JOC Article

Regioselective Synthesis of Indenols via Nickel-Catalyzed Carbocyclization Reaction

Dinesh Kumar Rayabarapu, Chun-Hui Yang, and Chien-Hong Cheng*

Department of Chemistry, Tsing Hua University, Hsinchu, Taiwan 300, ROC

chcheng@mx.nthu.edu.tw

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2-Halophenyl ketones **1a**−**e** (**1a**, *o*-$IC_6H_4COCH_3$) undergo carbocyclization with alkyl propiolates (**2a**, $CH_3(CH_2)_4C{\equiv}CCO_2CH_3$; **2b**, $TMSC{\equiv}CCO_2Et$ **2c**, $CH_3C{\equiv}CCO_2CH_3$; **2d**, $CH_3OCH_2C{\equiv}CCO_2CH_3$; **2e**, $CH_3(CH_2)_3C{\equiv}CCO_2CH_3$; **2f**, $PhC{\equiv}CCO_2CH_3$; and **2g**, $(CH_3)_3C{\equiv}CCO_2CH_3$) in the presence of Ni(dppe)Br_2 and zinc powder in acetonitrile at 80 °C to afford the corresponding indenol derivatives **3a**−**m** with remarkable regioselectivity in good to excellent yields. The nickel-catalyzed carbocyclization reaction was successfully extended to other simple disubstituted alkynes. Thus, the reaction of 2-halophenyl ketones **1a**−**e** with disubstituted alkynes (**2h**, $PhC{\equiv}CPh$; **2i**, $CH_3C_6H_4C{\equiv}CC_6H_4CH_3$; **2j**, $CH_3CH_2C{\equiv}CCH_2CH_3$; **2k**, $PhC{\equiv}CCH_3$; **2l**, $TMSC{\equiv}CCH_3$; and **2m**, $PhC{\equiv}C(CH_2)_3CH_3$) proceeded smoothly to afford the corresponding indenols **4a**−**t** in good to excellent yields. For unsymmetrical alkynes **2k**−**m**, the carbocyclization gave two regioisomers with regioselectivities ranging from 1:2 to 1:12 depending on the substituents on the alkyne and on the aromatic ring of halophenyl ketone. A possible mechanism for this nickel-catalyzed carbocyclization reaction is also proposed.

Introduction

The indenol moiety is an important and central structural unit present in various biologically active compounds. Some indenol derivatives have shown analgesic and myorelaxation activity,[1] and others are used as valuable intermediates for the synthesis of indenyl chrysanthemates that possess insecticidal properties.[2] Despite the high utility of indenols, only very few synthetic routes are available in the literature.[3−5] Recently, transition-metal-catalyzed carbocyclization proved to be a very powerful synthetic tool for the construction of carbocycles with various ring sizes.[6−9] Vicente and coworkers reported stoichiometric and catalytic synthesis of indenols from mono- and disubstituted alkynes and organomercuric compounds in the presence of palladium complexes,[4] whereas Yamamoto et al. described a palladium-catalyzed carbocyclization of *o*-bromophenyl ketones with disubstituted alkynes to give indenols.[5] Our continuous interest in nickel chemistry[10−13] led us to investigate the catalytic activity of nickel complexes for carbocyclization reactions. In a preliminary communication, we reported that nickel complexes effectively catalyzed the cyclization of *o*-iodophenyl ketones with propi-

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TABLE 1. Effect of Catalyst and Solvent on the Carbocyclization of 1c with 2a[a]

entry	catalyst	solvent	yield[b] (%)
1		CH_3CN	0
2[c]	Ni(dppe)Br_2	CH_3CN	0
3[d]	Zn	CH_3CN	0
4	Ni $(PPh_3)_2Br_2$/Zn	CH_3CN	26
5	Ni(dppm)Br_2/Zn	CH_3CN	57
6	Ni(dppe)Br_2/Zn	CH_3CN	86
7	Ni(dppb)Br_2/Zn	CH_3CN	21
8	Ni(bipy)Br_2/Zn	CH_3CN	trace
9	Ni(dppb)Br_2/Zn	Toluene	0
10	Ni(dppe)Br_2/Zn	DMF	19
11	Ni(dppe) Br_2/Zn	THF	51

[a] Unless stated otherwise, all reactions were carried out using *o*-iodophenyl ketone (**1c**) (0.50 mmol), methyl 2-octynoate (**2a**) (1.5 equiv), Ni catalyst (5 mol %), and Zn (2.75 equiv) in solvent (3.0 mL) at 80 °C under N_2 for 13 h. [b] Yields of **3g** were determined by ^{1}H NMR using mesitylene as an internal standard. [c] No Zn powder was used in the reaction. [d] No Ni catalyst was used in the reaction.

olates to give 2,3-disubstituted indenols in moderate to excellent yields with remarkably high regioselectivity.[14] Herein, we report the details of these studies and the results of the extension of this methodology to simple disubstituted alkynes.

Results and Discussion

Treatment of 2-iodoacetophenone **1a** (0.50 mmol) with methyl 2-octynoate **2a** (1.5 equiv) in the presence of Ni(dppe)Br_2 (dppe: bis(diphenylphosphino)ethane) (5 mol %) and zinc metal powder (2.75 equiv) in acetonitrile (3.0 mL) at 80 °C for 13 h gave the corresponding 2,3-disubstituted indenol **3a** in 87% isolated yield. The structure of **3a** that is derived from one molecule of **1a** and **2a** was confirmed by its ^{1}H NMR, ^{13}C NMR, and mass data. The reaction is highly regioselective, affording only a single regioisomer. The regiochemical assignment of the propiolate moiety was carefully established on the basis of the NOE experiments.[14]

To understand the nature of this nickel-catalyzed carbocyclization, the effect of solvent and nickel complexes used in the reaction of **1c** with **2a** was investigated. The results are summarized in Table 1. As shown in entries 1−3, in the absence of either nickel catalyst or zinc powder, no cyclization product **3g** was observed (Table 1, entries 1−3). Several nickel complexes, Ni$(PPh_3)_2Br_2$, Ni(dppm)Br_2, Ni(dppe)Br_2, Ni(bipy)Br_2, and Ni(dppb)Br_2, were also tested for the catalytic activity in acetonitrile. Among these complexes examined, Ni(dppe)Br_2 is most active catalyst for the cyclization of **1c** with **2a** furnishing **3g** in 86% yield (entry 6), while other nickel complexes gave **3g** in 21−57% yields (entries 4−8). The choice of solvent for the present catalytic reaction has a profound effect on the yield of product **3g**. Of the solvents screened (acetonitrile, THF, toluene, and DMF), only acetonitrile afforded a high yield of product **3g** (entry 6). DMF and THF gave low to moderate yields (entries 10 and 11), while toluene was totally inactive (entry 9).

This nickel-catalyzed carbocyclization was successfully extended to other substituted propiolates, and the results are demonstrated in Table 2. Thus, **1a** reacts with

SCHEME 1

1a: R^1 = H, R^2 = CH_3, X = I
1b: R^1 = H, R^2 = CH_3, X = Br
1c: R^1 = OCH_3, R^2 = CH_3, X = I
1d: R^1 = OCH_3, R^2 = $(CH_2)_3CH_3$, X = I
1e: R^1 = OCH_3, R^2 = Ph, X = I

2a: R^3 = $(CH_2)_4CH_3$, R^4 = CO_2CH_3
2b: R^3 = TMS, R^4 = $CO_2CH_2CH_3$
2c: R^3 = CH_3, R^4 = CO_2CH_3
2d: R^3 = CH_2OCH_3, R^4 = CO_2CH_3
2e: R^3 = *n*-Bu, R^4 = CO_2CH_3
2f: R^3 = Ph, R^4 = CO_2CH_3
2g: R^3 = *t*-Bu, R^4 = CO_2CH_3
2h: R^3 = Ph, R^4 = Ph
2i: R^3 = $PhCH_3$, R^4 = $PhCH_3$
2j: R^3 = CH_2CH_3, R^4 = CH_2CH_3
2k: R^3 = Ph, R^4 = CH_3
2l: R^3 = TMS, R^4 = CH_3
2m: R^3 = Ph, R^4 = $CH_2CH_2CH_2CH_3$

propiolates **2b**−**e** (**2b**, $TMSC{\equiv}CCO_2Et$; **2c**, $CH_3C{\equiv}CCO_2CH_3$; **2d**, $CH_3OCH_2C{\equiv}CCO_2CH_3$; **2e**, $CH_3(CH_2)_3C{\equiv}CCO_2CH_3$) in the presence of Ni(dppe)Br_2 and Zn in acetonitrile at 80 °C to provide the corresponding indenols **3b**−**e** in 86, 74, 68, and 87% yields, respectively (Scheme 1, Table 2, entries 2, 3, 7, and 8). A small amount of homotrimerization product ([2 + 2 + 2]) of propiolate was observed in the case of methyl 2-butynoate (**2c**). Similarly, **1a** underwent cyclization with **2f**, $PhC{\equiv}CCO_2CH_3$, smoothly to afford the desired carbocycle **3f** in 52% isolated yield. In all reactions using substituted propiolates as the alkyne substrates, only one regioisomer was detected in the carbocyclization product. The regiochemistry of these products suggests that the catalytic cyclization reaction follows a Michael-type addition pattern and is governed purely by the electronic properties rather than the steric factor of substrate **2**.

In a similar fashion, *o*-bromophenyl ketone (**1b**) underwent cyclization with propiolates **2a**−**c** smoothly to give the corresponding indenols **3a**−**c**, albeit in lower yields (Table 2, entries 4−6). The present carbocyclization can be extended to substituted *o*-iodophenyl ketones. Thus, treatment of **1c** bearing a methoxy group on the aromatic ring with propiolates **2a** and **2c** provided the corresponding substituted indenols **3g** and **3h** in 75 and 70% yields, respectively (Table 2, entries 10, 11), while the reaction of **1c** with propiolate **2g** $(CH_3)_3CC{\equiv}CCO_2CH_3$) bearing a sterically bulky *tert*-butyl group proceeded readily affording the desired indenol **3i** but in slightly lower yield (entry 12). In addition to **1a**−**c**, 1-(2-iodophenyl)-1-pentanone (**1d**) underwent carbocyclization with various propiolates **2a**−**c**,**f** efficiently to give the desired indenols **3j**−**m** in 85, 82, 88, and 48% yields, respectively (entries 13−16). Again, the carbocyclization reactions (entries 10−16) are completely regioselective giving only the Michael-type addition product.

The regiochemistry of products **3a**−**m** was assigned on the basis of the NOE experiments. As an example, the results of NOE experiments of compound **3g** are shown in Figure 1. Selective irradiation of methyl protons at δ 1.62 led to the enhancement of the signals at δ 3.37 for the hydroxy proton by 0.97% and at δ 7.37 for the aromatic proton H_b by 0.83%, respectively, whereas irradiation of the aromatic proton H_a at δ 6.90 resulted in the enhancement of the signals at δ 3.80 for the methoxy protons by 1.39% and at δ 2.84 for methylene

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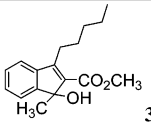
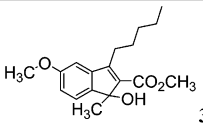
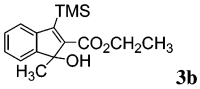
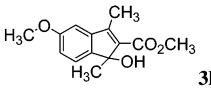
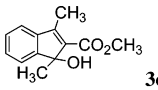
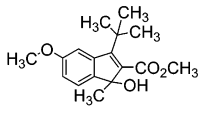
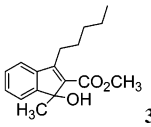
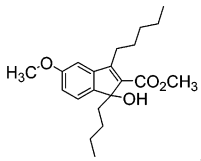
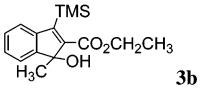
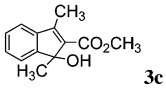
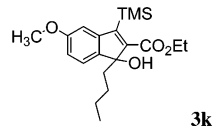
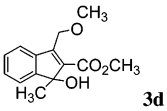
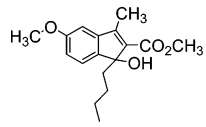
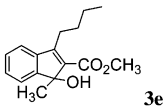
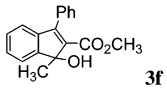
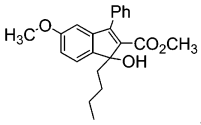
TABLE 2. Results of Nickel-Catalyzed Carbocyclization of *o*-Haloketone (1) with Propiolates (2)[a]

entry	ketone	propiolate	product	yield (%)[b]	entry	ketone	propiolate	product	yield (%)[b]
1	**1a**	**2a**	 **3a**	87 (94)	10	**1c**	**2a**	 **3g**	75 (86)
2	**1a**	**2b**	 **3b**	78 (86)	11	**1c**	**2c**	 **3h**	70 (75)
3	**1a**	**2c**	 **3c**	74	12	**1c**	**2g**	 **3i**	46
4	**1b**	**2a**	 **3a**	(85)	13	**1d**	**2a**	 **3j**	85 (92)
5	**1b**	**2b**	 **3b**	(76)					
6	**1b**	**2c**	 **3c**	(65)	14	**1d**	**2b**	 **3k**	82 (86)
7	**1a**	**2d**	 **3d**	68	15	**1d**	**2c**	 **3l**	88
8	**1a**	**2e**	 **3e**	(87)					
9	**1a**	**2f**	 **3f**	52	16	**1d**	**2f**	 **3m**	48

[a] Unless stated otherwise, all reactions were carried out using *o*-halophenyl ketone (0.50 mmol), propiolate (1.50 equiv), Ni(dppe)Br_2 (5.0 mol %), and Zn (2.75 equiv) in CH_3CN (3.0 mL) at 80 °C under N_2 (1 atm) for 13 h. [b] Isolated yields; yields in the parentheses were determined by ^1H NMR using mesitylene as an internal standard.

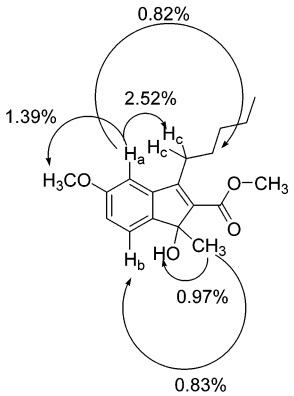
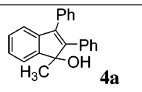
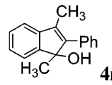
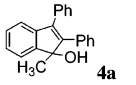
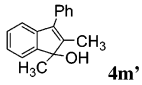
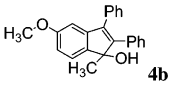
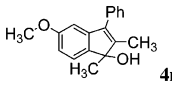
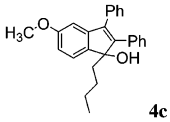
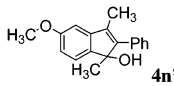
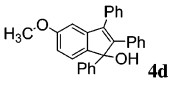
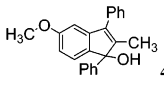
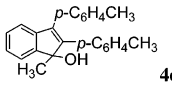
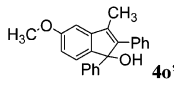
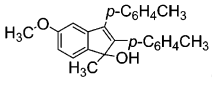
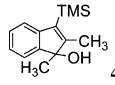
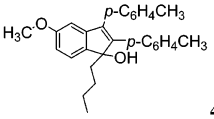
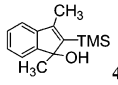
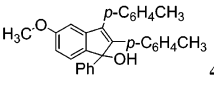
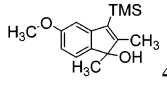
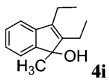
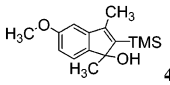
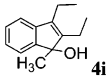
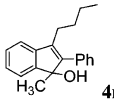
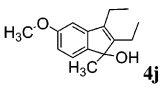
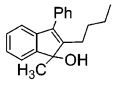
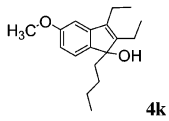
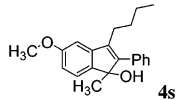
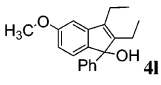
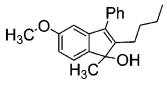
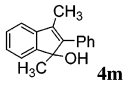
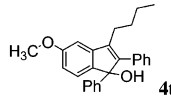
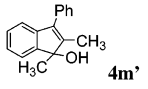
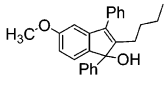


FIGURE 1.

protons by 2.52%. These NOE results strongly support the proposed structure of product **3g** shown in Figure 1.

Simple disubstituted alkynes also react with *o*-halophenyl ketones in the presence of Ni(dppe)Br_2 and zinc metal powder in acetonitrile at 80 °C to give the correponding indenol products. The results are summarized in Table 3. Treatment of diphenylacetylene (**2h**) with 2-iodoacetophenone (**1a**) and 2-iodo-3-methoxyphenyl ketones (**1c**−**e**) in the presence of Ni(dppe)Br_2 and zinc metal powder afforded the desired indenols **4a**−**d** in 87, 82, 80, and 86% isolated yields, respectively (Table 3, entries 1, 3−5). Similarly, the reaction of **2i**, $CH_3C_6H_4C{\equiv}CC_6H_4$-$CH_3$ with **1a** and **1c**−**e** provided the corresponding indenol products **4e**−**h** in 31, 54, 55, and 60% yields, respectively (entries 6−9). The carbocylization reaction also works with dialkylacetylenes. Accordingly, the reaction of **2j**, $CH_3CH_2C{\equiv}CCH_2CH_3$ with **1a**, **1c**−**e** afforded **4i**−**l** in 78, 54, 45, and 82% yields, respectively (entries 10, 12−14). For the carbocyclization of simple unsymmetrical alkynes, two regioisomers were formed as anticipated due to the lack of strong electronic control as observed for substituted propiolates (vide supra). Thus, the reaction of **1a** with $PhC{\equiv}CCH_3$ (**2k**) afforded two regioisomers **4m** and **4m′** in 70 and 23% yields, respec-

TABLE 3. Results of Nickel-Catalyzed Carbocyclization of 2-Halophenyl Ketones 1 with Alkynes 2[a]

entry	ketone	alkyne	product	yield(%)[b]	entry	ketone	alkyne	product	yield(%)[b]
1	**1a**	**2h**	 **4a**	87 (95)	16	**1b**	**2k**	 **4m**	54
2	**1b**	**2h**	 **4a**	70 (79)				 **4m'**	22
3	**1c**	**2h**	 **4b**	82 (94)	17	**1c**	**2k**	 **4n**	60
4	**1d**	**2h**	 **4c**	80				 **4n'**	31
5	**1e**	**2h**	 **4d**	86 (92)	18	**1e**	**2k**	 **4o**	86[c]
6	**1a**	**2i**	 **4e**	31 (34)				 **4o'**	
7	**1c**	**2i**	 **4f**	54	19	**1a**	**2l**	 **4p**	44 (47)
8	**1d**	**2i**	 **4g**	55				 **4p'**	(6)
9	**1e**	**2i**	 **4h**	60 (62)	20	**1c**	**2l**	 **4q**	62
10	**1a**	**2j**	 **4i**	78				 **4q'**	5
11	**1b**	**2j**	 **4i**	54	21	**1a**	**2m**	 **4r**	80
12	**1c**	**2j**	 **4j**	54 (68)				 **4r**	10
13	**1d**	**2j**	 **4k**	45	22	**1c**	**2m**	 **4s**	75
14	**1e**	**2j**	 **4l**	82				 **4s'**	18
15	**1a**	**2k**	 **4m**	70 (70)	23	**1d**	**2m**	 **4t**	57
			 **4m'**	23 (29)				 **4t'**	24

[a] Unless stated otherwise, all reactions were carried out using *o*-halophenyl ketone (0.50 mmol), alkyne (1.50 equiv), Ni(dppe)Br_2 (5.0 mol %), and Zn (2.75 equiv) in CH_3CN (3.0 mL) at 80 °C under N_2 (1 atm) for 13 h. [b] Isolated yields; yields in parentheses were determined by ^1H NMR using mesitylene as an internal standard. [c] Contains an inseparable mixture of two isomers.

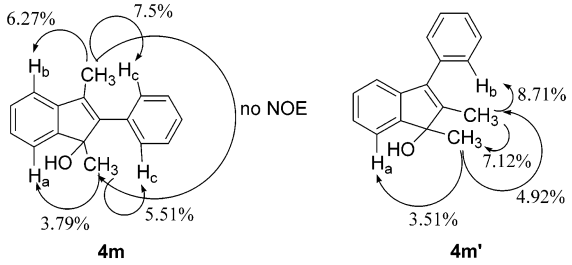


FIGURE 2.

tively (Table 3, entry 15). The regiochemistry of these two isomers **4m** and **4m′** was carefully assigned based on the NOE experiments. For **4m**, selective irradiation of methyl protons at δ 1.47 led to the enhancement of the signals at δ 7.41 aromatic protons by 5.51% and at δ 7.52 by 3.71%, respectively, whereas irradiation of the methyl protons at δ 2.09 attached to the double bond caused enhancement of the aromatic proton signals at δ 7.31 by 7.5% and at δ 7.52 by 6.27%. No NOE was detected between the two methyl groups at δ 1.47 and δ 2.09. These NOE results strongly support the proposed structure **4m** shown in Figure 2.

For **4m′**, the selective irradiation of methyl protons at δ 1.57 led to enhancement of the aromatic proton signal at δ 7.48 by 3.51% and methyl proton signal at δ1.99 by 4.92%, respectively, whereas irradiation of the methyl proton signal attached to the double bond at δ 1.99 resulted in enhancement of the signals at δ 7.45 by 8.71% and at δ 1.57 by 7.12%. The strong NOE effect between the two methyl groups at δ 1.57 and δ 1.99 clearly support the proposed structure **4m′** shown in Figure 2. It is interesting to mention that the major product **4m** has the phenyl group next to the hydroxy moiety.

Treatment of **1c** with **2k** afforded two regioisomers **4n** and **4n′** in 60 and 31% yields, respectively. Surprisingly, the observed regiochemistry for **4n** and **4n′** is opposite to that observed for **4m** and **4m′** (Table 3, entry 17). In the present case, the major isomer **4n** has two methyl groups adjacent to each other, whereas the major isomer **4m** has methyl group adjacent to phenyl group.

The nickel catalyst is also effective for the cyclization of 2-bromoacetophenone (**1b**) with alkynes **2h**−**j** (see entries 2, 11, and 16), but the yields are comparably lower than those from the corresponding iodo derivatives. Both **1a** and **1b** gave similar regioselectivity (the same major product **4m**) when reacted with unsymmetrical alkyne **2k** (entries 15 and 16).

The reaction of unsymmetrical acetylene **2l**, TMSC≡CCH_3, with **1a** and **1c** afforded two regioisomers **4p**/**4p′** and **4q**/**4q′** in 47/6% and 62/5% yields, respectively (entries 19 and 20). The regiochemistry of these isomers was carefully assigned based on the NOE experiments. Both the major isomers **4p** and **4q** have the TMS group away from hydroxy and methyl groups. In a similar fashion, the reaction of **1a** with acetylene **2m**, PhC≡$C(CH_2)_3CH_3$), afforded two regioisomers **4r** and **4r′** in 80% and 10% yields, respectively (Table 3, entry 21). Alkyne **2m** also reacts with other iodophenyl ketones **1c** and **1e** to furnish the corresponding regioisomers **4s**/**4s′** and **4t**/**4t′** in 75/18% and 57/24% yields, respectively.

A careful examination of the regiochemistry for the carbocyclization using unsymmetrical alkynes **2k**−**m** as substrates shows that in most cases the major products are the regioisomers (**4m**,**p**−**t**) in which the alkyne carbon bearing a less electron-donating group is connected to the keto group of **1** and the alkyne carbon with a more electron-donating substituent is attached to the ortho carbon of aryl ketone moiety. The electron-donating ability of the substituents in **2k**−**m** are CH_3 > Ph in PhC≡CCH_3 (**2k**); TMS > CH_3 in TMSC≡CCH_3 (**2l**); and $CH_3(CH_2)_3$ > Ph in PhC≡$C(CH_2)_3CH_3$) (**2m**). These unsymmetrical disubstituted alkynes **2k**−**m** do not have a strong electron-withdrawing group like the ester functionality in propiolates, but the Michael-type addition pattern still dominates the product distribution and the trend of regiochemistry is similar to that of propiolate products. The regiochemistry for the carbocyclization of **1c** with **2k** is an exception (Table 3, entry 17). While the exact reason is not known, the electron-donating ability of methoxy group in **1c** is likely responsible for the observed reverse regioselectivity.

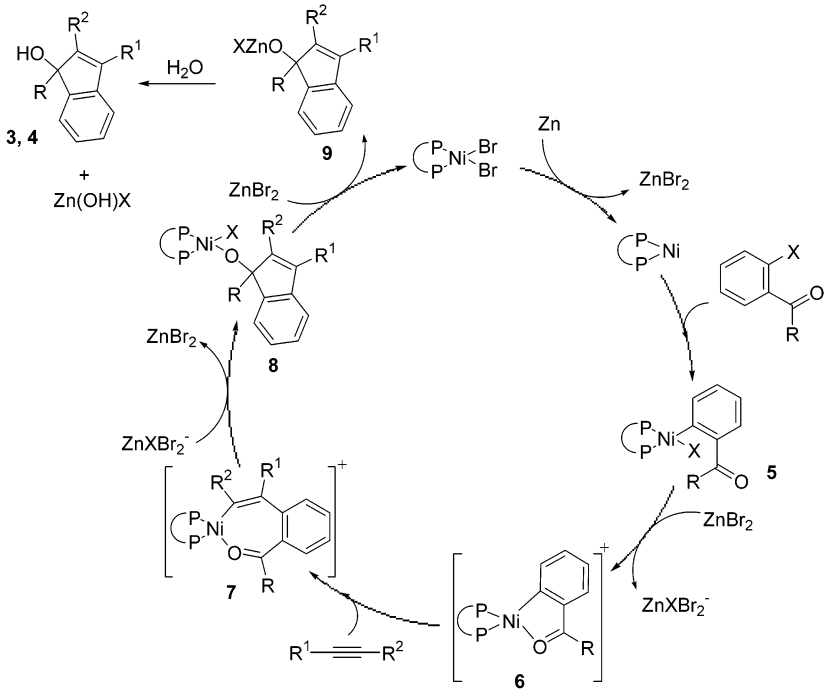
It is interesting to compare the difference between the current nickel-catalyzed carbocyclization and the palladium-catalyzed reaction reported previously.[5] The present nickel catalyst is very effective for *o*-iodophenyl ketones, while the palladium system prefers *o*-bromophenyl ketones to the corresponding iodo substrates. Second, the nickel catalyst system generally requires shorter reaction time i.e., ca. 13 h at 80 °C for the completion of reaction, whereas the reaction catalyzed by the palladium system was carried out at 100 °C and requires much longer reaction time. The low reducing power of KOAc/DMF in palladium system relative to zinc metal in the nickel system possibly accounts at least in part for the long reaction time and higher temperature in the palladium-catalyzed reaction. Third, the nickel-catalyzed carabocyclization appears to give slightly better yields and regioselectivity when compared to the palladium-catalyzed reactions. For example, the nickel system afforded **4a** in 87% yield while the palladium system produced the same product in 63% yield. Similarly the nickel system furnished **4m**/**4m′** in 70% and 23% yields respectively, whereas the palladium gave **4m** and **4m′** in 48% and 20% yields. Fourth, the Ni(dppe)Br_2/Zn system is very effective for the cyclization of *o*-halophenyl ketones with propiolates, but the cyclization by palladium complexes has not been explored previously.

On the basis of the above observations and the known organometallic chemistry of nickel, a catalytic cycle is proposed as shown in Scheme 2. Reduction of Ni(II) to Ni(0) by zinc metal powder[15] is likely the first step and initiates the catalytic cycle. Oxidative addition of aryl iodide to nickel(0) species to yield nickel(II) intermediate **5**. Regioselective insertion of alkyne (wherever applicable) into the nickel-aryl bond generates a seven-membered oxa-nickallocycle **7**.[16] Intramolecular nucleophilic addition of nickel−carbon bond of 7 to the carbonyl carbon leads to a nickel alkoxide intermediate **8**. Subsequent transmetalation with zinc halide furnishes zinc alkoxide **9** and a Ni(II) species. Reduction of the latter by zinc

(15) (a) Kende, A. S.; Liebeskindand, L. S.; Braitsen, D. M. *Tetrahedron Lett.* **1975**, 3375. (b) Zembayashi, M.; Tamao, K.; Yoshida, J.; Kumada, M. *Tetrahedron Lett.* **1977**, 4089.

(16) For nickel oxametallacycles, see: (a) Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3386. (b) Sato, Y.; Takanashi, T.; Mori, M. *Organometallics* **1999**, *18*, 4891.

SCHEME 2. Proposed Mechanism for the Nickel-Catalyzed Carbocyclization



metal regenerates the Ni(0) active catalyst. Zinc alkoxide **9** upon protonation is converted to the final product **3** and Zn(OH)X.

The observation that a bidentate phosphine ligand enhances the catalytic activity of nickel complex for carbocyclization supports the presence of catalytic intermediates **6** and **7** with cis structures.[17] The cis arrangement enhances the catalytic activity by promoting an intramolecular nucleophilic addition in **7** to give carbocyclization product **8**. For nickel catalyst with monodentate triphenylphosphine as ligand, the oxidative addition of aryl halide to Ni(0) gives *trans*-$NiL_2(Ar)X$ because of steric repulsion of the two phosphine ligands. The trans structure remains even after insertion of an alkyne into this Ni−Ar bond. Such a structure is unfavorable for further carbocyclization.

Conclusion

In conclusion, we have demonstrated that a nickel-bidentate ligand system effectively catalyzes the carbocyclization of *o*-halophenyl ketones with propiolates to afford indenol derivatives in moderate to excellent yields with remarkably high regioselectivity. This nickel-catalyzed carbocyclization reaction is successfully extended to simple disubstituted alkynes furnishing highly substituted indenols in moderate to good yields. The present bidentate nickel catalyst system is active for a broad range of alkynes under relatively mild reaction conditions.

Experimental Section

All reactions were conducted under nitrogen on a dual-manifold Schlenk line by using purified deoxygenated solvents and standard inert-atmosphere techniques, unless otherwise stated. Reagents and chemical were used as purchased without further purification. Substituted 2-iodophenyl ketones were prepared following literature procedures.[18] The nickel catalysts $Ni(PPh_3)_2X_2$[19a] and $Ni(dppe)Br_2$[19b] were synthesized according to reported procedures.

General Procedure for the Cyclization of Haloaryl Ketones 1 with Alkylpropiolates 2. A round-bottom side-arm flask (25 mL) containing *o*-iodoaryl ketone **1** (0.50 mmol), $Ni(dppe)Br_2$ (5.0 mol %), and zinc powder (2.75 equiv) was evacuated and purged with nitrogen gas three times. Freshly distilled CH_3CN (3.0 mL) was added followed by addition of propiolate **2** (1.5 equiv). The reaction mixture was heated with stirring at 80 °C for 13 h, cooled and diluted with dichloromethane, and stirred in the air for 15 min. The mixture was filtered through a Celite and silica gel pad and washed with dichloromethane several times. The filtrate was concentrated, and the residue was purified on a silica gel column using hexanes−ethyl acetate as eluent to afford the desired cyclization products **3**.

Acknowledgment. We thank the National Science Council of Republic of China (NSC 91-2113-M-007-053) for support of this research.

Supporting Information Available: NOE experimental data for compounds **3a** and **4n**,**n′**,**p**,**q**, the spectral data for all compounds, ^1H NMR spectra for compounds **3a**,**b**,**e**,**g**,**i**,**k** and **4a**,**b**,**e**,**j**,**l**,**m**,**p**,**p′**, and ^{13}C NMR spectra of compounds **3a** and **4a**,**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0346508

(17) Similar kind of catalytic activity for nickel−bidentate ligand system was observed for the arylation of aldehydes, see ref 12b.

(18) Hellwinkel, D.; Siegbert, S. *Chem. Ber.* **1987**, *120*, 1151.

(19) (a) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation*; Plenum Press: New York, 1991. (b) Colquhoun, H. M.; Holton, J.; Thompson, D. J.; Twigg, M. V. *New Pathways for Organic Synthesis-Practical Applications of Transition Metals*; Plenum Press: New York, 1988.