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Synthesis of Indenes by the Transition Metal-Mediated Carboannulation of Alkynes

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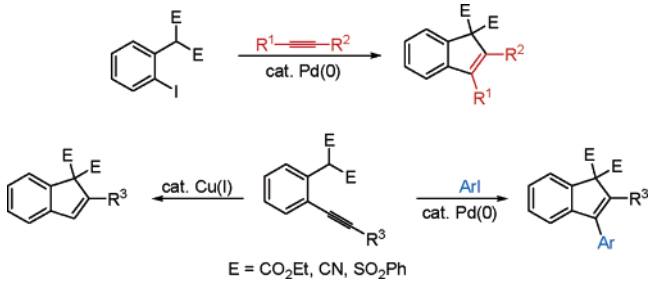

The synthesis of highly substituted indenes has been achieved by three different transition metal-mediated methods. The first method involves the palladium-catalyzed carboannulation of internal alkynes. The second method utilizes a two-step approach, which involves first the palladium/copper-catalyzed cross-coupling of terminal alkynes with appropriately functionalized aryl halides, followed by copper-catalyzed intramolecular cyclization. The third method involves intermolecular palladium-catalyzed arylation of the arylalkynes formed in the first step of the second method.

Introduction

The indene ring system is present in drug candidates possessing interesting biological activities[1] and metallocene complexes utilized in the catalysis of olefin polymerization.[2] Consequently, a number of approaches to the synthesis of the indene ring system have been developed, including the reduction/dehydration of indanones,[3] the cyclization of phenyl-substituted allylic alcohols,[4] and the ring expansion of substituted cyclopropenes.[5] Although these classical methods are quite effective in synthesizing simple indenes, they have certain drawbacks in the preparation of highly substituted indenes, namely the strong acid medium sometimes required, the lengthy reaction sequences often involved, and the low tolerance for important organic functionality. These drawbacks have prompted us to develop a general synthesis of indenes utilizing palladium- and copper-catalyzed annulation methodologies.

Transition metal-catalyzed annulation processes have proven very useful in organic synthesis.[6] The palladium-catalyzed annulation of alkynes is particularly effective for the synthesis of a wide variety of carbocycles and heterocycles.[7] We have successfully employed such annulation chemistry for the synthesis of indoles,[8] benzofurans,[9] isocoumarins,[10] isoquinolines,[11] carbolines,[12] indenones,[13] and polycyclic aromatic

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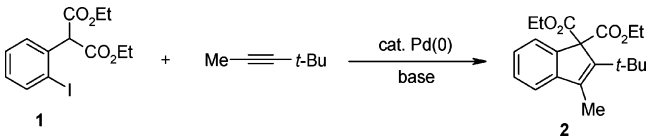
SCHEME 1



hydrocarbons.[14] The palladium-catalyzed synthesis of these carbo- and heterocycles has major 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. Most important organic functional groups are readily accommodated. The base-promoted Pd-catalyzed annulation of alkynes is especially useful for preparing acid-sensitive substances.[15] Recently, we have communicated our preliminary results on the synthesis of indenes by the palladium-catalyzed carboannulation of internal alkynes by appropriately functionalized aryl halides.[16] Herein, we wish to report the full details of that synthesis of indenes, plus additional approaches to indenes employing terminal alkynes plus copper- and palladium-catalyzed processes.

Results and Discussion

Synthesis of Indenes by the Palladium-Catalyzed Carboannulation of Internal Alkynes. Our initial studies were aimed at finding the optimal reaction conditions for the palladium-catalyzed carbonannulation of internal alkynes (Scheme 1). Our investigation began with the reaction of diethyl (2-iodophenyl)malonate (**1**) and 4,4-dimethyl-2-pentyne. The reaction was first attempted using 1 equiv of 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*-Bu_4NCl, and 2 equiv of KOAc in 1 mL of DMF at 80 °C. This reaction provided a 49% isolated yield of the desired indene **2** in 24 h, alongside a small amount of material, which appeared to arise by multiple insertion of the alkyne. To minimize the formation of multiple-insertion products, the concentration of the reactants was lowered by using 5 mL of DMF as the solvent. That reaction furnished an 86% yield of the indene product without any side products, but the reaction took 48 h to reach completion.

Additional reaction parameters were also studied. Using 5 mol % of PPh_3 as a ligand in this latter reaction did not increase the yield of the desired product. The use of other bases, such as K_2CO_3, Na_2CO_3, or organic amine bases, drastically reduced the yield of the desired product. Other Pd catalysts, such as $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, and $Pd_3(dba)_2{\cdot}CHCl_3$, have also been employed in this annulation reaction. None of them gave a higher yield than $Pd(OAc)_2$. LiCl was examined as an alternative to *n*-Bu_4NCl, and the yield was comparable. When less than 5 equiv of 4,4-dimethyl-2-pentyne were used, the reactions were slower, and the yields were lower.

On the basis of the above optimization efforts, the combination of 1 equiv 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 1). Having gained an understanding of the factors that influence the carboannulation process, we explored the scope and limitations of this method. Further carboannulation results are summarized in Table 1.

The reactions of **1** with symmetrical alkynes, such as 4-octyne and diphenyl acetylene, afforded good yields of the desired products (Table 1, entries 2 and 3). The results with the dialkyl acetylene are significant, since such alkynes have not always afforded particularly good results in analogous Pd-catalyzed annulation chemistry. 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 1; entries 1, 4, and 5). The assignment of regiochemistry is based on analogy with our earlier indole work.[8] In entry 5, a much lower yield (40%) of the indene product was isolated when KOAc was used as the base instead of K_2CO_3.

This process should tolerate considerable functionality. For example, the reaction of compound **1** with 3-phenyl-2-propyn-1-ol afforded a 51% yield of a single regioisomer (entry 6). The reactivity of other functionally substituted aryl halides has also been examined. The aryl halide **8** bearing two electron-donating methoxy groups reacts with 4,4-dimethyl-2-pentyne to afford a 74% yield of the desired indene (entry 7). Interestingly, when aryl bromide **10** was employed, a 46% yield of the corresponding indene could still be obtained (entry 8). Aryl halides with electron-withdrawing groups other than esters have also been allowed to react with various internal alkynes to afford moderate yields of the desired products (Table 1; entries 9−14). Several bases, such as KOAc, NaOAc, K_2CO_3, and Na_2CO_3, have been employed in many of these reactions and K_2CO_3 generally gave the highest yield of the desired annulation products (entries 9, 10, and 12). With certain alkynes, these latter functionally substituted aryl iodides gave back substantial amounts of the starting aryl halides for reasons that are not immediately obvious.

The mechanism shown in Scheme 2 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 insertion of the alkyne to form a vinylic palladium intermediate, (3) generation of a carbanion by the base, (4) intramolecular nucleophilic attack of the carbanion on the vinylic palladium intermediate to afford a palladacyclic intermediate, and (5) reductive elimination of the intermediate to furnish the indene and regenerate the Pd(0) catalyst.

The oxidative addition of aryl halides to Pd(0) is well-known and integral to a wide variety of Pd(0)-catalyzed processes.[17] Subsequent syn-addition of the resulting arylpalladium compound to internal alkynes has been widely employed in analogous palladium-catalyzed hydroarylation processes[18] and

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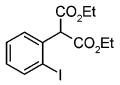
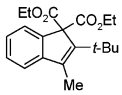
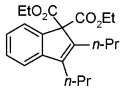
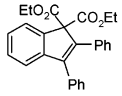
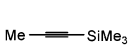
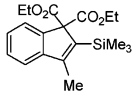
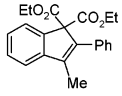
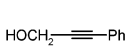
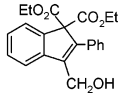
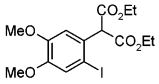
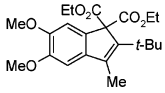
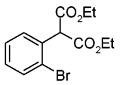
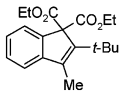
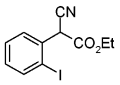
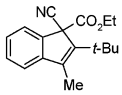
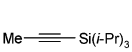
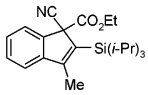
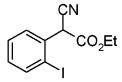
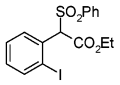
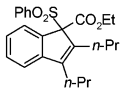
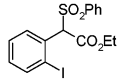
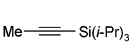
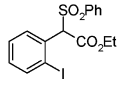
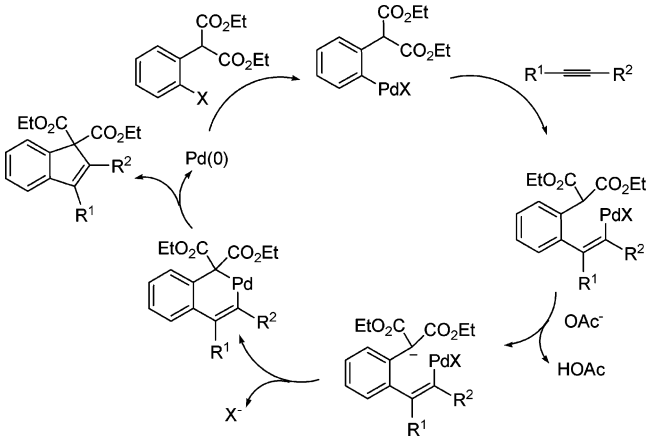
TABLE 1. Palladium-Catalyzed Carboannulation of Internal Alkynes by Aryl Halides[a]

entry	halide		alkyne	product		% isolated yield
1		**1**			**2**	86
2[b]	**1**				**3**	72
3[c]	**1**				**4**	70
4[d]	**1**				**5**	81
5[d]	**1**				**6**	63
6[b]	**1**				**7**	51
7		**8**			**9**	74
8		**10**			**2**	46
9[b,d]		**11**			**12**	65
10[b,d]	**11**				**13**	52
11	**11**				**11**	38
12[b,d]		**14**			**15**	45
13	**14**				**14**	57
14	**14**				**14**	68

[a] All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the aryl halide, 1.25 mmol of the alkyne, 5 mol % of $Pd(OAc)_2$, 0.25 mmol of *n*-Bu_4NCl, and 0.50 mmol of KOAc were stirred in 5 mL of DMF at 80 °C under an N_2 atmosphere for 48 h. [b] 0.25 mmol of LiCl was used instead of *n*-Bu_4NCl. [c] 0.50 mmol of the alkyne were employed. [d] 0.50 mmol of K_2CO_3 was used instead of KOAc.

assumed in many other alkyne insertion processes.[19] 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).

SCHEME 2



Analogous regiochemistry is also observed in all of our previous reported annulation chemistry.[7] The subsequent steps of this process are presumed to be palladacycle formation and subsequent reductive elimination. Although we have no actual proof of 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 heterocycle.[20] It stands to reason that analogous carbon-containing palladacycles would behave similarly.

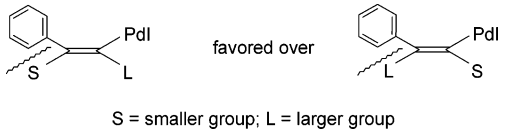


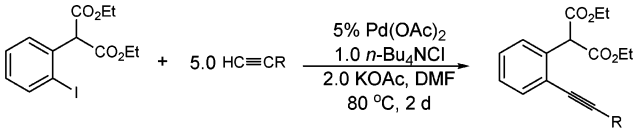
FIGURE 1. Steric effects on the regiochemistry of alkyne insertion.

Synthesis of Indenes by the Copper(I)-Catalyzed Carboannulation of Alkynes. We have also attempted to achieve the annulation of terminal alkynes utilizing this same methodology (Scheme 3). However, the reactions have only afforded acetylenic coupling products in high yields.

Preliminary efforts to cyclize the resulting diethyl [2-(1-octynyl)phenyl]malonate (**16**) by applying different Pd catalysts or bases gave poor results, suffering either low yields or no cyclization product at all (Scheme 4). The use of a strong base, such as *t*-BuOK or NaH, appeared essential to formation of the cyclization product **17** as noted later. However, a large amount of diethyl 2-[(1-octynyl)phenyl]malonate (**16**) was recovered in all cases.

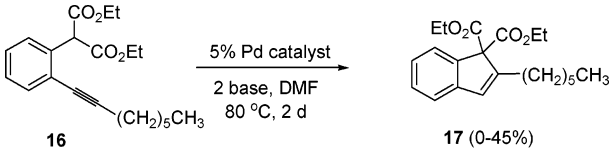
The cyclization of diethyl [2-(1-octynyl)phenyl]malonate (**16**) appears to involve intramolecular nucleophilic attack of a carbanion on the carbon−carbon triple bond. This type of cyclization has been achieved previously by several different methods. For example, Cacchi and Arcadi have observed the carbocyclization of N-substituted malonanilides using a stoichiometric amount of NaH.[21] The nature of the substituent linked to the acetylenic moiety was crucial for the success of this latter cyclization. Best results were obtained when the substituent was an aromatic ring bearing electron-withdrawing substituents.

SCHEME 3



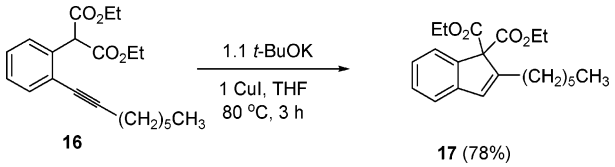
R	% yield
$(CH_2)_5CH_3$ (**16**)	93
CH_2OCH_3 (**20**)	84
$C(CH_3)_3$ (**30**)	87
Ph (**38**)	91

SCHEME 4



Pd catalyst: $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3{\cdot}CHCl_3$
base: KOAc, K_2CO_3, NaOEt, NEt_3, *t*-BuOK, NaH

SCHEME 5



Balme has reported an intramolecular cyclization of terminal alkynes in the presence of 20 mol % of $Pd(dppe)_2$ and 1.1 equiv of *t*-BuOK in THF as the solvent.[22] This procedure afforded a mixture of methylene cyclopentanes and methyl cyclopentenes. In a subsequent paper, Balme described a copper-catalyzed intramolecular cyclization using catalytic amounts of *t*-BuOK and CuI.[23] Compared to the previous palladium-catalyzed cyclization method, this procedure provided the desired methylene cyclopentanes in good yields at lower reaction temperatures and in shorter reaction times. 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 products.

Inspired by the preceding work, we have examined a similar copper-catalyzed intramolecular cyclization procedure in an attempt to cyclize diethyl [2-(1-octynyl)phenyl]malonate (**16**) (Scheme 5). Indeed, the use of stoichiometric amounts of CuI and *t*-BuOK afforded the desired cyclization product in a 78% yield when run in THF at 80 °C for 3 h. On the basis of the success of this copper-mediated intramolecular cyclization, we herein wish to report a two-step procedure for the carboannulation of terminal alkynes by appropriately functionalized aryl halides. The procedure involves the palladium/copper-catalyzed

(19) (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.

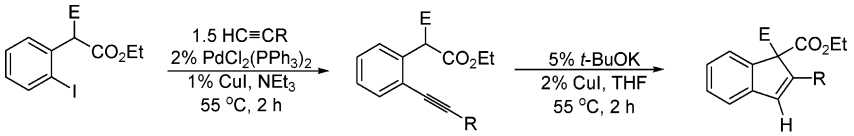
(20) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232. (b) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451.

(21) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Manna, F.; Pace, P. *Synlett* **1998**, 446.

(22) Monteiro, N.; Gore, G.; Balme, G. *Tetrahedron* **1992**, *48*, 10103.

(23) Bouyssi, D.; Monteiro, N.; Balme, G. *Tetrahedron Lett.* **1999**, *40*, 1297.

SCHEME 6



cross-coupling of terminal alkynes with aryl halides, followed by copper-catalyzed intramolecular cyclization.

Initial studies were aimed at finding the optimal reaction conditions for both the coupling and cyclization steps. With regard to the cross-coupling step, we found that the standard Sonogashira coupling procedure[24] often afforded somewhat higher yields of the coupling products than the procedure described in Scheme 3. In addition, Sonogashira coupling proceeds at a lower reaction temperature and shorter reaction times. On the basis of these results, we chose the Sonogashira coupling as the standard method for the initial cross-coupling step.

Next, we focused our attention on finding the best reaction conditions for the cyclization step. The reaction was first attempted using diethyl [2-(1-octynyl)phenyl]malonate (**16**, 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. As noted earlier, this reaction provided a 78% yield of the desired cyclization product **17** (Scheme 5). The reaction afforded an even higher 85% yield of the desired product when 5 mol % of *t*-BuOK, and 2 mol % of CuI were used. Interestingly, a 26% yield of the desired product was isolated when 1 equiv of *t*-BuOK and no CuI were employed. The reaction was also carried out by using diethyl [2-(1-octynyl)-phenyl]malonate (**16**, 0.25 mmol), 1.1 equiv of *t*-BuOK, and 1 equiv of CuI in other organic solvents, such as DMF, DMSO, and *t*-BuOH, and all of these reactions provided lower yields of the desired product. A reaction with 5 mol % of *t*-BuOK and 2 mol % of CuI at 55 °C afforded an excellent 96% yield of the desired product. An analogous reaction at 30 °C resulted in lower yields. Thus, the optimum reaction conditions developed involve 1 equiv of diethyl [2-(1-octynyl)phenyl]malonate (**16**, 0.25 mmol), 5 mol % of *t*-BuOK, and 2 mol % of CuI in 5 mL of THF at 55 °C for 2 h.

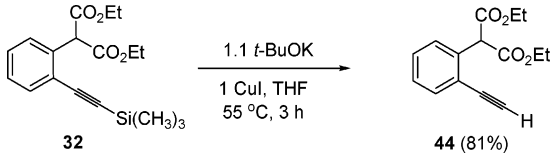
On the basis of the above optimization study, a two-step procedure has thus been developed for the synthesis of indenes by the carboannulation of terminal alkynes using suitably functionalized aryl halides. The procedure involves the palladium/copper-catalyzed Sonogashira coupling of terminal alkynes with aryl halides, followed by copper-catalyzed intramolecular cyclization of the intermediate alkyne (Scheme 6). A variety of indene derivatives have been synthesized by employing this methodology. The results are summarized in Table 2.

Both the coupling and cyclization reactions of diethyl (2-iodophenyl)malonate (E = CO_2Et) (**1**) with terminal alkynes bearing a long chain alkyl substituent afforded excellent yields of the desired products (entries 1 and 2). This two-step annulation methodology also tolerates a variety of functional groups in the terminal alkyne, including a methoxy (entry 3), a hydroxy (entry 4), an ester (entry 5), a diethoxyacetal (entry 6), and a cyano group (entry 7).

(24) Sonogashira, K. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1990; Vol. 3, p 521.

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)phenyl]malonate (**30**) in an excellent yield (entry 8). Subsequent cyclization of malonate **30** was slow and gave the corresponding cyclization product **31** in only a moderate yield. This result is reasonable considering the steric hindrance of the bulky *tert*-butyl group. An attempt to cyclize diethyl [2-(trimethylsilylethynyl)phenyl]-malonate (**32**) did not afford any cyclization product, and 82% of the coupling intermediate was recovered. Using stoichiometric amounts of both *t*-BuOK and CuI only resulted in formation of the desilylation product diethyl (2-ethynylphenyl)malonate (**44**) (Scheme 7).

SCHEME 7



Terminal alkynes bearing a carbocyclic ring have also been subjected to this annulation process. Both the coupling and cyclization reactions of diethyl (2-iodophenyl)malonate (**1**) with cyclohexyl acetylene (entry 10) or 1-ethynylcyclohexene (entry 11) provided the desired products in high yields. The coupling of diethyl (2-iodophenyl)malonate (**1**) with phenyl acetylene proceeded very well to give a 98% yield of the cross-coupled product **38** (entry 12). However, subsequent cyclization afforded the desired product **39** in only a moderate 61% yield. 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 (entries 13 and 14), although the former gave significantly lower yields in both steps.

The reactivity of other appropriately functionalized aryl halides has also been examined (entries 15−20). Both the cross-coupling and cyclization reactions of 1-octyne and ethyl cyano-(2-iodophenyl)acetate (**45**) afforded high yields of the desired products (entry 15). The cross-coupling of cyclohexyl acetylene with **45** gave a 76% yield of ethyl cyano[2-(cyclohexylethynyl)-phenyl]acetate (**48**), alongside a small amount of the cyclization product **49** (entry 16). The ethyl cyano[2-(cyclohexylethynyl)-phenyl]acetate (**48**) was then allowed to react with catalytic amounts of *t*-BuOK and CuI to generate the desired cyclization product **49** in 78% yield. A high yield of ethyl 1-cyano-2-phenyl-1*H*-indene-1-carboxylate (**50**) was obtained as the sole product under the Sonogashira conditions, when **45** and phenyl acetylene were employed (entry 17). While the Sonogashira reaction of halide **51** and phenylacetylene proceeded smoothly, the cyclization of ethyl [2-(phenylethynyl)phenyl](phenylsul-fonyl)acetate (**52**) was very slow under our normal reaction conditions and gave only a very low yield of the desired product

TABLE 2. Two-Step Annulation of Terminal Alkynes by Functionally Substituted Aryl Halides[a]

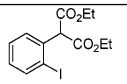
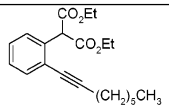
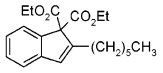
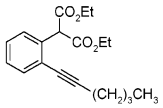
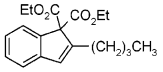
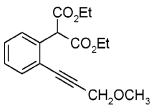
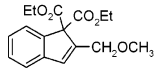
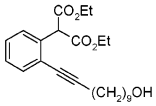
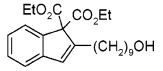
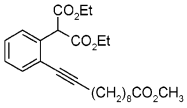
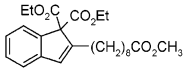
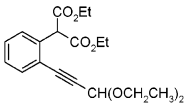
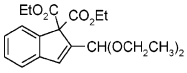
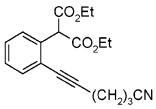
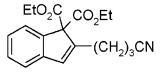
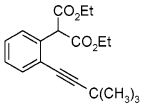
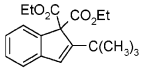
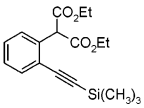
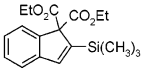
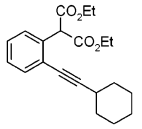
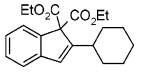
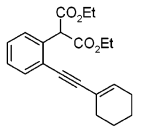
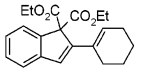
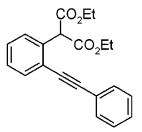
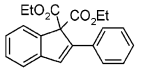
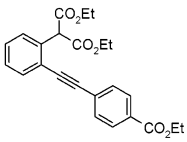
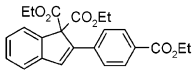
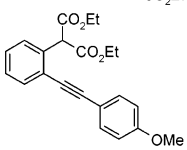
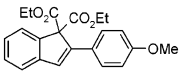
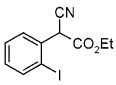
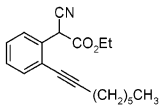
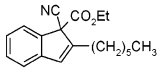
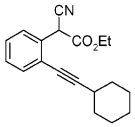
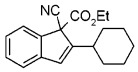
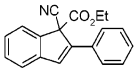
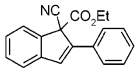
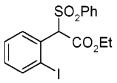
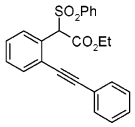
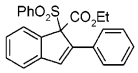
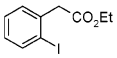
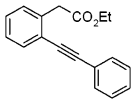
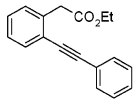
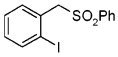
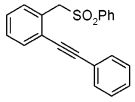
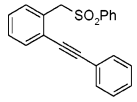
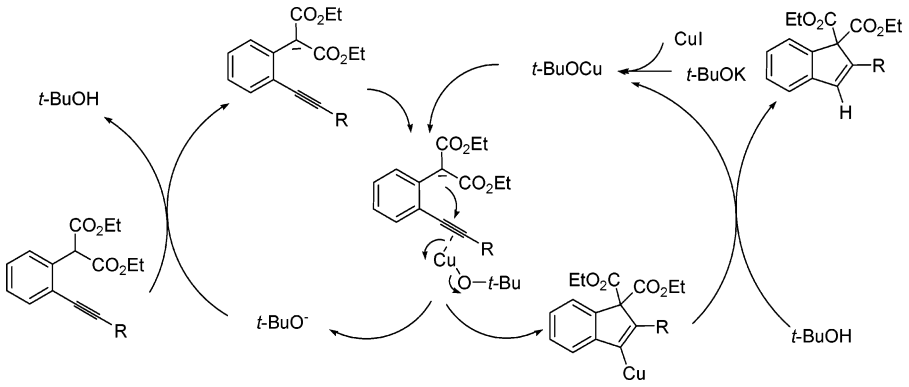
entry	aryl halide		coupling product		% yield	cyclization product		% yield
1		**1**		**16**	95		**17**	96
2	**1**			**18**	93		**19**	92
3	**1**			**20**	81		**21**	91
4	**1**			**22**	98		**23**	79
5	**1**			**24**	86		**25**	83
6	**1**			**26**	75		**27**	58[b]
7	**1**			**28**	62		**29**	68
8	**1**			**30**	94		**31**	69[c]
9	**1**			**32**	98		**33**	0[d]
10	**1**			**34**	91		**35**	92[c]
11	**1**			**36**	90		**37**	85[c]
12	**1**			**38**	98		**39**	61
13	**1**			**40**	63		**41**	65
14	**1**			**42**	86		**43**	96
15		**45**		**46**	92		**47**	83

Table 2 (Continued)

entry	aryl halide		coupling product		% yield	cyclization product		% yield
16	**45**			**48**	76[e]		**49**	78
17	**45**			**50**	86[f]			--
18		**51**		**52**	91		**53**	36[c,g]
19		**54**		**55**	98		**55**	78[c,g]
20		**56**		**57**	99		**57**	82[c,g]

[a] All reactions were run under the following reaction conditions, unless otherwise specified. Sonogashira coupling: 0.25 mmol of the aryl halide, 0.375 mmol of the alkyne, 2 mol % of $PdCl_2(PPh_3)_2$, and 1 mol % of CuI were stirred in 3 mL of NEt_3 at 55 °C for 2 h. Cu-catalyzed cyclization: 0.25 mmol of the intermediate, 5 mol % of *t*-BuOK, and 2 mol % of CuI in 5 mL of THF were stirred at 55 °C for 2 h. [b] A 21% yield of the intermediate **26** was recovered. [c] The Cu-catalyzed cyclization was run for 12 h. [d] An 82% yield of the alkyne **32** was recovered. [e] A 6% yield of **49** was isolated. [f] The reaction was run for 12 h. [g] 1.1 Equiv of *t*-BuOK and 1 equiv of CuI were used, and the reaction was run at 80 °C.

SCHEME 8



53 (entry 18). Even the use of stoichiometric amounts of both *t*-BuOK and CuI and an elevated temperature afforded only a modest 36% yield of indene **53**.

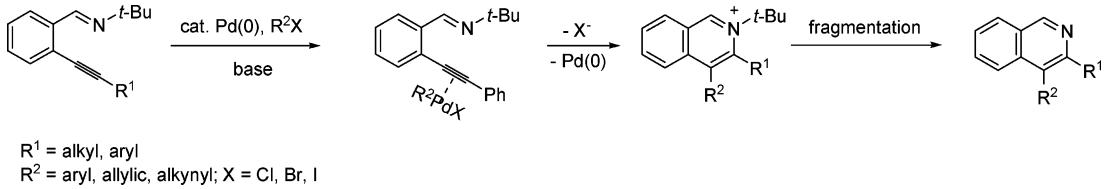
The cross-coupling of phenyl acetylene with ethyl (2-iodophenyl)acetate (**54**) or 1-iodo-2-(phenylsulfonylmethyl)-benzene (**56**) provided high yields of the desired cross-coupling products (entries 19 and 20). However, subsequent cyclization did not provide any of the desired indene products, even using stoichiometric amounts of both *t*-BuOK and CuI and an elevated temperature. The inertness of the intermediates **55** and **57** toward intramolecular cyclization can no doubt be attributed to the reduced acidity of the methylene hydrogens in these intermediates compared to the methyne hydrogen in the other intermediates bearing two electron-withdrawing groups.

The copper-catalyzed intramolecular cyclization presumably proceeds via (1) generation of a carbanion by the *tert*-butoxide, (2) coordination of the copper *tert*-butoxide to the alkyne triple bond, which activates the triple bond toward nucleophilic attack, (3) intramolecular nucleophilic attack of the carbanion on the activated triple bond to afford a vinylic copper intermediate, and (4) protonation of the resulting vinylic copper intermediate to furnish the indene and regenerate the copper catalyst and the *tert*-butoxide (Scheme 8).

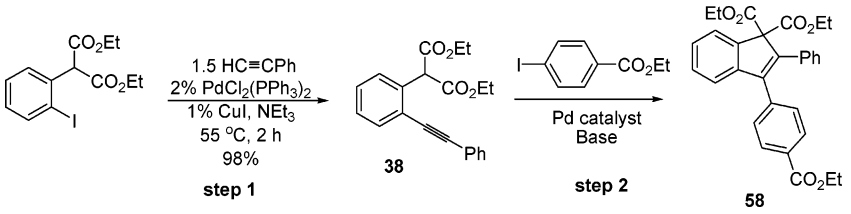
Synthesis of Indenes via Palladium-Catalyzed Cyclization of Diethyl 2-[2-(1-Alkynyl)phenyl]malonate by Organic Halides. Our group has recently reported an efficient synthesis of 3,4-disubstituted isoquinolines by the palladium-catalyzed cross-coupling of *o*-(1-alkynyl)benzaldimines and organic halides (Scheme 9).[11b,25] This method involves the intramolecular nucleophilic attack of a nitrogen atom on the triple bond promoted by coordination of a *σ*-aryl-, *σ*-allyl-, or *σ*-alkynylpalladium complex. 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 prompted us to explore analogous methodology for the synthesis of indenes. Following the

(25) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035.

SCHEME 9



SCHEME 10



completion of our work on this chemistry, Liang et al. reported very similar work on the synthesis of indenes by the palladium-catalyzed coupling of diethyl [2-(1-alkynyl)phenyl]malonates and aryl halides.[26] Herein, we wish to report the synthesis of 2,3-diarylindenes by the palladium-catalyzed arylation of aryl-alkynes bearing a neighboring carbon nucleophile by various aryl halides.

The starting 2-(1-alkynyl)phenylmalonates have been prepared by Sonogashira coupling of diethyl (2-iodophenyl)-malonate (**1**) with various terminal alkynes (Scheme 10). For example, diethyl 2-(phenylethynyl)phenylmalonate (**38**) was isolated in a 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 NEt_3.

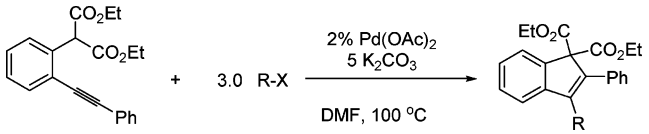
We next focused our attention on finding optimal reaction conditions for the palladium-catalyzed intermolecular cross-coupling of alkyne **38** with ethyl *p*-iodobenzoate (Scheme 10, step 2). The reaction was first attempted using our optimum reaction conditions for the synthesis of 3,4-disubstituted isoquinolines.[11b,25] The reaction was run using diethyl 2-(phenylethynyl)malonate (**38**) (0.25 mmol), 5 equiv of ethyl 4-iodobenzoate, 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 **58**, alongside a small amount of material, which appeared to arise by homo-coupling of the aryl halide. To minimize formation of the homo-coupling product, the amount of the aryl halide was decreased to 3 equiv. That reaction furnished a 77% yield of the desired product and a reduced amount of the homo-coupling product. Any further reduction in the amount of ethyl 4-iodobenzoate resulted in a much lower yield of the desired product.

The effect of different palladium catalysts on the outcome of the reaction has also been studied. $Pd(PPh_3)_4$ gave a higher yield of the desired product than other palladium catalysts studied [$Pd(OAc)_2$, $PdCl_2$, $PdCl_2(PPh_3)_2$, and $Pd_2(dba)_3{\cdot}CHCl_3$]. Decreasing the amount of $Pd(PPh_3)_4$ to 2 mol % provided the desired product in an improved 86% yield.

Other inorganic bases were examined as an alternative to K_2CO_3 [KOAc, Na_2CO_3, and Cs_2CO_3], and the yields were generally lower than the reaction using K_2CO_3 as the base. The use of organic bases, such as NEt_3 and pyridine, did not afford any of the desired product. Decreasing the amount of K_2CO_3 to 3 equiv gave a slightly lower 82% yield of the desired product than the reaction using 5 equiv of K_2CO_3. The yield was much lower when less than 3 equiv of K_2CO_3 were used.

When other organic solvents, such as DMSO and THF, were used, the reaction provided lower yields of the desired product. Raising the reaction temperature to 120 °C gave a 59% yield of the desired product and a large amount of homo-coupling product from the aryl iodide substrate was isolated. The reaction afforded an 84% yield of the desired product when the reaction was run at 80 °C. However, the reaction took 9 h to reach completion. On the basis of these optimization efforts, the combination of diethyl [2-(phenylethynyl)phenyl]malonate (**38**, 0.25 mmol), 3 equiv of the 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.

SCHEME 11



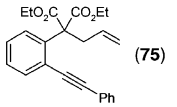
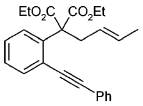
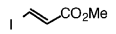
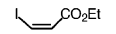
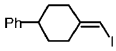
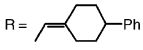
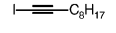
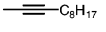
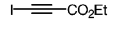
Having gained an understanding of the factors that influence the arylation process, we have explored the scope and limitations of this methodology (Scheme 11). The results are summarized in Table 3.

The reactions of diethyl [2-(phenylethynyl)phenyl]malonate (**38**) 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 3, entries 1−3). Similarly *p*- and *m*-iodonitrobenzenes reacted with alkyne **38** to give high yields of the desired products (entries 4 and 5). On the other hand, the reaction of *o*-iodonitrobenzene with alkyne **38** gave none of the desired arylation product for reasons that are not obvious and produced significant amounts of diethyl 2-phenyl-1*H*-indene-1,1-dicarboxylate (**39**) (entry 6). The reactions of *p*- and *m*-(trifluoromethyl)iodobenzenes with alkyne **38** generated the desired products in good yields, while *o*-(trifluoromethyl)-iodobenzene gave only a 53% yield of the desired product (entries 7−9). The lower yield of the desired product can presumably be attributed to the steric hindrance of the bulky ortho-substituted trifluoromethyl group.

The reactions of other electron-deficient aryl iodides with alkyne **38** also proceeded well, providing high yields of the desired indene derivatives (entries 10 and 11). None of the

(26) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-L.; Liang, Y.-M. *J. Org. Chem.* **2006**, *71*, 3325.

TABLE 3. Palladium-catalyzed Cyclization of Diethyl 2-(phenylethynyl) Phenylmalonate (38) using Various Organic Halides (Scheme 11)[a]

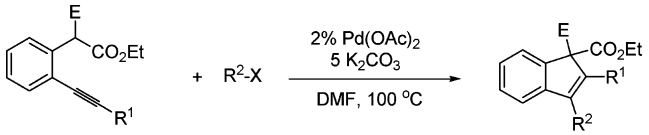
entry	RX	product	% yield
1	*p*-$EtO_2CC_6H_4I$	R = *p*-$EtO_2CC_6H_4$ (**58**)	86
2	*m*-$EtO_2CC_6H_4I$	R = *m*-$EtO_2CC_6H_4$ (**59**)	74
3	o-$EtO_2CC_6H_4I$	R = *o*-$EtO_2CC_6H_4$ (**60**)	78
4	*p*-$O_2NC_6H_4I$	R = *p*-$O_2NC_6H_4$ (**61**)	83
5	*m*-$O_2NC_6H_4I$	R = *m*-$O_2NC_6H_4$ (**62**)	82
6	*o*-$O_2NC_6H_4I$	R = H (**39**)	38[b]
7	*p*-$F_3CC_6H_4I$	R = *p*-$F_3CC_6H_4$ (**63**)	85
8	*m*-$F_3CC_6H_4I$	R = *m*-$F_3CC_6H_4$ (**64**)	91
9	*o*-$F_3CC_6H_4I$	R = *o*-$F_3CC_6H_4$ (**65**)	53
10	*p*-$CH_3COC_6H_4I$	R = *p*-$CH_3COC_6H_4$ (**66**)	94
11	*p*-ClC_6H_4I	R = *p*-ClC_6H_4 (**67**)	84
12	3-iodopyridine	R = H (**39**)	18
13	2-iodothiophene	R = 2-thienyl (**68**)	64
14	C_6H_5I	R = C_6H_5 (**69**)	72[b]
15	*p*-$H_3CC_6H_4I$	R = *p*-$H_3CC_6H_4$ (**70**)	69
16	*m*-$H_3CC_6H_4I$	R = *m*-$H_3CC_6H_4$ (**71**)	74
17	*o*-$H_3CC_6H_4I$	R = *o*-$H_3CC_6H_4$ (**72**)	73
18	*p*-$H_3COC_6H_4I$	R = *p*-$H_3COC_6H_4$ (**73**)	14[c]
19	C_6H_5Br	R = C_6H_5 (**69**)	75
20	C_6H_5Cl	R = H (**39**)	71
21	*p*-$O_2NC_6H_4Cl$	R = *p*-$O_2NC_6H_4$ (**61**)	34[d]
22	C_6H_5OTf	R = H (**39**)	38
23	allyl bromide	R = $CH_2CH{=}CH_2$ (**74**)	51[e]
24	diallyl carbonate	 (**75**)	86
25		 (**76**)	79
26		(**38**)	77
27		(**38**)	63
28		R = 	0
29		R =	0
30		R = 	0
31		(**38**)	10

[a] All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the alkyne **38**, 0.75 mmol of the aryl halide, 2 mol % of $Pd(OAc)_2$, 5 equiv of K_2CO_3 stirred in 5 mL of DMF at 100 °C for 3 h. [b] The reaction was run for 12 h. [c] A 17% yield of **69** was isolated. [d] A 55% yield of **39** was isolated. [e] The yield was determined by ^1H NMR spectroscopy.

desired arylation product was isolated when 3-iodopyridine was subjected to the palladium-catalyzed arylation (entry 12). Again, significant amounts of byproduct **39** were observed. The reaction of 2-iodothiophene and alkyne **38** afforded a moderate 64% yield of the desired indene product (entry 13).

SCHEME 12

SCHEME 13



E = CN, SO_2Ph, CO_2Et

The reactivity of relatively electron-rich aryl halides has also been examined. Iodobenzene has been allowed to react with diethyl [2-(phenylethynyl)phenyl]malonate (**38**) to give a 72% yield of the desired indene (entry 14). The *p*-, *m*-, and *o*-iodotoluenes reacted with alkyne **38** to afford the desired arylation products, but the yields are slightly lower than the reactions of the electron-deficient aryl halides (entries 15−17). When a strong 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 (entry 18). In this reaction, a significant amount of byproduct **69** was isolated. The formation of indene **69** is due to a competitive intermolecular cross-coupling process in which aryl−aryl exchange between the palladium center and the phosphine ligand in the organopalladium(II) complex[27] produces a phenylpalladium(II) complex (Scheme 12), which subsequently produces the observed side product.

Arylation using bromobenzene is nearly as effective as iodobenzene providing the desired arylation product in a good yield (entry 19). However, the reaction of chlorobenzene with alkyne **38** afforded only the reduction product **39** in a 71% yield (entry 20). On the other hand, attaching an electron-withdrawing nitro substituent to the chlorobenzene facilitated formation of the desired arylation product, although the 34% yield is still relatively low (entry 21). The reaction of phenyl triflate failed to produce any arylation product and once again afforded indene **39** in a 38% yield (entry 22).

We have also investigated the reactions of other organic halides. For example, allyl bromide reacted with alkyne **38** to yield an inseparable mixture of diethyl 3-allyl-2-phenyl-1*H*-indene-1,1-dicarboxylate (**74**, 51% yield) and diethyl 2-allyl-2-[2-(phenylethynyl)phenyl]malonate (**75**, 41% yield, entry 23). The yields were determined by ^1H NMR spectroscopy. The formation of alkyne **75** probably proceeds by a competitive S_N2 reaction, but it might also involve direct malonate anion attack on the expected π-allylpalladium intermediate. Using diallyl carbonate as an alternative source of allyl moiety only resulted in the formation of alkyne **75** in an 86% yield (entry 24). Crotyl chloride has also been subjected to this reaction. This reaction gave a high yield of the corresponding allylic-substituted alkyne, instead of the desired indene product (entry 25).

Vinylic halides, such as methyl *E*-3-iodoacrylate and ethyl *Z*-3-iodoacrylate, failed to produce any of the desired indene

(27) (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.

SCHEME 14

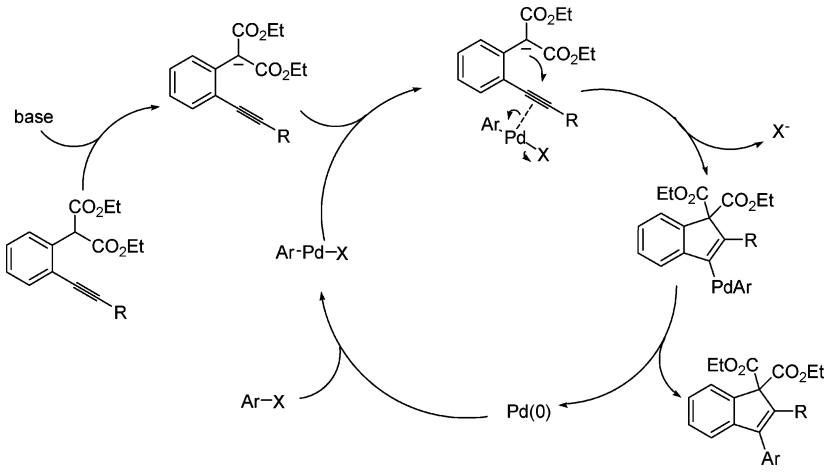


TABLE 4. Palladium-Catalyzed Arylation of Various Arylalkynes (Scheme 13)[a]

entry	E	R^1	alkyne	R^2X	product	% yield
1	CO_2Et	$(CH_2)_5CH_3$	**16**	*p*-$EtO_2CC_6H_4I$	**77**	61
2	CO_2Et	$(CH_2)_5CH_3$	**16**	*p*-$O_2NC_6H_4I$	**78**	63
3	CO_2Et	$(CH_2)_5CH_3$	**16**	*p*-$H_3COC_6H_4I$	**79**	9
4	CO_2Et	1-cyclohexenyl	**36**	*p*-$EtO_2CC_6H_4I$	**80**	83
5	CO_2Et	1-cyclohexenyl	**36**	*p*-$O_2NC_6H_4I$	**81**	87
6	CO_2Et	1-cyclohexenyl	**36**	*p*-$CH_3COC_6H_4I$	**82**	78
7	CN	$(CH_2)_5CH_3$	**46**	*p*-$EtO_2CC_6H_4I$	**83**	53
8	SO_2Ph	Ph	**52**	*p*-$EtO_2CC_6H_4I$	**84**	42

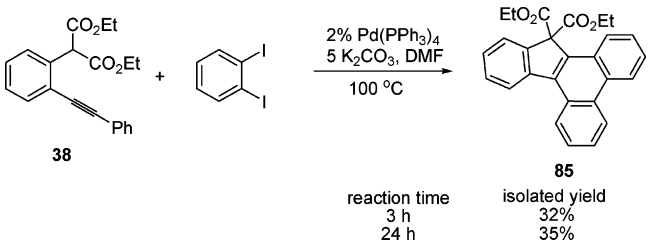
[a] All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the alkyne, 0.75 mmol of the aryl halide, 2 mol % of $Pd(OAc)_2$, and 5 equiv of K_2CO_3 were stirred in 5 mL of DMF at 100 °C for 3 h.

products, but gave back large amounts of the starting alkyne **38** (entries 26 and 27). The reaction of [4-(iodomethylene)-cyclohexyl]benzene resulted in a complex mixture with no obvious indene product (entry 28). The reactions of alkynyl iodides with alkyne **38** did not generate any of the desired indenes either (entries 29−31). A large amount of black oily material was obtained in each case, and the corresponding ^1H NMR spectrum was unrecognizable. On the other hand, a moderate yield of the desired 3,4-disubstituted isoquinoline was obtained (56%) in our earlier palladium-catalyzed cross-coupling of *o*-(1-alkynyl)benzaldimines and 1-iodo-1-decyne.[11b,25]

The reactivity of other arylalkynes bearing potential carbanion centers has also been examined (Scheme 13). For example, a 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 products (Table 4, 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 3. The arylalkyne **36** 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 (entries 4−6). Arylalkynes bearing different electron-withdrawing functional groups have also been subjected to this arylation reaction, and the reactions have afforded the desired arylation products in moderate yields (entries 7 and 8).

We propose the mechanism shown in Scheme 14 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, (3) coordination of the resulting organopalladium(II) intermediate to the alkyne triple bond to form an organopalladium π-complex, which activates the triple bond toward nucleophilic attack, (4) intramolecular nucleophilic attack of the carbanion on the activated carbon−carbon triple bond to afford a vinylic palladium intermediate, and (5) reductive elimination to form the arylation product and regenerate the Pd(0) catalyst. The observation that the yields of the reactions employing electron-deficient aryl halides are generally higher than those utilizing 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 by the carbanion. Liang has reported a similar mechanism,[26] but one involving trans addition of the arylpalladium intermediate to alkyne. This seems highly unlikely and is inconsistent with the many other reports of the backside attack of a nucleophile on an alkyne complexed to an arylpalladium intermediate.[11b,25,28]

SCHEME 15

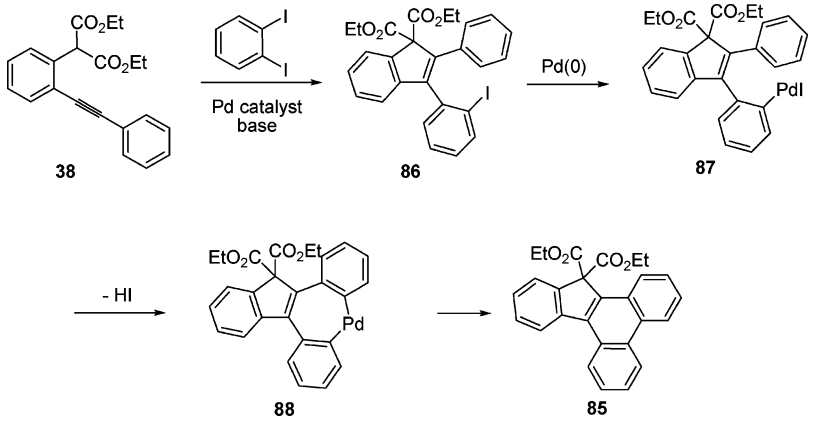


Interestingly, a double arylation product **85** (Scheme 15) has been isolated in a low yield when 1,2-diiodobenzene was allowed to react with diethyl [2-(phenylethynyl)phenyl]malonate (**38**). The formation of polycycle **85** is presumably due to subsequent intramolecular cyclization of the expected intermediate **86** bearing an iodophenyl group resulting in organopalladium species **88**, which subsequently undergoes reductive elimination to provide the double arylation product **85** (Scheme 16).[29]

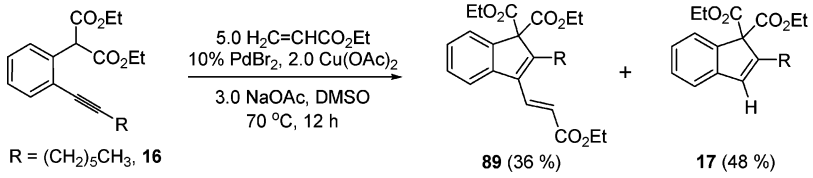
(28) (a) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 5327. (b) Cacchi, S.; Fabrizi, G.; Moro, L.; Pace, P. *Synlett* **1997**, 1367. (c) Wei, L.-M.; Lin, C.-F.; Wu, M.-J. *Tetrahedron Lett.* **2000**, *41*, 1215. (d) Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem.* **2002**, *67*, 2365.

(29) For analogous intramolecular arylations, see: (a) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (b) Parisien, M.; Damien, V. Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578.

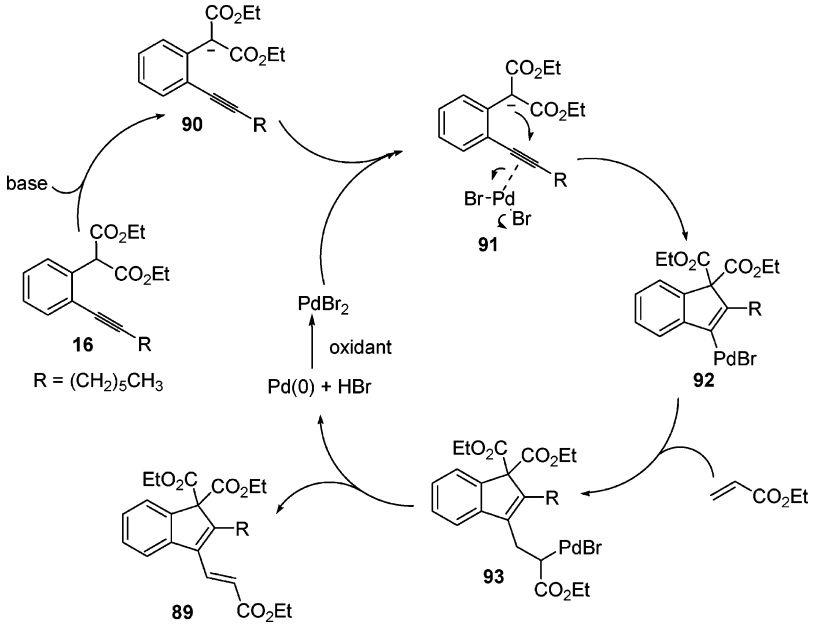
SCHEME 16



SCHEME 17



SCHEME 18



A Heck type reaction analogous to our earlier work on isoquinolines[11c,30] has also been examined employing diethyl [2-(oct-1-ynyl)phenyl]malonate (**16**) and ethyl acrylate (Scheme 17). The reaction yielded the desired olefinic indene product **89** in 36% yield, alongside a large amount of the direct cyclization product **17**. No further work has been carried out on optimizing this interesting process. Presumably, compound **89** is formed through a palladium(II) pathway (Scheme 18). The Pd(II) catalyst coordinates with the alkyne triple bond of the carbanion intermediate **90** to form a palladium complex **91**. Cyclization of the palladium complex **91** provides a vinylic palladium intermediate **92**. Subsequent cis addition of intermediate **92** to the carbon−carbon double bond of the acrylate affords an alkylpalladium intermediate **93**, which undergoes β-hydride elimination to furnish the olefinic indene **89** 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.

(30) Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 3557.

Conclusions

In conclusion, three different synthetic methods have been developed for preparing substituted indenes by the metal-mediated carboannulation of alkynes. The first method involves a palladium-catalyzed carboannulation of internal alkynes. The reactions proceed under relatively mild conditions, tolerate significant functionality, and generally give good yields. This annulation process exhibits excellent regioselectivity and is particularly suited for the synthesis of hindered indenes. The

second synthetic method for indene derivatives has been accomplished in high yields by the cross-coupling of terminal alkynes with functionally substituted aryl halides, followed by copper-catalyzed intramolecular cyclization. This process tolerates various functionality in the terminal alkynes and provides a convenient, general route to prepare 2-substituted indenes. The third synthesis of highly substituted indenes involves the palladium-catalyzed cross-coupling of arylalkynes bearing strong electron-withdrawing functional groups with 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 2,3-diarylindenes bearing electron-deficient aryl groups in the 3-position.

Experimental Section

General Procedure for the Palladium-Catalyzed Carboannulation of Internal Alkynes. To a solution of aryl halide (0.25 mmol) in DMF (5 mL) were added the alkyne (0.50−1.25 mmol), $Pd(OAc)_2$ (0.0125 mmol), LiCl (0.25 mmol) or *n*-Bu_4NCl (0.25 mmol), and the appropriate base (0.5 mmol). The reaction mixture was allowed to stir at 80 °C for 48 h. The resulting mixture was diluted with diethyl ether and washed with satd aq NH_4Cl. The organic layer was dried over anhydrous $MgSO_4$, filtered, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired product.

Diethyl 2-*tert*-Butyl-3-methyl-1*H*-indene-1,1-dicarboxylate (2) (Table 1, entry 1). Purification by flash chromatography (hexane/EtOAc) afforded the indicated compound in an 86% yield as a pale yellow oil: ^{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.

General Procedure for the Sonogashira Coupling of Terminal Alkynes and Functionally Substituted Aryl Halides. To a solution of 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 allowed to stir at 55 °C for 2 h. The mixture was then cooled to room temperature, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired product.

Diethyl [2-(Oct-1-ynyl)phenyl]malonate (16) (Table 2, entry 1). Purification by flash chromatography (hexane/EtOAc) afforded the indicated compound in a 95% yield as a pale yellow oil: ^{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.

General Procedure for the Copper-Catalyzed Intramolecular Cyclization to Indenes. To a solution of the alkyne (0.25 mmol) in THF (5 mL) were added CuI (0.005 mmol) and *t*-BuOK (0.0125 mmol). The reaction mixture was allowed to stir at 55 °C for 2 h. The mixture was cooled to room temperature, diluted with ether, and then washed with satd aq NH_4Cl. The organic layer was dried over anhydrous $MgSO_4$, filtered, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired product.

Diethyl 2-*n*-Hexyl-1*H*-indene-1,1-dicarboxylate (17) (Table 2, entry 1). Purification by flash chromatography (hexane/EtOAc) afforded the indicated compound in a 96% yield as a pale yellow oil: ^{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.

General Procedure for the Palladium-Catalyzed Arylation of Arylalkynes Bearing Various Carbon Nucleophiles. To a solution of the arylalkyne (0.25 mmol) in DMF (5 mL) were 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 allowed to stir at 100 °C for 3 h. The mixture was cooled to room temperature, diluted with ether, and washed with satd aq NH_4Cl. The organic layer was dried over anhydrous $MgSO_4$, filtered and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired product.

Diethyl 3-[4-(Ethoxycarbonyl)phenyl]-2-phenyl-1*H*-indene-1,1-dicarboxylate (58) (Table 3, entry 1). Purification by flash chromatography (hexane/EtOAc) afforded the indicated compound in an 86% yield as a pale yellow oil: ^{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), 7.17 (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.

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Supporting Information Available: General experimental procedures and characterization data for all new starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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