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Palladium-catalyzed approaches to indenes

by

Daohua Zhang

A thesis submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

Major: Organic Chemistry

Program of Study Committee:
Richard C. Larock (Major Professor)
George A. Kraus
John D. Corbett

Iowa State University

Ames, Iowa

2002

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Graduate College
Iowa State University

This is to certify that the master's thesis of

Daohua Zhang

has met the thesis requirements of Iowa State University

Signatures have been redacted for privacy

To my parents and wife,

for their love, patience, support and encouragement.

TABLE OF CONTENTS

LIST OF ABBREVIATION

Ac	acetyl
aq	aqueous
br	broad
Bu	butyl
cat	catalytic
d	day(s)
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
eq	equation
equiv	equivalent(s)
Et	ethyl
EtOAc	ethyl acetate
g	gram(s)
h	hour(s)
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
Me	methyl
min	minutes
mL	milliliter(s)
mol	mole(s)
mp	melting point
n	normal

NMR	nuclear magnetic resonance
Ph	phenyl
Pr	propyl
q	quartet
s	singlet
t	tertiary
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography

GENERAL INTRODUCTION

The development of new synthetic methods utilizing palladium catalysts is one of the most interesting areas in modern organic chemistry. In recent years, a wide variety of palladium-catalyzed reactions has been developed and applied to the synthesis of various organic compounds. These reactions have proven to be general in scope and often react with a high degree of regio- and stereospecificity. The encouraging development of organo-palladium chemistry has inspired us to develop new synthetic methods directed towards the synthesis of carbocycles using palladium catalysts. In this thesis three new methods have been developed to synthesize indenes by the palladium-catalyzed carboannulation of alkynes.

Thesis Organization

This thesis is divided into three chapters. Each chapter is presented with its own introduction, results and discussion, conclusions, experimental section and references. Following the third chapter is a general conclusion. The author of this manuscript has been the primary investigator for all papers reported in this thesis.

Chapter 1 describes the synthesis of indenes by the palladium-catalyzed carboannulation of internal alkynes by various aryl halides. The annulation proceeds under relatively mild reaction conditions and gives fair to good yields of indenes with high regioselectivity for unsymmetrical internal alkynes.

Chapter 2 reports the synthesis of indenes by the palladium-catalyzed coupling of terminal alkynes and aryl halides, followed by a copper-catalyzed intramolecular cyclization. This two-step annulation procedure has proven to be quite general for the synthesis of indenes from terminal alkynes bearing a variety of substituents.

Chapter 3 presents a new method for the synthesis of indenes by the palladium-catalyzed arylation of arylalkynes. This procedure, which involves cyclization and arylation in a single step, provides a convenient means of synthesizing indenes in high yields. This reaction also tolerates considerable functionality.

CHAPTER 1. SYNTHESIS OF INDENES BY THE PALLADIUM-CATALYZED CARBOANNULATION OF INTERNAL ALKYNES

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Abstract

A number of highly substituted indenes have been prepared in good yields by treating functionalized aryl halides with various internal alkynes in the presence of a palladium catalyst. The reaction is believed to proceed by regioselective arylpalladation of the alkyne and subsequent nucleophilic displacement of the palladium in the resulting vinylpalladium intermediate.

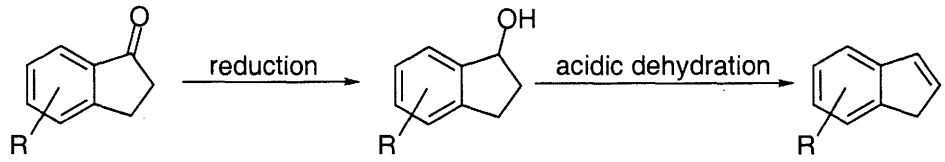
Introduction

Various indene derivatives have been used for regulating apoptosis,[1] or as endothelin receptor antagonists,[2] and inhibitors of human nonpancreatic secretory phospholipase.[3] Crixivan, an AIDS drug developed by Merck, contains an indane moiety, which can be generated from an indene precursor.[4] Indenes are also effective ligand systems for metallocene complexes, which act as highly active catalysts in olefin polymerization.[5] Furthermore, water swellable polymers useful in cosmetics and latexes are prepared from indene, maleic anhydride and divinylbenzene.[6]

Indenes have been generally prepared from the corresponding indanones (Scheme 1).[7] In this process an indanone is converted to the corresponding indanol by a reducing agent ($NaBH_4$, $LiAlH_4$ or KBH_4). The indanol is then transformed to the corresponding indene by dehydration. Acid catalysts, such as acetic acid, *p*-toluenesulfonic acid, HCl, H_2SO_4 and

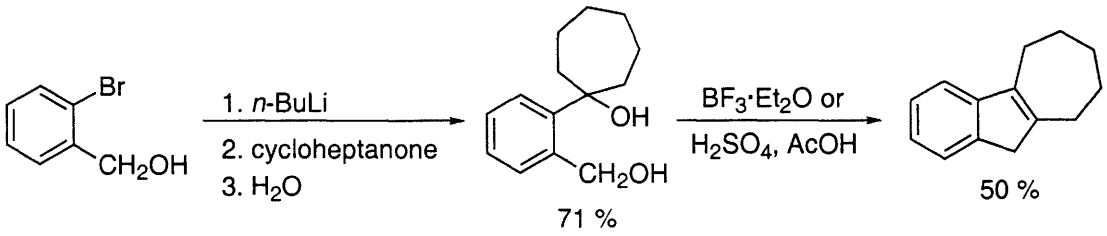
$KHSO_4$ are generally used in the dehydration step. The required indanones are usually prepared by cyclization of 3-arylalkanoic acids resulting from Reformatsky, Perkin, or Friedel-Crafts routes.[8] However, this general approach to indenes consists of several steps with low overall yields and possesses limited flexibility for the preparation of substituted indene derivatives.

Scheme 1



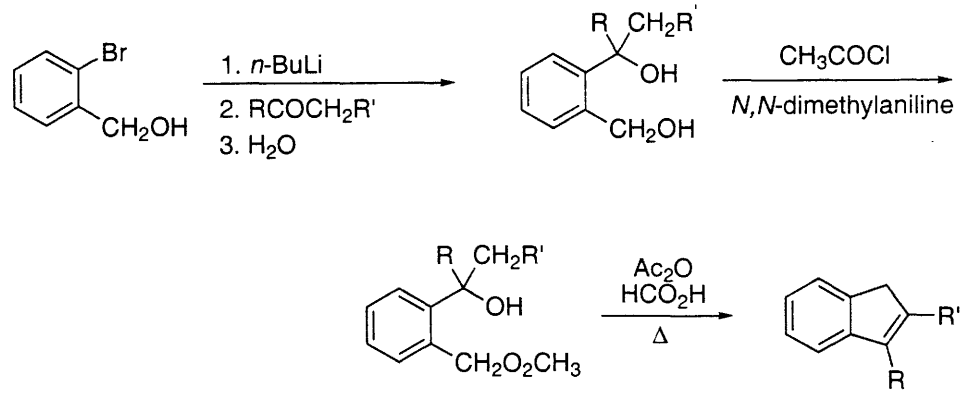
Parham and Egberg have reported an indene synthesis starting from readily available *o*-bromobenzyl alcohol that involves the formation of diols, which are converted to indenes by the action of protonic acids (Scheme 2).[9] Although this method is generally useful for preparing fused indenes, efforts to extend this chemistry to simple indenes resulted in low yields when acyclic ketones were employed.

Scheme 2



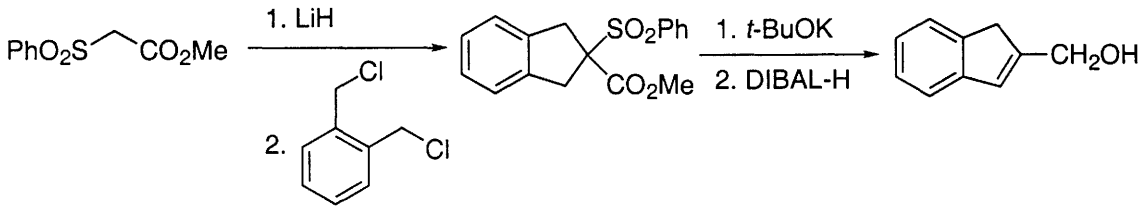
Parham later described an improved synthesis of indenes, which involves heating a monoacetate intermediate with hot acetic anhydride and formic acid (Scheme 3).[10] Acyclic indenes can be prepared by this procedure in moderate yields. Nevertheless, this method is not applicable to the preparation of indenes that are unstable to high reaction temperatures and a strong acid medium.

Scheme 3



Palandoken, McMillen and Nantz have reported a [4 + 1] approach to 2-substituted indenes from commercially available methyl phenylsulfonylacetate (Scheme 4).[11] Although the overall yield is reasonable (77 %), this procedure requires long reaction times and low reaction temperatures and is limited to the preparation of 2-substituted indenes.

Scheme 4

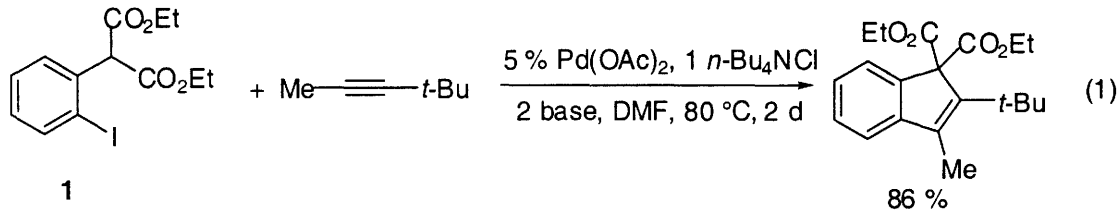


Indenes have also been prepared by the cyclization of phenyl-substituted allylic alcohols,[12] the ring expansion of substituted cyclopropenes,[13] and the solvolysis of alkynyl-amines in formic acid.[14] All these routes are of limited scope due to the strong acid medium, a long reaction sequence, and low tolerance of functionality. All these drawbacks have prompted us to develop a general synthesis of indenes utilizing palladium-catalyzed annulation methodology.

The palladium-catalyzed annulation of internal alkynes has proven to be a powerful method for the construction of a variety of carbo- and heterocycles.[15] For example, we have successfully employed this annulation chemistry for the synthesis of indoles,[16] benzofurans,[17]

isocoumarins,[18] isoquinolines,[19] indenones[20] and polycyclic aromatic hydrocarbons.[21] The palladium-catalyzed synthesis of carbo- and heterocycles has tremendous advantages over traditional annulation methods. For example, only catalytic amounts of palladium are employed, and the palladium catalyst is quite stable to air and moisture. Furthermore, the base-promoted Pd-catalyzed annulation of alkynes is especially useful for preparing acid-sensitive substances, such as indenes.[22]

During the course of earlier investigations of the palladium-catalyzed carboannulation of internal alkynes, Larock and Yum developed a new method of indene synthesis by the carboannulation of internal alkynes using aryl halides (eq 1).[23] For instance, in the presence of 5 mol % $Pd(OAc)_2$, 2 equiv of KOAc, and 1 equiv of *n*-Bu_4NCl in DMF at 80 °C, the reaction of diethyl (2-iodophenyl)malonate **1** with 4,4-dimethyl-2-pentyne affords an 86 % yield of the desired indene product after 2 d. Herein we wish to report the results of our continuing study of the carboannulation of internal alkynes by functionalized aryl halides.



1

Results and Discussion

Initial studies were aimed at finding the optimal reaction conditions for the palladium-catalyzed carboannulation of internal alkynes. Our investigation began with the reaction of diethyl (2-iodophenyl)malonate **1** and 4,4-dimethyl-2-pentyne, and the results are summarized in Table 1. Some of the experiments were performed by a former group member, Eul Kgun Yum.

The reaction was first attempted using diethyl (2-iodophenyl)malonate (**1**, 0.25 mmol), 5 equiv of 4,4-dimethyl-2-pentyne, 5 mol % of $Pd(OAc)_2$ as the catalyst, 1 equiv of *n*-BuN_4Cl,

and 2 equiv of KOAc in 1 mL of DMF at 80 °C (Table 1, entry 1). This reaction provided a moderate yield of the desired product with a small amount of material which appeared to arise by multiple insertion of the alkyne. To minimize the formation of the multiple-insertion products, the concentration of the reactants was lowered. The reaction furnished an 86 % yield of the carboannulation product without any side products, but the reaction required a longer reaction time (Table 1, entry 2).

Using 5 mol % of PPh_3 as a ligand in this reaction did not increase the yield of the desired product (Table 1, entry 3). The use of other inorganic bases, such as K_2CO_3 and Na_2CO_3, drastically reduced the yield of the desired product (Table 1, entries 4 and 5). The use of an organic base, such as triethylamine, afforded only a small amount of the desired product (Table 1, entry 6).

We also explored the effect of different palladium catalysts on the outcome of the reaction. $Pd(OAc)_2$ gave the best result based on our investigation (Table 1, entries 2 and 7-10). LiCl was examined as an alternative to *n*-Bu_4NCl, and the yield was comparable to the corresponding reaction using *n*-Bu_4NCl (Table 1, entry 11). When less than 5 equiv of 4,4-dimethyl-2-pentyne were used, the reactions were slower, and the yields were lower compared to the reaction with 5 equiv of 4,4-dimethyl-2-pentyne (Table 1, entries 12-14).

On the basis of the above optimization efforts, the combination of diethyl (2-iodophenyl) malonate **1** (0.25 mmol), 5 equiv of internal alkyne, 5 mol % of $Pd(OAc)_2$, 1 equiv of *n*-Bu_4NCl, and 2 equiv of KOAc in 5 mL of DMF at 80 °C for 2 days gave the best result (Table 1, entry 2).

Table 1. Optimization of the palladium-catalyzed carboannulation of 4,4-dimethyl-2-pentyne by diethyl (2-iodophenyl)malonate 1 (eq 1).[a]

entry	acetylene equiv	base	Pd catalyst	yield (%)
1[b,c,f]	5	KOAc	$Pd(OAc)_2$	49
2[f]	5	KOAc	$Pd(OAc)_2$	86
3[d,f]	5	KOAc	$Pd(OAc)_2$	85
4[f]	5	K_2CO_3	$Pd(OAc)_2$	49
5[f]	5	Na_2CO_3	$Pd(OAc)_2$	42
6	5	NEt_3	$Pd(OAc)_2$	22
7	5	KOAc	$PdCl_2$	46
8	5	KOAc	$PdCl_2(PPh_3)_2$	62
9	5	KOAc	$Pd(PPh_3)_4$	63
10	5	KOAc	$Pd_2(dba)_3{\cdot}CHCl_3$	55
11[e,f]	5	KOAc	$Pd(OAc)_2$	85
12[f]	4	KOAc	$Pd(OAc)_2$	85
13[f]	3	KOAc	$Pd(OAc)_2$	73
14[f]	2	KOAc	$Pd(OAc)_2$	60

[a] All reactions were run on a 0.25 mmol scale in 5 mL of DMF at 80 °C for 2 d unless otherwise noted. [b] 1 ML of DMF was used. [c] 1 D reaction time. [d] 5 Mol % of PPh_3 was added. [e] LiCl was used instead of *n*-Bu_4NCl. [f] Yum's result.

Having gained an understanding of the factors that influence the carboannulation process, we explored the scope and limitation of this annulation methodology. Further carboannulation results are summarized in Table 2. Some of the experiments were performed by a former group member, Eul Kgun Yum.

Table 2. Palladium-catalyzed carboannulation of internal alkynes by aryl halides.[a]

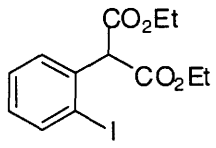
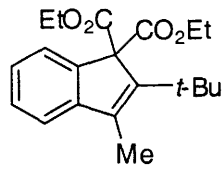
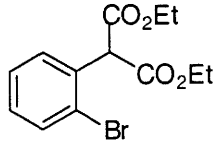
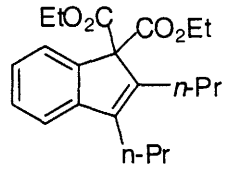
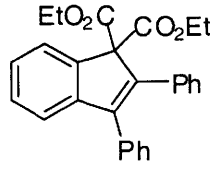
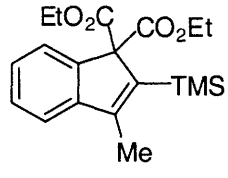
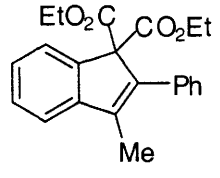
entry	halide	alkyne	product	yield (%)
1[b]	 **1**	Me—≡—*t*-Bu	 **2**	86
2	 **3**	Me—≡—*t*-Bu	**2**	46
3[b]	**1**	*n*-Pr—≡—*n*-Pr	 **4**	72
4[c]	**1**	Ph—≡—Ph	 **5**	70
5[b,d]	**1**	Me—≡—TMS	 **6**	81
6[b]	**1**	Me—≡—Ph	 **7**	63

Table 2. (continued)

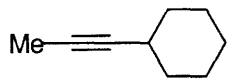
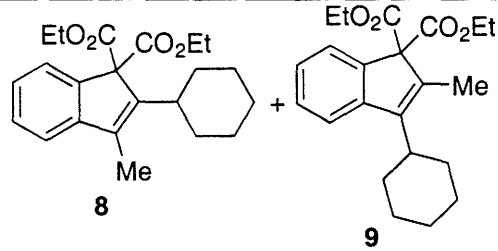
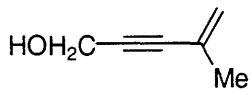
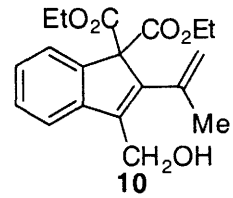
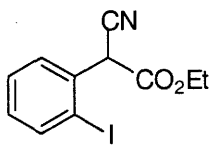
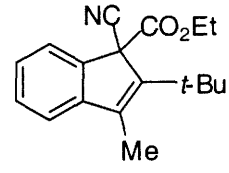
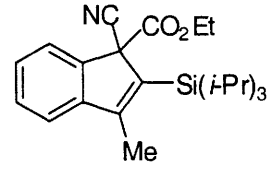
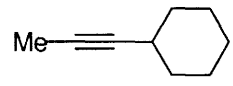
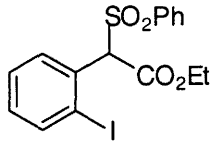
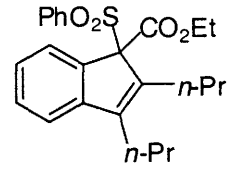
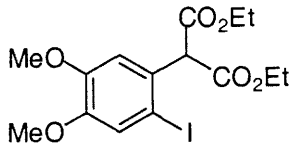
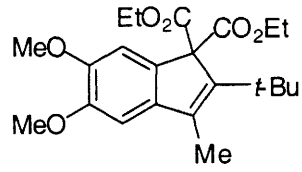
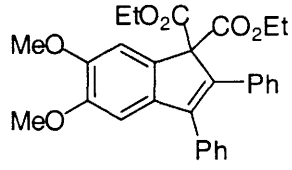
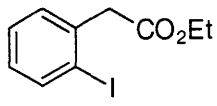
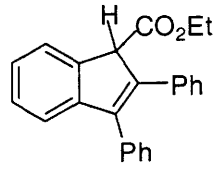
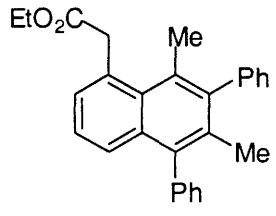
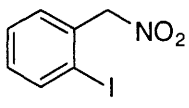
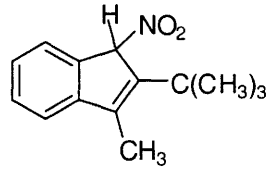
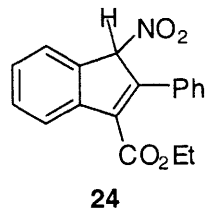
entry	halide	alkyne	product	yield (%)
7[b,e]	**1**		 **8** + **9**	63
8[b,f]	**1**		 **10**	40
9[d]	 **11**	Me—≡—*t*-Bu	 **12**	65
10[d]	**11**	Me—≡—Si(*i*-Pr)$_3$	 **13**	52
11	**11**	Ph—≡—Ph	**11**	38
12	**11**	*n*-Pr—≡—*n*-Pr	**11**	15
13	**11**	Me—≡—Ph	**11**	18
14	**11**		**11**	39
15[d]	 **14**	*n*-Pr—≡—*n*-Pr	 **15**	45
16	**14**	Me—≡—*t*-Bu	**14**	57
17	**14**	Me—≡—Si(*i*-Pr)$_3$	**14**	68

Table 2. (continued)

entry	halide	alkyne	product	yield (%)
18	**14**	Me—≡—Ph	**14**	70
19	 **16**	Me —≡— *t*-Bu	 **17**	74
20[c,f]	**16**	Ph—≡—Ph	 **18**	51
21[b,c]	 **19**	Ph—≡—Ph	 **20**	76
22[b,c]	**19**	Me—≡—Ph	 **21**	75
23[b,f]	 **22**	Me —≡— *t*-Bu	 **23**	50
24[b,f]	**22**	EtO_2C—≡—Ph	 **24**	50

[a] See the text and Experimental Section for the detailed procedure. [b] Yum's results. [c] 2 Equiv of the internal alkyne were used. [d] K_2CO_3 was used as the base, instead of KOAc. [e] A mixture of two regioisomers in a 6:1 ratio was obtained. [f] The reaction was run for 24 h.

The reaction of diethyl (2-bromophenyl)malonate **3** with 4,4-dimethyl-2-pentyne gave a much lower yield of the desired product compared with the reaction of the corresponding iodide (Table 2, entry 2). The low yield of the desired product is attributed to the stronger carbon-bromide bond, which can inhibit oxidative addition of the aryl bromide to the palladium(0) catalyst.

The reactions of diethyl (2-iodophenyl)malonate **1** with symmetrical alkynes, such as 4-octyne and diphenyl acetylene, afforded good yields of the desired products (Table 2, entries 3 and 4). 5 Equiv of diphenyl acetylene was also tried in the reaction with diethyl (2-iodophenyl)malonate **1,** only a 23 % yield of the desired annulation product was obtained.

The annulation process is highly regioselective for alkynes containing tertiary alkyl, trimethylsilyl, or phenyl groups, yielding a single regioisomer with the more sterically demanding group in the 2-position of the indene ring (Table 2; entries 1, 5 and 6). The assignment of regiochemistry is based on analogy with our earlier indole work.[23] In case of entry 5, a much lower yield (40 %) of the indene product **6** was isolated when KOAc was used rather than K_2CO_3. The reaction of diethyl (2-iodophenyl)malonate **1** with 1-cyclohexyl-1-propyne provided two regioisomers in a ratio of 6:1 with the major product having the cyclohexyl group in the 2-position of the indene (Table 2, entry 7). In this case the isomeric ratio was determined by GC and GC-MS, but only the major product was recognizable by ^{1}H NMR spectroscopy.

Next we explored the annulation of alkynes containing an hydroxy group (Table 2, entry 8). The reaction of diethyl (2-iodophenyl)malonate **1** with 4-methyl-4-penten-2-yn-1-ol afforded a 40% yield of the desired product. The regiochemistry of the product is uncertain, but both the ^{1}H and ^{13}C NMR spectra show only a single regioisomer.

The reactivity of other functionalized aryl halides bearing different electron-withdrawing groups has also been examined. For example, ethyl cyano(2-iodophenyl)acetate **11** has been

allowed to react with 4,4-dimethyl-2-butyne to afford a moderate yield of the desired indene **12** (Table 2, entry 9). Several bases, such as KOAc, NaOAc, K_2CO_3, and Na_2CO_3, were employed in these reactions, and K_2CO_3 gave the highest yield of the desired annulation products. The reaction of the acetate **11** and 1-triisopropylsilyl-1-propyne also gave the desired indene **13** in 52 % yield (Table 2, entry 10). However, the reactions of other internal alkynes and the acetate **11** were messy and significant amounts of the acetate **11** were recovered in all cases (Table 2, entries 11-14).

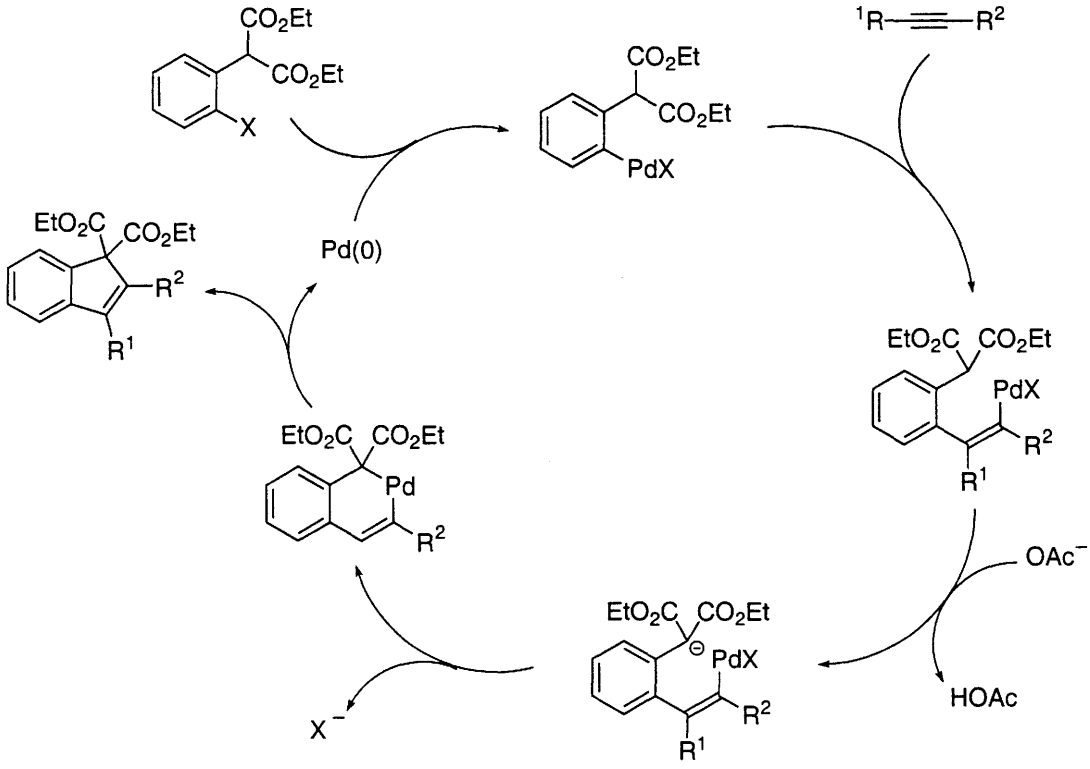
Ethyl (2-iodophenyl)(phenylsulfonyl)acetate **14** has been allowed to react with different internal alkynes (Table 2, entries 15-18). Only the reaction of 4-octyne afforded the desired indene **15** in a moderate yield (Table 2, entry 15). Significant amounts of the acetate **14** were recovered in the annulation reactions with other internal alkynes.

A relatively electron-rich aryl iodide, diethyl (2-iodo-4,5-dimethoxyphenyl)malonate **16**, was subjected to the palladium-catalyzed carboannulation (Table 2, entries 19 and 20). As expected, the yields of the desired indene product are slightly lower than the yields from annulation of the corresponding alkynes by diethyl (2-iodophenyl)malonate **1** (compare entries 1 and 4 with entries 12 and 13). The observation of lower yields can be explained by an electronic effect. Two methoxy substituents on the benzene ring significantly increase the electron density of the carbon-iodide bond, which consequently makes the bond less prone to nucleophilic attack by the palladium(0) catalyst.

The reaction of ethyl (2-iodopheny)lacetate **19** with diphenyl acetylene provided a 76% yield of the desired product (Table 2, entry 21). However, the reaction of the same ester with 1-phenyl-1-propyne afforded only a double insertion product **21** in high yield (Table 2, entry 22). The reaction of (2-iodophenyl)nitromethane **22** with 4,4-dimethyl-2-pentyne or ethyl 3-phenyl-2-propynoate afforded moderate yields of the desired products with only a small amount of multiple-insertion products (Table 2, entries 23 and 24).

The mechanism shown in Scheme 5 is proposed for this annulation process. It consists of the following key steps: (1) oxidative addition of the aryl halide to the Pd(0) catalyst, (2) arylpalladium coordination to the alkyne and then insertion of the alkyne to form a vinyl-palladium intermediate, (3) generation of a carbanion by the base, (4) intramolecular nucleophilic attack of the carbanion on the vinylpalladium intermediate to afford a palladocyclic intermediate, and (5) reductive elimination of the intermediate to furnish the indene and regenerate the Pd(0) catalyst.

Scheme 5



The oxidative addition of aryl halides to Pd(0) is well known and integral to a wide variety of Pd(0)-catalyzed processes.[24] The subsequent *syn*-addition of the arylpalladium compound to the alkyne has been established for the analogous palladium-catalyzed hydroarylation process[25] and assumed in many other alkyne insertion processes.[26] The high regioselectivity for unsymmetrical alkynes is probably due to the steric hindrance present in

the developing carbon-carbon bond. Alkyne insertion occurs so as to generate the least steric strain in the vicinity of the developing carbon-carbon bond rather than the longer carbon-palladium bond (Figure 1). Analogous regiochemistry is also observed in our previously reported indole synthesis.[16] The subsequent steps of this process are presumed to be palladacycle formation and the subsequent reductive elimination. Although we have no actual proof for the intermediacy of such palladacycles, a closely related heterocyclic arylpalladium amide has been reported and shown to undergo analogous thermal reductive elimination to form the corresponding aromatic nitrogen heterocycle.[27]

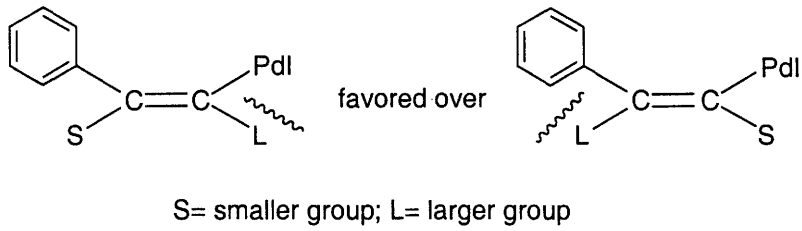


Figure 1. Steric effects on the regiochemistry of alkyne insertion

Conclusions

A general synthesis of highly substituted indenes has been developed using the palladium-catalyzed carboannulation of internal alkynes by functionalized aryl halides. The reactions proceed under relatively mild conditions and generally give good yields. This annulation process exhibits excellent regioselectivity and is particularly suited for the synthesis of hindered 2-substituted indenes.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz respectively. Thin layer chromatography was performed using commercially prepared

40-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254nm) and a basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5 %) + 300 mL of H_2O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. IR spectra were measured on a Bio-Rad FTS-7 spectrometer on salt plates.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. The following starting materials were prepared as indicated.

Diethyl (2-iodophenyl)malonate (1). Diethyl (2-iodophenyl)malonate was prepared in two steps from commercially available (2-iodophenyl)acetic acid. Ethyl (2-iodophenyl) acetate was prepared according to a modified literature procedure.[28] To a solution of (2-iodophenyl)acetic acid (1.00 g, 3.82 mmol) in 3 mL of ethanol was added 0.3 mL of concentrated sulfuric acid. The solution was then allowed to reflux for 3 h. The solution was poured into 8 mL of H_2O and extracted with 3 × 5 mL of ether. The ether extract was washed with 5 mL of H_2O, 5 mL of 5 % $NaHCO_3$, and 5 mL of brine, dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure, and the mixture was chromatographed using 4: 1 hexanes/EtOAc to afford the ester (1.45 g, 95 %) as a white solid: mp 125-126 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3 H), 3.77 (s, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 6.94 (m, 1 H), 7.28 (m, 2 H), 7.82 (d, J = 8.0 Hz, 1 H).

To a solution of ethyl (2-iodophenyl)acetate (0.54 g, 1.9 mmol) in 10 mL of diethyl carbonate was added NaH (0.19 g, 8.0 mmol). The resulting mixture was then allowed to stir at room temperature for 12 h. The mixture was poured into 20 mL of satd NH_4Cl (aq) and extracted with 3 × 10 mL of CH_2Cl_2. The ether extract was dried (Na_2SO_4) and filtered. The

solvent was evaporated under reduced pressure, and the mixture was chromatographed using 5:1 hexanes/EtOAc to afford diethyl (2-iodophenyl)malonate (0.59 g, 88 %) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 6 H), 4.24 (m, 4 H), 5.12 (s, 1 H), 7.00 (dt, J = 1.5, 7.5 Hz, 1 H), 7.36 (dt, J = 1.5, 7.5 Hz, 1 H), 7.47 (dd, J = 1.5, 7.5 Hz, 1 H), 7.86 (dd, J = 1.5, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 62.2, 62.4, 101.9, 128.8, 129.9, 130.0, 136.7, 139.8, 168.0; IR ($CHCl_3$, cm^{-1}) 2955, 2924, 1753, 1736, 1468; HRMS calcd for $C_{13}H_{15}IO_4$ 362.0015, found 362.0013.

Diethyl (2-bromophenyl)malonate (3). Diethyl (2-iodophenyl)malonate was prepared in two steps from commercially available (2-bromophenyl)acetic acid in the same manner as diethyl 2-iodophenylmalonate (**1**) was prepared. The indicated compound was prepared as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 6 H), 4.24 (m, 4 H), 5.20 (s, 1 H), 7.16 (dt, J = 1.5, 8.0 Hz, 1 H), 7.31 (dt, J = 1.5, 7.8 Hz, 1 H), 7.46 (dd, J = 1.4, 8.0 Hz, 1 H), 7.62 (dd, J = 1.5, 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 57.3, 62.1, 125.2, 127.7, 129.7, 130.3, 132.9, 133.0, 167.7; IR ($CHCl_3$, cm^{-1}) 3055, 2983, 1750, 1734, 1308; HRMS calcd for $C_{13}H_{15}BrO_4$ 314.0154, found 314.0157.

Ethyl cyano(2-iodophenyl)acetate (11). To a solution of (2-iodophenyl)acetonitrile (0.50 g, 2.1 mmol) in 10 mL of diethyl carbonate was added NaH (0.19 g, 8.0 mmol). The resulting mixture was then allowed to stir at room temperature for 12 h. The mixture was poured into 20 mL of satd NH_4Cl (aq) and extracted with 3 × 10 mL of CH_2Cl_2. The ether extract was dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure, and the mixture was chromatographed using 3:1 hexanes/EtOAc to afford ethyl cyano(2-iodophenyl)acetate (0.54 g, 82 %) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.2 Hz, 3 H), 4.30 (m, 2 H), 5.19 (s, 1 H), 7.10 (dt, J = 1.5, 7.8 Hz, 1 H), 7.44 (dt, J = 1.2, 7.5 Hz, 1 H), 7.60 (dd, J = 1.5, 7.8 Hz, 1 H), 7.90 (dd, J = 1.2, 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2,

48.3, 63.8, 100.0, 115.6, 129.5, 129.6, 131.1, 134.1, 140.4, 164.3; IR ($CHCl_3$, cm^{-1}) 3070, 2957, 1743, 1466, 1217; HRMS calcd for $C_{11}H_{10}INO_2$ 314.9756, found 314.9760.

Ethyl (2-iodophenyl)(phenylsulfonyl)acetate (14). Ethyl (2-iodophenyl)(phenylsulfonyl) acetate was prepared in two steps from commercially available (2-iodobenzyl) bromide. (2-Iodobenzyl)(phenyl)sulfone was prepared according to a modified literature procedure.[29] To a solution of (2-iodobenzyl)bromide (0.59 g, 2.0 mmol) in DMF (4 mL) was added $NaSO_2Ph$ (0.50 g, 3.0 mmol). The reaction mixture was stirred at 80 °C for 10 min, then poured into H_2O and stirred vigorously for 30 min. The precipitate was filtered, washed with H_2O and dried *in vacuo*. Recrystallization from 2:1 CH_2Cl_2/hexane afforded (2-iodobenzyl)(phenyl)sulfone (0.45 g, 63 %) as bright colorless needles: mp 131-132 °C; ^1H NMR ($CDCl_3$) δ 4.59 (s, 2 H), 7.00 (dt, J = 1.5, 7.8 Hz, 1 H), 7.44-7.53 (m, 3 H), 7.60-7.66 (m, 3 H), 7.73 (dd, J = 0.9, 7.8 Hz, 1 H).

To a solution of (2-iodobenzyl)(phenyl)sulfone (0.72 g, 2.0 mmol) in 10 mL of diethyl carbonate was added NaH (0.19 g, 8.0 mmol). The resulting mixture was then allowed to stir at room temperature for 12 h. The mixture was poured into 20 mL of satd NH_4Cl (aq) and extracted with 3 × 10 mL of CH_2Cl_2. The ether extract was dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure, and the mixture was chromatographed using 2:1 hexanes/EtOAc to afford ethyl (2-iodophenyl)(phenylsulfonyl)acetate (0.67 g, 78 %) as a white solid: mp 118-119 °C; ^1H NMR ($CDCl_3$) δ 1.15 (t, J = 7.2 Hz, 3 H), 4.15 (m, 2 H), 5.73 (s, 1 H), 7.00 (dt, J = 1.6, 7.8 Hz, 1 H), 7.33 (t, J = 7.5 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 2 H), 7.58 (t, J = 7.2 Hz, 1 H), 7.65 (d, J = 7.6 Hz, 2 H), 7.71 (t, J = 8.0 Hz, 1 H), 7.97 (dd, J = 1.5, 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 62.9, 103.8, 128.6, 129.1, 129.5, 131.1, 131.2, 134.5, 137.5, 140.0, 164.1; IR ($CHCl_3$, cm^{-1}) 3068, 2984, 1741, 1328, 1157; HRMS calcd for $C_{16}H_{15}ISO_4$ 329.9736, found 329.9742.

Diethyl (2-iodo-4,5-dimethoxyphenyl)malonate (16). Diethyl (2-iodo-4,5-dimethoxyphenyl)malonate was prepared in three steps from commercially available (3,4-dimethoxyphenyl)acetic acid. (2-Iodo-4,5-dimethoxyphenyl)acetic acid was prepared according to a modified literature procedure.[30] To a solution of (3,4-dimethoxyphenyl)acetic acid (3.92 g, 20.0 mmol) in CH_2Cl_2 (10 mL) and HOAc (10 mL), ICl (3.57 g, 22.0 mmol) in CH_2Cl_2 (40 mL) was added dropwise. The resulting mixture was stirred at room temperature for 12 h and then was quenched with NaS_2O_3 (aq). The organic layer was washed with brine (3 × 50 mL), dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure, and the residue triturated with ether to afford (2-iodo-4,5-dimethoxyphenyl)acetic acid (4.44 g, 69 %) as a yellow solid: mp 162-164 °C; ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 2 H), 3.86 (s, 6 H), 6.81 (s, 1 H), 7.24 (s, 1 H).

To a solution of (2-iodo-4,5-dimethoxyphenyl)acetic acid (2.00 g, 6.21 mmol) in 8 mL of ethanol was added 0.8 mL of concentrated sulfuric acid. The solution was then allowed to reflux for 3 h. The solution was poured into 10 mL of H_2O and extracted with 3 × 10 mL of ether. The ether extract was washed with 10 mL of H_2O, 10 mL of 5 % $NaHCO_3$, 10 mL of brine, dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure and the residue was recrystallized from 2:1 CH_2Cl_2/hexane to afford ethyl (2-iodo-4,5-dimethoxyphenyl)acetate (2.11 g, 97 %) as a white solid: mp 88-89 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3 H), 3.72 (s, 2 H), 3.86 (s, 6 H), 4.19 (q, J = 7.2 Hz, 2 H), 6.81 (s, 1 H), 7.24 (s, 1 H).

To a solution of (ethyl 2-iodo-4,5-dimethoxyphenyl)acetate (1.00 g, 3.1 mmol) in 12 mL of diethyl carbonate was added NaH (0.38 g, 13.7 mmol). The resulting mixture was then allowed to stir at room temperature for 12 h. The mixture was poured into 20 mL of satd NH_4Cl (aq) and extracted with 3 × 12 mL of CH_2Cl_2. The ether extract was dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure, and the residue was

chromatographed using 3:1 hexanes/EtOAc to afford diethyl (2-iodo-4,5-dimethoxyphenyl) malonate (1.13 g, 85 %) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3 H), 3.86 (s, 6 H), 4.24 (m, 4 H), 5.05 (s, 1 H), 7.06 (s, 1 H), 7.24 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 56.0, 56.2, 89.8, 112.2, 121.4, 128.6, 149.4, 168.0; IR ($CHCl_3$, cm^{-1}) 3055, 2937, 1749, 1733, 1029; HRMS calcd for $C_{15}H_{19}IO_6$ 422.0226, found 422.0234.

General procedure for the palladium-catalyzed carboannulation of internal alkynes. To a solution of the aryl halide (0.25 mmol) in DMF (5 mL) was added $Pd(OAc)_2$ (0.0125 mmol), LiCl (0.25 mmol) or *n*-Bu_4NCl (0.25 mmol), the appropriate base (0.50 mmol) and the alkyne (1.25 mmol). The reaction mixture was stirred under a nitrogen atmosphere at 80 °C for 48 h. The mixture was cooled, diluted with ether, and washed with satd NH_4Cl (aq). The organic layer was dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by column chromatography using hexanes/EtOAc as the eluent. The following compounds were prepared using the above general procedure.

Diethyl 2-*tert*-butyl-3-methyl-1*H*-indene-1,1-dicarboxylate (2). Obtained as a pale yellow oil in 86 % isolated yield (Table 2, entry 1): ^{1}H NMR ($CDCl_3$) δ 1.16 (t, J = 7.2 Hz, 6 H), 1.36 (s, 9 H), 2.29 (s, 3 H), 4.13 (m, 4 H), 7.13 (dt, J = 1.2, 7.5 Hz, 1 H), 7.19 (d, J = 7.8 Hz, 1 H), 7.31 (dt, J = 1.6, 7.5 Hz, 1 H), 7.47 (dt, J = 0.6, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.5, 14.1, 30.3, 34.4, 61.6, 70.9, 118.5, 122.3, 125.6, 128.5, 137.6, 140.7, 147.6, 149.1, 169.1; IR ($CHCl_3$, cm^{-1}) 2928, 2908, 1757, 1736, 1223, 1055; HRMS calcd for $C_{20}H_{26}O_4$ 330.1831, found 330.1835.

Diethyl 2,3-di-*n*-propyl-1*H*-indene-1,1-dicarboxylate (4). Obtained as a pale yellow oil in 72 % isolated yield (Table 2, entry 3): ^{1}H NMR ($CDCl_3$) δ 0.98 (m, 6 H), 1.24 (t, J = 6.9 Hz, 6 H), 1.47 (m, 2 H), 1.65 (m, 2 H), 2.58 (t, J = 8.1 Hz, 4 H), 4.20 (m, 4 H), 7.26 (m, 3 H), 7.56 (d, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.0, 14.7, 21.7, 22.8, 23.0, 29.41,

61.6, 119.0, 124.5, 125.2, 128.2, 140.3, 142.6, 142.7, 145.6, 168.8; IR ($CHCl_3$, cm^{-1}) 3067, 2959, 1732, 1466, 1367, 1229; HRMS calcd for $C_{21}H_{28}O_4$ 344.1988, found 344.1990.

Diethyl 2,3-diphenyl-1*H*-indene-1,1-dicarboxylate (5). Obtained as pale yellow crystals in 66 % isolated yield (Table 2, entry 4): mp 85-87 °C; ^1H NMR ($CDCl_3$) δ 1.07 (t, *J* = 7.2 Hz, 6 H), 4.14 (m, 4 H), 7.15-7.36 (m, 13 H), 7.69 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 61.9, 72.8, 121.3, 124.6, 126.7, 127.3, 127.6, 128.5, 128.7, 129.6, 130.3, 134.3, 135.1, 140.6, 141.0, 144.8, 145.1, 168.3; IR ($CHCl_3$, cm^{-1}) 3057, 3019, 2982, 1727, 1466, 1216; HRMS calcd for $C_{27}H_{24}O_4$ 412.1675, found 412.1680.

Diethyl 3-methyl-2-trimethylsilyl-1*H*-indene-1,1-dicarboxylate (6). Obtained as a pale yellow oil in 81 % isolated yield (Table 2, entry 5): ^1H NMR ($CDCl_3$) δ 0.45 (s, 9 H), 1.39 (t, *J* = 7.2 Hz, 6 H), 2.44 (s, 3 H), 4.33 (m, 4 H), 7.35-7.54 (m, 3 H), 7.63 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.24, 13.3, 13.4, 14.7, 61.6, 118.8, 124.0, 126.1, 128.2, 140.5, 143.1, 146.0, 152.1, 168.8; IR ($CHCl_3$, cm^{-1}) 2957, 1732, 1466, 1246; HRMS calcd for $C_{19}H_{26}O_4Si$ 346.1600, found 346.1604.

Diethyl 3-methyl-2-phenyl-1*H*-indene-1,1-dicarboxylate (7). Obtained as pale yellow crystals in 63 % isolated yield (Table 2, entry 6): mp 72-74 °C; ^1H NMR ($CDCl_3$) δ 1.06 (t, *J* = 7.2 Hz, 6 H), 2.10 (s, 3 H), 4.08 (m, 4 H), 7.22-7.67 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 11.9, 13.7, 30.0, 61.3, 119.7, 124.2, 126.3, 127.2, 127.6, 128.6, 129.3, 135.4, 129.4, 140.5, 140.7, 145.8, 168.3; IR ($CHCl_3$, cm^{-1}) 2984, 1729, 1472, 1246; HRMS calcd for $C_{22}H_{22}O_4$ 350.1518, found 350.1523.

Diethyl 2-cyclohexyl-3-methyl-1*H*-indene-1,1-dicarboxylate (8) and diethyl 3-cyclohexyl-2-methyl-1*H*-indene-1,1-dicarboxylate (9). Obtained as a pale yellow oil in 63 % isolated yield (Table 2, entry 7): ^1H NMR ($CDCl_3$) δ 1.25 (m, 6 H), 1.33-2.00 (m, 11 H), 2.20 (s, 3 H), 4.20 (m, 4 H), 7.15-7.57 (m, 4 H); ^{13}C NMR ($CDCl_3$, 6:1 mixture of isomers) δ 12.3, 12.4, 13.9, 26.2, 27.2, 30.2, 31.3, 37.8, 38.4, 61.6, 118.3, 118.4, 120.4, 124.0, 124.7,

125.3, 127.9, 128.2, 132.1, 134.6, 137.1, 139.4, 140.4, 143.7, 144.0, 145.6, 147.2, 168.5, 168.7; IR ($CHCl_3$, cm^{-1}, 6:1 mixture of isomers) 3055, 2980, 1732, 1470, 1234; HRMS calcd for $C_{22}H_{29}O_4$ 356.1988, found 356.1984.

Diethyl 3-(hydroxymethyl)-2-isopropenyl-1*H*-indene-1,1-dicarboxylate (10). Obtained as a pale yellow oil in 40 % isolated yield (Table 2, entry 8): ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 6.9 Hz, 6 H), 1.80 (s, 1 H), 2.18 (s, 3 H), 4.33 (q, J = 7.2 Hz, 4 H), 4.86 (s, 2 H), 5.08 (d, J = 2.4 Hz, 1 H), 5.37 (d, J = 2.4 Hz, 1 H), 7.42 (m, 2 H), 7.52 (t, J = 7.8 Hz, 1 H), 7.70 (t, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 23.5, 30.0, 57.4, 61.9, 118.3, 120.9, 124.3, 126.3, 128.6, 139.5, 140.4, 142.1, 143.7, 144.2, 167.9; IR ($CHCl_3$, cm^{-1}) 3019, 2982, 1730, 1468, 1242; HRMS calcd for $C_{19}H_{21}O_5$ 330.1468, found 330.1467.

Ethyl 2-*tert*-butyl-1-cyano-3-methyl-1*H*-indene-1-carboxylate (12). Obtained as a pale yellow oil in 65 % isolated yield (Table 2, entry 9): ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3 H), 1.44 (s, 9 H), 2.29 (s, 3 H), 4.23 (m, 2 H), 7.26 (m, 2 H), 7.38 (m, 1 H), 7.53 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.4, 14.1, 30.3, 34.4, 58.1, 63.4, 117.2, 119.6, 122.0, 126.9, 130.0, 138.4, 140.0, 145.4, 146.8, 167.1; IR ($CHCl_3$, cm^{-1}) 3014, 2964, 1747, 1222; HRMS calcd for $C_{18}H_{21}NO_2$ 283.1572, found 283.1576.

Ethyl 1-cyano-3-methyl-2-triisopropylsilyl-1*H*-indene-1-carboxylate (13). Obtained as a pale yellow oil in 52 % isolated yield (Table 2, entry 10): ^1H NMR ($CDCl_3$) δ 1.18 (m, 21 H), 1.52 (m, 3 H), 2.35 (s, 3 H), 4.17 (t, J = 7.2 Hz, 4 H), 7.33 (m, 2 H), 7.44 (m, 1 H), 7.60 (d, J = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.0, 13.7, 15.5, 19.1, 19.4, 60.7, 63.2, 117.8, 120.1, 122.0, 127.5, 129.6, 135.9, 142.9, 145.7, 156.6, 166.6; IR ($CHCl_3$, cm^{-1}) 3019, 2927, 1735, 1217; HRMS calcd for $C_{23}H_{33}NO_2Si$ 383.2281, found 383.2286.

Ethyl 1-phenylsulfonyl-2,3-di-*n*-propyl-1*H*-indene-1-carboxylate (15). Obtained as a pale yellow oil in 45 % isolated yield (Table 2, entry 15): ^1H NMR ($CDCl_3$) δ 1.84 (t, J = 7.2 Hz, 3 H), 1.07 (m, 5 H), 1.31 (t, J = 7.2 Hz, 3 H), 1.53 (m, 2 H), 2.18 (t, J = 8.0 Hz, 2 H),

2.42 (m, 1 H), 2.97 (m, 1 H), 4.29 (q, J = 7.2 Hz, 4 H), 6.89 (dd, J =1.5, 6.8 Hz, 1 H), 7.14 (t, J = 7.6 Hz, 2 H), 7.26 (m, 4 H), 7.38 (m, 1 H), 7.82 (dd, J = 1.8, 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.9, 15.3, 21.5, 23.3, 28.2, 29.0, 62.9, 85.2, 119.3, 125.9, 126.9, 127.7, 129.6, 130.0, 133.5, 136.8, 136.9, 146.1, 147.2, 165.3; IR ($CHCl_3$, cm^{-1}) 3016, 2963, 1716, 1419, 1224; HRMS calcd for $C_{24}H_{28}SO_4$ 412.1708, found 412.1713.

Diethyl 2-*tert*-butyl-5,6-dimethoxy-3-methyl-1*H*-indene-1,1-dicarboxylate (17). Obtained as a pale yellow oil in 74 % isolated yield (Table 2, entry 19): ^{1}H NMR ($CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 6 H), 1.34 (s, 1 H), 2.28 (s, 3 H), 3.86 (s, 3 H), 3.92 (s, 3 H), 4.12 (m, 4 H), 6.74 (s, 1 H), 7.06 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.7, 14.1, 30.3, 34.4, 56.3, 56.6, 61.6, 70.4, 102.3, 106.5, 132.6, 137.2, 140.5, 147.6, 147.8, 149.8, 169.3; IR ($CHCl_3$, cm^{-1}) 3054, 2983, 1754, 1734, 1497, 1265; HRMS calcd for $C_{22}H_{30}O_6$ 390.2042, found 390.2048.

Diethyl 5,6-dimethoxy-2,3-diphenyl-1*H*-indene-1,1-dicarboxylate (18). Obtained as a pale yellow oil in 51 % isolated yield (Table 2, entry 20): ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J = 7.2 Hz, 6 H), 3.76 (s, 1H), 3.86 (s, 1 H), 4.07 (m, 4 H), 6.74 (s, 1 H), 7.06-7.26 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 56.2, 56.4, 61.9, 104.5, 108.3, 127.0, 127.5, 127.8, 128.6, 129.5, 130.3, 133.4, 134.6, 135.2, 138.1, 139.4, 144.6, 148.4, 149.9, 168.6; IR ($CHCl_3$, cm^{-1}) 3052, 3019, 1724, 1300; HRMS calcd for $C_{29}H_{28}O_6$ 472.1886, found 472.1893.

Ethyl 2,3-diphenyl-1*H*-indene-1-carboxylate (20). Obtained as pale yellow crystals in 76 % isolated yield (Table 2, entry 21): mp 78-80 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3 H), 4.08 (s, 1 H), 4.22 (q, J = 7.2 Hz, 2 H), 7.06-7.84 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 40.8, 61.5, 118.8, 119.3, 124.6, 126.6, 127.8, 127.9, 128.3, 128.6, 129.0, 130.1, 131.1, 136.6, 137.0, 137.6, 138.1, 140.5, 140.7, 168.1; IR ($CHCl_3$, cm^{-1}) 3053, 2928, 1736, 1443, 1367; HRMS calcd for $C_{24}H_{20}O_2$ 340.1463, found 340.1458.

Ethyl (6,8-dimethyl-5,7-diphenyl-1-naphthyl)acetate (21). Obtained as pale yellow crystals in 75 % isolated yield (Table 2, entry 22): mp 128-129 °C; ^{1}H NMR ($CDCl_3$) δ 1.26

(t, J = 7.2 Hz, 3 H), 1.77 (s, 3 H), 2.50 (s, 3 H), 4.18 (q, J = 7.2 Hz, 2 H), 4.30 (s, 2 H), 7.24-7.48 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 14.7, 20.1, 22.2, 43.4, 60.0, 124.4, 126.6, 126.7, 127.4, 128.4, 128.5, 129.3, 130.2, 130.7, 130.8, 131.6, 134.0, 137.6, 141.1, 142.4, 143.2, 172.4; IR ($CHCl_3$, cm^{-1}) 2984, 2926, 1732, 1493, 1369; HRMS calcd for $C_{28}H_{26}O_2$ 394.1933, found 394.1936.

2-*tert*-Butyl-3-methyl-1-nitro-1*H*-indene (23). Obtained as a pale yellow oil in 50 % isolated yield (Table 2, entry 23): ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9 H), 2.16 (s, 3 H), 4.80 (s, 1 H), 7.03-7.30 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 29.6, 37.0, 68.6, 105.6, 120.4, 123.0, 125.3, 126.7, 127.8, 129.1, 136.0; IR ($CHCl_3$, cm^{-1}) 2961, 2870, 1695, 1597, 1487; HRMS calcd for $C_{14}H_{17}NO_2$ 231.1262, found 231.1261.

Ethyl 1-nitro-2-phenyl-1*H*-indene-3-carboxylate (24). Obtained as a pale yellow oil in 50 % isolated yield (Table 2, entry 24): ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.2 Hz, 3 H), 4.04 (q, J = 7.2 Hz, 2 H), 5.25 (s, 1 H), 7.11-7.57 (m, 7 H), 7.97 (d, J = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.5, 69.7, 80.6, 109.0, 122.4, 123.8, 126.5, 126.8, 127.9, 128.5, 129.0, 129.3, 130.0, 134.0, 161.1, 167.9; IR ($CHCl_3$, cm^{-1}) 3060, 2973, 1695, 1597, 1487; HRMS calcd for $C_{18}H_{15}NO_4$ 309.1002, found 309.1002.

References

1. Kikuchi, T.; Tottori, K.; Uwahodo, Y. PCT Int. Appl. 9621449, **1996**; *Chem. Abstr.* **1996**, *125*, 204539.
2. Mederski, W.; Dorsch, D.; Wilm, C.; Osswald, M.; Schmitges, C. Ger. Offen. 1971785, **1998**; *Chem. Abstr.* **1998**, *129*, 275905.
3. Dillard, R.; Hagishita, S.; Ohtani, M. PCT Int. Appl. 9603120, **1996**; *Chem. Abstr.* **1996**, *125*, 341826.

4. (a) Senanayake, C.; Roberts, F.; DiMichele, L.; Ryan, K.; Liu, J.; Fredenburgh, L.; Foster, B. *Tetrahedron Lett.* **1995**, *36*, 3993. (b) Bach, R. D.; Knight, J. W. *Org. Syn.* **1981**, *60*, 63.
5. Spaleck, W.; Antberg, M.; Dolle, V.; Klein, R.; Rohrmann, J.; Winter, A. *New J. Chem.* **1990**, *14*, 499.
6. Dirks, G.; Li, G. S.; Jones, J. F. U. S. Patent 4090998, **1978**; *Chem. Abstr.* **1978**, *89*, 147557.
7. (a) Prough, J.; Alberts, A.; Deanna, A.; Gilfillian, J.; Huff, R.; Smith, J.; Wiggins, J. *J. Med. Chem.* **1990**, *33*, 758. (b) Olivier, M.; Marechal, E. *Bull. Soc. Chim. Fr.* **1973**, 3092. (c) Normant, C. *Bull. Soc. Chim. Fr.* **1971**, 1351. (d) Ikeda, S.; Chatani, N.; Kajikawa, Y.; Ohe, K.; Murai, S. *J. Org. Chem.* **1992**, *57*, 2. (e) Becker, C.; McLaughlin, M. *Synlett*, **1991**, 642.
8. (a) Shriner, R. *Org. React.* **1942**, *1*, 1. (b) Johnson, A. *J. Org. React.* **1942**, *1*, 210.
9. Parham, W.; Egberg, D. *J. Org. Chem.* **1972**, *37*, 1545.
10. Parham, W.; Montgomery, W. *J. Org. Chem.* **1974**, *39*, 2048.
11. Palandoken, H.; McMillen, W. T.; Nantz, M. *Org. Prep. Proced. Int.* **1996**, *28*, 720.
12. Miller, W.; Pittman, C. *J. Org. Chem.* **1974**, *39*, 1955.
13. Yoshida, H.; Kato, M.; Ogata, T. *J. Org. Chem.* **1985**, *50*, 1145.
14. Ackroyd, J.; Pover, K. A.; Scheinmann, F. *Tetrahedron Lett.* **1982**, *23*, 5583.
15. Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111.
16. (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.
17. Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.
18. Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.
19. Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306.

20. Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579.

21. (a) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.

22. Rodd, E. H. *Chemistry of Carbon Compounds*, Vol. III, Elsevier, Amsterdam, **1954,** 82.

23. Yum, E. K. *Ph. D. dissertation*, Iowa State University, **1992.**

24. (a) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434. (b) Tsuji, J. *Palladium Reagents and Catalysts*, John Wiley & Sons, New York, **1995**, 5.

25. (a) Arcadi, A.; Cacchi, S.; Marinelli, F.; Nardelli, M. *Gazz. Chim. Ital.* **1986**, *116*, 725. (b) Cacchi, S. *Pure Appl. Chem.* **1990**, *62*, 713.

26. (a) Negishi, E. *Pure Appl. Chem.* **1992**, *64,* 323. (b) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 791. (c) Beydoun, N.; Pfeffer, M. *Synthesis* **1990**, 729.

27. (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232. (b) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451.

28. Harrison, L. W. *Ph. D. dissertation*, Iowa State University, **1989**.

29. Sperantio, D.; Hansen, H. J. *Helv. Chim. Acta.* **1995**, *78*, 765.

30. Qandil, A. M.; Miller, D. W.; Nichols, D. E. *Synthesis* **1999**, *12*, 2033.

CHAPTER 2. SYNTHESIS OF INDENES BY THE METAL-CATALYZED CARBOANNULATION OF TERMINAL ALKYNES

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Abstract

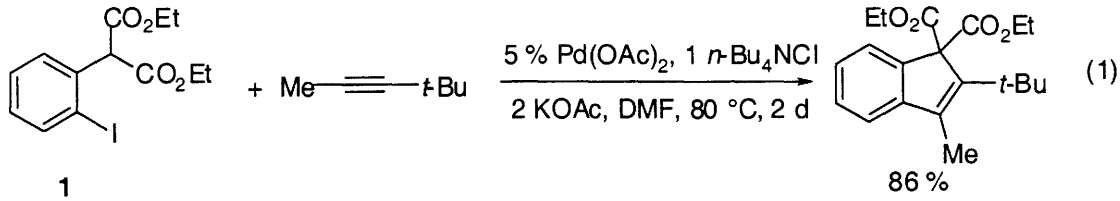
A variety of indene derivatives have been prepared in good to excellent yields via palladium/copper-catalyzed cross coupling of terminal alkynes with functionalized aryl halides, followed by copper-catalyzed intramolecular cyclization.

Introduction

The indene ring system is present in drug candidates possessing interesting biological activities[1] and metallocene complexes catalyzing olefin polymerization.[2] Consequently, it has encouraged the development of a number of approaches for the synthesis of the indene ring system, including the reduction/dehydration of indanones,[3] the cyclization of phenyl-substituted allylic alcohols,[4] and the ring expansion of substituted cyclopropenes.[5] All of these routes are of limited scope due to the strong acid medium required, a lengthy reaction sequence, and low tolerance of functionality. These drawbacks have prompted us to develop a general synthesis of indenes utilizing metal-catalyzed annulation methodology.

The palladium-catalyzed annulation of alkynes has proven to be extremely effective for the synthesis of a wide variety of carbo- and heterocycles.[6] For example, we have successfully employed this annulation chemistry for the synthesis of indoles,[7] benzofurans,[8] isocoumarins,[9] isoquinolines,[10] indenones[11] and polycyclic aromatic hydrocarbons.[12] The synthesis of indenes has also been achieved by the palladium-catalyzed carboannulation of

internal alkynes by aryl halides (eq 1).[13] For instance, in the presence of 5 mol % of $Pd(OAc)_2$, 2 equiv of KOAc, 1 equiv of *n*-Bu_4NCl in DMF at 80 °C, the reaction of diethyl (2-iodophenyl)malonate **1** with 4,4-dimethyl-2-pentyne affords an 86 % yield of the desired indene product after 2 d.



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However, this palladium-catalyzed annulation methodology cannot be applied to terminal alkynes. Attempts to achieve the annulation of terminal alkynes utilizing the same methodology have only afforded acetylenic coupling products in high yields (eq 2, Table 1).

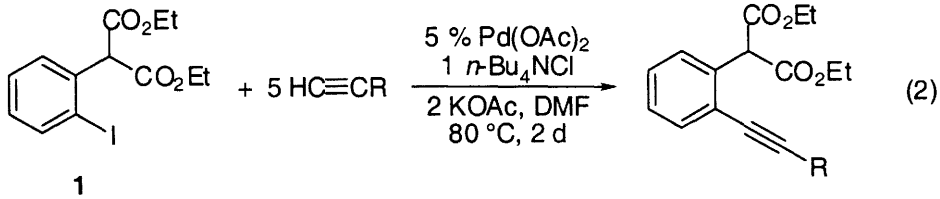

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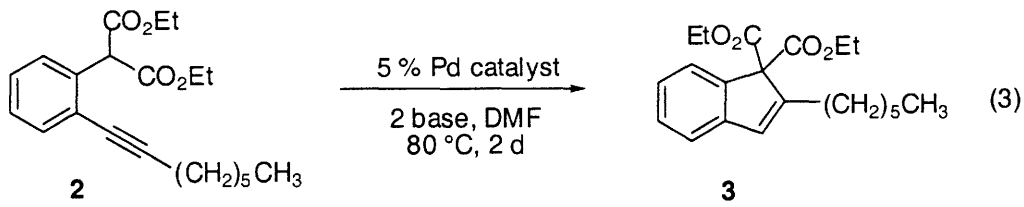
Table 1. Palladium-catalyzed carboannulation of terminal alkynes by aryl halide 1 (eq 2).[a]

entry	R	% yield
1	$(CH_2)_5CH_3$	93
2	$C(CH_3)_3$	87
3	CH_2OCH_3	84
4	Ph	91

[a] All reactions were run on a 0.25 mmol scale in 5 mL of DMF at 80 °C for 2 d.

Preliminary efforts to cyclize the resulting diethyl 2-(1-octynyl)phenyl-malonate **2** by applying different Pd catalysts or bases gave poor results, suffering either low yields or no cyclization product at all (eq 3, Table 2). The use of a strong base, such as *t*-BuOK or NaH, appears essential to the formation of the cyclization product **3** (Table 2, entries 6-9). A large amount of diethyl 2-(1-octynyl)phenylmalonate **2** was recovered in all cases.



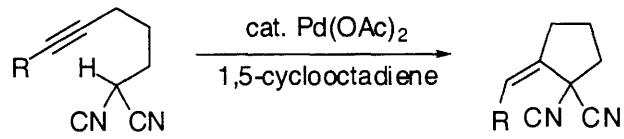
(3)

Table 2. Palladium-catalyzed carboannulation of diethyl 2-(2-octynyl)phenyl malonate 2 (eq 3).[a]

entry	Pd catalyst	base	% yield
1	$Pd(PPh_3)_4$	KOAc	0
2	$Pd_2(dba)_3{\cdot}CHCl_3$	KOAc	0
3	$Pd(OAc)_2$	K_2CO_3	0
4	$Pd(OAc)_2$	NaOEt	0
5	$Pd(OAc)_2$	NEt_3	0
6	$Pd(OAc)_2$	*t*-BuOK	42
7	$Pd(OAc)_2$	NaH	45
8	--	*t*-BuOK	36
9	--	NaH	43

[a] All reactions were run on a 0.25 mmol scale in 5 mL of DMF at 80 °C for 2 d.

The cyclization of diethyl 2-(1-octynyl)phenylmalonate **2** appears to involve an intramolecular nucleophilic attack of a carbanion on the carbon-carbon triple bond. This type of cyclization has been achieved by several different methods. For example, the intramolecular carbocyclization of internal alkynes bearing a carbon nucleophile proceeds very well under neutral conditions using $Pd(OAc)_2$-1,5-cyclooctadiene as the catalyst and ethanol as the solvent (eq 4).[14] The starting ε–alkynylmalonnitriles give the Z-isomers of the corresponding carbocyclic products in all cases (except when R = trimethylsilyl). Cyclization of the substrate bearing a terminal alkyne (R = H) is sluggish and affords the corresponding methylene cyclopentane product in only a 39 % yield. The low yield and slow reaction may be due to competitive oxidative addition of Pd(0) into the C-H bond of the terminal alkyne.[15]

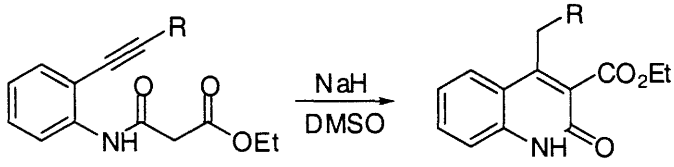


(4)

39-84 %

R = H, Me, $HO(CH_2)_3$, TBDMS-OCH_2, Ph, TMS

Cacchi and Arcadi have observed the carbocyclization of *N*-substituted malonanilides using a stoichiometric amount of NaH (eq 5).[16] The nature of the substituent linked to the acetylenic moiety R is crucial for the success of this cyclization. Best results are obtained when R is an aromatic ring bearing electron-withdrawing substituents.



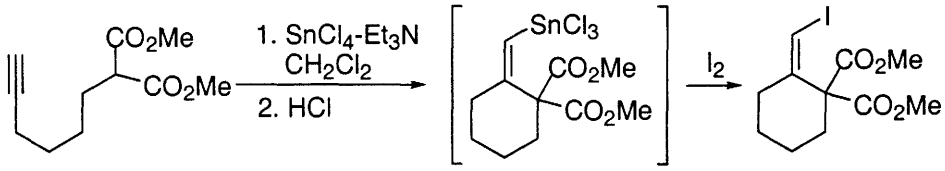
(5)

33-73 %

R= aryl, heteroaryl, vinylic

Taguchi has described an intramolecular carbostannation reaction of various active methyne-containing compounds having an alkynyl group in the presence of $SnCl_4$ and NEt_3 (Scheme 1).[17] Subsequent reaction of the resulting Sn intermediates with electrophiles provided functionalized cyclohexane derivatives.

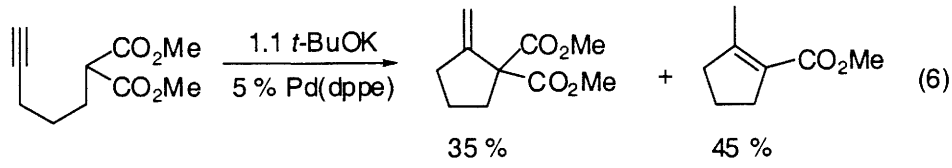
Scheme 1



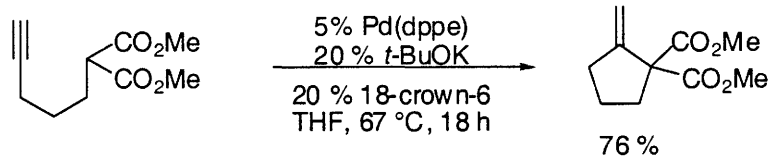
74 %

Balme, Gore, and Monteiro have reported an intramolecular cyclization of terminal alkynes in the presence of 20 mol % of Pd(dppe) and 1.1 equiv of *t*-BuOK in THF as the solvent. This procedure afforded a mixture of methylene cyclopentanes and methyl cyclopentenes (eq 6).[18] They found that the addition of 20 mol % of 18-crown-6 gave the

desired 2,2-difunctionalized methylene cyclopentanes as the sole product in good yields (eq 7).

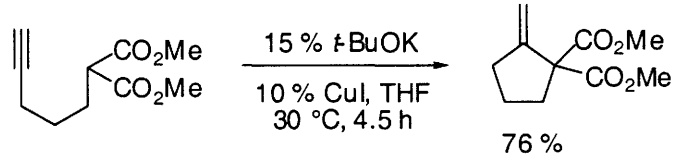


(6)



(7)

In a subsequent paper, Balme, Monteiro and Bouyssi described a copper-catalyzed intramolecular cyclization using catalytic amounts of *t*-BuOK and CuI (eq 8).[19] Compared to the previous palladium-catalyzed cyclization method, this procedure provides the desired methylene cyclopentanes in good yields at lower reaction temperatures and in shorter reaction times. Furthermore, this procedure avoids the use of 18-crown-6 as the additive. However, when this copper-catalyzed cyclization was applied to disubstituted alkynes, stoichiometric amounts of both *t*-BuOK and CuI were essential in order to afford reasonable yields of the desired cyclization product (eq 9).



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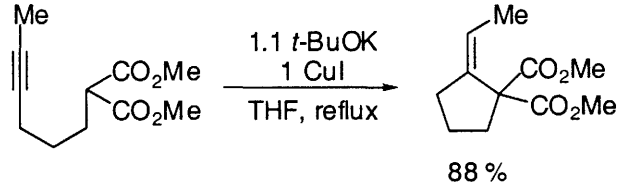
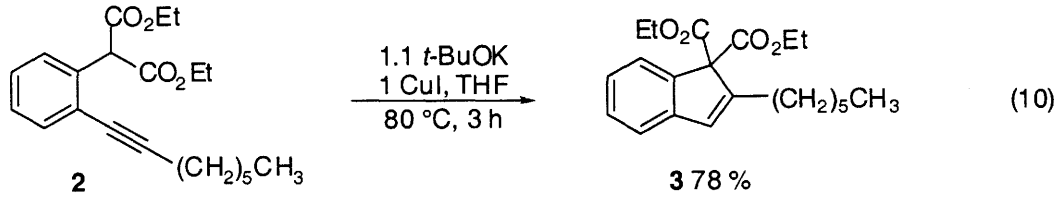


(9)

A similar copper-catalyzed intramolecuar cyclization procedure has been tried in an attempt to cyclize diethyl 2-(1-octynyl)phenylmalonate **2** (eq 10). Indeed, it afforded the desired cyclization product **3** in a 78 % yield.

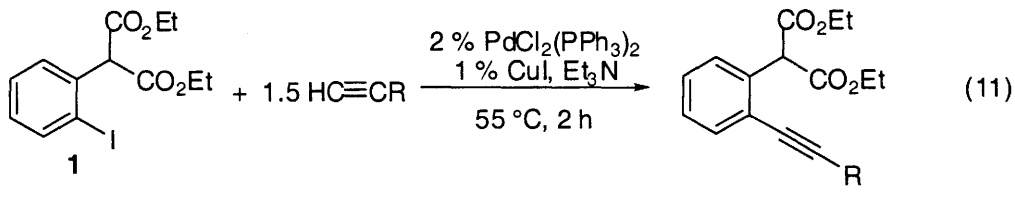


(10)

Based on the success of this copper-catalyzed intramolecular cyclization, we herein wish to report a convenient two-step procedure for the carboannulation of terminal alkynes by functionalized aryl halides. The procedure involves the palladium/copper-catalyzed cross coupling of terminal alkynes with aryl halides, followed by copper-catalyzed intramolecular cyclization.

Results and Discussion

Initial studies were aimed at finding optimal reaction conditions for both the coupling and cyclization steps. Regarding the cross coupling step, we found that the standard Sonogashira coupling procedure[20] often afforded somewhat higher yields of the coupling products than the procedure described in Table 1 (compare Table 3 and Table 1). In addition, Sonogashira coupling requires a lower reaction temperature and shorter reaction time. Based on these comparisons, we chose the Sonogashira coupling as the standard method for the cross coupling step.



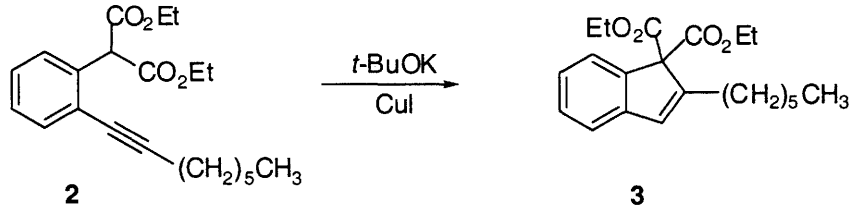
(11)

Table 3. Sonogashira coupling of terminal alkynes with aryl halide 1 (eq 11).[a]

entry	R	% yield
1	$(CH_2)_5CH_3$	95
2	$C(CH_3)_3$	94
3	CH_2OCH_3	81
4	Ph	98

[a] All reactions were run on a 0.25 mmol scale in 3 mL of Et_3N at 55 °C for 2 h.

Next, we focused on finding the best reaction conditions for the cyclization step (Table 4). The reaction was first attempted using diethyl 2-(1-octynyl)phenylmalonate **2** (0.25 mmol), 1.1 equiv of *t*-BuOK, and 1 equiv of CuI in 5 mL of THF at 80 °C for 3 h (Table 4, entry 1). This reaction provided a good yield of the desired cyclization product **3**. Using only catalytic amounts of both *t*-BuOK and CuI afforded an even higher yield of the desired product (Table 4, entries 2 and 3). On the other hand, no cyclization product was observed when only a catalytic amount of *t*-BuOK or CuI was applied (Table 4, entries 4 and 5). Using a stoichiometric amount of *t*-BuOK gave a low yield of the desired product (Table 4, entry 6). Running the reaction in other organic solvents, instead of THF, provided lower yields of the desired product (Table 4, entries 7-9). We also explored the effect of temperature on the outcome of the reaction. A temperature of 55 °C gave the highest yield based on our investigation (compare entries 3, 10 and 11 in Table 4). Thus, the optimum reaction conditions so far developed employ 1 equiv of diethyl 2-(1-octynyl)phenylmalonate **2** (0.25 mmol), 5 mol % of *t*-BuOK, and 2 mol % of CuI in 5 mL of THF at 55 °C (Table 4, entry 11).



2 **3** (12)

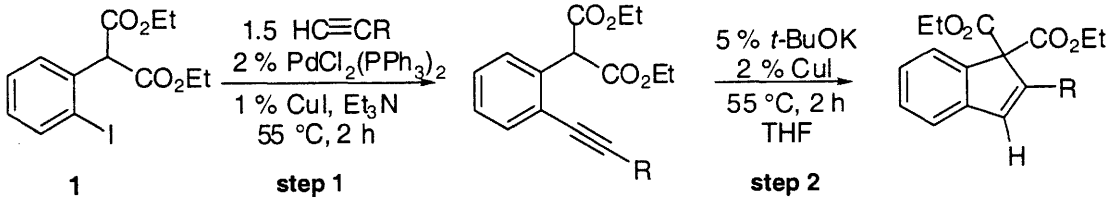
Table 4. Optimization of the copper-catalyzed intramolecular cyclization of diethyl 2-(1-octynyl)phenylmalonate 2 (eq 12).[a]

entry	*t*-BuOK (mol %)	CuI (mol %)	solvent	temperature (°C)	reaction time (h)	% yield
1	110	100	THF	80	3	78
2	15	10	THF	80	3	85
3	5	2	THF	80	3	84
4	0	2	THF	80	24	0
5	5	0	THF	80	24	0
6	100	0	THF	80	24	26
7	5	2	DMF	80	3	72
8	5	2	DMSO	80	3	43
9	5	2	*t*-BuOH	80	3	48
10	5	2	THF	30	3	27
11	5	2	THF	55	3	96

[a] All reactions were run on a 0.25 mmol scale in 5 mL of the solvent.

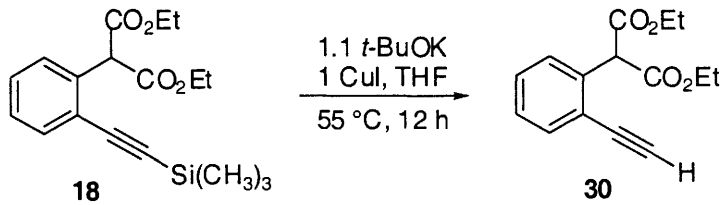
On the basis of the above optimization study, a two-step procedure has thus been developed for the synthesis of indenes by the carboannulation of terminal alkynes using functionalized aryl halides. The procedure involves the palladium/copper-catalyzed Sonogashira coupling of terminal alkynes with aryl halides, followed by copper-catalyzed intramolecular cyclization of the intermediate alkyne (Scheme 2). A variety of indene derivatives have been synthesized by employing this methodology. The results using a wide variety of terminal alkynes are summarized in Table 5.

Scheme 2



Both the coupling and cyclization reactions of terminal alkynes bearing a long chain alkyl substituent with diethyl (2-iodophenyl)malonate **1** afforded excellent yields of the desired products (Table 5, entries 1 and 2). This two-step annulation methodology also tolerates a variety of functional groups in the terminal alkyne, including a methoxy (Table 5, entry 3), an hydroxy (Table 5, entry 4), an ester (Table 5, entry 5), a diethoxy (Table 5, entry 6), and a cyano group (Table 5, entry 7).

Next we explored the annulation of terminal alkynes containing a sterically demanding substituent. The cross coupling of 3,3-dimethyl-1-butyne with diethyl (2-iodophenyl)-malonate (**1**) furnished diethyl 2-(3,3-dimethyl-1-butynyl)phenylmalonate **16** in an excellent yield (Table 5, entry 8). The subsequent cyclization of diethyl 2-(3,3-dimethyl-1-butynyl) phenylmalonate **16** was slow and gave the corresponding cyclization product **17** in a moderate yield. The result is reasonable considering the steric hindrance of the bulky *t*-butyl group. An attempt to cyclize diethyl 2-(trimethylsilylethynyl)phenylmalonate **18** didn't afford any cyclization product, and 82 % of the starting alkyne was recovered. Using stoichiometric amounts of both *t*-BuOK and CuI only resulted in the formation of the desilylation product diethyl (2-ethynylphenyl)malonate **30** (eq 13).



(13)

Table 5. Two-step annulation of terminal alkynes by aryl halide 1 (Scheme 2).[a]

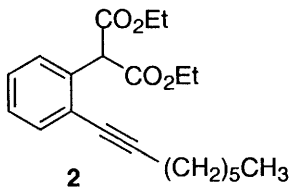
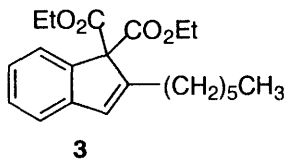
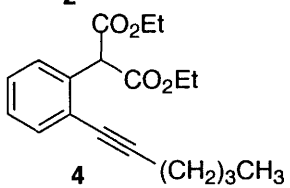
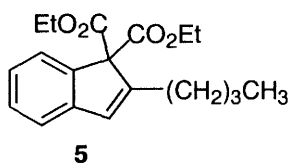
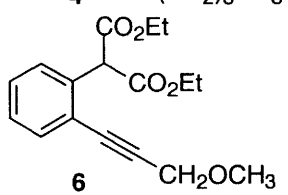
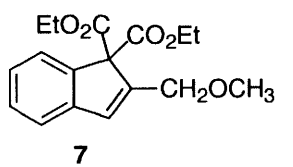
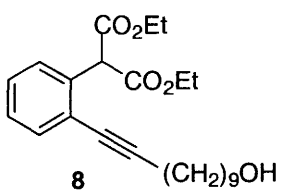
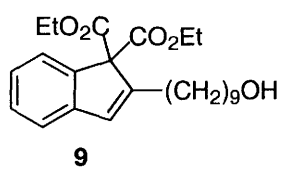
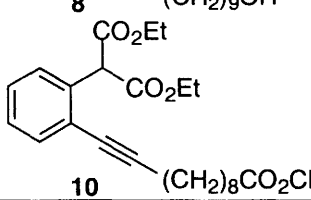
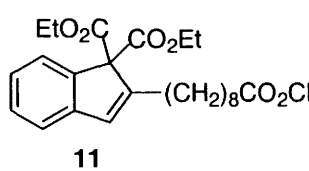
entry	R	coupling product	% yield	cyclization product	% yield
1	$(CH_2)_5CH_3$	 **2**	95	 **3**	96
2	$(CH_2)_3CH_3$	 **4**	93	 **5**	92
3	CH_2OCH_3	 **6**	81	 **7**	91
4	$(CH_2)_9OH$	 **8**	98	 **9**	79
5	$(CH_2)_8CO_2CH_3$	 **10**	86	 **11**	83

Table 5. (continued)

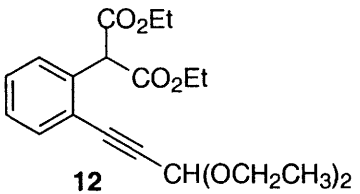
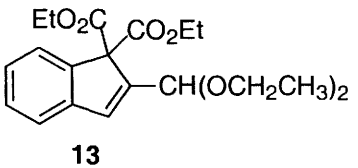
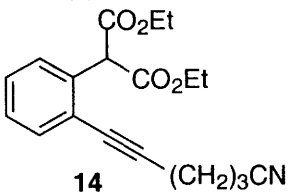
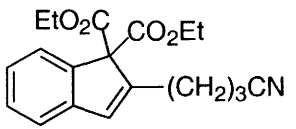
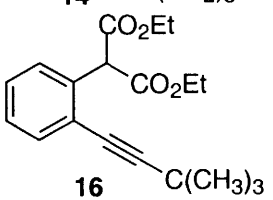
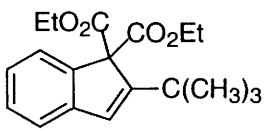
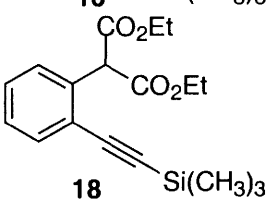
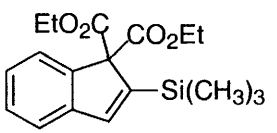
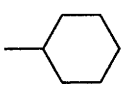
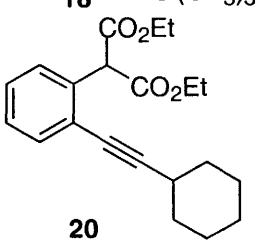
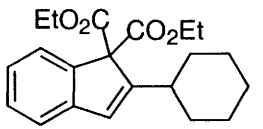
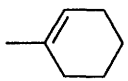
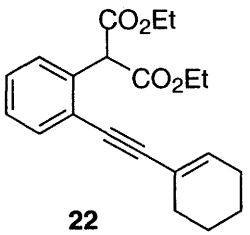
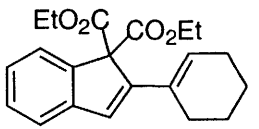
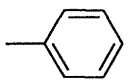
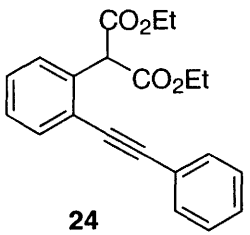
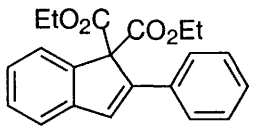
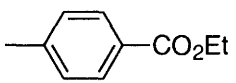
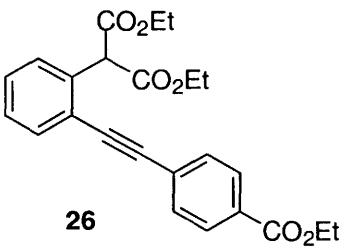
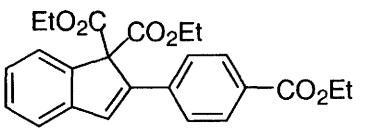
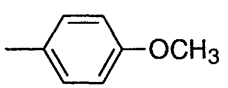
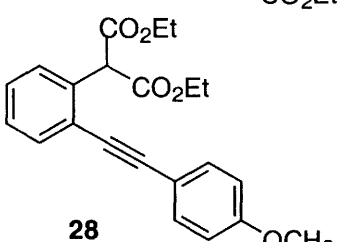
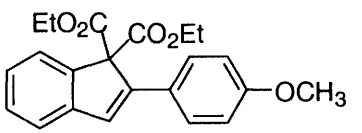
6	$CH(OCH_2CH_3)_2$	 **12**	75	 **13**	58[b]
7	$(CH_2)_3CN$	 **14**	62	 **15**	68
8	$C(CH_3)_3$	 **16**	94	 **17**	69[c]
9	$Si(CH_3)_3$	 **18**	98	 **19**	0[d]
10		 **20**	91	 **21**	92

Table 5. (continued)

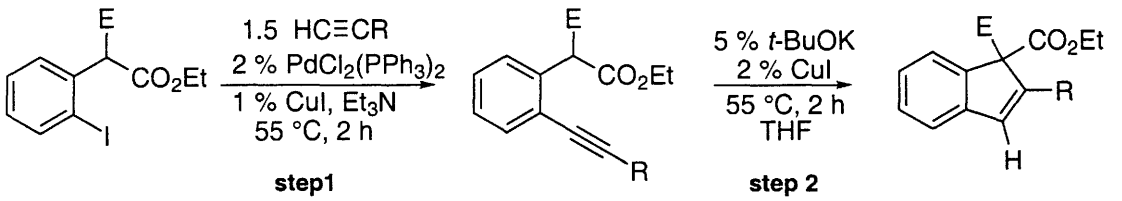
11		 **22**	90	 **23**	85
12		 **24**	98	 **25**	61
13		 **26**	63	 **27**	65
14		 **28**	86	 **29**	96

[a] See the text and Experimental Section for the detailed procedure. [b] A 21% yield of the intermediate **12** was recovered. [c] The reaction was run for 12 h. [d] An 82 % yield of the intermediate **18** was recovered.

Terminal alkynes bearing a carbocyclic ring have also been subjected to the annulation. Both coupling and cyclization reactions of diethyl (2-iodophenyl)malonate **1** and cyclohexyl acetylene (Table 5, entry 10) or 1-ethynylcyclohexene (Table 5, entry 11) have provided the desired products in high yields. The coupling of diethyl (2-iodophenyl)malonate **1** with phenyl acetylene proceeded very well to gave a 98 % yield of the cross coupled product **24**. However, subsequent cyclization afforded the desired product **25** in only a moderate 61 % yield (Table 5, entry 12). Terminal alkynes bearing an electron-deficient or electron-rich aromatic ring have also been allowed to react with diethyl (2-iodophenyl)malonate **1** to afford good yields of the desired products (Table 5, entries 13 and 14).

The reactivity of other functionalized aryl halides has also been examined (Scheme 3). The results are summarized in Table 6.

Scheme 3



Both the coupling and cyclization reactions of 1-octyne and ethyl cyano(2-iodophenyl) acetate **31** afforded high yields of the desired product (Table 6, entry 1). The cross coupling of cyclohexyl acetylene with ethyl cyano(2-iodophenyl)acetate **31** gave a 76 % yield of ethyl cyano[2-(cyclohexylethynyl)phenyl]acetate **34** alongside a small amount of the cyclization product **35** (Table 6, entry 2). The ethyl cyano[2-(cyclohexylethynyl)phenyl] acetate **34** was then allowed to react with catalytic amounts of *t*-BuOK and CuI to generate the desired cyclization product **35** in 78% yield. A high yield of ethyl 1-cyano-2-phenyl-1*H*-indene-1-carboxylate **36** was obtained as the sole product in the cross coupling of ethyl cyano(2-iodophenyl)acetate **31** and phenyl acetylene (Table 6, entry 3).

Table 6. Two-step annulation of terminal alkynes by various functionalized aryl halides (Scheme 3).[a]

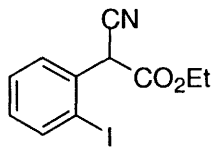
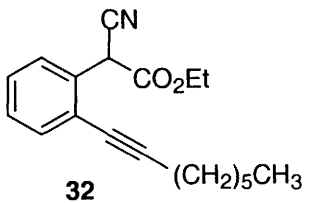
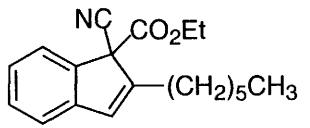
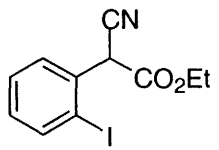
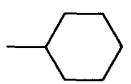
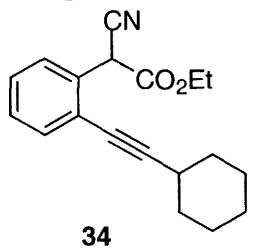
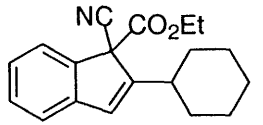
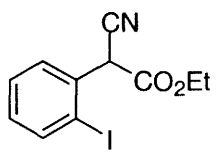
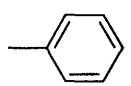
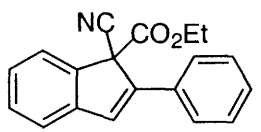
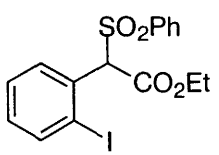
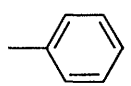
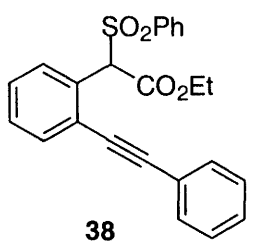
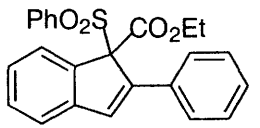
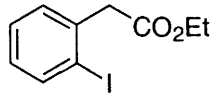
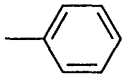
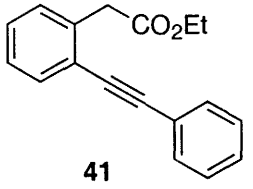
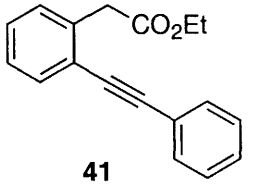
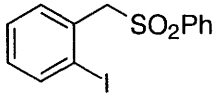
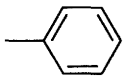
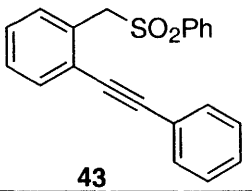
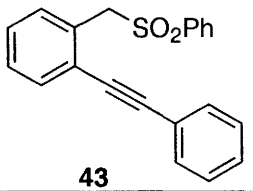
entry	aryl halides	R	coupling product	% yield	cyclization product	% yield
1	 **31**	$(CH_2)_5CH_3$	 **32**	92	 **33**	83
2	 **31**		 **34**	76[b]	 **35**	78
3	 **31**		 **36**	86[c]	--	--
4	 **37**		 **38**	91	 **39**	36[c,d,e]

Table 6. (continued)

5	 **40**		 **41**	98	 **41**	$78^{c,d,e}$
6	 **42**		 **43**	99	 **43**	$82^{c,d,e}$

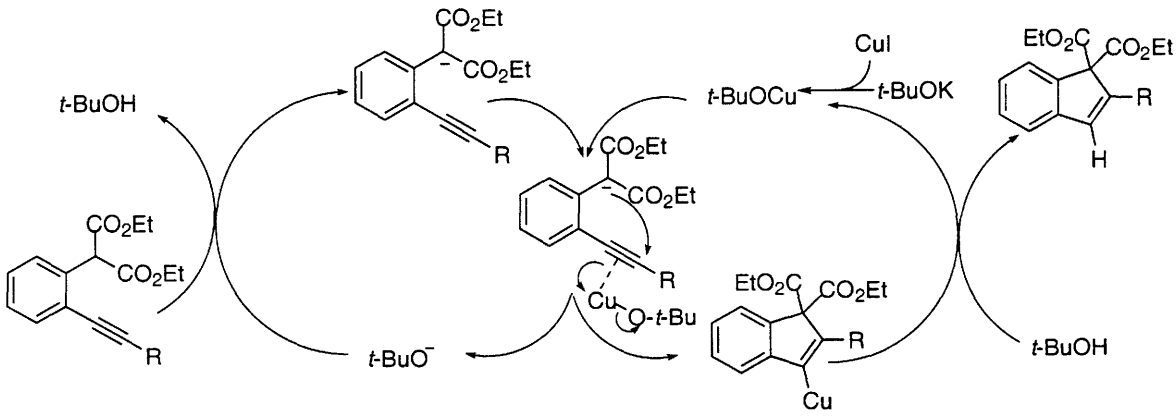
[a] See the text and Experimental Section for the detailed procedure. [b] A 6 % yield of **35** was isolated. [c] The reaction was run for 12 h. [d] 1.1 Equiv of t-BuOK and 1 equiv of CuI were used. [e] The reaction was run at 80 °C.

The cyclization of ethyl [2-(phenylethynyl)phenyl](phenylsulfonyl) acetate **38** was very slow under our normal reaction conditions and gave only a very low yield of the desired product **39** (Table 6, entry 4). The use of stoichiometric amounts of both *t*-BuOK and CuI and an elevated temperature afforded a modest 36 % yield of indene **39**.

The cross coupling of phenyl acetylene with ethyl (2-iodophenyl)acetate **40** or 1-iodo-2-(phenylsulfonylmethyl)benzene **42** provided high yields of the desired coupling products (Table 6, entries 5 and 6). However, the subsequent cyclization reaction didn't provide any of the desired indene products, even using stoichiometric amounts of both *t*-BuOK and CuI and an elevated temperature. The inertness of the intermediates **41** and **43** towards the intramolecular cyclization can no doubt be attributed to the weaker acidity of the methylene hydrogen in these intermediates compared to the methyne hydrogen in other intermediates bearing two electron-withdrawing groups.

The copper-catalyzed intramolecular cyclization presumably proceeds via (1) generation of a carbanion by the *t*-butoxide, (2) coordination of the copper *t*-butoxide to the alkyne triple bond, which activates the triple bond towards nucleophilic attack, (3) intramolecular nucleophilic attack of the carbanion on the activated triple bond to afford a vinylcopper intermediate, (4) protonation of the resulting vinylcopper intermediate to furnish the indene and regenerate the copper catalyst and the *t*-butoxide (Scheme 4).[19]

Scheme 4



Conclusions

In conclusion, the synthesis of various indene derivatives has been accomplished in high yields by the cross coupling of terminal alkynes with functionalized aryl halides, followed by the copper-catalyzed intramolecular cyclization. This process tolerates various functionality in the terminal alkyne and provides a convenient, general route to prepare 2-substituted indene derivatives.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz respectively. Thin layer chromatography was performed using commercially prepared 40-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254nm) and a basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5 %) + 300 mL of H_2O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. IR spectra were measured on a Bio-Rad FTS-7 spectrometer on salt plates.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. The following starting materials were prepared as indicated.

Diethyl (2-iodophenyl)malonate (1). Diethyl (2-iodophenyl)malonate was prepared in two steps from commercially available 2-iodophenylacetic acid. Ethyl (2-iodophenyl)acetate was prepared according to a modified literature procedure.[21] To a solution of (2-iodophenyl) acetic acid (1.00 g, 3.82 mmol) in 3 mL of ethanol was added 0.3 mL of concentrated sulfuric acid. The solution was then allowed to reflux for 3 h. The solution was poured into 8 mL of H_2O and extracted with 3 × 5 mL of ether. The ether extract was washed with 5 mL of H_2O, 5 mL of 5 % $NaHCO_3$, 5 mL of brine, dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure, and the mixture was chromatographed using 4:1 hexanes/EtOAc to afford the ester (1.45 g, 95 %) as a white solid: mp 125-126 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3 H), 3.77 (s, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 6.94 (m, 1 H), 7.28 (m, 2 H), 7.82 (d, J = 8.0 Hz, 1 H).

To a solution of ethyl (2-iodophenyl)acetate (0.54 g, 1.9 mmol) in 10 mL of diethyl carbonate was added NaH (0.19 g, 8.0 mmol). The resulting mixture was allowed to stir at room temperature for 12 h. The mixture was poured into 20 mL of satd NH_4Cl (aq) and extracted with 3 × 10 mL of CH_2Cl_2. The ether extract was dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure, and the mixture was chromatographed using 5:1 hexanes/EtOAc to afford diethyl (2-iodophenyl)malonate (0.59 g, 88 %) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 6 H), 4.24 (m, 4 H), 5.12 (s, 1 H), 7.00 (dt, J = 1.5, 7.5 Hz, 1 H), 7.36 (dt, J = 1.5, 7.5 Hz, 1 H), 7.47 (dd, J = 1.5, 7.5 Hz, 1 H), 7.86 (dd, J = 1.5, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 62.2, 62.4, 101.9, 128.8, 129.9, 130.0, 136.7, 139.8, 168.0; IR ($CHCl_3$, cm^{-1}) 2955, 2924, 1753, 1736, 1468; HRMS calcd for $C_{13}H_{15}IO_4$ 362.0015, found 362.0013.

Ethyl cyano(2-iodophenyl)acetate (31). To a solution of (2-iodophenyl)acetonitrile (0.50 g, 2.1 mmol) in 10 mL of diethyl carbonate was added NaH (0.19 g, 8.0 mmol). The resulting mixture was allowed to stir at room temperature for 12 h. The mixture was poured into 20 mL of satd NH_4Cl (aq) and extracted with 3 × 10 mL of CH_2Cl_2. The ether extract was dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure, and the mixture was chromatographed using 3:1 hexanes/EtOAc to afford ethyl cyano(2-iodophenyl) acetate (0.54 g, 82 %) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.2 Hz, 3 H), 4.30 (m, 2 H), 5.19 (s, 1 H), 7.10 (dt, J = 1.5, 7.8 Hz, 1 H), 7.44 (dt, J = 1.2, 7.5 Hz, 1 H), 7.60 (dd, J = 1.5, 7.8 Hz, 1 H), 7.90 (dd, J = 1.2, 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 48.3, 63.8, 100.0, 115.6, 129.5, 129.6, 131.1, 134.1, 140.4, 164.3; IR ($CHCl_3$, cm^{-1}) 3070, 2957, 1743, 1466, 1217; HRMS calcd for $C_{11}H_{10}INO_2$ 314.9756, found 314.9760.

Ethyl (2-iodophenyl)(phenylsulfonyl)acetate (37). Ethyl (2-iodophenyl)(phenyl-sulfonyl) acetate was prepared in two steps from commercially available 2-iodobenzyl bromide. (2-Iodobenzyl)(phenyl)sulfone was prepared according to a modified literature procedure.[29] To a solution of 2-iodobenzyl bromide (0.59 g, 2.0 mmol) in DMF (4 mL) was added $NaSO_2Ph$ (0.50 g, 3.0 mmol). The reaction mixture was stirred at 80 °C for 10 min, then poured into H_2O and stirred vigorously for 30 min. The precipitate was filtered, washed with H_2O and dried *in vacuo*. Recrystallization from 2:1 CH_2Cl_2/hexane afforded (2-iodobenzyl)(phenyl)sulfone (0.45 g, 63 %) as bright colorless needles: mp 131-132 °C; ^{1}H NMR ($CDCl_3$) δ 4.59 (s, 2 H), 7.00 (dt, J = 1.5, 7.8 Hz, 1 H), 7.44-7.53 (m, 3 H), 7.60-7.66 (m, 3 H), 7.73 (dd, J = 0.9, 7.8 Hz, 1 H).

To a solution of (2-iodobenzyl)(phenyl)sulfone (0.72 g, 2.0 mmol) in 10 mL of diethyl carbonate was added NaH (0.19 g, 8.0 mmol). The resulting mixture was allowed to stir at room temperature for 12 h. The mixture was poured into 20 mL of satd NH_4Cl (aq) and extracted with 3 × 10 mL of CH_2Cl_2. The ether extract was dried (Na_2SO_4) and filtered. The

solvent was evaporated under reduced pressure, and the mixture was chromatographed using 2:1 hexanes/EtOAc to afford ethyl (2-iodophenyl)(phenylsulfonyl)acetate (0.67 g, 78 %) as a white solid: mp 118-119 °C; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7.2 Hz, 3 H), 4.15 (m, 2 H), 5.73 (s, 1 H), 7.00 (dt, J = 1.6, 7.8 Hz, 1 H), 7.33 (t, J = 7.5 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 2 H), 7.58 (t, J = 7.2 Hz, 1 H), 7.65 (d, J = 7.6 Hz, 2 H), 7.71 (t, J = 8.0 Hz, 1 H), 7.97 (dd, J = 1.5, 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 62.9, 103.8, 128.6, 129.1, 129.5, 131.1, 131.2, 134.5, 137.5, 140.0, 164.1; IR ($CHCl_3$, cm^{-1}) 3068, 2984, 1741, 1328, 1157; HRMS calcd for $C_{16}H_{15}ISO_4$ 329.9736, found 329.9742.

General procedure for the Sonogashira coupling of terminal alkynes and aryl halides. To a solution of the aryl halide (0.25 mmol) in Et_3N (3 mL) was added $Pd(OAc)_2$ (0.005 mmol), CuI (0.0025 mmol), and the alkyne (0.375 mmol). The reaction mixture was stirred under a nitrogen atmosphere at 55 °C for 2 h. The mixture was then cooled, filtered, and concentrated. The residue was chromatographed using hexanes/EtOAc as the eluent. The following compounds were prepared using the above general procedure.

Diethyl (2-oct-1-ynylphenyl)malonate (2). Obtained as a pale yellow oil in 95 % isolated yield (Table 5, entry 1): ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.2 Hz, 3 H), 1.25-1.32 (m, 10 H), 1.44 (m, 2 H), 1.59 (m, 2 H), 2.41 (t, J = 7.2 Hz, 2 H), 4.21 (m, 4 H), 5.30 (s, 1 H), 7.24 (m, 2 H), 7.41 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.6, 22.6, 28.6, 28.7, 31.4, 55.7, 61.8, 78.2, 95.9, 124.6, 127.8, 127.9, 128.4, 132.0, 134.6, 168.3; IR ($CHCl_3$, cm^{-1}) 3058, 2982, 1751, 1734, 1266; HRMS calcd for $C_{21}H_{28}O_4$ 344.1988, found 344.1992.

Diethyl (2-hex-1-ynylphenyl)malonate (4). Obtained as a pale yellow oil in 93 % isolated yield (Table 5, entry 2): ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 3 H), 1.25 (m, 6 H), 1.49 (m, 4 H), 1.59 (m, 2 H), 2.44 (t, J = 6.9 Hz, 2 H), 4.22 (m, 4 H), 5.32 (s, 1 H), 7.26 (m, 2 H), 7.42 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.7, 14.1, 19.2, 20.0, 22.6, 30.7, 55.7, 61.8, 78.2, 95.8, 124.6,

127.8, 127.9, 128.4, 132.0, 134.7, 168.3; IR ($CHCl_3$, cm^{-1}) 3057, 2982, 1753, 1733, 1266; HRMS calcd for $C_{19}H_{24}O_4$ 316.1675, found 316.1678.

Diethyl [2-(3-methoxyprop-1-ynyl)phenyl]malonate (6). Obtained as a pale yellow oil in 81 % isolated yield (Table 5, entry 3): ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 6 H), 3.47 (s, 3 H), 4.23 (m, 4 H), 4.36 (s, 2 H), 5.29 (s, 1 H), 7.29 (m, 2 H), 7.49 (dd, J = 1.2, 7.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 55.7, 57.7, 60.4, 61.9, 84.0, 90.1, 123.2, 128.0, 128.7, 128.9, 132.5, 135.0, 168.1; IR ($CHCl_3$, cm^{-1}) 3054, 2928, 1749, 1713, 1266; HRMS calcd for $C_{17}H_{20}O_5$ 304.1311, found 304.1316.

Diethyl [2-(11-hydroxyundec-1-ynyl)phenyl]malonate (8). Obtained as a pale yellow oil in 98 % isolated yield (Table 5, entry 4): ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 6 H), 1.33-1.64 (m, 15 H), 2.43 (t, J = 7.2 Hz, 2 H), 3.62 (t, J = 6.6 Hz, 2 H), 4.23 (m, 4 H), 5.31 (s, 1 H), 7.27 (m, 2 H), 7.43 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 19.7, 26.0, 28.8, 29.1, 29.3, 29.6, 29.7, 33.0, 55.9, 62.0, 63.1, 76.9, 96.1, 124.8, 128.0, 128.1, 128.6, 132.2, 134.8, 168.5; IR ($CHCl_3$, cm^{-1}) 3421, 3054, 2931, 1748, 1732, 1265; HRMS calcd for $C_{24}H_{34}O_5$ 402.2406, found 402.2413.

Diethyl [2-(11-methoxy-11-oxoundec-1-ynyl)phenyl]malonate (10). Obtained as a pale yellow oil in 86 % isolated yield (Table 5, entry 5): ^1H NMR ($CDCl_3$) δ 1.26 (dt, J = 1.2, 7.2 Hz, 6 H), 1.33-1.64 (m, 12 H), 2.30 (t, J = 7.2 Hz, 2 H), 2.43 (t, J = 7.2 Hz, 2 H), 3.66 (s, 3 H), 4.23 (m, 4 H), 5.31 (s, 1 H), 7.27 (m, 2 H), 7.42 (t, J = 7.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.5, 24.9, 28.6, 28.9, 29.1, 29.2, 34.0, 51.4, 55.7, 61.7, 78.2, 95.8, 124.5, 127.8, 127.9, 128.4, 132.0, 134.6, 168.2, 174.2; IR ($CHCl_3$, cm^{-1}) 3056, 2934, 1734, 1266; HRMS calcd for $C_{25}H_{34}O_6$ 430.2355, found 430.2363.

Diethyl [2-(3,3-diethoxyprop-1-ynyl)phenyl]malonate (12). Obtained as a pale yellow oil in 75 % isolated yield (Table 5, entry 6): ^1H NMR ($CDCl_3$) δ 1.22 (m, 12 H), 3.66 (m, 2 H), 3.78 (m, 2 H), 4.17 (m, 4 H), 5.22 (s, 1 H), 5.47 (s, 1 H), 7.23 (dt, J = 1.2, 7.8 Hz, 1 H),

7.22 (dt, J = 1.2, 7.8 Hz, 1 H), 7.46 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 15.2, 55.5, 61.0, 61.9, 82.7, 89.5, 91.8, 122.4, 127.9, 128.8, 129.2, 132.6, 135.0, 167.0; IR ($CHCl_3$, cm^{-1}) 3054, 2981, 1749, 1733, 1266; HRMS calcd for $C_{20}H_{26}O_6$ 362.1736, found 362.17427.

Diethyl [2-(5-cyanopent-1-ynyl)phenyl]malonate (14). Obtained as a pale yellow oil in 62 % isolated yield (Table 5, entry 6): ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 6 H), 1.98 (m, 2 H), 2.57 (t, J = 7.2 Hz, 2 H), 2.63 (t, J = 7.2 Hz, 2 H), 4.24 (m, 4 H), 5.23 (s, 1 H), 7.27 (dt, J = 1.2, 7.2 Hz, 1 H), 7.33 (dt, J = 1.6, 7.8 Hz, 1 H), 7.45 (dt, J = 1.2, 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 16.2, 18.7, 24.6, 55.9, 61.9, 80.8, 92.4, 119.2, 123.7, 128.0, 128.4, 128.7, 132.2, 134.7, 168.1; IR ($CHCl_3$, cm^{-1}) 2984, 2254, 1748, 1732; $C_{19}H_{24}NO_4$ 327.1471, found 327.1475.

Diethyl [2-(3,3-dimethylbut-1-ynyl)phenyl]malonate (16). Obtained as a pale yellow oil in 94 % isolated yield (Table 5, entry 8): ^{1}H NMR ($CDCl_3$) δ 1.27 (dt, J = 0.8, 7.2 Hz, 6 H), 1.33 (d, J = 1.2 Hz, 9 H), 4.24 (m, 4 H), 5.28 (s, 1 H), 7.26 (m, 2 H), 7.40 (t, J = 7.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 28.22, 30.9, 55.9, 61.8, 104.0, 124.5, 127.8, 127.9, 128.3, 131.8, 134.8, 168.4; IR ($CHCl_3$, cm^{-1}) 3053, 2970, 1749, 1736, 1265; HRMS calcd for $C_{19}H_{24}O_4$ 316.1675, found 316.1678.

Diethyl [2-(trimethylsilylethynyl)phenyl]malonate (18). Obtained as a pale yellow oil in 98 % isolated yield (Table 5, entry 9): ^{1}H NMR ($CDCl_3$) δ 0.27 (s , 9 H), 1.28 (t, J = 7.2 Hz, 6 H), 4.25 (m, 4 H), 5.32 (s, 1 H), 7.29 (dt, J = 1.2, 7.2 Hz, 1 H), 7.35 (dt, J = 1.2, 7.5 Hz, 1 H), 7.44 (dd, J = 1.2, 7.8 Hz, 1 H), 7.49 (dd, J = 1.2, 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.08, 14.3, 56.0, 62.0, 100.2, 102.6, 123.8, 128.0, 128.6, 129.0, 132.4, 135.5, 168.3; IR ($CHCl_3$, cm^{-1}) 3054, 2984, 2156, 1749, 1732, 1266; HRMS calcd for $C_{18}H_{24}SiO_4$ 332.1444, found 332.1449.

Diethyl [2-(cyclohexylethynyl)phenyl]malonate (20). Obtained as a pale yellow oil in 91 % isolated yield (Table 5, entry 10): ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 6 H), 1.37

(m, 3 H), 1.57 (m, 3 H), 1.76 (m, 2 H), 1.86 (m, 2 H), 2.64 (m, 1 H), 4.23 (m, 4 H), 5.33 (s, 1 H), 7.26 (m, 2 H), 7.41 (d, J = 7.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.8, 24.8, 25.9, 29.8, 32.6, 55.8, 61.8, 78.2, 99.9, 124.6, 127.8, 127.9, 128.3, 131.9, 134.7, 168.4; IR ($CHCl_3$, cm^{-1}) 3054, 2933, 1749, 1733, 1265; HRMS calcd for $C_{21}H_{26}O_4$ 342.1831, found 342.1837.

Diethyl [2-(1-cyclohexenylethynyl)phenyl]malonate (22). Obtained as a pale yellow oil in 90 % isolated yield (Table 5, entry 11): ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 6 H), 1.64 (m, 4 H), 2.13 (m, 2 H), 2.22 (m, 2 H), 4.22 (m, 4 H), 5.26 (m, 2 H), 6.22 (m, 1 H), 7.28 (m, 2 H), 7.42 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.7, 22.5, 26.0, 29.3, 56.1, 62.0, 84.4, 96.8, 120.8, 124.5, 128.0, 128.3, 128.6, 132.0, 134.8, 135.9, 168.4; IR ($CHCl_3$, cm^{-1}) 3056, 2936, 1751, 1733, 1266; HRMS calcd for $C_{21}H_{24}O_4$ 340.1675, found 340.1678.

Diethyl [2-(phenylethynyl)phenyl]malonate (24). Obtained as a pale yellow oil in 98 % isolated yield (Table 5, entry 12): ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 6 H), 4.25 (m, 4 H), 5.40 (s, 1 H), 7.35 (m, 5 H), 7.49 (m, 1 H), 7.57 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 56.1, 61.9, 86.9, 94.6, 122.9, 123.8, 128.0, 128.5, 128.7, 128.8, 131.6, 132.1, 135.0, 168.2; IR ($CHCl_3$, cm^{-1}) 3055, 2986, 1749, 1733, 1266; HRMS calcd for $C_{21}H_{20}O_4$ 336.1362, found 336.1367.

Diethyl (2-{[4-(ethoxycarbonyl)phenyl]ethynyl}phenyl)malonate (26). Obtained as a pale yellow oil in 63 % isolated yield (Table 5, entry 13): ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 6 H), 1.37 (t, J = 7.2 Hz, 3 H), 4.22 (m, 4 H), 4.35 (q, J = 7.2 Hz, 2 H), 5.33 (s, 1 H), 7.32 (dt, J = 1.2, 7.6 Hz, 1 H), 7.35 (dt, J = 1.2, 7.6 Hz, 1 H), 7.46 (d, J = 7.6 Hz, 1 H), 7.56 (m, 3H), 8.00 (d, J = 7.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.4, 56.1, 61.2, 62.0, 89.7, 93.8, 123.2, 127.4, 128.1, 128.8, 129.2, 129.6, 130.2, 131.5, 132.3, 135.2, 166.0, 168.0; IR ($CHCl_3$, cm^{-1}) 3032, 2988, 1726, 1266; HRMS calcd for $C_{24}H_{24}O_6$ 408.1573, found 408.1580.

Diethyl {2-[(4-methoxyphenyl)ethynyl]phenyl}malonate (28). Obtained as a pale yellow oil in 86 % isolated yield (Table 5, entry 14): ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz,

6 H), 3.80 (s, 1 H), 4.22 (m, 4 H), 5.38 (s, 1 H), 6.87 (dt, J = 2.0, 9.2 Hz, 2 H), 7.31 (m, 2 H), 7.46 (m, 3 H), 7.53 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 55.4, 56.2, 61.9, 85.7, 94.8, 114.1, 115.0, 124.1, 128.0, 128.4, 128.6, 131.9, 133.1, 134.8, 160.0, 168.3; IR ($CHCl_3$, cm^{-1}) 3056, 2985, 1728, 1264; HRMS calcd for $C_{22}H_{22}O_5$ 366.1467, found 366.1472.

Ethyl cyano(2-oct-1-ynylphenyl)acetate (32). Obtained as a pale yellow oil in 92 % isolated yield (Table 6, entry 1): ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 6.9 Hz, 3 H), 1.26-1.37 (m, 7 H), 1.45 (m, 2 H), 1.60 (m, 2 H), 2.44 (t, J = 7.2 Hz, 2 H), 4.25 (m, 2 H), 5.28 (s, 1 H), 7.29-7.37 (m, 2 H), 7.46 (m, 1 H), 7.50 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 19.8, 22.8, 28.7, 28.9, 31.6, 42.0, 63.4, 77.7, 97.8, 115.9, 124.3, 128.3, 128.7, 129.2, 132.0, 132.8, 165.0; IR ($CHCl_3$, cm^{-1}) 3054, 2933, 2226, 1747, 1265; HRMS calcd for $C_{19}H_{23}NO_2$ 297.1729, found 297.1733.

Ethyl cyano[2-(cyclohexylethynyl)phenyl]acetate (34). Obtained as a pale yellow oil in 76 % isolated yield (Table 6, entry 2): ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3 H), 1.39 (m, 3 H), 1.57 (m, 3 H), 1.74 (m, 2 H), 1.90 (m, 2 H), 2.64 (m, 1 H), 4.26 (m, 2 H), 5.27 (s, 1 H), 7.33 (m, 2 H), 7.46 (m, 1 H), 7.50 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 25.0, 25.9, 29.8, 32.5, 41.9, 63.2, 77.2, 101.5, 115.8, 124.1, 128.1, 128.4, 129.0, 131.7, 132.5, 164.8; IR ($CHCl_3$, cm^{-1}) 3020, 2933, 2228, 1748, 1216; HRMS calcd for $C_{19}H_{21}NO_2$ 295.1572, found 295.1577.

Ethyl 1-cyano-2-phenyl-1*H*-indene-1-carboxylate (36). Obtained as a pale yellow oil in 86 % isolated yield (Table 6, entry 3): ^{1}H NMR ($CDCl_3$) δ 1.16 (t, J = 7.2 Hz, 3 H), 4.24 (m, 2 H), 7.36 (m, 2 H), 7.45 (m, 5 H), 7.69 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 56.7, 63.7, 116.6, 122.5, 123.0, 126.0, 127.5, 129.0, 129.1, 130.3, 131.1, 131.9, 140.0, 142.9, 143.3, 165.7; IR ($CHCl_3$, cm^{-1}) 3020, 2984, 2250, 1740, 1217; HRMS calcd for $C_{19}H_{15}NO_2$ 289.1103, found 289.1108.

Ethyl [2-(phenylethynyl)phenyl](phenylsulfonyl)acetate (38). Obtained as a pale yellow oil in 91 % isolated yield (Table 6, entry 4): ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3 H), 4.27 (m, 2 H), 6.00 (s, 1 H), 7.33-7.39 (m, 7 H), 7.42-7.46 (m, 3 H), 7.55 (m, 1 H), 7.65 (dd, J = 1.2, 7.2 Hz, 2 H), 7.99 (dd, J = 1.6, 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 62.8, 71.6, 86.1, 94.4, 122.5, 125.1, 128.5, 128.6, 128.7, 128.9, 129.4, 129.4, 129.5, 130.1, 131.6, 132.1, 134.1, 137.5, 164.4; IR ($CHCl_3$, cm^{-1}) 3056, 2985, 1740, 1265; HRMS calcd for $C_{24}H_{20}SO_4$ 404.1082, found 404.1088.

Ethyl [2-(phenylethynyl)phenyl]acetate (41). Obtained as a pale yellow oil in 98 % isolated yield (Table 6, entry 5): ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 7.2 Hz, 3 H), 3.90 (s, 2 H), 4.15 (q, J = 7.2 Hz, 2 H), 7.26-7.34 (m, 6 H), 7.52-7.55 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 40.4, 61.0, 87.5, 94.0, 123.3, 123.6, 127.2, 128.4, 128.5, 128.6, 130.0, 131.6, 132.1, 136.5, 171.3; IR ($CHCl_3$, cm^{-1}) 3056, 2982, 1733, 1265; HRMS calcd for $C_{18}H_{16}O_2$ 264.1150, found 264.1156.

1-Phenylethynyl-2-(phenylsulfonylmethyl)benzene (43). Obtained as a pale yellow oil in 99 % isolated yield (Table 6, entry 6): ^{1}H NMR ($CDCl_3$) 4.68 (s, 2 H), 7.26-7.37 (m, 10 H), 7.48 (t, J = 7.2 Hz, 2 H), 7.58 (d, J = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 60.8, 86.5, 93.7, 122.6, 124.7, 128.5, 128.6, 128.7, 128.8, 128.9, 129.9, 131.4, 131.6, 132.2, 133.7, 138.1; IR ($CHCl_3$, cm^{-1}) 3054, 2926, 1713, 1265; HRMS calcd for $C_{21}H_{16}SO_2$ 332.0871, found 332.0877.

General procedure for the copper-catalyzed intramolecular cyclization of the alkynes . To a solution of the alkyne (0.25 mmol) in THF (5 mL) was added CuI (0.005 mmol) and *t*-BuOK (0.0125 mmol). The reaction mixture was stirred under a nitrogen atmosphere at 55 °C for 2 h. The mixture was then cooled, diluted with ether, and washed with satd NH_4Cl (aq). The organic layer was dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by column chromatography

using hexanes/EtOAc as the eluent. The following compounds were prepared using the above general procedure.

Diethyl 2-*n*-hexyl-1*H*-indene-1,1-dicarboxylate (3). Obtained as a pale yellow oil in 96 % isolated yield (Table 5, entry 1): ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 3 H), 1.25 (t, J = 7.2 Hz, 6 H), 1.35 (m, 6 H), 1.66 (m, 2 H), 2.51 (m, 2 H), 4.21 (m, 4 H), 6.63 (t, J = 1.8 Hz, 1 H), 7.26 (m, 3 H), 7.57 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 22.9, 28.1, 28.7, 29.5, 30.0, 62.1, 72.2, 120.8, 125.0, 125.4, 128.8, 130.0, 140.9, 144.7, 148.5, 168.5; IR ($CHCl_3$, cm^{-1}) 3048, 2983, 1758, 1471; HRMS calcd for $C_{21}H_{28}O_4$ 334.1988, found 334.1994.

Diethyl 2-*n*-butyl-1*H*-indene-1,1-dicarboxylate (5). Obtained as a pale yellow oil in 92 % isolated yield (Table 5, entry 2): ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J = 7.2 Hz, 3 H), 1.27 (t, J = 7.2 Hz, 6 H), 1.48 (m, 2 H), 1.70 (m, 2 H), 2.56 (m, 2 H), 4.23 (m, 4 H), 6.66 (t, J = 1.6 Hz,1 H), 7.18-7.33 (m, 3 H), 7.61 (d, J = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 22.7, 28.3, 30.1, 61.9, 72.0, 120.6, 124.8, 125.3, 128.6, 129.7, 140.7, 144.5, 148.3, 168.3; IR ($CHCl_3$, cm^{-1}) 2959, 2932, 1732, 1467, 1235; HRMS calcd for $C_{19}H_{24}O_4$ 316.1675, found 316.1678.

Diethyl 2-methoxymethyl-1*H*-indene-1,1-dicarboxylate (7). Obtained as a pale yellow oil in 91 % isolated yield (Table 5, entry 3): ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3 H), 3.41 (s, 3 H), 4.20 (m, 4 H), 4.43 (d, J = 1.6 Hz, 2 H), 6.88 (d, J = 1.2 Hz, 1 H), 7.25 (m, 3 H), 7.61 (d, J = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 58.6, 62.2, 69.6, 70.5, 121.3, 125.1, 126.0, 128.7, 132.1, 140.8, 143.3, 143.5, 167.8; IR ($CHCl_3$, cm^{-1}) 2984, 1733, 1464, 1244; HRMS calcd for $C_{17}H_{20}O_5$ 304.1311, found 304.1316.

Diethyl 2-(9-hydroxy-1-nonyl)-1*H*-indene-1,1-dicarboxylate (9). Obtained as a pale yellow oil in 79 % isolated yield (Table 5, entry 4): ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7.2 Hz, 6 H), 1.30-1.66 (m, 15 H), 2.47 (t, J = 7.2 Hz, 2 H), 3.59 (t, J = 6.8 Hz, 2 H), 4.17 (m, 4 H), 6.60 (s, 1 H), 7.15 (dt, J = 1.2, 7.2 Hz, 1 H), 7.20 (d, J = 7.2 Hz, 1 H), 7.26 (t, J = 7.2 Hz, 1 H), 7.55 (d, J = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 25.8, 27.9, 28.5, 29.4, 29.5, 29.6,

32.8, 61.9, 63.0, 72.0, 120.6, 124.8, 125.3, 128.6, 129.7, 140.7, 144.5, 148.3, 168.5; IR ($CHCl_3$, cm^{-1}) 2930, 1733, 1725, 1242; HRMS calcd for $C_{24}H_{34}O_5$ 402.2406, found 402.2413.

Diethyl 2-(9-methoxy-9-oxo-1-nonyl)-1*H*-indene-1,1-dicarboxylate (11). Obtained as a pale yellow oil in 83 % isolated yield (Table 5, entry 5): ^1H NMR ($CDCl_3$) δ 1.22 (dt, J = 1.2, 7.2 Hz, 6 H), 1.36-1.64 (m, 12 H), 2.28 (t, J = 7.2 Hz, 2 H), 2.48 (m, 2 H), 3.64 (s, 3 H), 4.18 (m, 4 H), 6.60 (s, 1 H), 7.14-7.26 (m, 3 H), 7.54 (d, J = 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 25.0, 27.9, 28.5, 29.2, 29.3, 29.4, 29.5, 34.1, 54.5, 61.9, 72.0, 120.6, 124.8, 125.3, 128.6, 129.7, 140.7, 144.5, 148.2, 168.3, 174.4; IR ($CHCl_3$, cm^{-1}) 2982, 1734, 1718, 1240; HRMS calcd for $C_{25}H_{34}O_6$ 430.2355, found 430.2362.

Diethyl 2-diethoxymethyl-1*H*-indene-1,1-dicarboxylate (13). Obtained as a pale yellow oil in 58 % isolated yield (Table 5, entry 6): ^1H NMR ($CDCl_3$) δ 1.23 (m, 12 H), 3.61 (m, 2 H), 3.73 (m, 2 H), 4.18 (m, 4 H), 5.91 (d, J = 1.2 Hz, 1 H), 7.00 (s, 1 H), 7.24 (m, 1 H), 7.31 (m, 1 H), 7.63 (d, J = 7.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 15.3, 61.9, 62.1, 70.1, 99.1, 121.8, 124.9, 126.4, 128.6, 132.7, 141.7, 143.1, 144.3, 167.9; IR ($CHCl_3$, cm^{-1}) 3055, 2980, 1732, 1682, 1266; HRMS calcd for $C_{20}H_{26}O_6$ 362.1729, found 362.1734.

Diethyl 2-(3-cyano-1-propyl)-1*H*-indene-1,1-dicarboxylate (15). Obtained as a pale yellow oil in 68 % isolated yield (Table 5, entry 7): ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 6 H), 2.04 (t, J = 7.2 Hz, 2 H), 2.45 (t, J = 7.2, 2 H), 2.67 (m, 2 H), 4.20 (m, 4 H), 6.64 (s, 1 H), 7.24 (m, 3 H), 7.57 (d, J = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 16.8, 23.9, 27.6, 62.1, 71.9, 119.6, 120.9, 125.1, 125.8, 128.8, 130.9, 140.5, 145.1, 167.9; IR ($CHCl_3$, cm^{-1}) 3253, 2985, 2253, 1721, 1265; HRMS calcd for $C_{19}H_{24}NO_4$ 327.1471, found 327.1475.

Diethyl 2-*tert*-butyl-1*H*-indene-1,1-dicarboxylate (17). Obtained as a pale yellow oil in 69 % isolated yield (Table 5, entry 8): ^1H NMR ($CDCl_3$) δ 1.14 (t, J = 7.2 Hz, 6 H), 1.28 (s, 9 H), 4.11 (m, 4 H), 6.78 (s, 1 H), 7.11 (dt, J = 1.2, 7.6 Hz, 1 H), 7.23 (m, 2 H), 7.41 (d, J = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 31.2, 34.8, 61.6, 70.6, 120.6, 123.1, 125.4, 128.4,

131.2, 142.3, 144.1, 157.5, 168.8; IR ($CHCl_3$, cm^{-1}) 3057, 2965, 1750, 1715, 1222; HRMS calcd for $C_{19}H_{24}O_4$ 316.1675, found 316.1678.

Diethyl 2-cyclohexyl-1*H*-indene-1,1-dicarboxylate (21). Obtained as a pale yellow oil in 92 % isolated yield (Table 5, entry 10): ^1H NMR ($CDCl_3$) δ 1.23-1.35 (m, 11 H), 1.70-1.91 (m, 5 H), 2.53 (m, 1 H), 4.18 (m, 4 H), 6.64 (s, 1 H), 7.15 (dt, *J* = 1.2, 7.8 Hz, 1 H), 7.20 (d, *J* = 6.8 Hz, 1 H), 7.26 (dt, *J* = 1.2, 7.6 Hz, 1 H), 7.54 (dd, *J* = 1.2, 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 26.3, 26.9, 34.6, 38.1, 61.9, 71.9, 120.7, 124.8, 125.4, 128.6, 129.4, 140.2, 144.6, 153.9, 168.5; IR ($CHCl_3$, cm^{-1}) 3019, 2929, 1733, 1216; HRMS calcd for $C_{21}H_{26}O_4$ 342.1831, found 342.1837.

Diethyl 2-(1-cyclohexenyl)-1*H*-indene-1,1-dicarboxylate (23). Obtained as a pale yellow oil in 85 % isolated yield (Table 5, entry 11): ^1H NMR ($CDCl_3$) δ 1.15 (t, *J* = 7.2 Hz, 6 H), 1.61 (m, 2 H), 1.74 (m, 2 H), 2.20 (m, 2 H), 2.36 (m, 2 H), 4.17 (m, 4 H), 6.04 (t, *J* = 4.2 Hz, 1 H), 6.79 (s, 1 H), 7.16 (m, 1 H), 7.27 (m, 2 H), 7.53 (dd, *J* = 0.9, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.1, 22.8, 26.1, 26.7, 61.7, 69.7, 122.3, 123.6, 125.7, 128.3, 128.7, 129.0, 130.5, 142.2, 144.2, 147.9, 168.7; IR ($CHCl_3$, cm^{-1}) 2981, 1734, 1237; HRMS calcd for $C_{21}H_{24}O_4$ 340.1675, found 340.1678.

Diethyl 2-phenyl-1*H*-indene-1,1-dicarboxylate (25). Obtained as a pale yellow oil in 61 % isolated yield (Table 5, entry 12): ^1H NMR ($CDCl_3$) δ 1.07 (t, *J* = 7.2 Hz, 6 H), 4.14 (m, 4 H), 7.24-7.36 (m, 7 H), 7.62 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 62.1, 70.9, 121.7, 124.2, 126.3, 127.4, 127.9, 128.2, 128.9, 131.5, 134.1, 142.1, 143.7, 145.7, 168.3; IR ($CHCl_3$, cm^{-1}) 3019, 2988, 1734, 1217; HRMS calcd for $C_{21}H_{20}O_4$ 336.1362, found 336.1366.

Diethyl 2-[4-(ethoxycarbonyl)phenyl]-1*H*-indene-1,1-dicarboxylate (27). Obtained as a pale yellow oil in 65 % isolated yield (Table 5, entry 13): ^1H NMR ($CDCl_3$) δ 1.06 (t, *J* = 7.2 Hz, 6 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 4.12 (m, 4 H), 4.36 (q, *J*= 7.2 Hz, 2 H), 7.24-7.40 (m, 3 H), 7.65 (d, *J* = 8.4 Hz, 3 H), 8.00 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 14.4, 61.0, 62.2,

70.8, 122.1, 124.4, 127.0, 127.1, 129.1, 129.4, 129.5, 133.6, 138.4, 142.3, 143.1, 144.5, 166.4, 168.0; IR ($CHCl_3$, cm^{-1}) 3020, 2982, 1719, 1724, 1283; HRMS calcd for $C_{24}H_{24}O_6$ 408.1573, found 408.1580.

Diethyl 2-(4-methoxyphenyl)-1*H*-indene-1,1-dicarboxylate (29). Obtained as a pale yellow oil in 96 % isolated yield (Table 5, entry 14): ^1H NMR ($CDCl_3$) δ 1.08 (t, *J* = 7.2 Hz, 6 H), 3.80 (s, 1 H), 4.12 (m, 4 H), 6.87 (dt, *J* = 2.0, 9.2 Hz, 2 H), 7.18 (s, 1 H), 7.21 (m, 1 H), 7.32 (m, 2 H), 7.55 (dt, *J* = 2.0, 8.8 Hz, 2 H), 7.62 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 55.3, 62.0, 70.9, 113.6, 121.3, 124.1, 125.9, 126.7, 128.7, 128.9, 129.6, 141.9, 144.0, 145.3, 159.5, 168.5; IR ($CHCl_3$, cm^{-1}) 3068, 2981, 1734, 1253; HRMS calcd for $C_{22}H_{22}O_5$ 366.1467, found 366.1473.

Diethyl (2-ethynylphenyl)malonate (30). Obtained as a pale yellow oil in 81 % isolated yield (eq 9): ^1H NMR ($CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 6 H), 3.32 (s, 1 H), 4.25 (m, 4 H), 5.32 (s, 1 H), 7.29 (dt, *J* = 1.2, 7.6 Hz, 1 H), 7.38 (dt, *J* = 1.6, 7.6 Hz, 1 H), 7.52 (dt, *J* = 1.2, 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 55.5, 61.9, 81.2, 82.3, 122.6, 128.0, 128.8, 129.2, 132.8, 135.3, 168.0; IR ($CHCl_3$, cm^{-1}) 3297, 3053, 2983, 1749, 1733, 1265; HRMS calcd for $C_{15}H_{16}O_4$ 260.1049, found 260.1052.

Ethyl 1-cyano-2-*n*-hexyl-1*H*-indene-1-carboxylate (33). Obtained as a pale yellow oil in 83 % isolated yield (Table 6, entry 1): ^1H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 3 H), 1.27-1.1.47 (m, 9 H), 1.74 (m, 2 H), 2.49 (m, 2 H), 4.28 (m, 2 H), 6.71 (s, 1 H), 7.26 (t, *J* = 7.6 Hz, 1 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 7.38 (d, *J* = 7.6 Hz, 1 H), 7.57 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 22.6, 27.8, 28.2, 29.1, 31.7, 58.5, 63.5, 116.4, 121.5, 123.2, 126.4, 129.9, 130.8, 139.3, 144.0, 146.1, 165.4; IR ($CHCl_3$, cm^{-1}) 3020, 2930, 2246, 1743, 1217; HRMS calcd for $C_{19}H_{23}NO_2$ 297.1729, found 297.1733.

Ethyl 1-cyano-2-cyclohexyl-1*H*-indene-1-carboxylate (35). Obtained as a pale yellow oil in 78 % isolated yield (Table 6, entry 2): ^1H NMR ($CDCl_3$) δ 1.25-1.44 (m, 8 H), 1.72-

1.94 (m, 4 H), 2.21 (m, 1 H), 2.44 (m, 1 H), 4.24 (m, 2 H), 6.74 (m, 1 H), 7.24 (dt, J = 1.5, 7.5 Hz, 1 H), 7.29 (d, J = 6.9 Hz, 1 H), 7.36 (dt, J = 1.2, 7.5 Hz, 1 H), 7.52 (d, J = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 26.2, 26.6, 26.7, 33.1, 33.7, 38.6, 58.2, 63.6, 116.7, 121.8, 123.1, 126.7, 130.0, 130.8, 139.5, 144.1, 151.3, 165.9; IR ($CHCl_3$, cm^{-1}) 3020, 2932, 2250, 1710, 1217; HRMS calcd for $C_{19}H_{21}NO_2$ 295.1572, found 295.1577.

Ethyl 2-phenyl-1-phenylsulfonyl-1*H*-indene-1-carboxylate (39). Obtained as a pale yellow oil in 36 % isolated yield (Table 6, entry 4): ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3 H), 4.35 (m, 2 H), 6.96 (s, 1 H), 7.01 (dd, J = 1.2, 8.4 Hz, 2 H), 7.09 (t, J = 8.0 Hz, 2 H), 7.14 (d, J = 6.8 Hz, 1 H), 7.34-7.41 (m, 6 H), 7.51 (dt, J= 1.6, 8.0 Hz, 2 H), 7.96 (d, J = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 63.0, 84.0, 121.7, 126.2, 126.7, 127.4, 127.9, 128.3, 128.5, 130.0, 130.2, 132.7, 133.7, 134.3, 135.4, 138.1, 142.9, 143.9, 165.8; IR ($CHCl_3$, cm^{-1}) 3062, 2982, 1718, 1195; HRMS calcd for $C_{24}H_{20}SO_4$ 404.1082, found 404.1088.

References

1. (a) Kikuchi, T.; Tottori, K.; Uwahodo, Y. PCT Int. Appl. 9621449, **1996**; *Chem. Abstr.* **1996**, *125*, 204539. (b) Mederski, W.; Dorsch, D.; Wilm, C.; Osswald, M. Schmitges, C. Ger. Offen. 1971785, **1998**; *Chem. Abstr.* **1998**, *129*, 275905. (c) Dillard, R.; Hagishita, S.; Ohtani, M. PCT Int. Appl. 9603120, **1996**; *Chem. Abstr.* **1996**, *125*, 341826.
2. Spaleck, W.; Antberg, M.; Dolle, V.; Klein, R.; Rohrmann, J.; Winter, A. *New J. Chem.* **1990**, *14*, 499.
3. (a) Prough, J.; Alberts, A.; Deanna, A.; Gilfillian, J.; Huff, R.; Smith, J.; Wiggins, J. *J. Med. Chem.* **1990**, *33*, 758. (b) Olivier, M.; Marechal, E. *Bull. Soc. Chim. Fr.* **1973**, 3092. (c) Normant, C. *Bull. Soc. Chim. Fr.* **1971**, 1351. (d) Ikeda, S.; Chatani, N.; Kajikawa, Y.; Ohe, K.; Murai, S. *J. Org. Chem.* **1992**, *57*, 2. (e) Becker, C.; McLaughlin, M. *Synlett* **1991**, 642.

4. Miller, W.; Pittman, C. *J. Org. Chem.* **1974**, *39*, 1955.

5. Yoshida, H.; Kato, M.; Ogata, T. *J. Org. Chem.* **1985**, *50*, 1145.

6. Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111.

7. (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

8. Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.

9. Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.

10. Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306.

11. Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579.

12. (a) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.

13. Yum, E. K. *Ph. D. dissertation*, Iowa State University, **1992**.

14. Tsukada, N.; Yamanoto, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2477.

15. (a) Trost, B. M.; Chan, C.; Ruhter, C. *J. Am. Chem. Soc.* **1987**, *109*, 3486. (b) Trost, B. M.; Kottirsch, G. *J. Am. Chem. Soc.* **1990**, *112*, 2816.

16. Arcadi, A.; Cacchi, S.; Fabrizi. G.; Manna, F.; Pace, P. *Synlett* **1998**, *4*, 446.

17. Kitagawa, O.; Fujiwara, H.; Suzuki, T.; Taguchi, T.; Shio, M. *J. Org. Chem.* **2000**, *65*, 6819.

18. Monteiro, N.; Gore, G.; Balme, G. *Tetrahedron* **1992**, *48*, 10103.

19. Bouyssi, D.; Monteiro, N.; Balme, G. *Tetrahedron Lett.* **1999**, *40*, 1297.

20. Sonogashira, K. *Comprehensive Organic Synthesis*, Vol. 3, Pergamon, Oxford, **1990**, 521.

21. Harrison, L. W. *Ph. D. dissertation*, Iowa State University, **1989**.

CHAPTER 3. SYNTHESIS OF INDENES BY THE PALLADIUM-CATALYZED ARYLATION OF ARYLALKYNES BEARING A CARBON NUCLEOPHILE

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Abstract

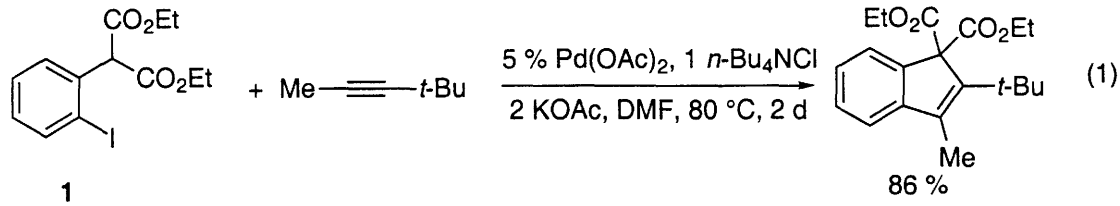
A number of highly substituted indenes have been prepared in good yields by treating arylalkynes bearing a carbon nucleophile with various aryl halides in the presence of a palladium catalyst. The reaction is believed to proceed by coordination of an arylpalladium (II) intermediate to the alkyne triple bond and subsequent intramolecular nucleophilic attack of the carbanion on the activated triple bond.

Introduction

The indene ring system is present in drug candidates possessing interesting biological activities[1] and metallocene complexes catalyzing olefin polymerization.[2] This has encouraged the development of a number of approaches for the synthesis of the indene ring system, including the reduction/dehydration of indanones,[3] the cyclization of phenyl-substituted allylic alcohols,[4] and the ring expansion of substituted cyclopropenes.[5] All these routes are of limited scope due to the strong acid medium employed, lengthy reaction sequences, and low tolerance of functionality.

The synthesis of indenes has also been achieved by the palladium-catalyzed carbo-annulation of internal alkynes by aryl halides (eq 1).[6] For instance, in the presence of 5 mol % of $Pd(OAc)_2$, 2 equiv of KOAc, 1 equiv of *n*-Bu_4NCl in DMF at 80 °C, the reaction of

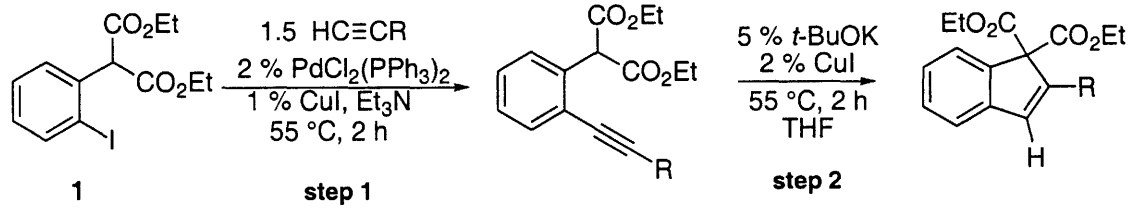
diethyl (2-iodophenyl)malonate **1** with 4,4-dimethyl-2-pentyne affords an 86 % yield of the desired indene product after 2 d.



(1)

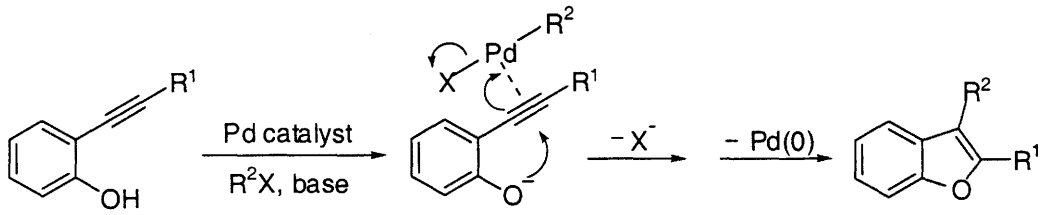
A two-step procedure has also been developed to synthesize various indene derivatives by the annulation of terminal alkynes by aryl halides (Scheme 1).[7] The procedure involves the Pd/Cu-catalyzed Sonogashira coupling[8] of terminal alkynes with aryl halides, followed by copper-catalyzed intramolecular cyclization of the aryl alkyne intermediate. The copper-catalyzed intramolecular cyclization presumably proceeds by intramolecular nucleophilic attack of the carbanion on the triple bond activated by coordination to copper.

Scheme 1



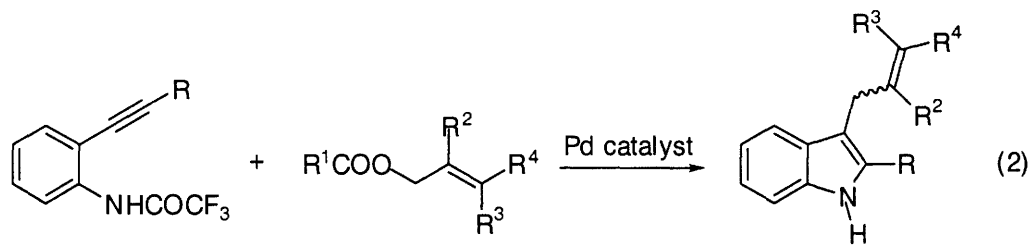
The transition metal-catalyzed cyclization of alkynes containing nucleophilic centers close to the carbon-carbon triple bond has proven to be extremely effective for the synthesis of a wide variety of carbo- and heterocycles.[9] This type of cyclization can also be promoted by vinylic, allyllic, aryl and alkynylpalladium complexes. For example, Cacchi and coworkers have developed a valuable new route to the synthesis of 2,3-disubstituted benzofurans by palladium-catalyzed heterocyclization (Scheme 2).[10] The furan ring is generated through a cyclization reaction promoted by σ-vinyl- or σ-arylpalladium complexes and involving the nucleophilic attack of a phenoxide onto the carbon-carbon triple bond coordinated to palladium.

Scheme 2



R^1 = alkyl, vinylic, aryl
R^2 = vinylic, aryl; X = I, OTf

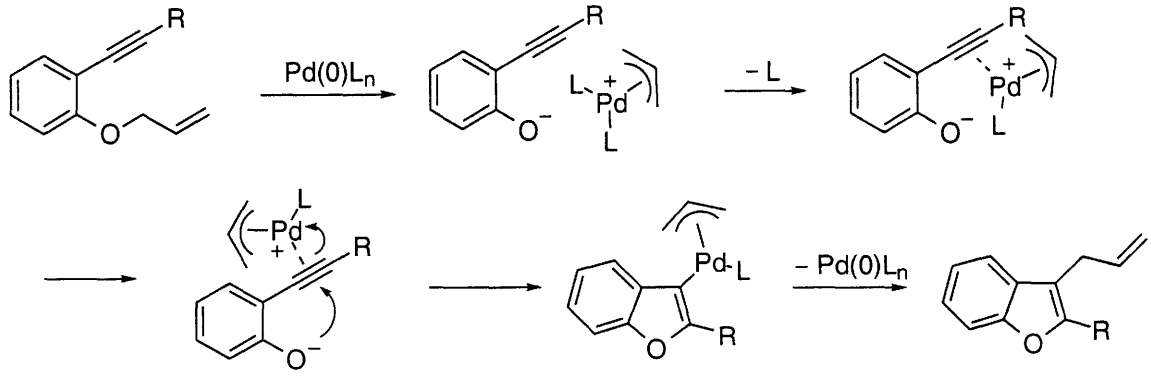
Cacchi later described a regioselective synthesis of 3-allylic indoles by the palladium-catalyzed cyclization of *o*-alkynyltrifluoroacetanilides promoted by allyl esters (eq 2).[11] Thus, η^3-allyl-palladium complexes have been successfully utilized to promote the cyclization of alkynes containing nitrogen nucleophiles. The reaction exhibits remarkable regioselectivity and almost exclusively forms 3-allylic indoles with the indolyl moiety bound to the less substituted allyl terminus. Some loss of olefin geometry is observed.



(2)

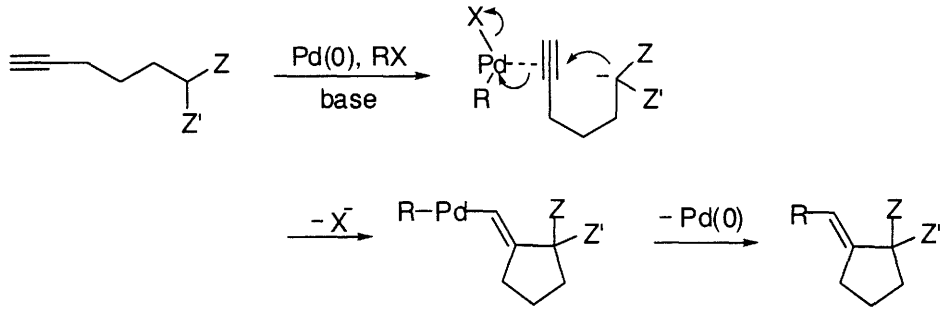
Monterio and Balme have adopted a similar palladium-catalyzed heteroallylation method to synthesize 2-substituted-3-allylic benzofurans (Scheme 3).[12] To avoid the direct *endo-dig* cyclization of *o*-alkynylphenols,[10,13] they started from *o*-alkynyl(allyloxy)benzenes to generate η^3-allylpalladium complexes *in situ*. In this way, the allylic moiety can be internally delivered, allowing the reaction to occur in a completely neutral medium.

Scheme 3



Balme and Gore have also developed a stereospecific synthesis of arylidene and allylidene cyclopentanes by palladium-catalyzed carbocyclization (Scheme 4).[14] Vinylic and aryl halides react with ε-acetylenic β-diesters, β-keto esters and β-sulfonyl esters in the presence of a Pd(0) catalyst to provide in good yields of cyclopentane derivatives with an *E* configuration. This process is believed to proceed by intramolecular nucleophilic attack of the carbanion on the triple bond activated by coordination of the σ-aryl- or σ-vinylpalladium complexes.

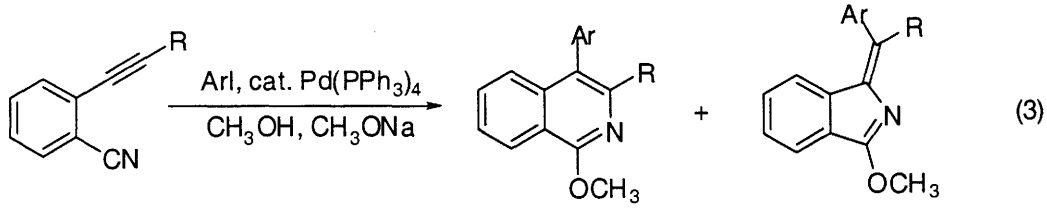
Scheme 4



Z = CO_2Me; Z' = CO_2Me, COMe, SO_2Ph
R = aryl, vinylic; X = Br, I

Wei, Lin and Wu have described a new strategy for the synthesis of 3,4-disubstituted isoquinolines and diarylmethylidene isoindoles employing the cross-coupling and cyclization of

2-alkynylbenzonitriles with aryl iodides (eq 3).[15] The reaction of 2-(2-phenylethynyl)benzonitrile with aryl iodides affords the corresponding isoindole products in 18-56 % yields. When 2-(1-hexynyl)benzonitrile was employed in this reaction, a mixture of isoquinolines and isoindoles were obtained in low yields.

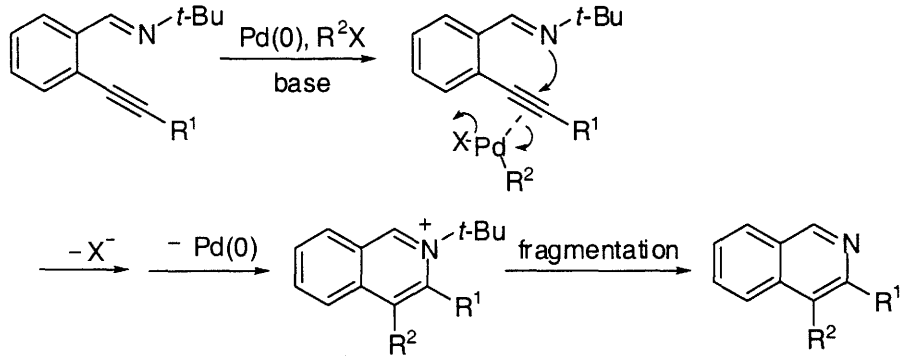


(3)

R = Ph, *n*-Bu
Ar = Ph, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$

Larock and Dai has recently reported a more efficient synthesis of 3,4-disubstituted isoquinolines by palladium-catalyzed cross coupling of *o*-(1-akynyl)benzaldimines and organic halides (Scheme 5).[16] This method also involves intramolecular nucleophilic attack of a nitrogen atom on the triple bond promoted by coordination of a σ-aryl-, σ- allyl, or σ-alkynylpalladium complex.

Scheme 5

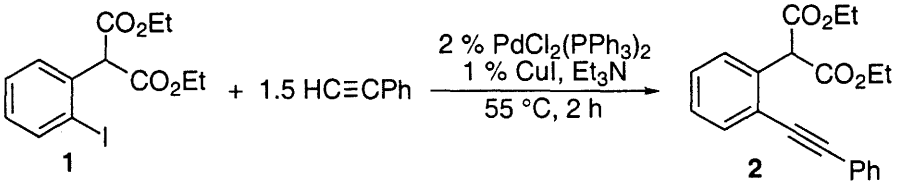


R^1 = alkyl, aryl
R^2 = aryl, allylic, alkynyl; X = Cl, Br, I

This successful utilization of *o*-(1-alkynyl)benzaldimines as precursors for the synthesis of 3,4-disubstituted isoquinolines and our continuing interest in palladium-catalyzed intramolecular cyclizations has prompted us to explore the extension of this methodology to the synthesis of indenes. Herein we wish to report the synthesis of 3,4-diarylsubstituted indenes by the palladium-catalyzed carboarylation of arylalkynes bearing a carbon nucleophile by various aryl halides.

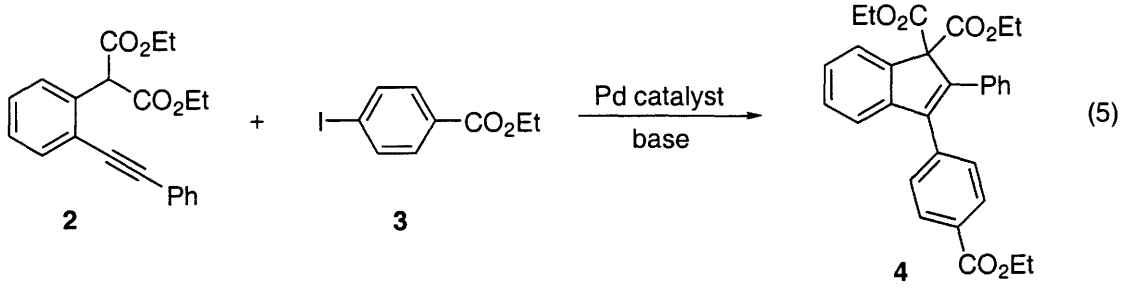
Results and Discussion

The starting 2-(1-alkynyl)phenylmalonates have been prepared by Sonogashira coupling of diethyl (2-iodophenyl)malonate **1** with various terminal alkynes. For example, diethyl 2-(phenylethynyl)phenylmalonate **2** was isolated in 98 % yield when diethyl (2-iodophenyl)malonate **1** was treated with phenylacetylene in the presence of 2 mol % of $PdCl_2(PPh_3)_2$ and 1 mol % of CuI in Et_3N (eq 4).



(4)

Initial studies were aimed at finding optimal reaction conditions for the palladium-catalyzed intramolecular carbocyclization of this alkyne by ethyl *p*-iodobenzoate (eq 5). The results are summarized in Table 1.



(5)

Table 1. Optimization of the palladium-catalyzed arylation of diethyl [2-(phenylethynyl)phenyl]malonate 2 (eq5).[a]

entry	aryl halide **3** equiv	Pd catalyst	pd catalyst (mol %)	base	base equiv	solvent	temperature (°C)	% yield
1	5	$Pd(PPh_3)_4$	5	K_2CO_3	5	DMF	100	68
2	3	$Pd(PPh_3)_4$	5	K_2CO_3	5	DMF	100	77
3	2	$Pd(PPh_3)_4$	5	K_2CO_3	5	DMF	100	47
4	3	$Pd(OAc)_2$	5	K_2CO_3	5	DMF	100	62
5	3	$PdCl_2$	5	K_2CO_3	5	DMF	100	45
6	3	$PdCl_2(PPh_3)_2$	5	K_2CO_3	5	DMF	100	72
7	3	$Pd_2(dba)_3 \cdot CHCl_3$	5	K_2CO_3	5	DMF	100	52
8	3	$Pd(PPh_3)_4$	2	K_2CO_3	5	DMF	100	86
9	3	$Pd(PPh_3)_4$	2	KOAc	5	DMF	100	50[b]
10	3	$Pd(PPh_3)_4$	2	Na_2CO_3	5	DMF	100	38[c]
11	3	$Pd(PPh_3)_4$	2	Cs_2CO_3	5	DMF	100	75
12	3	$Pd(PPh_3)_4$	2	pyridine	5	DMF	100	0[d]
13	3	$Pd(PPh_3)_4$	2	NEt_3	5	DMF	100	0[e]
14	3	$Pd(PPh_3)_4$	2	K_2CO_3	3	DMF	100	82
15	3	$Pd(PPh_3)_4$	2	K_2CO_3	2	DMF	100	70
16	3	$Pd(PPh_3)_4$	2	K_2CO_3	3	DMSO	100	68
17	3	$Pd(PPh_3)_4$	2	K_2CO_3	3	THF	100	63

Table 1. (continued)

18	3	$Pd(PPh_3)_4$	2	K_2CO_3	3	DMF	120	59
19	3	$Pd(PPh_3)_4$	2	K_2CO_3	3	DMF	80	84[f]

[a] All reactions were run on a 0.25 mmol scale in 5 mL of the solvent for 3 h. [b] An 8 % yield of **2** was recovered. [c] A 12 % yield of **2** was recovered. [d] A 50 % yield of **2** was recovered. [e] An 84 % yield of **2** was recovered. [f] The reaction was run for 9 h.

The reaction was first attempted using the optimum reaction condition for the synthesis of 3,4-disubstituted isoquinolines.[16] The reaction was run using diethyl 2-(phenylethynyl) phenylmalonate **2** (0.25 mmol), 5 equiv of ethyl 2-iodobenzoate **3**, 5 mol % of $Pd(PPh_3)_4$, and 5 equiv of K_2CO_3 in 5 mL of DMF at 100 °C. After 3 h, the reaction afforded a 68 % yield of the desired arylation product **4** alongside a small amount of material which appeared to arise by homo-coupling of the aryl halide (Table 1, entry 1). To minimize the formation of the homo-coupling product, the amount of the aryl halide was deceased to 3 equiv. The reaction furnished a 77 % yield of the desired product and a reduced amount of the homo-coupling product (Table 1, entry 2). Any further reduction in the amount of ethyl 2-iodo-benzoate **3** resulted in a much lower yield of the desired product (Table 1, entry 3).

We have also explored the effect of different palladium catalysts on the outcome of the reaction (Table 1, entries 2 and 4-7). $Pd(PPh_3)_4$ have given the best result based on our investigation. Decreasing the amount of $Pd(PPh_3)_4$ to 2 mol % provided the desired product in an improved 86 % yield (Table 1, entry 8).

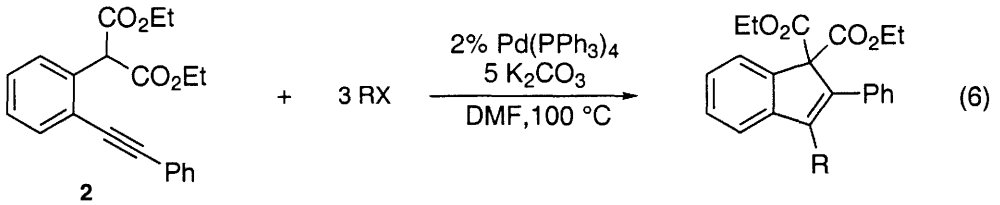
Other inorganic bases were examined as an alternative to K_2CO_3 and the yields were generally lower than that from the reaction using K_2CO_3 as the base (Table 1, entries 9-11). The use of organic bases, such as NEt_3 and pyridine, didn't afforded any of the desired product (Table 1, entries 12 and 13). Decreasing the amount of K_2CO_3 to 3 equiv gave a slightly lower yield of the desired product than the reaction using 5 equiv of K_2CO_3 (Table 1, entry 14). The yield was much lower when less than 3 equiv of K_2CO_3 were used (Table 1, entry 15).

The reaction provided lower yields of the desired product when other organic solvents were used instead of DMF (Table 1, entries 16 and 17). Raising the reaction temperature to 120 °C gave a low yield of the desired product and a large amount of homo-coupling product from the aryl iodide substrate was isolated (Table 1, entry 18). The reaction afforded a high

yield of the desired product when the reaction was run at 80 °C. However, the reaction took a much longer time to complete (Table 1, entry 19).

On the basis of the above optimization efforts, the combination of diethyl 2-(phenylethynyl)phenylmalonate **2** (0.25 mmol), 3 equiv of aryl halide, 2 mol % of $Pd(OAc)_2$, and 5 equiv of K_2CO_3, in 5 mL of DMF at 100 °C for 3 h gave the best result (Table 1, entry 8).

Having gained an understanding of the factors that influence the arylation process, we have explored the scope and limitation of this methodology (eq 6). The results are summarized in Table 2.

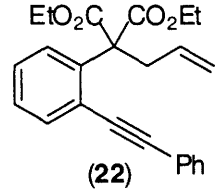
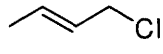
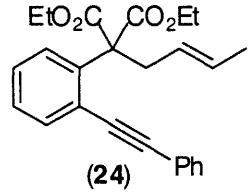
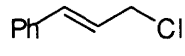
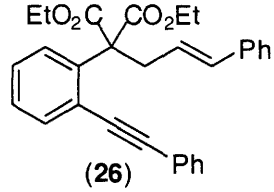
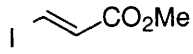
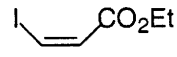
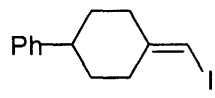
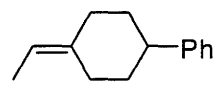
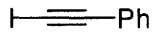
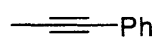
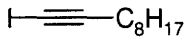
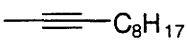
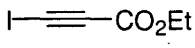


(6)

Table 2. Palladium-catalyzed cyclization of diethyl 2-(phenylethynyl)phenyl malonate 2 using various organic halides (eq 6).[a]

entry	RX	product	% yield
1	*p*-$EtO_2CC_6H_4I$	R = *p*-$EtO_2CC_6H_4$ (**4**)	86
2	*m*-$EtO_2CC_6H_4I$	R = *m*-$EtO_2CC_6H_4$ (**5**)	74
3	o-$EtO_2CC_6H_4I$	R = *o*-$EtO_2CC_6H_4$ (**6**)	78
4	*p*-$O_2NC_6H_4I$	R = *p*-$O_2NC_6H_4$ (**7**)	83
5	*m*-$O_2NC_6H_4I$	R = *m*-$O_2NC_6H_4$ (**8**)	82
6	*o*-$O_2NC_6H_4I$	R = H (**9**)	38[b]
7	*p*-$F_3CC_6H_4I$	R = *p*-$F_3CC_6H_4$ (**10**)	85
8	*m*-$F_3CC_6H_4I$	R = *m*-$F_3CC_6H_4$ (**11**)	91
9	*o*-$F_3CC_6H_4I$	R = *o*-$F_3CC_6H_4$ (**12**)	53[c]
10	*p*-$CH_3COC_6H_4I$	R = *p*-$CH_3COC_6H_4$ (**13**)	94
11	*p*-ClC_6H_4I	R = *p*-ClC_6H_4 (**14**)	84
12	3-iodopyridine	R = H (**9**)	18
13	2-iodothiophene	2-thienyl (**15**)	64
14	C_6H_5I	R = C_6H_5 (**16**)	72[b]
15	*p*-$H_3CC_6H_4I$	R = *p*-$H_3CC_6H_4$ (**17**)	69

Table 2. (continued)

16	*m*-$H_3CC_6H_4I$	R = *m*-$H_3CC_6H_4$ (**18**)	74
17	*o*-$H_3CC_6H_4I$	R = *o*-$H_3CC_6H_4$ (**19**)	73
18	*p*-$H_3COC_6H_4I$	R =*p*-$H_3COC_6H_4$ (**20**)	14[c]
19	C_6H_4Br	R = C_6H_5 (**16**)	75
20	C_6H_4Cl	R = H (**9**)	71
21	*p*-$O_2NC_6H_4Cl$	R = *p*-$O_2NC_6H_4$ (**7**)	34[e]
22	C_6H_4OTf	R = H (**9**)	38
23	allyl bromide	R = $CH_2CH{=}CH_2$ (**21**)	51[f]
24	diallyl carbonate	 (**22**)	86
25	 **23**	 (**24**)	79
26	 **25**	 (**26**)	83
27	 **27**	(**2**)	77
28	 **28**	(**2**)	63
29	 **29**	R = 	o[g]
30	 **30**	R = 	0[h]
31	 **31**	R = 	0[h]
32	 **32**	(**2**)	10[h]

[a] See the text and Experimental Section for the detailed procedure. [b] The reaction was run for 12 h. [c] A 17 % yield of **9** was isolated. [d] A 23 % yield of **15** was isolated. [e] A 55 % yield of **9** was

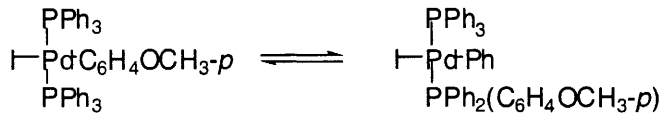
isolated. [f] The yield was determined by ^{1}H NMR spectroscopy. [g] The reaction was messy and there were many spots shown on tlc plate. [h]. A large amount of unrecognizable polymer was obtained.

The reactions of diethyl 2-(phenylethynyl)phenylmalonate **2** with ethyl *p*-, *m*- and *o*-iodobenzoates afforded the desired indenes in good yields, indicating that there is no significant steric effect in this reaction (Table 2, entries 1-3). Similarly *p*- and *m*-iodonitrobenzenes reacted with alkyne **2** to give high yields of the desired products (Table 2, entries 4 and 5). On the other hand, the reaction of *o*-iodonitrobenzene with alkyne **2** gave none of the desired arylation product for reasons that are not obvious and produced significant amounts of hydrogen-containing indene cyclization product **9** (Table 2, entry 6). The reactions of *p*- and *m*-(trifluoromethyl)iodobenzenes with alkyne **2** generated the desired products in good yields, while *o*-(trifluoromethyl)iodobenzene gave only a 53 % yield of the desired product (Table 2, entries 7-9). The low yield of the desired product is attributed to the steric hindrance of the bulky *o*-substituted trifluoromethyl group.

The reactions of other electron-deficient aryl iodides with alkyne **2** also proceeded well providing high yields of the desired indene derivatives (Table 2, entries 10 and 11). None of the desired arylation product was isolated when 3-iodopyridine was subjected to the palladium-catalyzed arylation (Table 2, entry 12). Again, significant amounts of indene **9** were observed. The reaction of 2-iodothiophene and diethyl 2-(phenylethynyl)phenyl-malonate **2** afforded a moderate yield of the desired indene product (Table 2, entry 13).

The reactivity of relatively electron-rich aryl halides has also been examined. For example, iodobenzene has been allowed to react with diethyl 2-(phenylethynyl)phenyl-malonate **2** to give a 72 % yield of the desired indene product (Table 2, entry 14). The *P*-, *m*- and *o*-iodotoluenes reacted with alkyne **2** to afford the desired arylation products, but the yields are slightly lower than the reactions of the electron-deficient aryl halides (Table 2, entries 15-17). When a very electron-rich aryl halide, such as *p*-iodoanisole, was employed

in this arylation reaction, only a 14 % yield of the desired arylation product was isolated (Table 2, entry 18). In this reaction, a significant amount of phenyl-containing indene **16** was also isolated after the arylation reaction. Presumably the formation of indene **16** is due to aryl-aryl exchange between the palladium center and the phosphine ligand in the organopalladium(II) complex, which produces a phenylpalladium(II) complex, which produces the observed side-product (eq 7).[17]



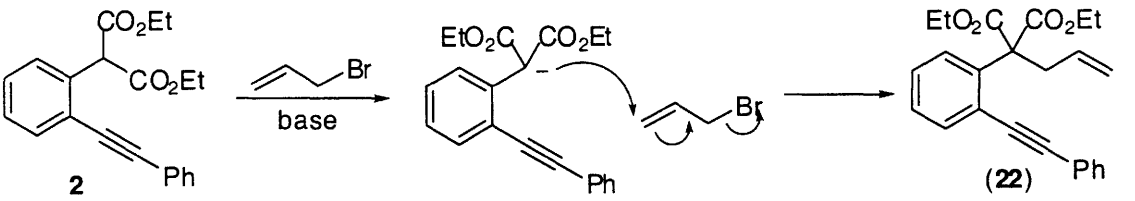
(7)

Arylation using bromobenzene is nearly as effective as iodobenzene providing the desired arylation product in good yield (Table 2, entry 19). However, the reaction of chlorobenzene with diethyl [2-(phenylethynyl)phenyl]malonate **2** only afforded the reduction product **9** in 71% yield (Table 2, entry 20). On the other hand, attaching an electron-withdrawing substituent to the chlorobenzene facilitated formation of the desired arylation product although the yield is still relatively low (Table 2, entry 21). The reaction of phenyl triflate failed to produce any arylation product and once again afforded indene **9** in 38 % yield (Table 2, entry 22).

We have also investigated the reactions of other organic halides. For example, allyl bromide reacted with diethyl 2-(phenylethynyl)phenylmalonate **2** to yield an inseparable mixture of diethyl 3-allyl-2-phenyl-1*H*-indene-1,1-dicarboxylate **21** (51 %) and diethyl 2-(but-3-enyl)-2-[2-(phenylethynyl)phenyl]malonate **22** (41 %; Table 2, entry 23). The yields were determined by ^{1}H NMR spectroscopy. The formation of alkyne **22** probably proceeds by a competitive S_N2 reaction, but it might also involve direct malonate anion attack on the expected π-allylpalladium intermediate (Scheme 6). Using diallyl carbonate as an alternative allyl moiety source only result in alkyne **22** in 86 % yield (Table 2, entry 24). Other allylic halide, such as crotyl chloride or cinamyl chloride, has also been subject to this reaction, the

both reactions gave high yield of the corresponding alkynes, instead of the desired indene products (Table 2, entries 25 and 26).

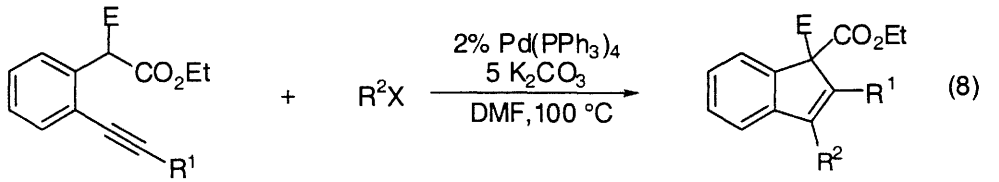
Scheme 6



Vinylic halides, such as methyl *E*-3-iodoacrylate **27** and ethyl *Z*-3-iodoacrylate **28**, failed to produce any of the desired arylation products, but gave large amounts of the starting alkyne **2** (Table 2, entries 27 and 28). The reaction of (4-iodomethylene)cyclohexylbenzene was messy and there were many spots shown on tlc plate (Table 2, entry 29). The reactions of alkynyl iodides with diethyl 2-(phenylethynyl)phenylmalonate **2** did not generate any of the desired arylation product either (Table 2, entries 30-32). A large amount of black oily polymer was obtained in all cases, and the corresponding ^{1}H NMR spectrum was unrecognizable. Presumably, a polymer is formed by the palladium-catalyzed polymerization of these alkynyl iodides. On the other hand, A moderate yield of the desired 3,4-disubstituted isoquinoline was obtained (56 %) in Dai's palladium-catalyzed cross-coupling of *o*-(1-alkynyl)benzaldimines and 1-iodo-1-decyne.[16]

The reactivity of other arylalkynes bearing potential carbanion centers has also been examined. For example, the malonate-containing arylalkyne bearing a long chain alkyl group on the end of the acetylene has been allowed to react with various aryl halides to furnish the desired indene derivatives (Table 3, entries 1-3). The reactions of electron-deficient halides have given much higher yields than the reaction of the electron-rich halide *p*-iodoanisole. This observation is consistent with the results reported in Table 2. The arylalkyne **33** bearing a cyclohexenyl group on the end of the acetylene has also reacted with

various aryl halides to generate the desired indene derivatives in good yields (Table 3, entries 4-6).



(8)

Table 3. Palladium-catalyzed arylation of various arylalkynes (eq 8).[a]

entry	E	R^1	alkyne	R^2X	product	% yield
1	CO_2Et	$(CH_2)_5CH_3$	**33**	*p*-$EtO_2CC_6H_4I$	**34**	61
2	CO_2Et	$(CH_2)_5CH_3$	**33**	*p*-$O_2NC_6H_4I$	**35**	63
3	CO_2Et	$(CH_2)_5CH_3$	**33**	*p*-$H_3COC_6H_4I$	**36**	9
4	CO_2Et	1-cyclohexenyl	**37**	*p*-$EtO_2CC_6H_4I$	**38**	83
5	CO_2Et	1-cyclohexenyl	**37**	*p*-$O_2NC_6H_4I$	**39**	87
6	CO_2Et	1-cyclohexenyl	**37**	*p*-$CH_3COC_6H_4I$	**40**	78
7	CN	$(CH_2)_5CH_3$	**41**	*p*-$EtO_2CC_6H_4I$	**42**	53
8	CN	$(CH_2)_5CH_3$	**41**	*p*-$O_2NC_6H_4I$	--	--[b]
9	CN	$(CH_2)_5CH_3$	**41**	*p*-$F_3COC_6H_4I$	--	--[b]
10	SO_2Ph	Ph	**43**	*p*-$EtO_2CC_6H_4I$	**44**	42
11	SO_2Ph	Ph	**43**	*p*-$CH_3COC_6H_4I$	**45** (R^2 = H)	61
12	SO_2Ph	Ph	**43**	*p*-$O_2NC_6H_4I$	**45** (R^2 = H)	53
13	SO_2Ph	$(CH_2)_5CH_3$	**46**	*p*-$EtO_2CC_6H_4I$	--	--[b]
14	SO_2Ph	$(CH_2)_5CH_3$	**46**	*p*-$O_2NC_6H_4I$	--	--[b]

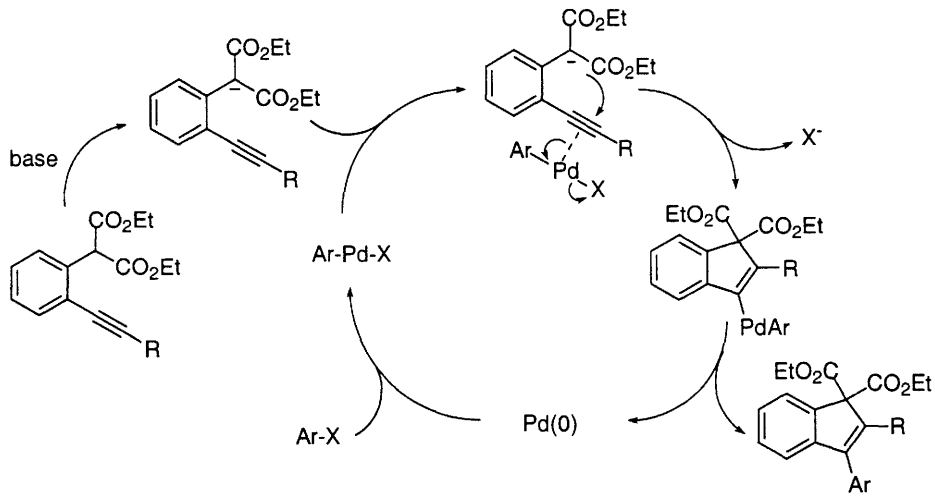
[a] See the text and Experimental Section for the detailed procedure. [b] The reaction was messy and the products isolated after column chromatography were not recognizable.

Arylalkynes bearing different electron-withdrawing functional groups have also been subjected to this arylation reaction. The reaction of the arylalkyne **41** and ethyl 4-iodobenzoate afforded the desired indene product **42** in a moderate yield (Table 3, entry 7). However, reactions of the arylalkyne **41** and other aryl iodides, such as 4-iodonitrobenzene or 4-iodobenzotrifluoride, were messy and didn't give any of the desired products (Table 3, entries 8 and 9). Ethyl [2-(phenylethynyl)phenyl](phenylsulfonyl)acetate **43** has also been subjected to this cyclization reaction, but only the reaction with ethyl 4-iodobenzoate afforded a 42 %

yield of the desired product (Table 3, entry 10). The reactions with 4-iodoaceto-phenone and 4-iodonitrobenzene didn't give any of the desired products and a large amount of starting acetate **43** was recovered in both cases (Table 3, entries 11 and 12). The reactions of ethyl (2-oct-1-ynylphenyl)(phenylsulfonyl)acetate **46** and aryl iodides, such as ethyl 4-iodobenzoate and 4-iodonitrobenzene, were messy and no recognizable products could be isolated (Table 3, entries 13 and 14).

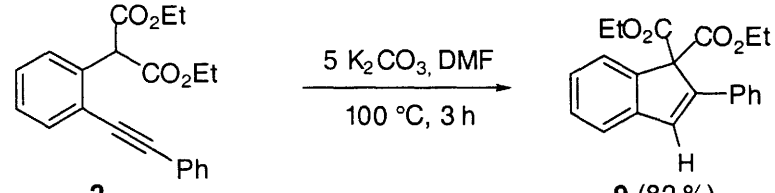
We propose the mechanism shown in Scheme 7 for this process. It consists of the following key steps: (1) generation of a carbanion by the base, (2) oxidative addition of the aryl halide to the Pd(0) catalyst,[18] (3) coordination of the resulting organopalladium(II) intermediate to the alkyne triple bond to form a palladium π-complex, which activates the triple bond towards nucleophilic attack,[9] (4) intramolecular nucleophilic attack of the carbanion on the activated carbon-carbon triple bond to afford a vinylpalladium inter-mediate,[19] and (5) reductive elimination to form the arylation product and regenerate the Pd(0) catalyst.[20]

Scheme 7

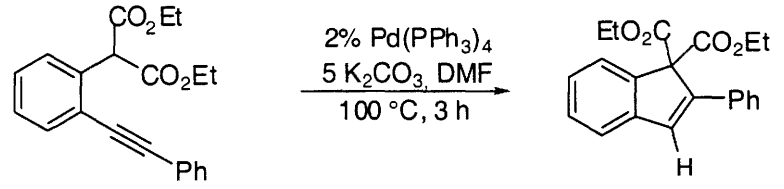


The observation that yields of the reactions employing electron-deficient aryl halides are often higher than electron-deficient aryl halides can be explained by this mechanism. The

arylpalladium(II) intermediates derived from electron-deficient aryl halides more strongly coordinate to the alkyne triple bond, making the alkyne triple bond more prone to nucleophilic attack of the carbanion. The coordination step is crucial to formation of the indene product, because, without it, the alkyne substrate can cyclize by a base-promoted or a palladium-catalyzed process to the hydrogen-containing indene **9** (eqs 9 and 10).

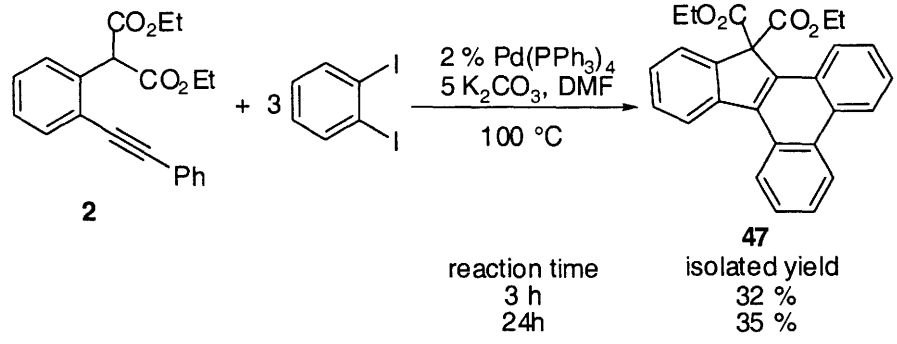


(9)



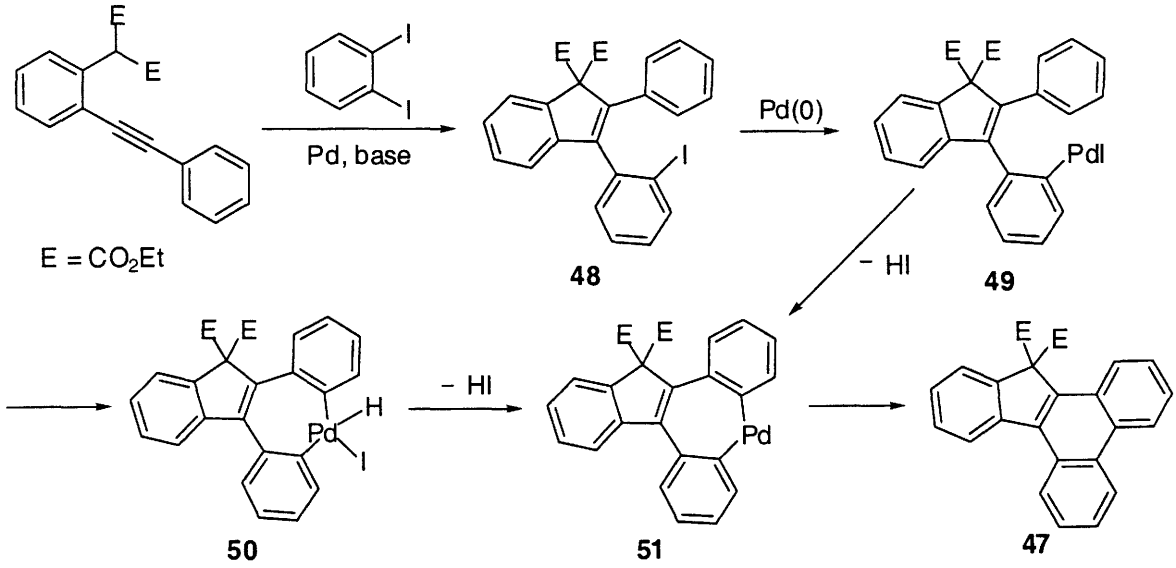
(10)

A double arylation product **47** (eq 11) has been isolated in a low yield when 1,2-diiodoben-zene was allowed to react with diethyl 2-(phenylethynyl)phenylmalonate **2**. The formation of polycyclic **47** is presumably due to cyclization of the expected intermediate **48** bearing an iodophenyl group by either oxidative addition of a neighboring aryl C-H bond to the resulting organopalladium species **49** to produce an organopalladium(IV) intermediate **50**, which subsequently undergoes two rapid reductive eliminations to provide the double arylation product **47** or possibly direct electrophilic aromatic substitution of intermediate **49** to produce intermediate **51** directly (Scheme 8).

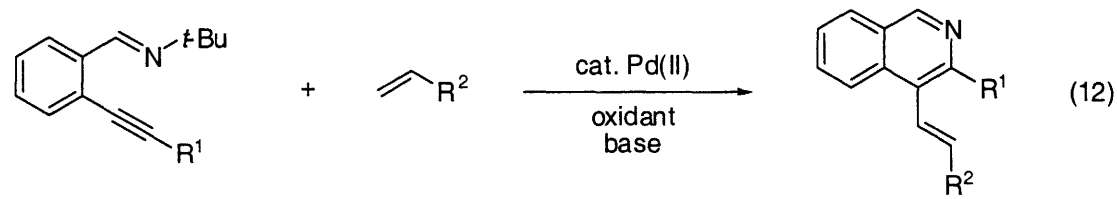


(11)

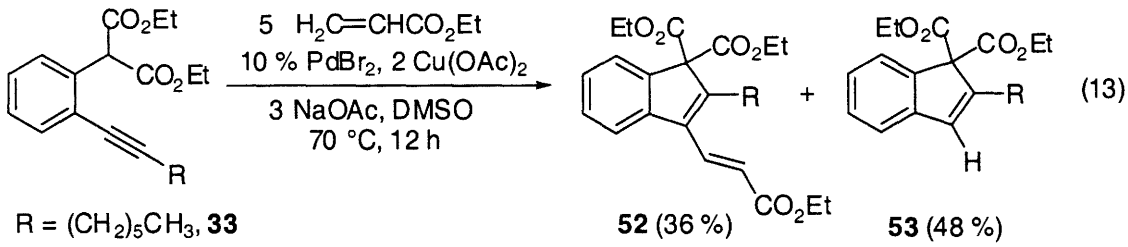
Scheme 8



Qinhua Huang, a group member, has reported a synthesis of isoquinolines by palladium-catalyzed cyclization, followed by a Heck reaction (eq 12).[21] A variety of 4-(1-alkenyl)-3-arylisoquinolines have been prepared by this Pd(II)-catalyzed reaction in good yields. Inspired by his work, a similar reaction has been tried in the reaction of diethyl 2-(oct-1-ynylphenyl)phenylmalonate **33** and ethyl acrylate (eq 13). The reaction yielded the desired olefinated indene product **52** with a large amount of direct cyclization product **53**. Presumably compound **52** is formed through a palladium(II) pathway (Scheme 9).[21] The Pd(II) catalyst coordinates with the alkyne triple bond of the carbanion intermediate **54** to form a palladium complex **55**. The cyclization of the palladium complex **55** provides a vinylpalladium intermediate **56**. The subsequent *cis* addition of intermediate **56** to the carbon-carbon double bond of the acrylate affords an alkylpalladium intermediate **57**, which undergoes β-hydride elimination to furnish the olefinated indene product **52** and Pd(0). The Pd(0) generated can be reoxidized back to $PdBr_2$ by the $Cu(OAc)_2$ oxidant present in the reaction mixture.



(12)



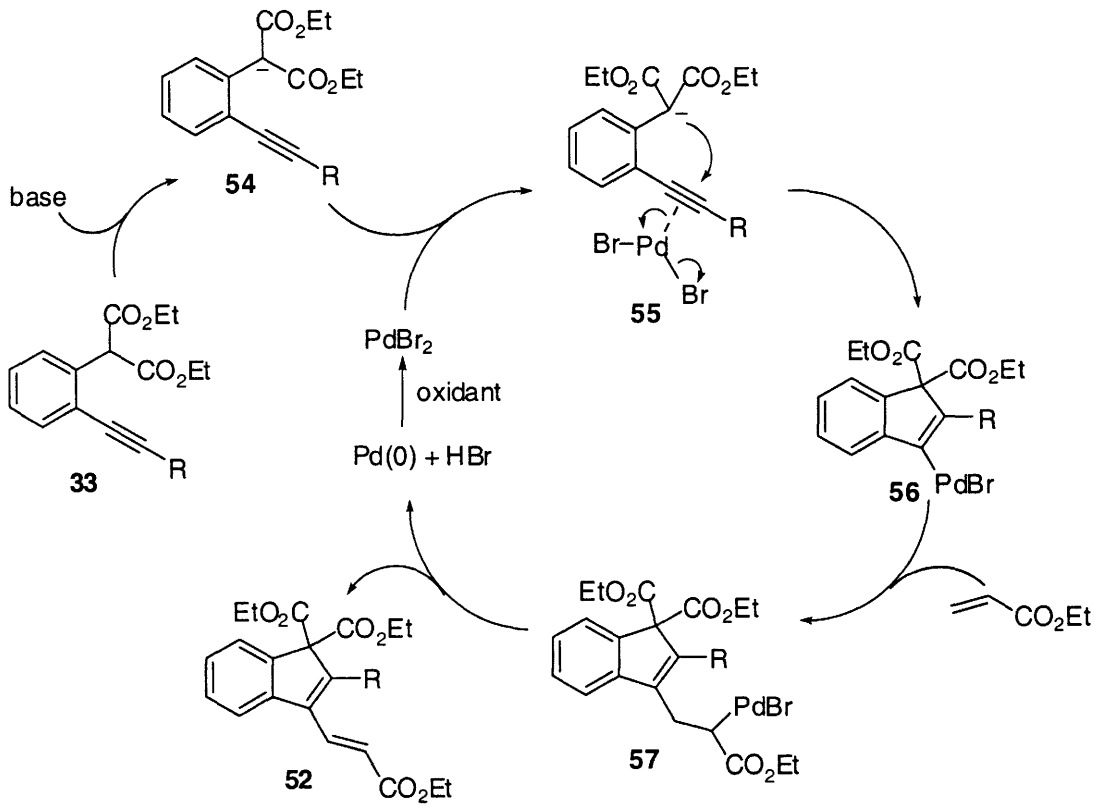
(13)

R = $(CH_2)_5CH_3$, **33**

52 (36 %)

53 (48 %)

Scheme 9



Conclusions

In conclusion, a general, efficient synthesis of highly substituted indene derivatives has been accomplished in high yields by the palladium-catalyzed cross-coupling of arylalkynes bearing strong electro-withdrawing functional groups like esters, nitriles, and sulfones and various aryl halides. This process involves both arylation and cyclization of the arylalkynes in a single step and is particularly suited for the synthesis of 3,4-diaryl substituted indenes from electron-deficient aryl halides.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz respectively. Thin layer chromatography was performed using commercially prepared 40-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254nm) and a basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5 %) + 300 mL of H_2O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. IR spectra were measured on a Bio-Rad FTS-7 spectrometer on salt plates.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. The following starting materials were prepared as indicated.

Diethyl (2-iodophenyl)malonate (1). Diethyl (2-iodophenyl)malonate was prepared in two steps from commercially available (2-iodophenyl)acetic acid.

Ethyl (2-iodophenyl)acetate was prepared according to a modified literature procedure.[22] To a solution of (2-iodophenyl)acetic acid (1.00 g, 3.82 mmol) in 3 mL of ethanol was added

0.3 mL of concentrated sulfuric acid. The solution was then allowed to reflux for 3 h. The solution was poured into 8 mL of H_2O and extracted with 3 × 5 mL of ether. The ether extract was washed with 5 mL of H_2O, 5 mL of 5 % $NaHCO_3$, 5 mL of brine, dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure, and the mixture was chromatographed using 4:1 hexanes/EtOAc to afford the ester (1.45 g, 95 %) as a white solid: mp 125-126 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3 H), 3.77 (s, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 6.94 (m, 1 H), 7.28 (m, 2 H), 7.82 (d, J = 8.0 Hz, 1 H).

To a solution of ethyl (2-iodophenyl)acetate (0.54 g, 1.9 mmol) in 10 mL of diethyl carbonate was added NaH (0.19 g, 8.0 mmol). The resulting mixture was allowed to stir at room temperature for 12 h. The mixture was poured into 20 mL of satd NH_4Cl (aq) and extracted with 3 × 10 mL of CH_2Cl_2. The ether extract was dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure, and the mixture was chromatographed using 5:1 hexanes/EtOAc to afford diethyl (2-iodophenyl)malonate (0.59 g, 88 %) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 6 H), 4.24 (m, 4 H), 5.12 (s, 1 H), 7.00 (dt, J = 1.5, 7.5 Hz, 1 H), 7.36 (dt, J = 1.5, 7.5 Hz, 1 H), 7.47 (dd, J = 1.5, 7.5 Hz, 1 H), 7.86 (dd, J = 1.5, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 62.2, 62.4, 101.9, 128.8, 129.9, 130.0, 136.7, 139.8, 168.0; IR ($CHCl_3$, cm^{-1}) 2955, 2924, 1753, 1736, 1468; HRMS calcd for $C_{13}H_{15}IO_4$ 362.0015, found 362.0013.

General procedure for the preparation of arylalkynes bearing a carbon nucleophile. The arylalkynes bearing a carbon nucleophile are prepared by Sonogashira coupling of aryl halides with terminal alkynes.[8] To a solution of the aryl halide (0.25 mmol) in Et_3N (3 mL) was added $Pd(OAc)_2$ (0.005 mmol), CuI (0.0025 mmol), and the alkyne (0.375 mmol). The reaction mixture was stirred under a nitrogen atmosphere at 55 °C for 2 h. The mixture was then cooled, filtered, and concentrated. The residue was chromatographed using

hexanes/EtOAc as the eluent. The following compounds were prepared using the above general procedure.

Diethyl [2-(phenylethynyl)phenyl]malonate (2). Obtained as a pale yellow oil in 98 % isolated yield (eq 4): ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 6 H), 4.25 (m, 4 H), 5.40 (s, 1 H), 7.35 (m, 5 H), 7.49 (m, 1 H), 7.57 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 56.1, 61.9, 86.9, 94.6, 122.9, 123.8, 128.0, 128.5, 128.7, 128.8, 131.6, 132.1, 135.0, 168.2; IR ($CHCl_3$, cm^{-1}) 3055, 2986, 1749, 1733, 1266; HRMS calcd for $C_{21}H_{20}O_4$ 336.1362, found 336.1367.

Diethyl (2-oct-1-ynylphenyl)malonate (33). Obtained as a pale yellow oil in 95 % isolated yield (Table 3, entry 1): ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J= 7.2 Hz, 3 H), 1.25-1.32 (m, 10 H), 1.44 (m, 2 H), 1.59 (m, 2 H), 2.41 (t, J = 7.2 Hz, 2 H), 4.21 (m, 4 H), 5.30 (s, 1 H), 7.24 (m, 2 H), 7.41 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.6, 22.6, 28.6, 28.7, 31.4, 55.7, 61.8, 78.2, 95.9, 124.6, 127.8, 127.9, 128.4, 132.0, 134.6, 168.3; IR ($CHCl_3$, cm^{-1}) 3056, 2983, 2932, 1750, 1716, 1221; IR ($CHCl_3$, cm^{-1}) 3058, 2982, 1751, 1734, 1266; HRMS calcd for $C_{21}H_{28}O_4$ 344.1988, found 344.1992.

Diethyl 2-(1-cyclohexenylethynyl)phenylmalonate (37). Obtained as a pale yellow oil in 90 % isolated yield (Table 3, entry 4): ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 6 H), 1.64 (m, 4 H), 2.13 (m, 2 H), 2.22 (m, 2 H), 4.22 (m, 4 H), 5.26 (m, 2 H), 6.22 (m, 1 H), 7.28 (m, 2 H), 7.42 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.7, 22.5, 26.0, 29.3, 56.1, 62.0, 84.4, 96.8, 120.8, 124.5, 128.0, 128.3, 128.6, 132.0, 134.8, 135.9, 168.4; IR ($CHCl_3$, cm^{-1}) 3056, 2936, 1751, 1733, 1266; HRMS calcd for $C_{21}H_{24}O_4$ 340.1675, found 340.1678.

Ethyl cyano(2-oct-1-ynylphenyl)acetate (41). Obtained as a pale yellow oil in 92 % isolated yield (Table 3, entry 7): ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3 H), 1.39 (m, 3 H), 1.57 (m, 3 H), 1.74 (m, 2 H), 1.90 (m, 2 H), 2.64 (m, 2 H), 4.26 (m, 2 H), 5.27 (s, 1 H), 7.33 (m, 2 H), 7.46 (m, 1 H), 7.50 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 19.8, 22.8, 28.7, 28.9, 31.6, 42.0, 63.4, 77.7, 97.8, 115.9, 124.3, 128.3, 128.7, 129.2, 132.0, 132.8, 165.0; IR

($CHCl_3$, cm^{-1}) 3054, 2933, 2226, 1747, 1265; HRMS calcd for $C_{19}H_{23}NO_2$ 297.1729, found 297.1733.

Ethyl [2-(phenylethynyl)phenyl](phenylsulfonyl)acetate (43). Obtained as a pale yellow oil in 91 % isolated yield (Table 3, entry 8): ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3 H), 4.27 (m, 2 H), 6.00 (s, 1 H), 7.33-7.39 (m, 7 H), 7.42-7.46 (m, 3 H), 7.55 (m, 1 H), 7.65 (dd, J = 1.2, 7.2 Hz, 2 H), 7.99 (dd, J = 1.6, 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 62.8, 71.6, 86.1, 94.4, 122.5, 125.1, 128.5, 128.6, 128.7, 128.9, 129.4, 129.4, 129.5, 130.1, 131.6, 132.1, 134.1, 137.5, 164.4; IR ($CHCl_3$, cm^{-1}) 3056, 2985, 1740, 1265; HRMS calcd for $C_{24}H_{20}SO_4$ 404.1082, found 404.1088.

General procedure for the palladium-catalyzed arylation of arylalkynes bearing a carbon nucleophile. To a solution of the arylalkyne (0.25 mmol) in DMF (5 mL) was added $Pd(PPh_3)_4$ (0.005 mmol), K_2CO_3 (1.25 mmol), and the aryl halide (0.75 mmol). The reaction mixture was stirred under a nitrogen atmosphere at 100 °C for 3 h. The mixture was then cooled, diluted with ether, and washed with satd NH_4Cl (aq). The organic layer was dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by column chromatography using hexanes/EtOAc as the eluent. The following compounds were prepared using the above general procedure.

Diethyl 3-[4-(ethoxycarbonyl)phenyl]-2-phenyl-1*H*-indene-1,1-dicarboxylate (4). Obtained as a pale yellow oil in 86 % isolated yield (Table 2, entry 1): ^1H NMR ($CDCl_3$) δ 1.09 (t, J = 7.2 Hz, 6 H), 1.37 (t, J = 7.2 Hz, 3 H), 4.14 (m, 4 H), 4.35 (q, J = 7.2 Hz, 2 H), 7.17 (m, 5 H), 7.25 (m, 1 H), 7.34 (m, 2 H), 7.39 (d, J = 8.4 Hz, 2 H), 7.69 (dd, J = 1.2, 7.6 Hz, 1 H), 8.00 (d, J = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 14.4, 61.1, 62.1, 73.0, 121.1, 124.8, 126.9, 127.6, 127.7, 128.8, 129.6, 129.7, 130.3, 134.7, 139.1, 140.9, 141.8, 144.0, 144.4, 166.4, 168.0; IR ($CHCl_3$, cm^{-1}) 3065, 2982, 1718, 1275; HRMS calcd for $C_{30}H_{28}O_6$ 484.1886, found 484.1895.

Diethyl 3-[3-(ethoxycarbonyl)phenyl]-2-phenyl-1*H*-indene-1,1-dicarboxylate (5). Obtained as a pale yellow oil in 74 % isolated yield (Table 2, entry 2): ^{1}H NMR ($CDCl_3$) δ 1.09 (t, J = 7.2 Hz, 6 H), 1.37 (t, J = 7.2 Hz, 3 H), 4.14 (m, 4 H), 4.35 (q, J = 7.2 Hz, 2 H), 7.16-7.28 (m, 6 H), 7.34 (m, 3 H), 7.44 (m, 1 H), 7.71 (d, J = 7.2 Hz, 1 H), 7.98 (dt, J = 1.6, 7.6 Hz, 1 H), 8.10 (t, J = 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 14.4, 61.1, 62.1, 73.0, 121.1, 124.8, 126.9, 127.5, 127.7, 128.6, 128.8,129.0, 130.3, 130.5, 130.8, 134.2, 134.6, 134.7, 140.9, 141.5, 144.0, 144.7, 166.4, 168.1; IR ($CHCl_3$, cm^{-1}) 3067, 2982, 1730, 1257; HRMS calcd for $C_{30}H_{28}O_6$ 484.1886, found 484.1892.

Diethyl 3-[2-(ethoxycarbonyl)phenyl]-2-phenyl-1*H*-indene-1,1-dicarboxylate (6). Obtained as a pale yellow oil in 78 % isolated yield (Table 2, entry 3): ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7.2 Hz, 3 H), 0.95 (t, J = 7.2 Hz, 3 H), 1.24 (t, J = 7.2 Hz, 3 H), 4.04 (m, 4 H), 4.28 (m, 2 H), 6.90 (m, 1 H), 7.15 (m, 4 H), 7.27 (m, 4 H), 7.37 (m, 2 H), 7.67 (m, 1 H), 8.05 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.5, 13.8, 14.2, 61.5, 61.8, 62.3, 72.8, 120.6, 124.7, 126.6, 127.4, 127.7, 128.1, 128.9, 130.2, 130.8, 131.8, 131.9, 132.6, 135.2, 135.6, 139.6, 140.4, 146.0, 146.1, 167.7, 167.8, 169.1; IR ($CHCl_3$, cm^{-1}) 3019, 2982, 1725, 1702, 1217; HRMS calcd for $C_{30}H_{28}O_6$ 484.1886, found 484.1892.

Diethyl 3-(4-nitrophenyl)-2-phenyl-1*H*-indene-1,1-dicarboxylate (7). Obtained as a pale yellow oil in 83 % isolated yield (Table 2, entry 4): ^{1}H NMR ($CDCl_3$) δ 1.08 (t, J = 7.2 Hz, 6 H), 4.15 (m, 4 H), 7.23 (m, 6 H), 7.36 (m, 2 H), 7.49 (d, J = 8.8 Hz, 2 H), 7.71 (d, J = 7.6 Hz, 1 H), 8.16 (d, J = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 62.2, 73.2, 120.8, 123.8, 125.0, 127.2, 127.9, 128.0, 129.0, 130.2, 130.6, 134.3, 140.9, 141.4, 142.9, 143.1, 143.8, 147.2, 167.7; IR ($CHCl_3$, cm^{-1}) 3024, 2985, 1716, 1235; HRMS calcd for $C_{27}H_{23}NO_6$ 457.1525, found 457.1531.

Diethyl 3-(3-nitrophenyl)-2-phenyl-1*H*-indene-1,1-dicarboxylate (8). Obtained as a pale yellow oil in 82 % isolated yield (Table 2, entry 5): ^{1}H NMR ($CDCl_3$) δ 1.09 (t, J = 7.2

Hz, 6 H), 4.15 (m, 4 H), 7.23 (m, 6 H), 7.36 (m, 2 H), 7.46 (d, J = 8.0 Hz, 1 H), 7.60 (d, J = 7.6 Hz, 1 H), 7.72 (d, J = 7.2 Hz, 1 H), 8.13 (d, J = 8.4 Hz, 1 H), 8.24 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 62.2, 73.1, 120.7, 122.8, 124.4, 125.0, 127.2, 127.9, 129.0, 129.6, 130.3, 134.2, 135.9, 136.1, 140.9, 142.6, 142.9, 143.9, 148.4, 167.7; IR ($CHCl_3$, cm^{-1}) 3019, 2983, 1727, 1715, 1219; HRMS calcd for $C_{27}H_{23}NO_6$ 457.1525, found 457.1531.

Diethyl 2-phenyl-1*H*-indene-1,1-dicarboxylate (9). Obtained as a pale yellow oil in 38 % isolated yield (Table 2, entry 6): ^{1}H NMR ($CDCl_3$) δ 1.07 (t, J = 7.2 Hz, 6 H), 4.14 (m, 4 H), 7.24-7.36 (m, 7 H), 7.62 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 62.1, 70.9, 121.7, 124.2, 126.3, 127.4, 127.9, 128.2, 128.9, 131.5, 134.1, 142.1, 143.7, 145.7, 168.3; IR ($CHCl_3$, cm^{-1}) 3019, 2988, 1734, 1217; HRMS calcd for $C_{21}H_{20}O_4$ 336.1362, found 336.1366.

Diethyl 2-phenyl-3-[4-(trifluoromethyl)phenyl]-1*H*-indene-1,1-dicarboxylate (10). Obtained as a pale yellow oil in 85 % isolated yield (Table 2, entry 7): ^{1}H NMR ($CDCl_3$) δ 1.09 (t, J = 7.2 Hz, 6 H), 4.15 (m, 4 H), 7.23 (m, 6 H), 7.35 (m, 2 H), 7.45 (d, J = 8.4 Hz, 2 H), 7.58 (d, J = 8.0 Hz, 2 H), 7.72 (d, J = 7.6Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 62.1, 73.1, 121.0, 122.8, 124.9, 125.5, 127.0, 127.7, 127.8, 128.9, 130.0, 130.3, 134.6, 138.2, 140.9, 141.0, 142.1, 143.6, 144.4, 168.0; IR ($CHCl_3$, cm^{-1}) 3006, 2982, 1732, 1247; HRMS calcd for $C_{28}H_{23}F_3O_4$ 480.1548, found 480.1555.

Diethyl 2-phenyl-3-[3-(trifluoromethyl)phenyl]-1*H*-indene-1,1-dicarboxylate (11). Obtained as a pale yellow oil in 91 % isolated yield (Table 2, entry 8): ^{1}H NMR ($CDCl_3$) δ 1.09 (t, J = 7.2 Hz, 6 H), 4.15 (m, 4 H), 7.23 (m, 6 H), 7.37 (m, 3 H), 7.49 (d, J = 7.6 Hz, 1 H), 7.54 (d, J = 7.6 Hz, 1 H), 7.63 (s, 1 H), 7.72 (d, J = 6.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 62.1, 73.0, 120.9, 124.6, 124.9, 126.4, 126.5, 127.0, 127.7, 127.8, 128.9, 129.0, 130.3, 133.0, 134.5, 135.2, 141.0, 142.1, 143.5, 144.3, 168.0; IR ($CHCl_3$, cm^{-1}) 3057, 2983, 1729, 1266; HRMS calcd for $C_{28}H_{23}F_3O_4$ 480.1548, found 480.1556.

Diethyl 2-phenyl-3-[2-(trifluoromethyl)phenyl]-1*H*-indene-1,1-dicarboxylate (12). Obtained as a pale yellow oil in 53 % isolated yield (Table 2, entry 9): ^{1}H NMR ($CDCl_3$) δ 1.07 (m, 6 H), 4.13 (m, 4 H), 6.82 (m, 1 H), 7.11-7.17 (m, 5 H), 7.28 (m, 2 H), 7.37 (d, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 7.66-7.73 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.6, 13.8, 61.9, 62.0, 72.4, 121.1, 124.0, 126.7, 126.8, 126.9, 127.4, 127.5, 128.2, 128.7, 129.4, 131.9, 132.1, 133.6, 134.3, 140.3, 141.8, 142.5, 146.4, 168.0, 168.2; IR ($CHCl_3$, cm^{-1}) 3067, 2982, 1734, 1717, 1220; HRMS calcd for $C_{28}H_{23}F_3O_4$ 480.1548, found 480.1556.

Diethyl 3-(4-acetylphenyl)-2-phenyl-1*H*-indene-1,1-dicarboxylate (13). Obtained as a pale yellow oil in 94 % isolated yield (Table 2, entry 10): ^{1}H NMR ($CDCl_3$) δ 1.09 (t, *J* = 7.2 Hz, 6 H), 2.59 (s, 3 H), 4.14 (m, 4 H), 7.20 (m, 5 H), 7.28 (m, 1 H), 7.35 (m, 2 H), 7.43 (dt, *J* = 1.8, 8.7 Hz, 2 H), 7.70 (m, 1 H), 7.92 (dt, *J* = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 26.7, 62.1, 73.0, 121.0, 124.8, 126.9, 127.6, 127.7, 128.5, 128.8, 129.9, 130.3, 134.7, 136.3, 139.5, 141.0, 142.0, 143.9, 144.4, 168.0, 197.7; IR ($CHCl_3$, cm^{-1}) 2980, 1733, 1685, 1221; HRMS calcd for $C_{29}H_{26}O_5$ 454.1780, found 454.1786.

Diethyl 3-(4-chlorophenyl)-2-phenyl-1*H*-indene-1,1-dicarboxylate (14). Obtained as a pale yellow oil in 84 % isolated yield (Table 2, entry 11): ^{1}H NMR ($CDCl_3$) δ 1.08 (t, *J* = 7.2 Hz, 6 H), 4.14 (m, 4 H), 7.17-7.37 (m, 12 H), 7.70 (d, *J* = 7.2Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 62.2, 73.1, 121.2, 125.0, 127.1, 127.7, 127.9, 129.0, 130.5, 130.6, 131.2, 133.0, 133.9, 135.0, 141.1, 141.4, 143.9, 144.8, 168.3; IR ($CHCl_3$, cm^{-1}) 3019, 2983, 1725, 1714, 1218; HRMS calcd for $C_{27}H_{23}ClO_4$ 446.1285, found 446.1292.

Diethyl 2-phenyl-3-thien-2-yl-1*H*-indene-1,1-dicarboxylate (15). Obtained as a pale yellow oil in 64 % isolated yield (Table 2, entry 13): ^{1}H NMR ($CDCl_3$) δ 1.08 (t, *J*= 7.2 Hz, 6 H), 4.14 (m, 4 H), 7.00 (dd, *J* = 3.6, 5.1 Hz, 1 H), 7.13 (dd, *J* = 1.2, 3.6 Hz, 1 H), 7.25 –7.45 (m, 8 H), 7.63(d, *J* = 7.2 Hz, 1 H), 7.69 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 62.2, 62.3, 73.3, 121.6, 124.9, 126.6, 127.1, 127.2, 127.9, 128.0, 128.3, 130.0, 130.7, 135.3,

135.5, 138.1, 140.8, 141.4, 144.4, 168.2; IR ($CHCl_3$, cm^{-1}) 3001, 2984, 1714, 1363, 1223; HRMS calcd for $C_{25}H_{22}SO_4$ 418.1239, found 418.1245.

Diethyl 2,3-diphenyl-1*H*-indene-1,1-dicarboxylate (16). Obtained as white crystals in 72 % isolated yield (Table 2, entry 14): mp 85-87 °C; ^1H NMR ($CDCl_3$) δ 1.07 (t, *J*= 7.2 Hz, 6 H), 4.14 (m, 4 H), 7.15-7.36 (m, 13 H), 7.69 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 61.9, 72.8, 121.3, 124.6, 126.7, 127.3, 127.6, 127.8, 128.5, 128.7, 129.6, 130.3, 134.3, 135.1, 140.6, 141.0, 144.8, 145.1, 168.3; IR ($CHCl_3$, cm^{-1}) 3057, 3019, 2982, 1727, 1466, 1216; HRMS calcd for $C_{27}H_{24}O_4$ 412.1675, found 412.1680.

Diethyl 3-(4-methylphenyl)-2-phenyl-1*H*-indene-1,1-dicarboxylate (17). Obtained as a pale yellow oil in 69 % isolated yield (Table 2, entry 15): ^1H NMR ($CDCl_3$) δ 1.08 (t, *J*= 7.2 Hz, 6 H), 2.34 (s, 3 H), 4.15 (m, 4 H), 7.12-7.35 (m, 12 H), 7.68 (d, *J* = 6.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 21.6, 62.1, 73.0, 121.5, 124.7, 126.8, 127.4, 127.7, 127.8, 128.7, 128.9, 129.4, 129.7, 129.8, 130.5, 130.6, 135.5, 137.7, 141.2, 145.0, 145.4, 168.6; IR ($CHCl_3$, cm^{-1}) 3019, 2983, 1732, 1728, 1216; HRMS calcd for $C_{28}H_{26}O_4$ 426.1831, found 426.1837.

Diethyl 3-(3-methylphenyl)-2-phenyl-1*H*-indene-1,1-dicarboxylate (18). Obtained as a pale yellow oil in 74 % isolated yield (Table 2, entry 16): ^1H NMR ($CDCl_3$) δ 1.08 (t, *J*= 7.2 Hz, 6 H), 2.30 (s, 3 H), 4.14 (m, 4 H), 7.09-7.36 (m, 12 H), 7.70 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 21.7, 62.1, 72.9, 121.5, 124.7, 126.8, 126.9, 127.4, 127.8, 128.5, 128.6, 128.7, 128.8, 129.8, 130.3, 130.5, 134.4, 138.2, 141.2, 145.1, 145.5, 168.5; IR ($CHCl_3$, cm^{-1}) 3021, 2983, 1728, 1218; HRMS calcd for $C_{28}H_{26}O_4$ 426.1831, found 426.1837.

Diethyl 3-(2-methylphenyl)-2-phenyl-1*H*-indene-1,1-dicarboxylate (19). Obtained as a pale yellow oil in 73 % isolated yield (Table 2, entry 17): ^1H NMR ($CDCl_3$) δ 1.02 (t, *J*= 7.2 Hz, 6 H), 1.12 (t, *J*= 7.2 Hz, 3 H), 2.06 (s, 3 H), 4.12 (m, 4 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 7.13 (m, 3 H), 7.19-7.31 (m, 8 H), 7.69 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.7, 13.9, 19.6, 61.8, 62.0, 72.2, 121.3, 124.1, 125.9, 126.6, 127.3, 127.6, 128.0, 128.8, 129.1, 129.7,

130.5, 134.2, 135.0, 136.7, 140.8, 140.9, 144.5, 145.9, 168.0, 168.8; IR ($CHCl_3$, cm^{-1}) 3019, 2983, 1728, 1717, 1219; HRMS calcd for $C_{28}H_{26}O_4$ 426.1831, found 426.1837.

Diethyl 3-(4-methoxyphenyl)-2-phenyl-1*H*-indene-1,1-dicarboxylate (20). Obtained as a pale yellow oil in 14 % isolated yield (Table 2, entry 18): ^1H NMR ($CDCl_3$) δ 1.08 (t, *J*= 7.2 Hz, 6 H), 3.80 (s, 3 H), 4.14 (m, 4 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 7.17-7.36 (m, 10 H), 7.68 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 55.2, 61.9, 72.7, 113.9, 121.2, 124.6, 126.5, 126.6, 127.1, 127.6, 128.7, 130.4, 130.8, 135.3, 139.9, 141.0, 144.4, 145.3, 159.1, 168.4; IR ($CHCl_3$, cm^{-1}) 2980, 1732, 1510, 1247; HRMS calcd for $C_{28}H_{26}O_5$ 442.1780, found 442.1785.

Diethyl 2-allyl-2-(2-phenylethynyl)phenylmalonate (22). Obtained as a pale yellow oil in 86 % isolated yield (Table 2, entry 24): ^1H NMR ($CDCl_3$) δ 1.21 (t, *J*= 7.2 Hz, 6 H), 3.31 (d, *J* = 7.2 Hz, 2 H), 4.22 (m, 4 H), 4.92 (d, *J* = 10.2 Hz, 1 H), 5.00 (d, J = 17.1 Hz, 1 H), 5.84 (m, 1 H), 7.24-7.37 (m, 6 H), 7.55-7.58 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 39.7, 61.9, 64.1, 88.4, 95.0, 118.0, 122.9, 123.2, 127.2, 127.9, 128.2, 128.5, 128.6, 131.3, 133.9, 134.2, 139.5, 170.2; IR ($CHCl_3$, cm^{-1}) to be done; HRMS to be done.

Diethyl 3-[4-(ethoxycarbonyl)phenyl]-2-hexyl-1*H*-indene-1,1-dicarboxylate (34). Obtained as a pale yellow oil in 61 % isolated yield (Table 3, entry 1): ^1H NMR ($CDCl_3$) δ 0.78 (t, *J*= 7.2 Hz, 6 H), 1.12 (m, 6 H), 1.26 (t, *J* = 7.2 Hz, 8 H), 1.40 (t, *J* = 7.2 Hz, 3 H), 2.58 (t, *J* = 8.0 Hz, 2 H), 4.22 (m, 4 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 6.98 (d, *J* = 7.2 Hz, 1 H), 7.23 (m, 2 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 7.2 Hz, 1 H), 8.13 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 14.4, 22.6, 27.6, 29.1, 29.7, 31.4, 61.1, 62.1, 71.9, 119.8, 124.9, 126.0, 128.6, 128.9, 129.8, 129.9, 139.6, 140.1, 142.6, 143.4, 145.4, 166.5, 168.4; IR ($CHCl_3$, cm^{-1}) 2981, 2930, 1730, 1273; HRMS calcd for $C_{30}H_{36}O_6$ 492.2512, found 492.2521.

Diethyl 2-hexyl-3-(4-nitrophenyl)-1*H*-indene-1,1-dicarboxylate (35). Obtained as a pale yellow oil in 63 % isolated yield (Table 3, entry 2): ^1H NMR ($CDCl_3$) δ 0.78 (t, *J*= 7.2 Hz, 6 H), 1.14 (m, 6 H), 1.27 (t, *J* = 7.2 Hz, 8 H), 2.59 (t, *J* = 7.6 Hz, 2 H), 4.23 (m, 4 H),

6.95 (d, J = 6.8 Hz, 1 H), 7.26 (m, 2 H), 7.56 (d, J = 8.4 Hz, 2 H), 7.63 (d, J = 6.8 Hz, 1 H), 8.32 (d, J = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 27.6, 29.2, 29.7, 31.4, 62.2, 72.0, 119.6, 124.0, 125.1, 126.3, 128.7, 129.9, 140.0, 141.5, 141.9, 144.6, 144.7, 147.4, 168.1; IR ($CHCl_3$, cm^{-1}) 2981, 2930, 1732, 1243; HRMS calcd for $C_{27}H_{31}NO_6$ 465.2151, found 465.2160.

Diethyl 2-hexyl-3-(4-methoxyphenyl)-1*H*-indene-1,1-dicarboxylate (36). Obtained as a pale yellow oil in 9 % isolated yield (Table 3, entry 3): ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J= 7.2 Hz, 6 H), 1.13-1.32 (m, 14 H), 2.58 (t, J = 8.0 Hz, 2 H), 3.87 (s, 3 H), 4.21 (m, 1 H), 7.00 (d, J = 8.8 Hz, 2 H), 7.06 (d, J = 7.2 Hz, 1 H), 7.21 (t, J = 7.2 Hz, 1 H), 7.27 (t, J = 7.2 Hz, 1 H), 7.32 (d, J = 8.4 Hz, 2 H), 7.61 (d, J = 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.2, 22.7, 27.6, 29.1, 29.8, 31.5, 55.3, 61.9, 71.6, 114.2, 120.0, 125.6, 126.9, 127.8, 128.4, 130.0, 140.1, 142.1, 143.1, 146.2, 159.1, 168.8; IR ($CHCl_3$, cm^{-1}) 3053, 2985, 2926, 1714, 1265; HRMS calcd for $C_{28}H_{34}O_5$ 450.2406, found 450.2414.

Diethyl 2-cyclohex-1-en-1-yl-3-[4-(ethoxycarbonyl)phenyl]-1*H*-indene-1,1-dicarboxylate (38). Obtained as a pale yellow oil in 83 % isolated yield (Table 3, entry 4): ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 6 H), 1.42 (t, J = 7.2 Hz, 3 H), 1.53 (m, 4 H), 2.00 (m, 4 H), 4.19 (m, 4 H), 4.41 (t, J = 7.2 Hz, 2 H), 5.60 (s, 1 H), 7.15 (d, J = 7.6 Hz, 1 H), 7.27 (m, 2 H), 7.52 (d, J = 8.0 Hz, 2 H), 7.60 (d, J = 7.2 Hz, 1 H), 8.10 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.4, 21.8, 22.9, 25.9, 29.1, 61.1, 61.9, 72.0, 120.5, 124.4, 126.3, 128.6, 129.1, 129.6, 129.7, 130.9, 132.4, 140.2, 140.7, 141.8, 144.8, 144.9, 166.6, 168.3; IR ($CHCl_3$, cm^{-1}) 3055, 2983, 2934, 1716, 1269; HRMS calcd for $C_{30}H_{32}O_6$ 488.2199, found 488.2206.

Diethyl 2-cyclohex-1-en-1-yl-3-(4-nitrophenyl)-1*H*-indene-1,1-dicarboxylate (39). Obtained as a pale yellow oil in 87 % isolated yield (Table 3, entry 5): ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 6 H), 1.54 (m, 4 H), 1.98 (m, 2 H), 2.05 (m, 2 H), 4.22 (m, 4 H), 5.59 (s,

1 H), 7.14 (m, 1 H), 7.30 (m, 2 H), 7.63 (m, 3 H), 8.30 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.9, 23.0, 26.1, 29.4, 62.2, 72.2, 120.5, 123.9, 124.9, 126.9, 127.8, 128.6, 128.9, 130.3, 131.9, 132.4, 140.9, 142.7, 144.2, 146.3, 147.3, 168.1; IR ($CHCl_3$, cm^{-1}) 3055, 2984, 1733, 1719, 1265; HRMS calcd for $C_{27}H_{27}NO_6$ 461.1838, found 416.1846.

Diethyl 2-cyclohexy-1-en-1-yl-3-[4-(acetylphenyl)phenyl]-1*H*-indene-1,1-dicarboxylate (40). Obtained as a pale yellow oil in 78 % isolated yield (Table 3, entry 6): ^{1}H NMR ($CDCl_3$) δ 1.24 (t, *J*= 7.2 Hz, 6 H), 1.53 (m, 4 H), 2.00 (m, 4 H), 2.66 (s, 3 H), 4.22 (m, 4 H), 5.60 (s, 1 H), 7.16 (d, *J* = 7.6 Hz, 1 H), 7.28 (m, 2 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 7.60 (d, *J* = 7.2 Hz, 1 H), 8.02 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 21.8, 22.9, 25.9, 26.7, 29.1, 61.9, 72.0, 120.5, 124.4, 126.4, 128.4, 128.6, 129.4, 131.0, 132.4, 136.2, 140.6, 140.7, 141.7, 144.7, 145.0, 168.3, 197.9; IR ($CHCl_3$, cm^{-1}) 3056, 2983, 2934, 1739, 1716, 1268; HRMS calcd for $C_{29}H_{30}O_5$ 458.2093, 458.2101.

Ethyl 1-cyano-3-[4-(ethoxycarbonyl)phenyl]-2-hexyl-1*H*-indene-1-carboxylate (42). Obtained as a pale yellow oil in 53 % isolated yield (Table 3, entry 7): ^{1}H NMR ($CDCl_3$) δ 1.24 (t, *J*= 7.2 Hz, 6 H), 1.20-1.31 (m, 9 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 1.60 (m, 2 H), 2.48 (m, 1 H), 2.58 (m, 1 H), 4.28 (m, 2 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 7.09 (d, *J* = 7.6 Hz, 1 H), 7.34 (m, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.61 (d, *J* = 7.2 Hz, 1 H), 8.18 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 14.4, 22.5, 27.6, 28.6, 29.5, 31.3, 58.3, 61.2, 63.6, 116.4, 120.9, 123.2, 127.1, 128.8, 129.8, 130.0, 130.5, 138.0, 138.9, 140.8, 144.0, 144.7, 165.6, 166.3; IR ($CHCl_3$, cm^{-1}) 2983, 2930, 1741, 1715, 1266; HRMS calcd for $C_{28}H_{31}NO_4$ 445.2253, found 445.2261.

Ethyl 3-[4-(ethoxycarbonyl)phenyl]-2-phenyl-1-(phenylsulfonyl)-1*H*-indene-1-carboxylate (44). Obtained as a pale yellow oil in 42 % isolated yield (Table 3, entry 10): ^{1}H NMR ($CDCl_3$) δ 1.25 (t, *J*= 7.2 Hz, 3 H), 1.37 (t, *J* = 7.2 Hz, 3 H), 4.35 (m, 4 H), 6.91 (d, *J* = 8.4 Hz, 3 H), 7.06 (d, *J* = 7.2 Hz, 2 H), 7.11-7.24 (m, 7 H), 7.37 (m, 2 H), 7.47 (m, 1 H),

7.93 (d, J = 8.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.4, 61.2, 63.0, 85.4, 121.1, 126.3, 127.3, 127.6, 127.8, 128.2, 129.0, 129.9, 130.0, 130.1, 130.2, 130.6, 132.4, 133.7, 135.7, 137.4, 137.8, 138.8, 145.2, 146.8, 165.8, 166.2; IR ($CHCl_3$, cm^{-1}) 2982, 1739, 1717, 1272; HRMS calcd for $C_{33}H_{28}SO_6$ 552.1607, found 552.1616.

Ethyl 2-phenyl-1-phenylsulfonyl-1*H*-indene-1-carboxylate (45). Obtained as a pale yellow oil in 61 % isolated yield (Table 3, entry 11): ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3 H), 4.35 (m, 2 H), 6.96 (s, 1 H), 7.01 (dd, J = 1.2, 8.4 Hz, 2 H), 7.09 (t, J = 8.0 Hz, 2 H), 7.14 (d, J = 6.8 Hz, 1 H), 7.34-7.41 (m, 6 H), 7.51 (dt, J= 1.6, 8.0 Hz, 2 H), 7.96 (d, J = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 63.0, 84.0, 121.7, 126.2, 126.7, 127.4, 127.9, 128.3, 128.5, 130.0, 130.2, 132.7, 133.7, 134.3, 135.4, 138.1, 142.9, 143.9, 165.8; IR ($CHCl_3$, cm^{-1}) 3062, 2982, 1718, 1195; HRMS calcd for $C_{24}H_{20}SO_4$ 404.1082, found 404.1088.

Diethyl 13*H*-indeno[1,2-*l*]phenanthrene-13,13-dicarboxylate (47). Obtained as a pale yellow oil in 35 % isolated yield (eq 11): ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J= 7.2 Hz, 6 H), 4.10 (m, 4 H), 7.41 (t, J = 7.6 Hz, 1 H), 7.61 (m, 3 H), 7.75 (m, 2 H), 7.88 (d, J = 7.6 Hz, 1 H), 8.21 (d, J = 8.0 Hz, 1 H), 8.40 (d, J = 7.6 Hz, 1 H), 8.74 (d, J = 7.6 Hz, 1 H), 8.86 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 62.2, 68.7, 123.1, 123.3, 123.7, 124.8, 124.9, 126.5, 126.6, 126.8, 126.9, 127.0, 127.1, 128.5, 128.7, 129.1, 130.8, 131.9, 136.4, 137.5, 142.6, 142.9, 168.9; IR ($CHCl_3$, cm^{-1}) 3053, 2984, 1749, 1265; HRMS calcd for $C_{27}H_{22}O_4$ 410.1518, found 410.1526.

Diethyl 3-[(1*E*)-3-ethoxy-3-oxoprop-1-enyl]-2-hexyl-1*H*-indene-1,1-dicarboxylate (52). Obtained as a pale yellow oil in 36 % isolated yield (eq 13): ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J= 6.9 Hz, 3 H), 1.22-1.49 (m, 17 H), 2.73 (m, 2 H), 4.15-4.33 (m, 6 H), 6.55 (d, J = 16.5 Hz, 1 H), 7.27 (dt, J = 0.9, 7.5 Hz, 1 H), 7.37 (dt, J = 0.9, 7.5 Hz, 1 H), 7.56 (d, J = 7.5 Hz, 1 H), 7.62 (d, J = 7.2 Hz, 1 H), 7.77 (d, J = 16.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 14.5, 16.6, 22.8, 28.4, 30.1, 30.5, 31.7, 60.9, 62.4, 72.0, 120.7, 121.5, 125.4, 126.4, 128.9,

136.2, 136.9, 140.2, 142.7, 151.2, 167.3, 168.1; IR ($CHCl_3$, cm^{-1}) 3054, 2985, 1727, 1718, 1265; HRMS calcd for $C_{26}H_{34}O_6$ 442.2355, found 442.2362.

Diethyl 2-hexyl-1*H*-indene-1,1-dicarboxylate (53). Obtained as a pale yellow oil in 48 % isolated yield (eq 13): ^1H NMR ($CDCl_3$) δ 0.91 (m, 3 H), 1.25 (t, J = 7.2 Hz, 6 H), 1.35 (m, 6 H), 1.66 (m, 2 H), 2.51 (m, 2 H), 4.21 (m, 4 H), 6.63 (t, J = 1.8 Hz, 1 H), 7.26 (m, 3 H), 7.57 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 22.9, 28.1, 28.7, 29.5, 30.0, 62.1, 72.2, 120.8, 125.0, 125.4, 128.8, 130.0, 140.9, 144.7, 148.5, 168.5; IR ($CHCl_3$, cm^{-1}) 3048, 2983, 1758, 1471; HRMS calcd for $C_{21}H_{28}O_4$ 334.1988, found 334.1994.

References

1. (a) Kikuchi, T.; Tottori, K.; Uwahodo, Y. PCT Int. Appl. 9621449, **1996**; *Chem. Abstr.* **1996**, *125*, 204539. (b) Mederski, W.; Dorsch, D.; Wilm, C.; Osswald, M. Schmitges, C. Ger. Offen. 1971785, **1998**; *Chem. Abstr.* **1998**, *129*, 275905. (c) Dillard, R.; Hagishita, S.; Ohtani, M. PCT Int. Appl. 9603120, **1996**; *Chem. Abstr.* **1996**, *125*, 341826.
2. Spaleck, W.; Antberg, M.; Dolle, V.; Klein, R.; Rohrmann, J.; Winter, A. *New J. Chem.* **1990**, *14*, 499.
3. (a) Prough, J.; Alberts, A.; Deanna, A.; Gilfillian, J.; Huff, R.; Smith, J.; Wiggins, J. *J. Med. Chem.* **1990**, *33*, 758. (b) Olivier, M.; Marechal, E. *Bull. Soc. Chim. Fr.* **1973**, 3092. (c) Normant, C. *Bull. Soc. Chim. Fr.* **1971**, 1351. (d) Ikeda, S.; Chatani, N.; Kajikawa, Y.; Ohe, K.; Murai, S. *J. Org. Chem.* **1992**, *57*, 2. (e) Becker, C.; McLaughlin, M. *Synlett*, **1991**, 642.
4. Miller, W.; Pittman, C. *J. Org. Chem.* **1974**, *39*, 1955.
5. Yoshida, H.; Kato, M.; Ogata, T. *J. Org. Chem.* **1985**, *50*, 1145.
6. Yum, E. K. *Ph. D. dissertation*, Iowa State University, **1992**.
7. Zhang, D. *M. S. Thesis*, Iowa State University, **2002**.

8. Sonogashira, K. *Comprehensive Organic Synthesis*, Vol. 3, Pergamon, Oxford, **1990**, 521.

9. (a) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111. (b) Monteiro, N.; Balme, G. *Synlett* **1998**, 746. (c) Chowdhury, C.; Chaudhuri, G.; Guha, S.; Mukherjee, A. K.; Kundu, N. G. *J. Org. Chem.* **1998**, *63*, 1863. (d) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 5327. (e) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Paola, P. *Synlett* **1997**, 1363. (f) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280. (g) Cavicchioli, M.; Decortiat, S.; Gore, J.; Balme, G. *Tetrahedron* **1996**, *52*, 11463.

10. Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.

11. Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001.

12. Monteiro, N.; Balme, G. *Synlett* **1998**, 746.

13. Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin trans. 1* **1997**, 2815.

14. Fournet, G.; Balme, G.; Van Hemelryck, B.; Gore, J. *Tetrahedron Lett.* **1990**, *31*, 5147.

15. Wei, L.; Lin, C.; Wu, M. *Tetrahedron Lett.* **2000**, *41*, 1215.

16. Dai, G.; Larock, R. C. *Organic Lett.* **2001**, *3*, 4035.

17. (a) Kong, K. C.; Cheng, C. H. *J. Am. Chem. Soc.* **1991**, *113*, 6313. (b) Goodson, E. F.; Wallow, I. T.; Novak, M. B. *J. Am. Chem. Soc.* **1997**, *119*, 12441.

18. (a) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434. (b) Tsuji, J. *Palladium Reagents and Catalysts*, John Wiley & Sons, New York, **1995**, 5.

19. (a) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280. (b) Monteiro, N.; Balme, G. *Synlett* **1998**, 746. (c) Fournet, G.; Balme, G.; Van Hemelryck, B.; Gore, J. *Tetrahedron Lett.* **1990**, *31*, 5147. (d) Dai, G.; Larock, R. C. *Organic Lett.* **2001**, *3*, 4035.

20. (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232. (b) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451.

21. Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 3557.

22. Harrison, L. W. *Ph. D. dissertation*, Iowa State University, **1989**.

GENERAL CONCLUSIONS

In this thesis several palladium-catalyzed carboannulation methods have been developed for a variety of indene derivatives.

Chapter 1 describes the synthesis of indenes by the palladium-catalyzed carboannulation of internal alkynes by functionalized aryl halides. The annulation proceeds under relatively mild reaction conditions and gives good yields of indenes. This annulation process also exhibits excellent regioselectivity and is particularly suited for the synthesis of hindered 2-substituted indenes.

Chapter 2 deals with a palladium/copper-catalyzed coupling of terminal alkynes and aryl halides, followed by a copper-catalyzed intramolecular cyclization. This two-step annulation procedure has proven to be quite general for the synthesis of indenes from terminal alkynes bearing a variety of substituents.

Chapter 3 presents a new method for the synthesis of indenes by the palladium-catalyzed arylation of arylalkynes bearing a carbon nucleophile. This procedure, which involves cyclization and arylation in a single step, provides a convenient means of synthesizing indenes in high yields . This reaction also tolerates considerable functionality, and is particularly suited for the synthesis of 3,4-diaryl substituted indenes from electron-deficient aryl halides.

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