienes **1a–c** *N*-methoxycarbonyl and *N*-*p*-tolylsulfonyl-7-azabenzonorbornadienes[27] were synthesized according to the reported procedures.

Reaction of methyl but-2-ynoate with oxabenzonorbornadiene (1a) to give 2a, 2b and 3

To a 50 ml round-bottomed side-arm flask was added **1a** (0.144 g, 1.00 mmol), $NiCl_2(PPh_3)_2$ (0.0325 g, 0.0500 mmol), PPh_3 (0.210 g, 0.801 mmol) and zinc powder (0.180 g, 2.75 mmol). The system was evacuated and purged with nitrogen gas three times. To the system was added freshly distilled toluene (2.0 ml) and methyl but-2-ynoate (0.118 g, 1.20 mmol). The reaction mixture was stirred at room temperature for 24 h. The solution was filtered through Celite and silica gel, and the filtrate was concentrated. The residue was separated on a silica gel column using hexanes–dichloromethane as eluent to afford **2a** (0.076 g), **2b** (0.052 g) and **3** (0.245 g) in 58, 40 and 92% yields, respectively. The TLC R_f values of **2a**, **2b** and **3** are 0.62, 0.50 and 0.45, respectively, using hexane–ethyl acetate (v/v = 4/1) as the eluent. Important spectral data of these products are listed below.

(1*R,3*R**,10*S**,12*S**)-19,20-Dioxahexacyclo[10.6.1.1^{3,10}.0^{2,11}.0^{4,9}.0^{13,18}]icosa-4,6,8,13,15,17-hexaene 2a.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 4 H, benzo), 7.08 (m, 4 H, benzo), 5.32 (dd, J = 3.4 Hz, J = 1.8 Hz, 2 H, bridgehead), 4.69 (s, 2 H, bridgehead), 2.80 (dd, J = 3.4 Hz, J = 1.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.97 (s), 143.64 (s), 127.03 (d), 126.42 (d), 119.93 (d), 119.35 (d), 80.21 (d, O–C, bridgehead), 51.00 (d), 50.10 (d); MS: [*m*/*z*, (%)] 262 (M^+, 59.0), 233 (91.1), 215 (91.0), 118 [$(C_8H_6O)^+$, 100]; HRMS: calcd for $C_{18}H_{14}O_2$ 262.0995, found 262.0970.

(1*R,3*S**,10*R**,12*S**)-19,20-Dioxahexacyclo[10.6.1.1^{3,10}.0^{2,11}.0^{4,9}.0^{13,18}]icosa-4,6,8,13,15,17-hexaene 2b.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (dd, J = 5.2 Hz, J = 3.0 Hz, 4 H, benzo), 7.67 (dd, J = 5.3 Hz, J = 3.0 Hz, 4 H, benzo), 5.46 (s, 4 H, bridgehead), 2.06 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.48 (s), 126.57 (d), 119.08 (d), 81.31 (d, O–C, bridgehead), 51.22 (d); MS: [*m*/*z*, (%)] 262 (M^+, 7.2), 233 (5.5), 215 (29.0), 202 (22.7), 189 (8.2), 165 (6.9), 118 [$(C_8H_6O)^+$, 100]; HRMS: calcd for $C_{18}H_{14}O_2$ 262.0995, found 262.000.

Dimethyl 2,4-dimethylisophthaloate 3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, J = 8.0 Hz, 1 H, aromatic H), 7.06 (d, J = 8.0 Hz, 1 H, aromatic H), 3.90 (s, 3 H, $COOCH_3$), 3.85 (s, 3 H, $COOCH_3$), 2.47 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.56 (C=O), 170.11 (C=O), 167.63 (s), 138.72 (s), 136.31 (d), 136.22 (d), 128.04 (s), 127.34 (d), 52.11 (q), 51.88 (q) 19.71 (q), 17.98 (q); MS: [*m*/*z*, (%)] 222 (M^+, 47.2), 207 [$(M - CH_3)^+$, 79.7], 191 [$(M - OCH_3)^+$, 100], 162 [$(M - COOCH_3)^+$, 45.5]; HRMS: calcd for $C_{12}H_{14}O_4$ 222.0893, found 222.0897.

The reaction of **1a** and various alkynes in the presence of $NiCl_2(PPh_3)_2$, PPh_3 and zinc powder also led to the formation

of **2a** and **2b**. The reaction conditions and the yields are listed in Table 1.

A similar procedure was employed for the reaction of **1e** with methyl but-2-ynoate to give **3** and **16** in 94 and 72% yields, respectively. The spectral data of compound **16** follow.

(1*R,3*R**,10*S**,12*S**)-5,8,14,17-Tetramethyl-19,20-dioxahexacyclo[10.6.1.1^{3,10}.0^{2,11}.0^{4,9}.0^{13,18}]icosa-4,6,8,13,15,17-hexaene 16.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91 (s, 2 H, benzo), 6.77 (s, 2 H, benzo), 5.40 (dd, J = 2.97 Hz, J = 1.8 Hz, 2 H, bridgehead), 4.67 (s, 2 H, bridgehead), 2.76 (dd, J = 3.01 Hz, J = 1.7 Hz, 2 H), 2.39 (s, 6 H, 2 × CH_3), 2.23 (s, 6 H, 2 × CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.99 (s), 141.89 (s), 128.28 (d), 127.77 (d), 126.29 (s), 125.81 (s), 78.98 (d, O–C, bridgehead), 76.04 (d, O–C, bridgehead), 49.61 (d), 18.20 (q), 17.95 (q); MS (FAB): [*m*/*z*, (%)] 319 (M + 1, 10.1), 173 ($C_{12}H_{13}O$, 88.3), 146 ($C_{10}H_{10}O$, 100); HRMS (M + 1): calcd for $C_{22}H_{23}O_2$ 319.1698, found 319.1674.

General procedure for the isolation of [2 + 2 + 2] cocyclotrimerization products. To a 50 ml round-bottomed side-arm flask was added an oxa- or azabenzonorbornadiene (1.00 mmol), $NiCl_2(PPh_3)_2$ (0.0325 g, 0.0500 mmol), PPh_3 (0.210 g, 0.801 mmol) and zinc powder (0.180 g, 2.75 mmol). The system was evacuated and purged with nitrogen gas three times. To the system was added freshly distilled toluene (2.0 ml) and an alkyne (mono alkyne, 2.0 mmol; bisalkyne, 1.0 mmol). The reaction mixture was stirred for 24 h at a specified temperature as shown in Table 2. The solution was filtered through Celite and silica gel, and the filtrate was concentrated. The residue was separated on a silica gel column using hexanes–dichloromethane as eluent to afford the [2 + 2 + 2] products. Compounds **5a**–**d** were thus prepared following the above procedure. The corresponding minor isomers **4a**–**d** cannot be separated from **5a**–**d** completely. Due to thermal instability, no purifications on silica gel column were carried out for **4e**, **4i**–**j**. The residues from concentration of the filtrates were used directly for spectral analysis. For compounds **6a**–**d**, the reaction temperature was 18 °C and the reaction time was 48 h. Selected spectral data are listed below:

(1*R,8*S**,9*R**,14*S**)-10,13-Dipropyl-15-oxatetracyclo-[6.6.1.0^{2,7}.0^{9,14}]pentadeca-2,4,6,10,12-pentaene 5a.** Yield 69%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (m, 2 H, benzo), 7.14 (m, 2 H, benzo), 5.47 (br s, 2 H, cyclohexadiene), 5.17 (s, 2 H, O–CH, bridgehead), 2.62 (br s, 2 H, =CH, *endo* cyclohexadiene), 2.08 (t, J = 8.0 Hz, 4 H, CH_2, propyl), 1.46 (m, 4 H, CH_2, propyl), 0.96 (t, J = 9.0 Hz, 6 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.12 (s), 135.64 (s), 126.53 (d), 121.28 (d), 118.88 (d), 86.80 (d, O–C, bridgehead), 41.08 (d), 34.45 (t), 22.26 (t), 13.85 (q); MS: [*m*/*z*, (%)] 280 (M^+, 0.5), 237 [(M − C_3H_7)$^+$, 3.5], 162 [(M − C_8H_6O)$^+$, 17.5], 133 (54.4), 118 ($C_8H_6O^+$, 100); HRMS: calcd for $C_{20}H_{24}O$ 280.1828, found 280.1802.

(1*R,8*S**,9*R**,14*S**)-10,13-Dibutyl-15-oxatetracyclo-[6.6.1.0^{2,7}.0^{9,14}]pentadeca-2,4,6,10,12-pentaene 5b.** Yield 62%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (m, 2 H, benzo), 7.16 (m, 2 H, benzo), 5.47 (br s, 2 H, cyclohexadiene), 5.16 (s, 2 H, O–CH, bridgehead), 2.62 (br s, 2 H, =CH, *endo* cyclohexadiene), 2.11 (t, J = 8.0 Hz, 4 H, CH_2, butyl), 1.39 (m, 8 H, CH_2, butyl), 0.93 (t, J = 9.0 Hz, 6 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.09 (s), 135.90 (s), 126.53 (d), 121.10 (d), 118.90 (d), 86.79 (d, O–C, bridgehead), 41.05 (d), 31.99 (t), 31.49 (t), 22.60 (t), 14.06 (q); MS: [*m*/*z*, (%)] 308 (M^+, 0.6), 190 [(M − C_8H_6O)$^+$, 29.5], 147 (16.8), 118 ($C_8H_6O^+$, 100), 105 (68.4); HRMS: calcd for $C_{22}H_{28}O$ 308.2142, found 308.2143.

(1*R,8*S**,9*R**,14*S**)-10,13-Dipentyl-15-oxatetracyclo-[6.6.1.0^{2,7}.0^{9,14}]pentadeca-2,4,6,10,12-pentaene 5c.** Yield 61%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 2 H, benzo), 7.16 (m, 2 H, benzo), 5.46 (br s, 2 H, cyclohexadiene), 5.16 (s, 2 H, O–CH, bridgehead), 2.61 (br s, 2 H, =CH, *endo* cyclohexadiene), 2.11 (t, J = 8.0 Hz, 4 H, CH_2, pentyl), 1.35 (m, 12 H, CH_2), 0.9 (t, 6 H, J = 9.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.00 (s), 135.97 (s), 125.55 (d), 121.08 (d), 118.92 (d), 86.80 (d, O–C, bridgehead), 41.05 (d), 32.29 (t), 31.89 (t), 29.00 (t), 22.61 (t), 14.11 (q); MS: [*m*/*z*, (%)] 336 (M^+, 0.8), 279 [(M − C_4H_8)$^+$, 16.0], 218 [(M − C_8H_6O)$^+$, 27], 118 ($C_8H_6O^+$, 100); HRMS: calcd for $C_{24}H_{32}O$ 336.2455, found 336.2451.

(1*R,8*S**,9*R**,14*S**)-10,13-Dipropyl-15-[(4-methylphenyl)-sulfonyl]-15-azatetracyclo[6.6.1.0^{2,7}.0^{9,14}]pentadeca-2,4,6,10,12-pentaene 5d.** Yield 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 6.0 Hz, 2 H, tosyl), 6.97–6.90 (m, 6 H, benzo tosyl), 5.38 (br s, 2 H, cyclohexadiene), 4.79 (s, 2 H, N–CH, bridgehead), 2.55 (br s, 2 H, =CH, *endo* cyclohexadiene), 2.26 (s, 3 H, CH_3), 2.05 (m, 4 H, CH_2, propyl), 1.43 (m, 4 H, CH_2, propyl), 0.94 (t, J = 9.0 Hz, 6 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.13 (s), 143.79 (s), 136.42 (s), 135.96 (s), 128.71 (d), 127.74 (d), 126.46 (d), 122.82 (d), 119.94 (d), 71.39 (d, N–C, bridgehead), 43.19 (d), 34.51 (t), 22.47 (t), 21.28 (q), 13.88 (q); MS (FAB): [*m*/*z*, (%)] 334 (M + 1, 3.6), 271 ($C_{15}H_{13}NSO_2^+$, 100), 231 (24.8), 91 (46.1); HRMS (M+1): calcd for $C_{27}H_{32}NSO_2$ 434.2154, found 434.2155.

(1*R,8*S**,9*R**,14*S**)-10,12-Diphenyl-15-oxatetracyclo-[6.6.1.0^{2,7}.0^{9,14}]pentadeca-2,4,6,10,12-pentaene 4e.** Yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (m, 10 H, phenyl), 7.25 (m, 4 H, benzo), 6.70 (br s, 1 H, cyclohexadiene), 6.05 (d, J = 3.6 Hz, 1 H, cyclohexadiene), 5.41 (s, 1 H, O–CH, bridgehead), 5.22 (s, 1 H, O–CH, bridgehead), 3.36 (d, J = 11 Hz, 1 H, *endo* cyclohexadiene), 3.10 (dd, J = 11 Hz, J = 3.6 Hz, 1 H, =CH, *endo* cyclohexadiene); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 146.10 (s), 145.20 (s), 140.80 (s), 135.52 (s), 132.50 (s), 132.48 (s), 129.10 (d), 128.71 (d), 128.25 (d), 128.24 (d), 127.51 (d), 127.48 (d), 127.00 (d), 126.10 (d), 125.90 (d), 125.20 (d), 122.26 (d), 122.10 (d), 118.75 (d), 118.31 (d), 86.62 (d, O–C, bridgehead), 85.52 (d, O–C, bridgehead), 42.60 (d), 42.25 (d); MS: [*m*/*z*, (%)] 262 [(M − $C_{18}H_{14}$)$^+$, 57.9], 230 [(M −C_8H_6O)$^+$, 100], 183 (28.2), 152 (20.9), 118 ($C_8H_6O^+$, 53.2).

(1*R,8*S**,9*R**,14*S**)-10,12-Diphenyl-15-[(4-methylphenyl)-sulfonyl]-15-azatetracyclo[6.6.10^{2,7}.0^{9,14}]pentadeca-2,4,6,10,12-pentaene 4f.** Yield 93%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57–7.31 (m, 12 H, phenyl tosyl), 7.15–6.93 (m, 4 H, benzo), 6.92 (d, J = 8.14 Hz, 2 H, tosyl), 6.57 (s, 1 H, cyclohexadiene), 5.94 (d, J = 4.21 Hz, 1 H, cyclohexadiene), 5.04 (s, 1 H, N–CH, bridgehead), 4.87 (s, 1 H, N–CH, bridgehead), 3.24 (d, J = 11.31 Hz, 1 H, *endo* cyclohexadiene), 3.02 (dd, J = 11.35 Hz, J = 4.25 Hz, 1 H, =CH, *endo* cyclohexadiene), 2.26 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.67 (s), 143.88 (s), 142.75 (s), 140.66 (s), 140.15 (s), 136.35 (s), 136.01 (s), 135.96 (s), 129.15 (d), 128.85 (d), 128.80 (d), 128.76 (d), 128.49 (d), 128.41 (d), 127.79 (d), 127.73 (d), 127.39 (d), 127.22 (d), 126.90 (d), 126.08 (d), 125.87 (d), 125.66 (d), 123.61 (d), 121.32 (d), 120.43 (d), 120.21 (d), 119.60 (d), 71.46 (d, N–C, bridgehead), 69.40 (d, N–C, bridgehead), 43.81 (d), 43.64 (d), 21.33 (q); MS (FAB): [*m*/*z*, (%)] 502 [(M+ 1)$^+$, 4.8], 271 ($C_{15}H_{13}NSO_2^+$, 100), 231 (32.9), 91 ($C_7H_7^+$, 45.4); HRMS (M + 1): calcd for $C_{33}H_{28}NSO_2$ 502.1841, found 502.1815.

(1*R,8*S**,9*R**,14*S**)-10,12-Di(cyclohex-1-enyl)-15-oxatetracyclo[6.6.1.0^{2,7}.0^{9,14}]pentadeca-2,4,6,10,12-pentaene 4g.** Yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 2 H, benzo), 7.18 (m, 2 H, benzo), 6.30 (br s, 1 H, cyclohexadiene), 6.01 (br t, J = 3.9 Hz, 1 H, cyclohexenyl), 5.92 (br t, J = 3.9 Hz, 1 H, cyclohexenyl), 5.74 (d, J = 2.8 Hz, 1 H, cyclohexadiene), 5.33 (s, 1 H, O–CH, bridgehead), 5.28 (s, 1 H, O–CH, bridgehead), 2.89 (s, 1 H, *endo* cyclohexadiene), 2.88 (d, J = 2.8 Hz, 1 H, =CH, *endo* cyclohexadiene), 2.25 (m, 8 H, –CH_2–, cyclohexenyl), 1.66

(m, 8 H, CH_2, cyclohexenyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.74 (s), 145.25 (s), 135.95 (s), 135.27 (s), 135.23 (s), 135.04 (s), 126.68 (d), 126.64 (d), 124.41 (d), 123.07 (d), 119.36 (d), 118.32 (d), 118.24 (d), 117.47 (d), 87.51 (d, O–C, bridgehead), 86.72 (d, O–C, bridgehead), 42.56 (d), 40.71 (d), 26.40 (t), 26.22 (t), 25.78 (t), 22.95 (t), 22.38 (t), 22.25 (t); MS (FAB): [*m*/*z*, (%)] 356 [(M − H)$^+$, 17.9], 255 (87.9), 238 [(M − C_8H_6O)$^+$, 100], 118 ($C_8H_6O^+$, 76.4); HRMS (M − 1): calcd for $C_{26}H_{27}O$ 355.2064, found 355.2058.

(1*R,8*S**,9*R**,14*S**)-10,12-Di(cyclohex-1-enyl)-15-[(4-methylphenyl)sulfonyl]-15-azatetracyclo[6.6.1.0^{2,7}.0^{9,14}]pentadeca-2,4,6,10,12-pentaene 4h.** Yield 90%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, J = 8.1 Hz, 2 H, tosyl), 7.11–6.85 (m, 6 H, benzo tosyl), 6.24 (s, 1 H, cyclohexadiene), 5.99 (br s, 1 H, cyclohexenyl), 5.81 (br s, 1 H, cyclohexenyl), 5.58 (br s, 1 H, cyclohexenyl), 4.84 (s, 1 H, N–CH, bridgehead), 4.76 (s, 1 H, N–CH, bridgehead), 2.82 (br s, 2 H, =CH, *endo* cyclohexadiene), 2.28 (s, 3 H, CH_3), 2.23 (m, 8 H, –CH_2–, cyclohexenyl), 1.66 (m, 8 H, CH_2, cyclohexenyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.20 (s), 138.18 (s), 136.92 (s), 135.98 (s), 135.55 (s), 134.45 (s), 128.77 (d), 127.91 (d), 126.72 (d), 124.22 (d), 123.08 (d), 120.31 (d), 119.14 (d), 118.36 (d), 117.51 (d), 71.55 (d, N–C, bridgehead), 70.26 (d, N–C, bridgehead), 43.17 (d), 41.87 (d), 26.32 (t), 26.21 (t), 25.81 (t), 22.93 (t), 22.88 (t), 22.30 (t), 22.27 (t), 21.38 (q); MS (FAB): [*m*/*z*, (%)] 509 (M$^+$, 2.1), 271 ($C_{15}H_{13}NSO_2^+$, 91.6), 91 (C_7H_7)$^+$; HRMS (FAB): calcd for $C_{33}H_{35}NSO_2$ 509.2388, found 509.2398.

(1*S,8*R**,9*S**,14*R**)-10,12-Diphenyl-3-methoxy-15-oxatetracyclo[6.6.1.0^{2,7}.0^{9,14}]pentadeca-2,4,6,10,12-pentaene 4i and (1*S**,8*R**,9*S**,14*R**)-10,12-diphenyl-6-methoxy-15-oxatetracyclo[6.6.1.0^{2,7}.0^{9,14}]pentadeca-2,4,6,10,12-pentaene 4i′.** Combined yield 72%. The following two sets of spectral data are for compounds **4i** and **4i′**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–6.80 (m, 13 H, phenyl, benzo), 6.70 (s, 1 H, cyclohexadiene), 6.02 (d, J = 4.5 Hz, 1 H, cyclohexadiene), 5.60 (s, 1 H, O–CH, bridgehead), 5.24 (s, 1 H, O–CH, bridgehead), 3.86 (s, 3 H, OCH_3), 3.31 (d, J = 11.5 Hz, 1 H, *endo* cyclohexadiene), 3.11 (dd, J = 11.5 Hz, J = 4.5 Hz, 1 H, =CH, *endo* cyclohexadiene); MS (FAB): [*m*/*z*, (%)] 337 [(M + 1)$^+$, 15.0], 361 [(M − O)$^+$, 16.8], 307 (13.63).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–6.80 (m, 13 H, phenyl, benzo), 6.75 (s, 1 H, cyclohexadiene), 6.10 (d, J = 4.5 Hz, 1 H, cyclohexadiene), 5.52 (s, 1 H, O–CH, bridgehead), 5.38 (s, 1 H, O–CH, bridgehead), 3.86 (s, 3 H, OCH_3), 3.31 (d, J = 11.5 Hz, 1 H, *endo* cyclohexadiene), 3.04 (dd, J = 11.5 Hz, J = 4.5 Hz, 1 H, =CH, *endo* cyclohexadiene); MS (FAB): [*m*/*z*, (%)] 337 [(M + 1)$^+$, 15.0], 361 [(M − O)$^+$, 16.8], 307 (13.63).

(1*S,8*R**,9*S**,14*R**)-3,6-Dimethoxy-10,12-diphenyl-15-oxatetracyclo[6.6.1.0^{2,7}.0^{9,14}]pentadeca-2,4,6,10,12-pentaene 4j.** Yield 74%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (m, 10 H, phenyl), 6.79 (s, 1 H, cyclohexadiene), 6.71 (br s, 2 H, dimethoxybenzo), 6.09 (d, J = 4.4 Hz, 1 H, cyclohexadiene), 5.58 (s, 1 H, O–CH, bridgehead), 5.50 (s, 1 H, O–CH, bridgehead), 3.83 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.32 (d, J = 11.6 Hz, 1 H, *endo* cyclohexadiene), 3.11 (dd, J = 11.6 Hz, J = 4.4 Hz, 1 H, =CH, *endo* cyclohexadiene); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.69 (s), 146.46 (s), 141.72 (s), 141.11 (s), 139.42 (s), 135.67 (s), 135.47 (s), 134.98 (s), 128.74 (d), 128.52 (d), 128.35 (d), 127.34 (d), 127.19 (d), 126.05 (d), 125.82 (d), 125.49 (d), 122.52 (d), 121.89 (d), 85.15 (d, O–C, bridgehead), 84.08 (d, O–C, bridgehead), 56.16 (q, OCH_3), 56.01 (q, OCH_3), 42.84 (d), 41.96 (d); MS: [*m*/*z*, (%)] 408 (M$^+$, 0.1), 230 [(M − $C_{18}H_{14}$)$^+$, 100], 178 [($C_{10}H_{10}O_3$)$^+$, 1.16]; HRMS: calcd for $C_{28}H_{24}O_3$ 408.1725, found 408.1717.

(1*S,2*R**,10*S**,11*R**)-18-Oxapentacyclo[9.6.1.0^{2,10}.0^{4,8}.0^{12,17}]-octadeca-3,8,12,14,16-pentaene 6a.** Yield 62%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (m, 2 H, benzo), 7.15 (m, 2 H, benzo), 5.52 (br s, 2 H, =CH, cyclohexadiene), 5.16 (s, 2 H, O–CH, bridgehead), 2.69 (br s, 2 H, *endo* cyclohexadiene), 2.34 (m, 4 H, 2 × CH_2), 1.77 (m, 1 H), 1.62 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.22 (s), 139.65 (s), 126.54 (d), 118.89 (d), 115.37 (d), 86.62 (d, O–C, bridgehead), 42.03 (d), 31.38 (t), 24.48 (t); MS (FAB): [*m*/*z*, (%)] 236 (M$^+$, 5.1), 154 (16.6), 136 (15.1), 118 [(C_8H_6O)$^+$, (C_9H_{10})$^+$, 100]; HRMS: calcd for $C_{17}H_{16}O$ 236.1201, found 236.1198.

(1*S,2*R**,11*S**,12*R**)-19-Oxapentacyclo[10.6.1.0^{2,11}.0^{4,9}.-0^{13,18}]nonadeca-3,9,13,15,17-pentaene 6b.** Yield 70%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (m, 2 H, benzo), 7.13 (m, 2 H, benzo), 5.39 (br s, 2 H, =CH, cyclohexadiene), 5.15 (s, 2 H, O–CH, bridgehead), 2.62 (br s, 2 H, *endo* cyclohexadiene), 2.26 (m, 4 H, 2 × CH_2), 1.57 (m, 4 H, 2 × CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.09 (s), 133.59 (s), 126.54 (d), 119.95 (d), 118.89 (d), 86.63 (d, O–C, bridgehead), 41.28 (d), 29.83 (t), 23.13 (t); MS (FAB): [*m*/*z*, (%)] 250 (M$^+$, 9.4), 233 (22.3), 132 [(M − C_8H_6O)$^+$, 8.2], 118 [(C_8H_6O)$^+$, 100]; HRMS: calcd for $C_{18}H_{18}O$ 250.1357, found 250.1363.

(1*S,2*R**,10*S**,11*R**)-18-[(4-Methylphenyl)sulfonyl]-18-azapentacyclo[9.6.1.0^{2,10}.0^{4,8}.0^{12,17}]octadeca-3,8,12,14,16-pentaene 6c.** Yield 71%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (d, J = 8.23 Hz, 2 H, tosyl H), 6.99–6.91 (m, 6 H, aromatic), 5.43 (br s, 2 H, =CH, cyclohexadiene), 4.78 (s, 2 H, N–CH, bridgehead), 2.61 (br s, 2 H, *endo* cyclohexadiene H), 2.31 (m, 4 H, 2 × CH_2), 2.27 (s, 3 H, CH_3), 1.76 (m, 1 H), 1.64 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.39 (s), 142.64 (s), 140.43 (s), 136.05 (s), 128.75 (d), 127.82 (d), 126.56 (d), 119.86 (d), 114.59 (d), 70.90 (d, N–C, bridgehead), 42.87 (d), 31.41 (t), 24.54 (t), 21.36 (q); MS (FAB): [*m*/*z*, (%)] 390 (M + 1, 6.7), 271 ($C_{15}H_{13}NSO_2^+$, 100), 155 (25.4), 91 (45.4); HRMS (M+1): calcd for $C_{24}H_{24}NSO_2$ 390.1528, found 390.1518.

(1*S,2*R**,11*S**,12*R**)-19-[(4-Methylphenyl)sulfonyl]-19-azapentacyclo[10.6.1.0^{2,11}.0^{4,9}.0^{13,18}]nonadeca-3,9,13,15,17-pentaene 6d.** Yield 75%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, J = 8.27 Hz, 2 H, tosyl H), 7.01–6.92 (m, 6 H, aromatic), 5.32 (br s, 2 H, =CH, cyclohexadiene), 4.79 (s, 2 H, N–CH, bridgehead), 2.57 (br s, 2 H, *endo* cyclohexadiene H), 2.28 (s, 3 H, CH_3), 2.25 (m, 4 H, 2 × CH_2), 1.59 (m, 4 H, 2 × CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.62 (s), 142.65 (s), 135.61 (s), 134.38 (s), 128.76 (d), 127.76 (d), 126.54 (d), 119.83 (d), 119.06 (d), 70.88 (d, N–C, bridgehead), 42.08 (d), 29.77 (t), 23.03 (t), 21.34 (q); MS (FAB): [*m*/*z*, %)] 404 (M + 1, 3.3), 271 ($C_{15}H_{13}NSO_2^+$, 100), 155 (23.5), 91 (47.7); HRMS (M+1): calcd for $C_{25}H_{26}NSO_2$ 404.1684, found 404.1675.

Diels–Alder cycloaddition of *in situ* generated isobenzofuran or isoindole with 1a. To a 50 ml round-bottomed side-arm flask consisting of **6c** (or **6d**) (0.0720 mmol) and **1a** (0.0104 g, 0.0720 mmol) was added freshly distilled xylene (5.0 ml). The system was evacuated and purged with nitrogen gas three times. The reaction mixture was then heated at 90 °C for 7.5 h. The solvent was removed under vacuum and the resulting solid was purified by silica gel column using a mixture of hexanes–ethyl acetate (v/v = 7/3) as eluent to give **10** in 70% yield.

(1*S,3*S**,10*R**,12*R**)-20-[(4-Methylphenyl)sulfonyl]-19-oxa-20-azahexacyclo[10.6.1.1^{3,10}.0^{2,11}.0^{4,9}.0^{13,18}]icosa-4,6,8,13,15,17-hexaene 10.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, J = 7.6 Hz, 2 H, tosyl H), 7.12 (m, 4 H, benzo), 7.07 (m, 4 H, benzo), 6.94 (d, J = 6.4 Hz, 2 H, tosyl H), 5.07 (br s, 2 H, O–CH, bridgehead), 4.66 (s, 2 H, N–CH, bridgehead), 2.95 (br s, 2 H), 2.27 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.13 (s), 142.84 (s), 141.24 (s), 136.26 (s), 129.85 (d), 128.92 (d), 127.82 (d), 127.35 (d), 126.87 (d), 126.67 (d), 120.43 (d), 118.94 (d), 77.69 (d, C–O,

bridgehead), 65.42 (d, N–C, bridgehead), 49.26 (d), 21.33 (q); MS (FAB): [*m*/*z*, (%)] 416 [(M + 1)$^+$, 28.8], 272 (85.9), 271 (100), 245 (72.5), 91(75.2); HRMS (M + 1): calcd for $C_{25}H_{22}NSO_3$ 416.1320, found 416.1352.

Similarly, **11** and **12**, **13** and **14** and **15** were prepared by reacting **6a** with cyclohex-2-en-1-one, dimethyl acetylenedicarboxylate and *N*-methoxycarbonyl-7-azabenzonorborndiene at 60 °C in toluene for 3 h. The combined yields of these products is 77, 60 and 68%. Selected spectral data of these products follow.

(1*S,2*S**,7*R**,8*R**)-15-Oxatetracyclo[6.6.1.0^{2,7}.0^{9,14}]-pentadeca-9,11,13-trien-3-one 11.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 2 H, benzo), 7.17 (m, 2 H, benzo), 5.75 (s, 1 H, O–CH, bridgehead), 5.12 (br s, 1 H, O–CH, bridgehead), 2.44–2.27 (m, 4 H, CH & CH_2), 2.19 (m, 1 H), 2.00 (m, 1 H), 1.72 (m, 1 H), 1.56 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.53 (C=O, s), 145.33 (s), 144.43 (s), 126.86 (d), 126.77 (d), 119.27 (d), 118.99 (d), 84.27 (d, C–O, bridgehead), 81.91 (d, C–O, bridgehead), 51.97 (d), 42.38 (d), 38.98 (t), 27.92 (t), 20.59 (t).

(1*S,2*R**,7*S**,8*R**)-15-Oxatetracyclo[6.6.1.0^{2,7}.0^{9,14}]pentadeca-9,11,13-trien-3-one 12.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.15 (m, 4 H, benzo), 5.59 (d, J = 5.5 Hz, 1 H, O–CH, bridgehead), 5.33 (d, 1 H, J = 4.9 Hz, O–CH, bridgehead), 3.15 (m, 1 H, CH), 2.99 (m, 1 H, CH), 2.06 (m, 1 H, CH), 2.00 (m, 1 H), 1.49–1.29 (m, 2 H, CH_2), 0.91 (m, 1 H), 0.67 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.5 (C=O, s), 143.75 (s), 143.19 (s), 127.05 (d), 126.68 (d), 121.81 (d), 120.98 (d), 83.24 (d, C–O, bridgehead), 80.77 (d, C–O, bridgehead), 50.69 (d), 39.92 (t), 38.49 (d), 24.38 (t), 20.24 (t).

Dimethyl 11-oxatricyclo[6.2.1.0^{2,7}]undeca-2,4,6,9-tetraene-9,10-dicarboxylate 13. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (m, 2 H, benzo), 7.07 (m, 2 H, benzo), 5.97 (s, 2 H, O–CH, bridgehead), 3.81 (s, 6 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.78 (C=O, s), 151.19 (s), 146.12 (s), 126.12 (d), 121.48 (d), 84.79 (d, C–O, bridgehead), 52.38 (d).

Methyl (1*S,2*S**,3*S**,10*R**,11*R**,12*R**)-19-oxa-20-azahexacyclo[10.6.1.1^{3,10}.0^{2,11}.0^{4,9}.0^{13,18}]icosa-4,6,8,13,15,17-hexaene-20-carboxylate 14.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (m, 4 H, benzo), 7.04 (m, 4 H, benzo), 5.38 (dd, J = 3.5 Hz, J = 1.9 Hz, 2 H, O–CH, bridgehead), 4.67 (s, 2 H, N–CH, bridgehead), 3.68 (s, 3 H, OCH_3), 2.69 (dd, J = 3.4 Hz, J = 1.9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.68 (C=O, s), 147.27 (s), 145.72 (s), 127.40 (d), 126.63 (d), 119.65 (d), 119.32 (d), 81.09 (d, C–O, bridgehead), 62.58 (d, C–N, bridgehead), 52.12 (d), 51.82 (q); MS (FAB): [*m*/*z*, (%)] 319 (M$^+$, 8.3), 320 (M + 1, 68.3), 245 (41.8), 175 (100), 118 (C_8H_6O, 40.8); HRMS (M + 1): calcd for $C_{20}H_{18}NO_3$ 320.1286, found 320.1273.

Methyl (1*R,2*S**,3*S**,10*R**,11*R**,12*S**)-19-oxa-20-azahexacyclo[10.6.1.1^{3,10}.0^{2,11}.0^{4,9}.0^{13,18}]icosa-4,6,8,13,15,17-hexaene-20-carboxylate 15.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (m, 4 H, benzo), 7.03 (m, 4 H, benzo), 5.25 (s, 2 H, O–CH, bridgehead), 4.57 (s, 2 H, N–CH, bridgehead), 3.19 (s, 3 H, OCH_3), 1.97 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.64 (C=O, s), 146.20 (s), 145.48 (s), 127.22 (d), 126.42 (d), 120.23 (d), 119.49 (d), 80.21 (d, C–O, bridgehead), 50.72 (d, C–N, bridgehead), 51.03 (q), 49.62 (d); MS (FAB): [*m*/*z*, (%)] 320 (M + 1, 68.3), 176 (96.40), 175 (100), 118 (C_8H_6O, 40.5); HRMS (M + 1): calcd for $C_{20}H_{18}NO_3$ 320.1286, found 320.1268.

Acknowledgements

We are grateful to the National Science Council of the Republic of China for financial support of this research (NSC 87-2811-M-007-0042). TS thanks NSC for a Post Doctoral fellowship.

References

1 W. Friedrichsen, *Adv. Heterocycl. Chem.*, 1980, **26**, 135; B. Rickborn, *Isobenzofurans* in *Advances in Theoretically Interesting Molecules*, ed. R. P. Thummel, JAI Press, Greenwich, CT, 1989, vol. 1, ch. 1; W. Friedrichsen, in *Houben-Weyl*, *Methoden der Organischen Chemie*, ed. R. Kreher, Thieme Verlag, Stuttgart, 1994, vol. E6b, pp. 163–216.
2 P. Vogel, D. Fattori, F. Gasparini and C. Le Drian, *Synlett*, 1990, **56**, 2128; P. Renaud and J.-P Vionnet, *J. Org. Chem.*, 1993, **58**, 5895; T. A. Eggette, H. de Koning and H. O. Huisman, *J. Chem. Soc., Perkin Trans. 1*, 1978, 980; G. Just and S. Kim, *Tetrahedron Lett.*, 1976, 1063.
3 A. Padwa, C. O. Kappe and T. S. Reger, *J. Org. Chem.*, 1996, **61**, 4888.
4 A. Padwa, C. O. Kappe, J. E. Cochran and J. P. Snyder, *J. Org. Chem.*, 1997, **62**, 2786.
5 Y.-M. Man, T. C. W. Mak and H. N. C. Wong, *J. Org. Chem.*, 1990, **55**, 3214; R. N. Warrener, D. N. Butler, W. Y. Liao, I. G. Pitt and R. A. Russsell, *Tetrahedron Lett.*, 1991, **32**, 1889; H. Takeshita, A. Mori, S. Sugiyama and T. Tsuda, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 3988; C. W. Chan and H. N. C. Wong, *J. Am. Chem. Soc.*, 1988, **110**, 462; K. Blatter and A.-D. Schlueter, *Chem. Ber.*, 1989, **122**, 1351; H. Takeshita, Y. J. Yan, N. Kato, A. Mori and T. Nozoe, *Tetrahedron Lett.*, 1995, **36**, 5195; R. N. Warrener, S. Wang, D. N. Butler and R. A. Russell, *Synlett*, 1997, **1**, 44.
6 C. S. LeHoullier and G. W. Gribble, *J. Org. Chem.*, 1983, **48**, 1682; J. R. Malpass, G. Sun, J. Fawcett and R. N. Warrener, *Tetrahedron Lett.*, 1998, **39**, 3083.
7 L. F. Fieser and M. J. Haddadin, *J. Am. Chem. Soc.*, 1964, **86**, 2081; L. F. Fieser and M. J. Haddadin, *Can. J. Chem.*, 1965, **43**, 1599; R. N. Warrener, *J. Am. Chem. Soc.*, 1971, **93**, 2346; J. Luo and H. Hart, *J. Org. Chem.*, 1989, **54**, 1762; S. E. Whitney, M. Winters and B. Rickborn, *J. Org. Chem.*, 1990, **55**, 929.
8 G. M. Priestley and R. N. Warrener, *Tetrahedron Lett.*, 1972, 4295.
9 K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 539; M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, **96**, 49; I. Ojima, M. Tzamarioudaki, Z. Li and R. J. Donovan, *Chem. Rev.*, 1996, **96**, 635.
10 S. H. Lecker, N. H. Nguen and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 1986, **108**, 856; E. Negishi, L. S. Harring, Z. Owczarczyk, M. M. Mohamud and M. Ay, *Tetrahedron Lett.*, 1992, **33**, 3253; H. E. Helson, K. P. C. Vollhardt and Z.-Y. Yang, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 114; R. Grigg, R. Scott and P. Stevenson, *Tetrahedron Lett.*, 1982, **23**, 2691.
11 N. E. Schore, *Chem. Rev.*, 1988, **88**, 1081; B. M. Trost, *Science*, 1996, **96**, 49.
12 A. J. Chalk, *J. Am. Chem. Soc.*, 1972, **94**, 5928; H. Suzuki, K. Itoh, Y. Ishii, K. Simon and J. A. Ibers, *J. Am. Chem. Soc.*, 1976, **98**, 8494; E. D. Sternberg and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 1980, **102**, 4841; E. D. Sternberg and K. P. C. Vollhardt, *J. Org. Chem.*, 1984, **49**, 1574; G. J. Balaich and I. P. Rothwell, *J. Am. Chem. Soc.*, 1993, **115**, 1581; F. Slowinski, C. Aubert and M. Malacria, *Tetrahedron Lett.*, 1999, **40**, 707.
13 R. Grigg, R. Scott and P. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1365; Z. Zhou, L. P. Battaglia, G. P. Chiusoli, M. Costa, M. Nardelli, C. Pelizzi and G. Predieri, *J. Chem. Soc., Chem. Commun.*, 1990, 1632; Z. Zhou, M. Costa and G. P. Chiusoli, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1399; Y. Yamamoto, H. Kitahara, R. Ogawa and K. Itoh, *J. Org. Chem.*, 1998, **63**, 9610.
14 T.-Y. Hsiao, K. C. Santhosh, K.-F. Liou and C.-H. Cheng, *J. Am. Chem. Soc.*, 1998, **120**, 12232.
15 T. Sambaiah, L.-P. Li, D.-J. Huang, C.-H. Lin, D. K. Rayabarapu and C.-H. Cheng, *J. Org. Chem.*, 1999, **64**, 3663.
16 S. Ikeda, N. Mori and Y. Sato, *J. Am. Chem. Soc.*, 1997, **119**, 4779; S. Ikeda, H. Watanabe and Y. Sato, *J. Org. Chem.*, 1998, **63**, 7026; N. Mori, S. Ikeda and Y. Sato, *J. Am. Chem. Soc.*, 1999, **121**, 2722.
17 For preliminary communication see: D.-J. Huang, T. Sambaiah and C.-H. Cheng, *New J. Chem.*, 1998, **22**, 1147.
18 C. D. Smith, *J. Am. Chem. Soc.*, 1966, **88**, 4273; J. Meinwald, J. C. Meinwald and T. N. Baker, *J. Am. Chem. Soc.*, 1964, **86**, 4074.
19 T. Tsuda, S. Morikawa, R. Sumiya and T. Saegusa, *J. Org. Chem.*, 1988, **53**, 3140; T. Tsuda, R. Sumiya and T. Saegusa, *Synth. Commun.*, 1987, **17**, 147.
20 D.-J. Huang and C.-H. Cheng, *J. Organomet. Chem.*, 1995, **490**, C1.
21 J. J. Eisch and J. E. Galle, *J. Organomet. Chem.*, 1975, **96**, C23; J. J. Eisch, A. M. Piotrowski, K. I. Han, C. Kruger and Y. H. Tsay, *Organometallics*, 1985, **4**, 224. For production of a cobaltacyclopentadiene complex, see: Y. Wakatsuki, O. Nomura, K. Kitaura,

K. Morokuma and H. Yamazaki, *J. Am. Chem. Soc.*, 1983, **105**, 1907.
22 D. R. McAlister, J. E. Bercaw and R. G. Bergman, *J. Am. Chem. Soc.*, 1977, **99**, 1666.
23 For production of cobaltacyclopentene complex, see: Y. Wakatsuki, K. Aoki and H. Yamazaki, *J. Am. Chem. Soc.*, 1974, **96**, 5284; Y. Wakatsuki, K. Aoki and H. Yamazaki, *J. Am. Chem. Soc.*, 1979, **101**, 123.
24 J.-P. Duan and C.-H. Cheng, *Tetrahedron Lett.*, 1993, **34**, 4019; J.-P. Duan and C.-H. Cheng, *Organometallics*, 1995, **14**, 1608; C.-C. Feng, M. Nandi, T. Sambaiah and C.-H. Cheng, *J. Org. Chem.*, 1999, **64**, 3538.
25 L. S. Hegedus, in *Transition Metals in the Synthesis of Complex Organic Molecules*, University Science Books, Mill Valley, California, 1994, ch. 8, pp. 248–255.
26 H. M. Colquhoun, D. J. Thompson and M. V. Twigg, *Carbonylation*, Plenum Press, New York, 1991; H. M. Colquhoun, J. Holton, D. J. Thompson and M. V. Twigg, *New Pathways For Organic Synthesis-Practical Applications of Transition Metals*, Plenum Press, New York, 1988.
27 G. M. L. Cragg, R. G. F. Giles and G. H. P. Roos, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1339.

Paper a907654i