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Carbopalladation of Nitriles: Synthesis of Benzocyclic Ketones and Cyclopentenones via Pd-Catalyzed Cyclization of ω-(2-Iodoaryl)alkanenitriles and Related Compounds

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An efficient procedure for the synthesis of 2,2-disubstituted benzocyclic ketones by intramolecular carbopalladation of nitriles has been developed. The cyclization of substituted 3-(2-iodoaryl)-propanenitriles affords indanones in high yields. The reaction is compatible with a wide variety of functional groups. This methodology has been extended to the synthesis of tetralones and cyclopentenones.

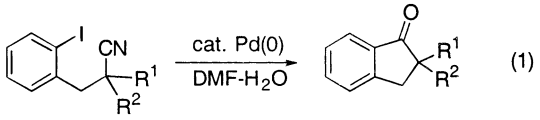
Introduction

Benzocyclic ketones are versatile and useful synthetic intermediates in the agrochemical and pharmaceutical industries.[1] The 2-alkyl-1-indanone core is prominently featured in many pharmaceutical products, such as the antihypertensive drug (+)-Indacrinone, the diuretic MK473, and the β-blocker Spirendolol.[1a] Some indanone derivatives also exhibit bronchodilatory activity.[2] Indanones serve as important building blocks in the synthesis of steroids, gibberellic acid, fredericamycin A, and other natural products,[2,3] and are frequently used as precursors to medicinal substances, such as nonsteroidal 5α-reductase inhibitors, 5-hydroxytryptamine-receptor agonists, dopamine-receptor antagonists, and other agents against Alzheimer's disease.[4]

α-Tetralones have been used as precursors to chiral benzocyclic amines that provide key intermediates for a number of pharmaceutical preparations with neurotropic and psychotropic activity.[1d] Other biologically active substances synthesized from tetralones include lignans (such as podophyllotoxin and Justicidins A−F) and diterpenes (heliosporin E and the aglycon moiety of various pseudopterosins),[5] antitumor and antileukemic HIV reverse transcriptase-inhibiting benzo[*c*]phenanthridine alkaloids,[6] angucyclin antibiotics,[7] anthracyclins, tetracyclins, and estrone derivatives.[8]

Traditionally, benzocyclic ketones have been synthesized by the intramolecular Friedel−Crafts acylation of β-arylpropionic and γ-arylbutyric acids and their derivatives.[6a,9] The strongly acidic conditions required by this method, especially when the aromatic ring is deactivated, restrict the variety of functional groups that are tolerated. There can also be problems with the regioselectivity of the cyclization. Intermolecular routes to benzocyclic ketones include the Vilsmeier−Haack cyclization of substituted styrenes,[1c] the tandem Knoevenagel condensation−cycloaddition,[3a] the Wittig−Horner reaction of phthalide-3-phosphonates and ketones,[3b] and various carbonylation processes.[10] Complex benzocyclic ketones may be synthesized by derivatization of simple indanones and tetralones, but this approach often suffers from poor yields.[11] Specific indanone targets have also been prepared via indirect, highly specific routes.[8,12]

In a continuation of our work on developing useful, new synthetic organic methodology based on the carbopalladation of nitriles,[13] we have explored the possibility of synthesizing indanones by the Pd-catalyzed cyclization of 3-(2-iodoaryl)propanenitriles (eq 1).[14] Here, we wish



(1)

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TABLE 1. Optimization of the Pd-Catalyzed Cyclization of 2,2-Dimethyl-3-(2-iodophenyl)propanenitrile (eq 2, $n = 1$, R^1, $R^2 = Me$)[a]

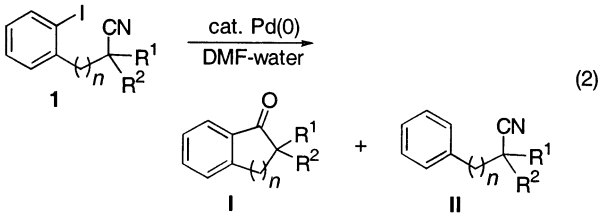
entry	catalyst	phosphine	argon	NEt_3 (equiv)	time (h)	yield (%)[b] I	yield (%)[b] II
1	10% $Pd(dba)_2$		−	1	72	34[c]	0
2	10% $Pd(OAc)_2$	20% PPh_3	+	1.2	10	85[d]	8
3	10% $Pd(OAc)_2$	20% PPh_3	+	1.2	12	88	12
4	10% $Pd(OAc)_2$	20% PPh_3	−	1.2	12	80	9
5	10% $Pd(OAc)_2$	20% PPh_3	+	1	12	60	10
6	10% $Pd(OAc)_2$	20% PPh_3	−	1	12	72	12

[a] All reactions were run at 130 °C in 9:1 DMF−water. [b] Yields determined by GC-MS and ^1H NMR spectral analysis. [c] Only 62% conversion of the starting material. [d] 95% conversion of the starting material.

to report the full details of our investigation of the scope and limitations of this process, which has been found to afford 2,2-disubstituted benzocyclic ketones in high yields.

Results and Discussion

2,2-Dimethyl-3-(2-iodophenyl)propanenitrile (**1a**, R^1, R^2 = Me, $n = 1$, eq 2) was chosen as the model system for the cyclization. We began the optimization work by first attempting to apply our previous carbopalladation reaction conditions (Table 1, entry 1).[13] The target, 2,2-dimethyl-1-indanone (**2a**, Table 2), was formed in a moderate yield accompanied by a considerable amount of unreacted **1a** even after a long reaction time.



(2)

We then turned our attention to a catalytic system consisting of $Pd(OAc)_2$ and PPh_3,[15] and also employed 1.2 equiv of triethylamine as a base and a possible reducing agent for Pd(II). Under these conditions, we detected the formation of two products (eq 2), the target indanone **I** and a minor product **II**, which apparently resulted from reduction of the carbon−iodine bond of the starting material. Such reduction is a well-known process that has been observed in many other palladium-catalyzed reactions of organic halides.[16]

Since a small amount of the starting material was detected in the reaction mixture after 10 h (Table 1, entry 2), we allowed the reaction to proceed until all of **1a** was consumed (entry 3). After 12 h, the reaction was complete and the results were comparable to those reported in entry 2. It was also established that an inert atmosphere is not essential for the success of the cyclization as the target product was obtained in a high yield when the reaction was conducted in air (entry 4). Reducing the amount of triethylamine decreased the yield of the indanone (entries 5 and 6). On the basis of the results of our optimization study, the following reaction conditions were adopted as our general procedure for the palladium-catalyzed cyclization of 3-(2-iodoaryl)propanenitriles:[17] 0.25 mmol of the substrate, 10 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, and 1.2 equiv of NEt_3 in 5 mL of a 9:1 DMF−water mixture are stirred at 130 °C under Ar until consumption of the starting material is complete.

We propose the following mechanism for this cyclization (Scheme 1). Oxidative addition of the aryl iodide to a Pd(0) species, produced by reduction of $Pd(OAc)_2$, leads to the arylpalladium intermediate **A**. Intramolecular addition of the arylpalladium species across the cyano group in **A** affords an iminopalladium intermediate, which is then hydrolyzed to the corresponding indanone **I**.[18] The Pd(II) species is then reduced again to Pd(0), which returns to the catalytic cycle. As we have proposed elsewhere,[19] the reduction of Pd(II) to Pd(0) is most likely effected by triethylamine.[20] Alternatively, the arylpalladium intermediate **A** may undergo reduction, which results in formation of the byproduct **II**. The exact mechanism of this reduction, as well as the identity of the reducing agent, is unknown at this time (vide infra).

Having established a procedure for the cyclization, we synthesized a variety of substituted 3-(2-iodoaryl)propanenitriles to investigate the scope and limitations of our methodology. One of the advantages of this process is in fact the ease of preparation of the starting materials from commercially available precursors. Thus, a number of alkanenitriles were alkylated with 2-iodobenzyl bromide to produce representative substrates **1a**−**i** (eq 3). A similar procedure utilizing the ability of the cyano group to stabilize the neighboring carbanion was the key step in the preparation of 3-(2-iodophenyl)propanenitriles functionalized at the benzylic position (**1j**−**n**, Scheme 2).

(14) For a preliminary communication, see: Pletnev, A. A.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 2133.

(15) Similar reaction conditions were found to induce nitrile carbopalladation previously, see: (a) Yang, C.-C.; Tai, H.-M.; Sun, P.-J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2843. (b) Deng, J.-H.; Tai, H.-M.; Yang, C.-C. *J. Chin. Chem. Soc.* **2000**, *47*, 327.

(16) For example, see: (a) Quan, L. G.; Lamrani, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4827. (b) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619.

(17) Cyclization of the corresponding aryl bromide was found to be ineffective, producing mostly the reduction byproduct and only trace amounts of **2a**.

(18) The exact mechanism of this hydrolysis is unclear. For example, it may involve hydrolysis of the C−N double bond in the iminopalladium intermediate to produce **I** and $IPdNH_2$, with the latter further reacting with water to afford ammonia and IPdOH or an equivalent Pd(II) species. Alternatively, reaction of the iminopalladium intermediate with water may lead directly to IPdOH and the indanone imine, which is then hydrolyzed to **I**.

(19) Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *68*, 9276.

(20) This reduction presumably proceeds via oxidative addition of the α-C−H bond of triethylamine to Pd, followed by fragmentation of the resulting species. See also: (a) McCrindle, R.; Ferguson, G.; Arsenault, G. J.; McAlees, A. J. *J. Chem. Soc., Chem. Commun.* **1983**, 571 and references therein. (b) Murahashi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348. (c) Murahashi, S.-I.; Watanabe, T. *J. Am. Chem. Soc.* **1979**, *101*, 7429.

TABLE 2. Synthesis of Indanones by the Pd-Catalyzed Cyclization of 3-(2-Iodoaryl)propanenitriles (eq 2, $n = 1$)[a]

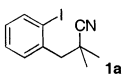
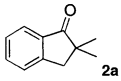
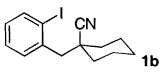
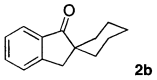
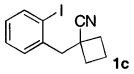
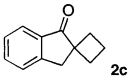
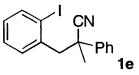
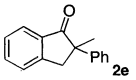
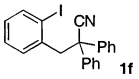
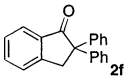
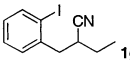
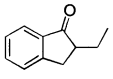
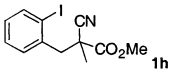
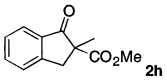
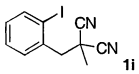
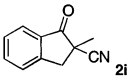
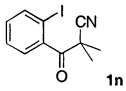
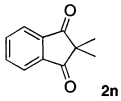
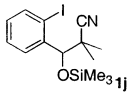
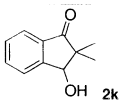
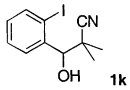
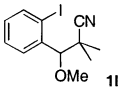
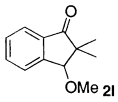
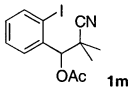
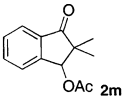
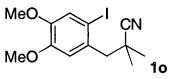
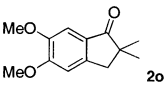
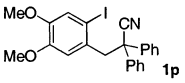
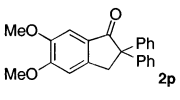
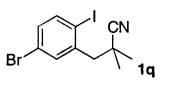
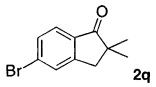
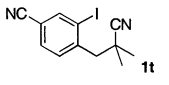
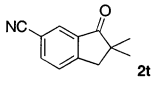
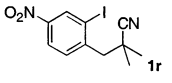
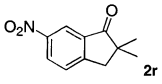
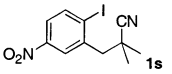
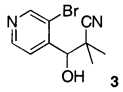
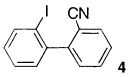
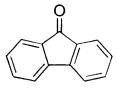
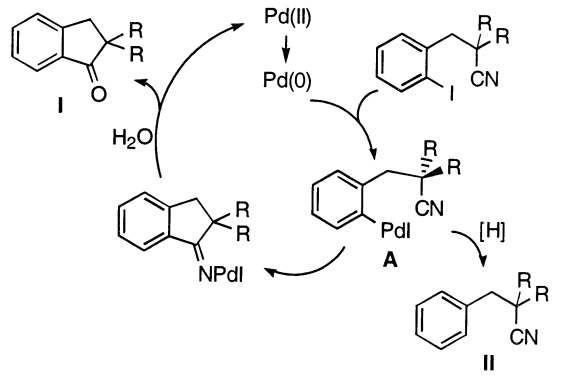
entry	nitrile	time (h)	indanone (**I**)	% yield[b]	
				I	**II**
1	 **1a**	12	 **2a**	88	12
2	 **1b**	12	 **2b**	86	8
3	 **1c**	12	 **2c**	83[c]	17
4	 **1e**	12	 **2e**	82	6
5	 **1f**	15	 **2f**	92	7
6	 **1g**	12	 **2g**	30	50
7	 **1h**	12	 **2h**	78, 73[c]	trace
8	 **1i**	12	 **2i**	89[c]	0
9	 **1n**	15	 **2n**	83	6
10	 **1j**	15	 **2k**	80	trace
11	 **1k**	12	**2k**	80	5
12	 **1l**	36	 **2l**	77(79)[d]	19(19)
13	 **1m**	40	 **2m**	80[c,e]	14
14	 **1o**	29	 **2o**	75[c]	trace
15	 **1p**	18	 **2p**	84[c]	0

Table 2. (Continued)

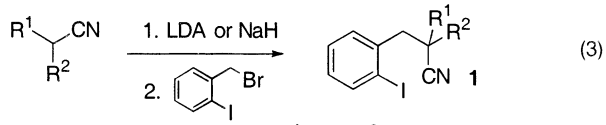
entry	nitrile	time (h)	indanone (**I**)	% yield[b] I	% yield[b] II
16	 **1q**	15	 **2q**	64(68)[c,f]	trace
17	 **1t**	12	 **2t**	43	48
18	 **1r**	12	 **2r**	35	64
19	 **1s**	12	-	0	98
20	 **3**	12	-	0	99
21	 **4**	12	 **5**	56	24

[a] See the Experimental Section for the reaction conditions. [b] Yields determined by ^{1}H NMR spectral analysis unless specified otherwise. Yields in parentheses are corrected for unreacted starting material. [c] Isolated yield. [d] 97% conversion of the starting material. [e] 87% conversion after 36 h. [f] Approximately 5% of the starting material and 3% of 2,2-dimethylindanone were also isolated.

SCHEME 1



3-(2-Iodoaryl)propanenitriles **1o**−**q** were prepared via alkylation of the appropriate alkanenitriles with substituted 2-iodobenzylic bromides derived from the corresponding *o*-iodobenzylic alcohols as shown in Schemes 3 and 4. A different approach was implemented for the synthesis of electron-poor substrates **1r** and **1s**, which were obtained from nitration of the parent compound **1a** (Scheme 5). Compound **1r** was further transformed into 3-(2-iodo-4-cyanophenyl)-2,2-dimethylpropanenitrile (**1t**) by a reduction−Sandmeyer reaction sequence.



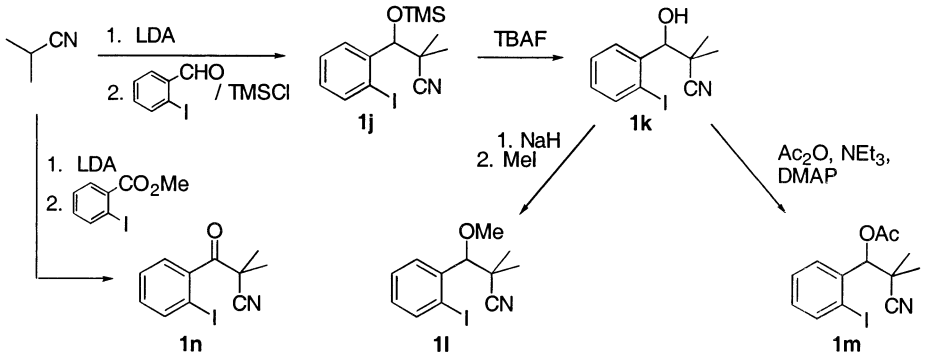
(3)

	R^1	R^2		R^1	R^2
1a	Me	Me	**1f**	Ph	Ph
1b	-$(CH_2)_5$-		**1g**	H	Et
1c	-$(CH_2)_3$-		**1h**	Me	CO_2Me
1d	-$(CH_2)_2$-		**1i**	Me	CN
1e	Me	Ph			

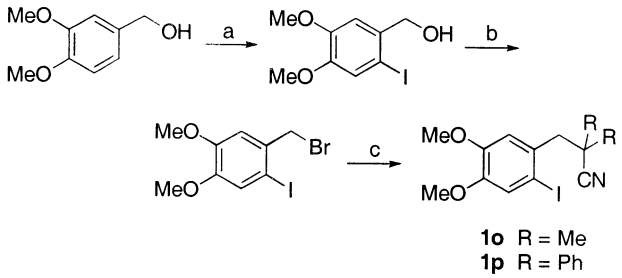
With various 3-(2-iodoaryl)propanenitriles **1** in hand, we explored the scope and limitations of their palladium-catalyzed cyclization to indanones. The results of this study are presented in Table 2. In most cases, the corresponding indanones were obtained in very good yields. As we observed during the optimization studies with **1a** (entry 1), minor amounts of reduction byproducts were often formed in the cyclization of other 2,2-disubstituted 3-(2-iodoaryl)propanenitriles. Given the small scale on which this reaction has usually been run, it has sometimes proven difficult to separate the two products by column chromatography, so the yields of all known products were determined by analysis of the GC-MS and ^{1}H NMR spectral data obtained from the reaction mixtures. Several of the reactions were also performed on a larger scale and the isolated yields of the products were found to be consistent with the yields that were determined spectroscopically.

As expected, cycloalkanecarbonitriles **1b** and **1c** underwent successful cyclization and afforded spirocyclic indanones **2b** and **2c**, the skeletons of which are related to several pharmaceutical and biologically active substances (Table 2, entries 2 and 3).[1a,3b,4a] 2-Methyl-2-phenyl-1-indanone (**2e**) and 2,2-diphenyl-1-indanone (**2f**) were obtained in high yields (entries 4 and 5) despite our concern that organopalladium species **A** (Scheme 1), derived from 2-aryl-3-(2-iodophenyl)propanenitriles, might undergo intramolecular attack on the aryl substituent,

SCHEME 2

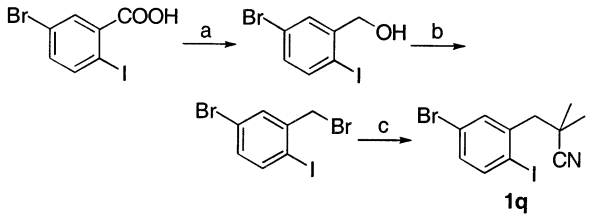


SCHEME 3[a]



[a] Reagents and conditions: (a) CF_3COOAg, I_2, CH_2Cl_2, rt; (b) CBr_4, PPh_3, CH_2Cl_2, 0 °C; (c) alkylation of isobutyronitrile or diphenylacetonitrile.

SCHEME 4[a]



[a] Reagents and conditions: (a) $BH_3{\cdot}SMe_2$, THF, 0 °C to rt; (b) CBr_4, PPh_3, CH_2Cl_2, 0 °C; (c) alkylation of isobutyronitrile.

resulting in the formation of a dihydrophenanthrene derivative.[21] Cyclization of the secondary nitrile **1g** resulted in only a modest yield of the target, 2-monosubstituted indanone **2g**, with the major product being the dehalogenated starting material (entry 6). This represents a limitation of the current protocol (see the discussion below). However, this limitation can be overcome by the decarboalkoxylation of 1-indanone-2-carboxylate esters,[22a] such as **2h**, which is readily prepared from methyl 2-cyano-3-(2-iodophenyl)-2-methylpropanoate (**1h**) using our cyclization procedure (entry 7). Another α-functionalized propanenitrile, **1i**, also cyclized efficiently and afforded indanone **2i** without formation of the reduction byproduct (entry 8).

The cyclization has been found to tolerate a wide variety of functional groups (entries 7−18). 1,3-Indandione derivatives **2k**−**n** were readily obtained from *β*-functionalized 3-(2-iodoaryl)propanenitriles **1j**−**n** containing keto, hydroxy, ether, and ester groups (entries 9−13). Only the trimethylsilyloxy group of **1j** did not survive the cyclization conditions, affording instead the deprotected hydroxyindanone **2k** (entry 10). Since the silyl derivative of **2k** was never detected in the reaction mixture during GC-MS monitoring, it appears that **1j** underwent deprotection before engaging in the palladium-catalyzed cyclization, either due to the ease of desilylation under our reaction conditions or because the bulk of the trimethylsilyl group inhibited the oxidative addition of **1j** to the Pd(0) catalyst. The long reaction times reported in entries 12 and 13 are probably caused by intramolecular chelation of the methoxy and acetoxy groups to the palladium moiety in the arylpalladium intermediates produced from **1l** and **1m**.

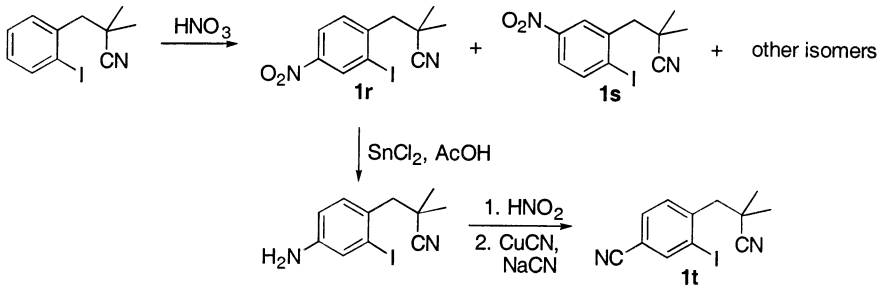
Substituents on the arene ring appear to have a pronounced effect on the success of the carbopalladation. The electron-rich substrates **1o** and **1p** readily produced the corresponding indanones **2o** and **2p** (entries 14 and 15), although these two reactions required longer reaction times than those of the parent systems, most probably due to the more sluggish oxidative addition of **1o** and **1p** to the Pd(0) catalyst. The slightly electron-deficient **1q** afforded only a modest yield of 5-bromo-2,2-dimethyl-1-indanone (**2q**), demonstrating the chemoselectivity of our procedure and resulting in an aryl bromide poised for other palladium-catalyzed processes. Strong electron-withdrawing groups, on the other hand, inhibited the carbopalladation considerably, making reduction of the arylpalladium intermediate the predominant reaction (entries 17−19). As we have proposed previously,[14,19] the palladium center in intermediate **A** (Scheme 1) must have sufficient electron density to be able to add to the carbon−nitrogen triple bond. Obviously, the nucleophilicity of the arylpalladium species suffers with the introduction of electron-withdrawing groups on the arene ring. We have found that the yields of the corresponding indanones decrease with the increase in electron-withdrawing ability of the substituent in the aromatic ring of the 3-(2-iodoaryl)propanenitrile as quantified by the Hammett parameter *σ* (entries 17−19).[23] Heterocyclic 3-(2-haloaryl)propanenitrile **3** also failed to furnish any cyclization product, probably because of the electron-poor nature of the pyridine system (entry 20).

(21) For an example of such a process, see: Qabaja, G.; Jones, G. B. *J. Org. Chem.* **2000**, *65*, 7187.

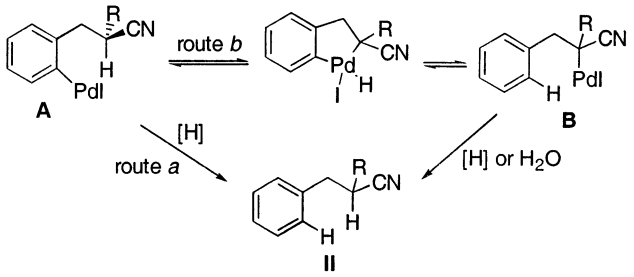
(22) (a) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999; p 1542. (b) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999; p 571.

(23) Values of *σ* for the substituents in **1q**−**t**: 0.232 (*p*-Br, **1q**), 0.678 (*m*-CN, **1t**), 0.710 (*m*-NO_2, **1r**), 0.778 (*p*-NO_2, **1s**) [from: Jaffe, H. H. *Chem. Rev.* **1953**, *53*, 191].

SCHEME 5



SCHEME 6



9-Fluorenone (**5**) was obtained in a 56% yield from 2-cyano-2′-iodobiphenyl (**4**) in what we believe to be the first example of the addition of an *aryl*palladium to an *arene*nitrile (entry 21). The modest yield is most probably caused by steric factors that hinder coordination of the arylpalladium to the carbon−nitrogen triple bond prior to the carbopalladation step.

The low yield and the considerable amount of reduction byproduct in the cyclization of 2-(2-iodobenzyl)butanenitrile (**1g**, Table 2, entry 6) prompted us to look closer at our proposed mechanism (Scheme 1). The oxidative addition of **1g** to the Pd(0) catalyst is evidently successful, but the intermediate **A** is apparently reduced faster than it cyclizes. Presumably, intermediate **A** adopts a conformation where the palladium center is oriented toward the smallest substituent on the α-carbon of the nitrile. In tertiary nitriles, the smallest substituent on the α-carbon is the cyano group itself, so the conformation of **A** is close to the one shown in Scheme 1, which is favorable for the cyclization. However, when formed from secondary nitriles such as **1g**, intermediate **A** prefers the conformation shown in Scheme 6, where the palladium is oriented toward the hydrogen, which is now the smallest group on the α-carbon of the nitrile. Obviously, the cyano group in such a conformation is too far away from the palladium for successful intramolecular attack, and **A** is eventually reduced to the byproduct **II** (route *a*, Scheme 6).

We also considered the possibility that the α-hydrogen plays a more active role in the reduction (route *b*). It seemed conceivable that the palladium species **A** could insert into the activated α-C−H bond of the alkanenitrile and then migrate to the α-position and furnish intermediate **B**, which could later be reduced or hydrolyzed. This would account for the reduction of the original carbon−iodine bond in **1g**. However, such a mechanism is not possible for the tertiary nitriles **1r** and **1s**, where the reduction predominates (Table 2, entries 18 and 19). To test this idea, we prepared an α-deuterated version of **1g** and carried out the cyclization under our standard conditions. No deuterium incorporation into the benzene ring was observed in the reduction product, nor was any of the deuterium label lost from the α-position of the nitrile. These results strongly discount the likelihood of route *b* (Scheme 6).

Using the cyclization of 2-(2-iodobenzyl)butanenitrile as a model system, we attempted to find reaction conditions that would substantially increase the yield of the 2-monosubstituted indanone (Table 3). Different phosphine ligands were tried to stabilize the arylpalladium intermediate **A** (Scheme 1) or make it more nucleophilic, thus promoting its attack on the cyano group. However, no improvement over the use of PPh_3 was observed (entries 1−14). Omitting the phosphine altogether resulted in a significant increase in the reaction time, but failed to improve the indanone-to-byproduct ratio (entry 15). Using tricyclohexylphosphine, which was employed by Yamamoto in a mechanistically similar intramolecular addition of an arylpalladium intermediate to ketones,[16a] with several organic and inorganic bases was also explored to no avail (entries 16−20). Especially surprising was the almost complete absence of the cyclization product in reactions using Na_2CO_3 and NaOAc since these were the bases used successfully by Yamamoto for the ketone cyclization. Two other Pd catalysts gave poorer results than did $Pd(OAc)_2$ (entries 21 and 22). No advantage was obtained when we tried using a chloride source (entries 23 and 24).

Since alkylamine bases having α-C−H bonds can be a source of reduction of the Pd(II) intermediates,[20] we decided to explore different organic bases (entries 25−31). First, we reduced the amount of triethylamine in hopes that this would lead to a decrease in the amount of the reduction byproduct, but the only result of this modification was an increase in the reaction time (entry 25). Using diisopropylamine, which has fewer α-C−H bonds than Et_3N and therefore can be expected to be less reducing, seemed to improve the indanone-to-byproduct ratio. However, the overall yield of **2g** remained unsatisfactory (entry 26). The use of several other amines with no α-hydrogens, as well as *i*-Pr_2NEt, only led to an increase in the amount of reduction (entries 27−30). From these results, it appears that our standard base of choice, triethylamine, may not be responsible for reduction of the arylpalladium intermediate **A** (Scheme 6).

Finally, we considered the possibility that **A** may be reduced by formate anion,[24] formed under our reaction conditions from DMF and water. Reactions run in the

(24) (a) Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1 and references therein. (b) Cacchi, S.; Felici, M.; Pietroni, B. *Tetrahedron Lett.* **1984**, *25*, 3137.

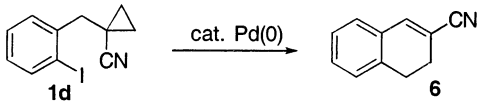
TABLE 3. Optimization of the Pd-Catalyzed Cyclization of 2-(2-Iodobenzyl)butanenitrile (eq 2, $n = 1$, $R^1 = H$, $R^2 = Et$)[a]

				yield (%) (GC ratio **I/II**)[b]	
entry	catalyst (10 mol %)	phosphine or arsine	base (equiv)	**I**	**II**
1	$Pd(OAc)_2$	20% PPh_3	NEt_3 (1.2)	30	50
2	$Pd(OAc)_2$	20% P(*o*-Tol)$_3$	NEt_3 (1.2)	30	49
3	$Pd(OAc)_2$	20% $AsPh_3$	NEt_3 (1.2)	14	51
4	$Pd(OAc)_2$	20% P(2-furyl)$_3$	NEt_3 (1.2)	(1:9.3)[c]	
5	$Pd(OAc)_2$	20% dppf	NEt_3 (1.2)	22[d]	39
6	$Pd(OAc)_2$	10% dppf	NEt_3 (1.2)	24	38
7	$Pd(OAc)_2$	10% dppe	NEt_3 (1.2)	16	55
8	$Pd(OAc)_2$	20% dppe	NEt_3 (1.2)	23	58
9	$Pd(OAc)_2$	20% BINAP	NEt_3 (1.2)	20	40
10	$Pd(OAc)_2$	20% dppp	NEt_3 (1.2)	10	55
11	$Pd(OAc)_2$	20% TPPTS[e]	NEt_3 (1.2)	16	57
12	$Pd(OAc)_2$	20% TTMPP[f]	NEt_3 (1.2)	(1:1.8)	
13	$Pd(OAc)_2$	20% (di-*tert*-butylphosphino)ferrocene	NEt_3 (1.2)	32	44
14	$Pd(OAc)_2$	20% 2-(di-*tert*-butylphosphino)biphenyl	NEt_3 (1.2)	16	23
15	$Pd(OAc)_2$		NEt_3 (1.2)	(1:2.2)[g]	
16	$Pd(OAc)_2$	20% PCy_3	NEt_3 (1.2)	27	69
17	$Pd(OAc)_2$	20% PCy_3	pyridine (1.2)	26	51[c]
18	$Pd(OAc)_2$	20% PCy_3	2,6-di-*tert*-butyl-4-methylpyridine (1.2)	10	67[c]
19	$Pd(OAc)_2$	20% PCy_3	Na_2CO_3 (2)	0	34
20	$Pd(OAc)_2$	20% PCy_3	NaOAc (2)	trace	34
21	$PdCl_2$	20% PPh_3	NEt_3 (1.2)	15	55
22	$PdCl_2(PPh_3)_2$		NEt_3 (1.2)	17	58
23	$Pd(OAc)_2$	20% PPh_3	NEt_3 (1.2)	20[h]	54
24	$Pd(OAc)_2$	20% PPh_3	NEt_3 (1.2)	7[i]	80
25	$Pd(OAc)_2$	20% PPh_3	NEt_3 (0.5)	24[j]	33
26	$Pd(OAc)_2$	20% PPh_3	*i*-Pr_2NH (1.2)	48	51
27	$Pd(OAc)_2$	20% PPh_3	2,2,6,6-tetramethylpiperidine (1.2)	(1:4.8)[k]	
28	$Pd(OAc)_2$	20% PPh_3	Ph_2NH (1.2)	16[l]	77
29	$Pd(OAc)_2$	20% PPh_3	NPh_3 (1.2)	12[m]	79
30	$Pd(OAc)_2$	20% PPh_3	*i*-Pr_2NEt (1.2)	9	53
31	$Pd(OAc)_2$	20% PPh_3	pyridine (1.2)	29	38[c]
32	$Pd(OAc)_2$	20% PPh_3	NEt_3 (1.2)	trace[n,o]	48
33	$Pd(OAc)_2$	20% PPh_3	NPh_3 (1.2)	trace[n,p]	11
34	$Pd(OAc)_2$	20% PPh_3	NEt_3 (1.2)	31[q]	24

[a] All reactions were run at 130 °C under Ar in 9:1 DMF−water unless specified otherwise. [b] All yields have been determined by ^1H NMR spectral analysis whenever practical. GC ratios were obtained straight from the reaction mixtures. [c] The reaction time was 36 h. [d] The same result was obtained at 100 °C. [e] TPPTS = tris(3-sulfonatophenyl)phosphine, sodium salt. [f] TTMPP = tris(2,4,6-trimethoxyphenyl)phosphine. [g] The reaction time was 84 h. [h] 1 equiv of *n*-Bu_4NCl was employed in the reaction. [i] 1 equiv of LiCl was employed in the reaction. [j] The reaction time was 24 h. [k] Low conversion after 12 h. [l] The reaction time was 48 h. [m] The reaction time was 29 h. [n] This reaction was run for 7 days in dry DMA. [o] 76% conversion of the starting material. [p] 12% conversion of the starting material. [q] This reaction was run for 5 days in 9:1 DMA−water; 85% conversion of the starting material.

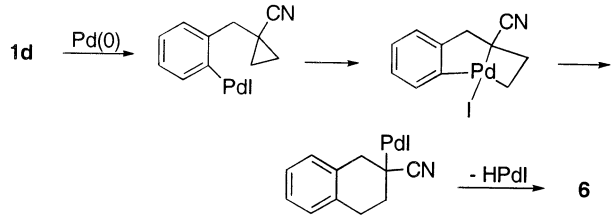
absence of water using DMA as a solvent were extremely slow and produced only traces of the desired compound **2g** (entries 32 and 33). A reaction using a 9:1 DMA−water mixture required an unreasonably long time and afforded **2g** in only a very modest yield (entry 34). Even though not using DMF seemed to somewhat suppress the reduction (entries 32−34), the formation of the reduced starting material indicated the presence of another reducing agent, the identity of which remains unknown. The role of DMF was further discounted when we found no deuterium incorporation into the reduction byproduct after the reaction was run under our standard conditions in a mixture of DMF-d_7 and D_2O.

An interesting process was observed in the attempted cyclization of 1-(2-iodobenzyl)cyclopropanecarbonitrile (**1d**). Instead of the expected spirocyclic indanone, this reaction produced 2-cyano-3,4-dihydronaphthalene (**6**) in a 58% yield (eq 4). The identity of the product was



(4)

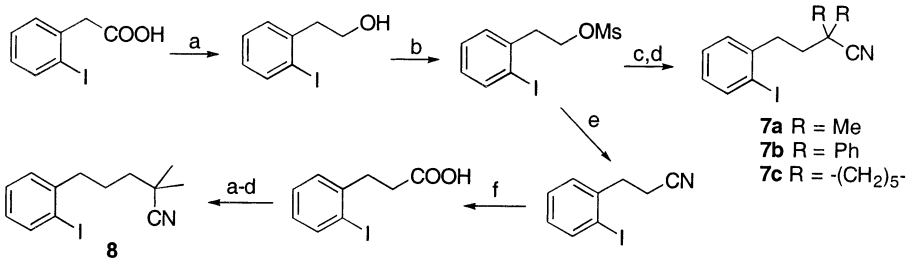
SCHEME 7. Proposed Mechanism for the Formation of 6



confirmed by synthesizing it independently from β-tetralone and TMSCN. Evidently, instead of attacking the cyano group, the arylpalladium intermediate formed from **1d** induces cyclopropane ring-opening perhaps by a process like that illustrated in Scheme 7. Examples of such ring-opening are well documented in cases where it leads to stable π-allylpalladium complexes.[25] In our case, the process is probably driven by the eventual formation of a conjugated system.

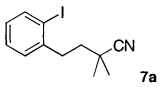
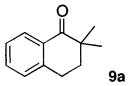
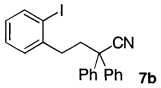
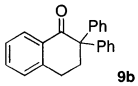
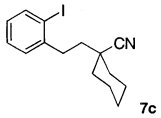
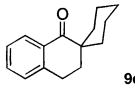
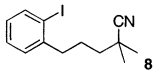
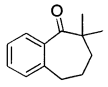
(25) (a) Larock, R. C.; Yum, E. K. *Tetrahedron* **1996**, *52*, 2743. (b) Balme, G.; Fouret, G.; Gore, J. *Tetrahedron Lett.* **1986**, *27*, 3855. (c) Blomberg, M. R. A.; Siegbahn, P. E. M.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 4450.

SCHEME 8[a]



[a] Reagents and conditions: (a) BH_3·SMe_2, THF, 0 °C to rt; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt; (c) NaI, acetone, reflux; (d) alkylation of corresponding alkanenitrile; (e) KCN, 18-crown-6, acetone, reflux; (f) aq KOH, reflux; then H_3O^+.

TABLE 4. Synthesis of Tetralones and a Benzosuberone by the Pd-Catalyzed Cyclization of *ω*-(2-Iodophenyl)alkanenitriles (eq 2)[a]

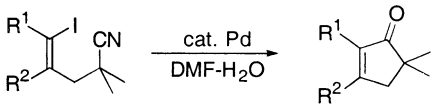
entry	nitrile	time (h)	benzocyclic ketone (**I**)	% yield[b]	
				I	**II**
1	 **7a**	24	 **9a**	69	16
2	 **7b**	24	 **9b**	55[c]	18
3	 **7c**	24	 **9c**	64	15
4	 **8**	36	 **10**	41	45

[a] See the Experimental Section for the reaction conditions. [b] All yields were determined by ^{1}H NMR spectral analysis unless specified otherwise. [c] Isolated yield.

Encouraged by the success of the cyclization of 2,2-disubstituted 3-(2-iodoaryl)propanenitriles, we decided to investigate the possibility of synthesizing benzocyclic ketones other than indanones. The starting materials for the six- and seven-membered-ring cyclization were prepared from commercially available 2-iodophenylacetic acid as shown in Scheme 8, and introduced into the reaction under our standard reaction conditions.

Subsequent cyclization proceeded in reasonable yields. Thus, 4-(2-iodophenyl)-2,2-dimethylbutanenitrile (**7a**) afforded tetralone **9a** in a 69% yield (Table 4, entry 1). Cyclization of other 4-(2-iodophenyl)butanenitriles was also reasonably successful (entries 2 and 3). Surprisingly, even 5-(2-iodophenyl)pentanenitrile (**8**) cyclized to produce a seven-membered-ring benzosuberone derivative **10** (entry 4). The efficacy of this six- and seven-membered-ring formation is remarkable considering that the greater conformational flexibility present in these longer chain substrates must significantly reduce the likelihood of achieving the conformation necessary for intramolecular addition of the arylpalladium species to the cyano group. This difficulty in achieving a favorable conformation is undoubtedly responsible for the increased reaction times compared to the five-membered-ring cyclizations.

We have also extended the scope of this methodology to the synthesis of cyclopentenones (eq 5). Cyclopentenones are common carbon skeletal structures in many natural products, such as jasmonates, muscones, rethrolones, prostaglandins, etc.[26] They are also important in the pharmaceutical industry as many exhibit very useful biological activity, including antitumor, antiviral, and antimicrobial properties.[27] Traditional routes to cyclopentenones include the Dieckmann condensation of 1,4-diketones,[28] the Nazarov cyclization,[26c,29] the Pauson−



(5)

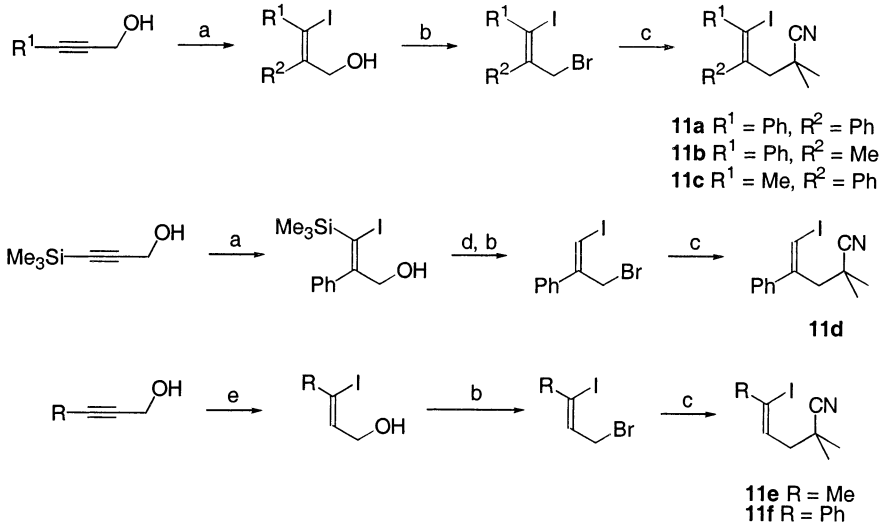
(26) (a) Satoh, T.; Yoshida, M.; Ota, H. *Tetrahedron Lett.* **2001**, *42*, 9241. (b) Hailes, H. C.; Isaac, B.; Javaid, M. H. *Tetrahedron Lett.* **2001**, *42*, 7325. (c) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429. (d) Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 867.

(27) (a) Miler, J. A.; Pugh, A. W.; Ullah, G. M.; Welsh, G. M. *Tetrahedron Lett.* **2001**, *42*, 955. (b) Trost, B. M.; Pinkerton, A. B. *J. Org. Chem.* **2001**, *66*, 7714.

(28) Ellison, F. A. *Synthesis* **1973**, 397.

(29) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.

SCHEME 9[a]



[a] Reagents and conditions: (a) PhMgBr or CH_3MgBr, cat. CuI, THF, 0 °C; then I_2, −78 °C to rt; (b) CBr_4, PPh_3, CH_2Cl_2, 0 °C; (c) alkylation of isobutyronitrile; (d) CH_3ONa, methanol, reflux; (e) Red-Al, THF, 0 °C; then I_2, −78 °C to rt.

Khand reaction,[30] and other variations of carbonylative cycloaddition processes.[27b,31] Many of these methods, however, suffer from the use of strongly acidic or basic conditions or sensitive organometallic reagents, often in stoichiometric amounts.

For our studies, we synthesized a variety of substituted 5-iodopent-4-enenitriles **11** as shown in Scheme 9. Copper-catalyzed addition of Grignard reagents to the appropriate propargylic alcohols, followed by quenching with iodine and conversion of the resulting allylic alcohols, provided allylic bromides that were used in the alkylation of isobutyronitrile to afford 4-substituted vinylic substrates **11a**−**d**. Compounds **11e** and **11f** were made via a similar route starting with reduction of the corresponding propargylic alcohols with Red-Al.

Cyclization of the 4,5-disubstituted 5-iodo-2,2-dimethylpent-4-enenitriles **11a**−**c** proved successful as highly substituted cyclopentenones **12a**−**c** were obtained in very good yields (Table 5, entries 1−3). In contrast with the benzocyclic ketone synthesis (eq 2), none of the reduction byproduct was detected in the reaction mixtures. 5,5-Dimethyl-3-phenylcyclopentenone (**12d**) was prepared from **11d** in a 67% yield (entry 4). Substrates **11e** and **11f** failed to give rise to their expected cyclization products (entries 5 and 6). The major product of the attempted cyclization of **11f** was identified from GC-MS analysis as 2,2-dimethyl-5-phenylpent-4-ynenitrile, which probably arises from **11f** by base-promoted dehydroiodination.[22b]

Since reduction of the carbon−iodine bond of the vinylic substrates **11** was not observed, we prepared the secondary nitrile **13** and subjected it to our standard cyclization conditions. The 5-monosubstituted cyclopentenone **14** was obtained in a 63% isolated yield (entry 14). Even though the reduction byproduct corresponding to **II** in eq 2 was formed in about 5% yield (as determined by analysis of the GC-MS data obtained from the reaction mixture), this problem does not appear to present any significant limitations for the synthesis of 5-monosubstituted cyclopentenones.

Conclusions

We have developed a general and efficient method for the synthesis of 2,2-disubstituted benzocyclic ketones from *ω*-(2-iodoaryl)alkanenitriles. The procedure affords indanones and tetralones in good to excellent yields and is compatible with a wide variety of functional groups. The suitability of this methodology for the preparation of various cyclopentenones has also been demonstrated.

Experimental Section

General. ^1H 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 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short-wavelength UV light (254 nm) and 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. All reagents were used directly as obtained commercially unless otherwise noted. $Pd(OAc)_2$ was donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. PPh_3 was also donated by Kawaken Fine Chemicals Co., Ltd.

General Procedure for the Pd-Catalyzed Cyclization of *ω*-(2-Iodoaryl)alkanenitriles. All reactions were performed under an Ar atmosphere. A 0.25-mmol sample of the *ω*-(2-iodoaryl)alkanenitrile, 0.025 mmol (10 mol %) of $Pd(OAc)_2$, and 0.05 mmol (20 mol %) of Ph_3P were dissolved in 4.5 mL of DMF and 0.5 mL of water, and 0.3 mmol (1.2 equiv) of Et_3N was added to the solution. The reaction mixture was stirred at 130 °C for the appropriate amount of time. Then, the reaction mixture was allowed to cool to room temperature and poured into 25 mL of diethyl ether. The ether solution was washed with aq NH_4Cl and dried over Na_2SO_4. The identity of all known products was established by GC-mass spectrometry and ^1H NMR spectroscopy of the reaction mixtures. The yields of known products were determined by ^1H NMR spectroscopy by integration of the appropriate outstanding

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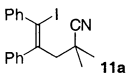
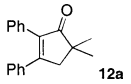
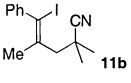
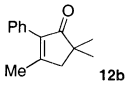
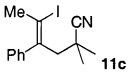
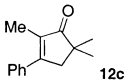
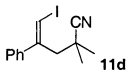
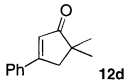
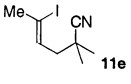
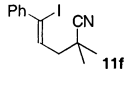
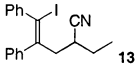
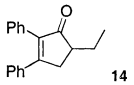
(31) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5881.

TABLE 5. Synthesis of Cyclopentenones by the Pd-Catalyzed Cyclization of 5-Iodopent-4-enenitriles (eq 5)[a]

entry	nitrile	time (h)	cyclopentenone	% yield[b]
1	 **11a**	12	 **12a**	94
2	 **11b**	12	 **12b**	72
3	 **11c**	12	 **12c**	82
4	 **11d**	12	 **12d**	67[c]
5	 **11e**	12	-	0
6	 **11f**	12	-	0
7	 **13**	12	 **14**	63

[a] See the Experimental Section for the reaction conditions. [b] Isolated yield unless specified otherwise. [c] Yield determined by ^{1}H NMR spectral analysis.

signals using 1,4-dimethoxybenzene as an internal standard. New products were isolated by column chromatography on a silica gel column.

The following known compounds were prepared using the above procedure: 2,2-dimethyl-1-indanone (**2a**),[32] spiro[cyclohexane-1,2′-indan]-1′-one (**2b**),[33] 2-methyl-2-phenyl-1-indanone (**2e**),[34] 2,2-diphenyl-1-indanone (**2f**),[35] 2-ethyl-1-indanone (**2g**),[36] 3-hydroxy-2,2-dimethyl-1-indanone (**2k**),[37] 3-methoxy-2,2-dimethyl-1-indanone (**2l**),[38] 2,2-dimethyl-1,3-indandione (**2n**),[39] 2,2-dimethyl-6-nitro-1-indanone (**2r**),[40] 9-fluorenone (**5**),[41] 2,2-dimethyl-1-tetralone (**9a**),[42] 3′,4′-dihydrospiro[cyclohexane-1,2′-(1′H)-naphthalen]-1′-one (**9c**),[43] 6,6-dimethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one (**10**),[44] 3,5,5-trimethyl-2-phenylcyclopent-2-en-1-one (**12b**),[45] and 5,5-dimethyl-3-phenylcyclopent-2-en-1-one (**12d**).[46]

Methyl 2-methyl-1-indanone-2-carboxylate (2h) was obtained as a white solid, mp 57−58 (lit.[47] mp 57−58 °C), in a 73% isolated yield from **1h** according to the general procedure after column chromatography using 4:1 hexanes/ethyl acetate. The 78% yield determined by ^{1}H NMR spectroscopy was obtained straight from the reaction mixture. The spectral properties were identical with those previously reported.[47]

5,6-Dimethoxy-2,2-dimethyl-1-indanone (2o) was obtained in a 75% isolated yield from **1o** according to the general procedure after column chromatography using 2:1 hexanes/ethyl acetate: white solid, mp 97−98 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 6H), 2.92 (s, 2H), 3.92 (s, 3H), 3.97 (s, 3H), 6.85 (s, 1H), 7.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.4, 42.6, 45.7, 56.0, 56.1, 104.8, 107.4, 127.8, 147.3, 149.4, 155.5, 210.1; IR (neat) 3066, 2984, 2867, 2832, 1684 cm^{-1}; HRMS *m*/*z* 220.11016 (calcd for $C_{13}H_{16}O_3$, 220.10994).

5,5-Dimethyl-2,3-diphenylcyclopent-2-en-1-one (12a) was obtained as a yellow oil in a 94% isolated yield from **11a** according to the general procedure after column chromatography using 4:1 hexanes/ethyl acetate: ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 6H), 2.93 (s, 2H), 7.21−7.34 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 25.5, 43.4, 46.6, 127.7, 128.1, 128.3, 129.5, 129.7, 132.5, 135.7,

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(35) (a) Klumpp, D. A.; Lau, S.; Garza, M.; Schick, B.; Kantardjieff, K. *J. Org. Chem.* **1999**, *64*, 7635. (b) Beringer, F. M.; Daniel, W. J.; Galton, S. A.; Rubin, G. *J. Org. Chem.* **1966**, *31*, 4315.
(36) Suzuki, T.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1997**, *119*, 6774.
(37) Berner, D.; Cox, D. P.; Dahn, H. *Helv. Chim. Acta* **1982**, *65*, 2061.
(38) Cawley, J. J.; Petrocine, D. V. *J. Org. Chem.* **1976**, *41*, 2608.
(39) Dolbier, W. R., Jr.; Matsui, K.; McCullagh, L.; Anapolle, K. E. *J. Org. Chem.* **1979**, *44*, 2842.
(40) Enas, J. D.; Garcia, J. G.; Mathis, C. A.; Gerdes, J. M. *J. Fluorine Chem.* **1993**, *63*, 233.
(41) This compound was identified by comparing its ^{1}H NMR spectrum to the ^{1}H NMR spectrum of an authentic sample obtained from Aldrich Chemical Co., Inc.
(42) (a) Farcasiu, D.; Schlosberg, R. H. *J. Org. Chem.* **1982**, *47*, 151. (b) Burdon, M. G.; Moffatt, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 5855.
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137.0, 164.5, 211.7 (1 sp^2 carbon missing due to overlap); IR (neat) 3055, 3023, 2961, 2926, 1694 cm^{-1}; HRMS *m/z* 262.13617 (calcd for $C_{19}H_{18}O$, 262.13577).

Characterization of all other cyclization products prepared in this study can be found in the Supporting Information.

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Supporting Information Available: Preparation and characterization of the starting materials; references to the preparation methods and characterization data for all known products; characterization data for all new compounds (including copies of ^1H and ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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