C–H Activation

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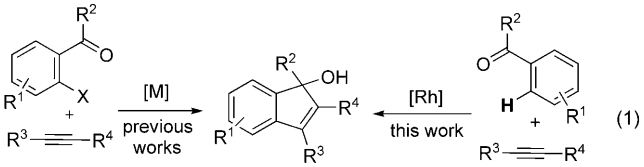
Regioselective Synthesis of Indenols by Rhodium-Catalyzed C–H Activation and Carbocyclization of Aryl Ketones and Alkynes**

*Krishnamoorthy Muralirajan, Kanniyappan Parthasarathy, and Chien-Hong Cheng**

Substituted indenol moieties are an important structural unit present in various biologically active compounds that possess analgesic, insecticidal, and myorelaxation properties.[1,2] Despite the high utility of indenols, only few synthetic routes are reported in the literature.[2,3–6]

Transition-metal-catalyzed carbocyclization is a powerful method for the construction of indenol derivatives in organic synthesis.[7] In this context, Liebeskind et al. reported a stoichiometric reaction of alkynes with *ortho*-manganated acetophenones to give indenols.[2a] Vicente et al. also described the stoichiometric reaction of palladium(II) complexes of 2-acylaryl with alkynes to afford indenol derivatives.[3] Carbocyclization of *o*-haloaromatic ketones or aldehydes with alkynes to give substituted indenols were reported by Yamamoto and co-workers[4] as well as our research group.[5] Later, Murakami and co-workers described a regioselective rhodium-catalyzed carbocyclization reaction of *o*-formylphenylboronic acid with alkynes to give substituted inden-1-ol derivatives.[6] However, the above methods for synthesizing indenol derivatives required halides or boronic acids and sometimes harsh reaction conditions [Eq. (1)]. To



(1)

the best of our knowledge, there is no effective method for the synthesis of indenols using ketone-assisted C–H activation/carbocylization, although a limited number of examples are available using a ketone as the directing group for the C–H bond activation.[8,9e]

In 1999, Woodgate and co-workers reported the first example of a ketone-assisted C–H activation/cyclopentaannulation reaction to give indenols using a ruthenium complex as the catalyst.[8g] Very recently, Shibata and co-workers reported a C–H bond activation/carbocyclization reaction of aromatic ketones and alkynes catalyzed by a cationic iridium complex to afford benzofulvenes in which indenols were obtained as minor products.[8h] Our continuous interest in metal-catalyzed C–H activation[9] and carbocylization reactions[6] prompted us to explore the reaction of aryl ketones with alkynes. Herein, we report the synthesis of substituted indenols from aryl ketones and alkynes through rhodium-catalyzed C–H activation/carbocyclization. Recently, many C–H activation reactions catalyzed by Rh–Cp* complexes have been reported.[10]

Treatment of acetophenone **1a** with diphenyl acetylene **2a** in the presence of 1.0 mol% of $[\{RhCp^*Cl_2\}_2]$, 5 mol% of $AgSbF_6$, and 2.0 equivalents of $Cu(OAc)_2{\cdot}H_2O$ in *tert*-amyl alcohol at 120 °C for 1 hour gave indenol product **3a** in 91% yield (Table 1, entry 1). The structure of **3a** was confirmed by its ^1H and ^{13}C NMR spectra and mass spectrometry data.

The choice of silver salt and oxidant were very crucial for the success of the present catalytic reaction. A series of silver salts and oxidants were examined for the reaction of **1a** with **2a** (for detailed studies, see the Supporting Information).[11] Among them, the combination of $AgSbF_6$ and $Cu(OAc)_2{\cdot}H_2O$ gave the best results and afforded **3a** in 91% yield. In the absence of either the silver salt or an oxidant, the reaction of **1a** with **2a** afforded only a trace amount of **3a**. The use of oxygen or benzoquinone as the oxidant was ineffective. The choice of solvent was also vital to the catalytic reaction. The best solvent was *tert*-amyl alcohol in which **3a** was obtained in 91% yield. 1,2-dichloroethane was also an effective solvent and gave **3a** in 61% yield. Other solvents such as *t*BuOH, MeOH, EtOH, and acetic acid were less effective for the catalytic reaction and gave **3a** in 42, 16, 16, and 36% yield, respectively.

Under the optimal reaction conditions described above, various substituted acetophenones (**1b–f**) were treated with diphenyl acetylene **2a** and gave the corresponding indenol derivatives. Thus, 4-methylacetophenone **1b** afforded **3b** in 89% yield (entry 2). Electron-rich 3,4-dimethoxyacetophenone **1c** reacted nicely with **2a** and gave **3c** in 76% yield (entry 3). In the reaction, there are two possible C–H bond activation sites at C2 and C6 of **1c**, but the reaction occurred only at C6 and is likely a result of the steric bulk of the methoxy group at C3. Electron-withdrawing 4-fluoroacetophenone **1d** provided functionalized indenol **3d** in 80% yield (entry 4). The present catalytic reaction is also compatible with halo substituents on the aromatic ring of acetophenone **1**. Thus, the reaction of 4-chloro-, 4-bromo-, and 4-iodoacetophenones **1e–g** with **2a** gave the corresponding indenol **3e**,

[*] K. Muralirajan, Dr. K. Parthasarathy, Prof. Dr. C.-H. Cheng
Department of Chemistry
National Tsing Hua University
Hsinchu 30013, Taiwan (China)
Fax: (+886) 3572-4698
E-mail: chcheng@mx.nthu.edu.tw
Homepage: http://mx.nthu.edu.tw/%7Echcheng

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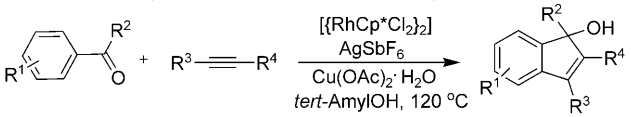
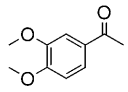
Table 1: Results of rhodium-catalyzed C–H activation and carbocylization of aryl ketones with alkynes.[a]



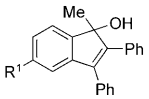
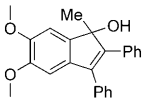
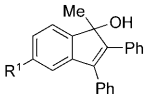
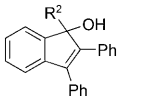
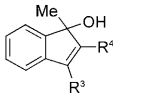
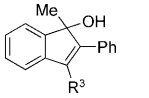
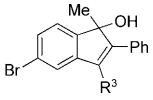
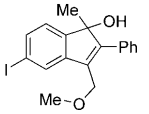
1a–k **2a–i** **3a–x**

1a: R^1 = H, R^2 = Me
1b: R^1 = 4-Me, R^2 = Me
1c:



1d: R^1 = 4-F, R^2 = Me
1e: R^1 = 4-Cl, R^2 = Me
1f: R^1 = 4-Br, R^2 = Me
1g: R^1 = 4-I, R^2 = Me
1h: R^1 = 4-Ph, R^2 = Me
1i: R^1 = H, R^2 = Et
1j: R^1 = H, R^2 = $CH(CH_3)_2$
1k: R^1 = H, R^2 = Ph

2a: R^3, R^4 = Ph
2b: R^3, R^4 = 4-MeC_6H_4
2c: R^3, R^4 = 4-$OMeC_6H_4$
2d: R^3, R^4 = 4-BrC_6H_4
2e: R^3, R^4 = CH_2OMe
2f: R^3 = Me, R^4 = Ph
2g: R^3 = Et, R^4 = Ph
2h: R^3 = Cpr, R^4 = Ph
2i: R^3 = CH_2OMe, R^4 = Ph

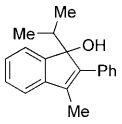
Entry	Ketone	Alkyne	Product	Yield [%][b]
1	**1a**	**2a**	 **3a**: R^1 = H	91
2	**1b**	**2a**	**3b**: R^1 = Me	89
3	**1c**	**2a**	 **3c**	76[c]
4	**1d**	**2a**	**3d**: R^1 = F	80
5	**1e**	**2a**	 **3e**: R^1 = Cl	77
6	**1f**	**2a**	**3f**: R^1 = Br	79
7	**1g**	**2a**	**3g**: R^1 = I	93
8	**1h**	**2a**	**3h**: R^1 = Ph	78
9	**1i**	**2a**	 **3i**: R^2 = Et	76
10	**1j**	**2a**	**3j**: R^2 = $CH(CH_3)_2$	83
11	**1k**	**2a**	**3k**: R^2 = Ph	81
12	**1a**	**2b**	 **3l**: R^3,R^4 = 4-MeC_6H_4	84
13	**1a**	**2c**	**3m**: R^3,R^4 = 4-$OMeC_6H_4$	79
14	**1a**	**2d**	**3n**: R^3,R^4 = 4-BrC_6H_4	86
15	**1a**	**2e**	**3o**: R^3,R^4 = CH_2OMe	73
16	**1a**	**2f**	 **3p**: R^3 = Me	77
17	**1a**	**2g**	**3q**: R^3 = Et	73
18	**1a**	**2h**	**3r**: R^3 = Cpr	61
19	**1a**	**2i**	**3s**: R^3 = CH_2OMe	78
20	**1f**	**2f**	 **3t**: R^3 = Me	74
21	**1f**	**2h**	**3u**: R^3 = Cpr	62
22	**1f**	**2i**	**3v**: R^3 = CH_2OMe	81
23	**1g**	**2i**	 **3w**	84

3f, and **3g** in 77, 79 and 93% yield, respectively (entries 5–7). The phenyl substituent in acetophenone **1h** provided **3h** in 78% yield (entry 8). The effect of changing the methyl group in acetophenone **1a** to another substituents was also investigated. Thus, propiophenone **1i** and isobutyrophenone **1j** reacted effectively with **2a** and provided **3i** and **3j** in 76 and 83% yield, respectively (entries 9 and 10). Finally, the reaction of bulkier benzophenone **1k** with **2a** also proceeded smoothly and afforded product **3k** in good yield (entry 11).

In addition to **2a**, other symmetrical alkynes (**2b–d**) were also tested for the present reaction. Thus, methyl- (**2b**), methoxy- (**2c**), and bromo- (**2d**) substituted diphenylacetylenes underwent C–H activation and carbocylization with **1a** and afforded the corresponding indenols **3l–n** in good yields (entries 12–14). The present catalytic reaction was successfully extended to the aliphatic alkyne **2e** and gave **3o** in 73% yield (entry 15).

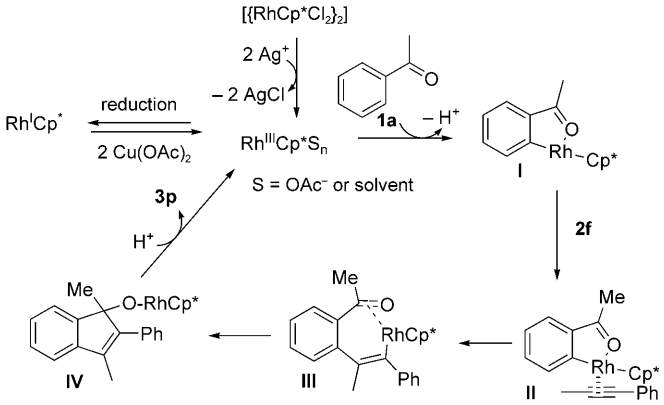
To understand the regioselectivity of the present reaction, unsymmetrical alkynes were used as the substrates for the reaction with **1a**. Thus, 1-phenyl-1-propyne (**2f**) and 1-phenyl-1-butyne (**2g**) gave the single regioisomeric products **3p** and **3q** in 77 and 73% yield, respectively (entries 16 and 17). Similarly, excellent regioselectivity was observed in the reaction of phenylcyclopropylacteylene **2h** and propargylic ether **2i** with **1a**, and afforded **3r** and **3s** in 61 and 78% yield, respectively (entries 18 and 19). Encouraged by the above results, we further examined the reaction of 4-bromoacetophenone **1f** with **2f**, **2h**, and **2i** and these reactions afforded highly regioselective indenols **3t**, **3u**, and **3v** in 74, 62, and 81% yield, respectively (entries 20–22). Similarly, 4-iodoacetophenone **1g** and isobutyrophenone **1j** reacted with **2i** and **2f** in a highly regioselective manner and gave indenol derivatives **3w** and **3x** in 84 and 79% yield, respectively (entries 23 and 24).

Table 1: (Continued)

Entry	Ketone	Alkyne	Product	Yield [%][b]
24	**1j**	**2f**	 **3x**	79

[a] Unless otherwise mentioned, all reactions were carried out using aryl ketone **1** (1.00 mmol), alkyne **2** (1.20 mmol), [{RhCp*Cl_2}$_2$] (1.0 mol%), $AgSbF_6$ (5.0 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol), and *tert*-amyl alcohol (2.5 mL) at 120°C for 1 h. [b] Yield of isolated product. [c] Reaction time was 30 min. Cpr = cyclopropyl.

On the basis of known metal-catalyzed, directing-group-assisted C–H bond activation/carbocyclization reactions,[5–10,12] a possible mechanism is proposed to account for the present catalytic reaction (Scheme 1). The catalytic cycle



Scheme 1. Proposed mechanistic pathway for the formation of indenol derivatives.

is likely initiated by the removal of chloride by Ag^+ in [{RhCp*Cl_2}$_2$]. Coordination of **1a** to the rhodium species and subsequent *ortho* C–H bond activation forms a five-membered rhodacycle **I**. Regioselective insertion of alkyne **2f** into the rhodium–carbon bond of intermediate **II** gives seven-membered rhodacycle **III** with the keto group π-bonded to the rhodium center.[10k] Subsequent intramolecular insertion of the C=O group into the rhodium–alkenyl bond affords rhodium alkoxide intermediate **IV**. Protonation of this alkoxide provides the final product **3p** and regenerates the active Rh^{III} species.

The role of $AgSbF_6$ probably involves removal of the chloride ligands from the [{RhCp*Cl_2}$_2$] complex to generate a more active rhodium complex which likely contains acetate or solvent as ligands in addition to Cp*. The catalytic activity of the rhodium catalyst system increases as the amount of $AgSbF_6$ relative to the rhodium dimer [{RhCp*Cl_2}$_2$] increases from 1.0 to 5.0 equivalents (see the Supporting Information).[11] These results suggest that as one of the chloride ligands in the dimer is removed by Ag^+, the rhodium system starts to show catalytic activity. Based on the amount of Ag^+ used, it is likely that the highest catalytic activity is reached as the four chloride atoms of the dimer are all removed.

Based on the stoichiometry of the reaction, there should be no redox reaction involved. However, during the catalytic reaction the solvent or substrates appear to reduce the active Rh^{III} species. As a result, the catalytic reaction requires the presence of $Cu(OAc)_2{\cdot}H_2O$ to achieve higher product yields. An evidence for the involvement of solvent as a reducing agent for the Rh^{III} species is the observation that [{RhCp*Cl_2}$_2$] in the presence of $AgSbF_6$ (5 equiv) readily reacted with the solvent *tert*-amyl alcohol to give a black metal-like precipitate and unknown organic compounds. Thus, an important role of $Cu(OAc)_2{\cdot}H_2O$ likely involves oxidation of the reduced rhodium species to regenerate the active Rh^{III} species.[12e] In addition, $Cu(OAc)_2{\cdot}H_2O$ also possibly provides the OAc^- source for the active rhodium species.[10d,e]

In conclusion, we have developed a rhodium-catalyzed, chelating-assisted C–H activation of aryl ketones and the reaction with alkynes to afford substituted indenols in good to excellent yields. The catalytic reaction is highly regioselective with unsymmetrical alkynes. In addition, this appears to be the effective method to describe C–H activation/carbocyclization using ketone as a directing group for C–H activation. Further applications of this method in natural product synthesis and a detailed mechanistic investigation are in progress.

Experimental Section

General procedure for the rhodium-catalyzed synthesis of indenol derivatives: A sealed tube containing [{RhCp*Cl_2}$_2$] (1.0 mol%), $AgSbF_6$ (5.0 mol%), and $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol) was evacuated and purged with nitrogen three times. Then, *t*-amyl alcohol (2.5 mL), aryl ketone **1** (1.00 mmol), and alkyne **2** (1.20 mmol) were sequentially added to the system by syringe under nitrogen and the reaction mixture was stirred at 120°C for 1 h. When the reaction was complete, the mixture was cooled and diluted with CH_2Cl_2 (10 mL). The mixture was filtered through a pad of Celite and the Celite was washed with CH_2Cl_2 (50 mL). The filtrate was concentrated and the residue was purified by column chromatography on silica gel (eluent: *n*-hexane/EtOAc 10:4) to give the corresponding pure product **3**.

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[1] a) Kurakay Co. , Ltd. Jpn. Kokai Tokkyo Koho, JP 81, 113, 740 (C1.C07C69/017), Sept 7, **1981** [*Chem. Abstr.* **1982**, *96*, 68724b]; b) Kurakay Co. , Ltd. Jpn. Kokai Tokkyo Koho, JP 82 04, 945 (C1. C07C69/013), Jan 11, **1982** [*Chem. Abstr.* **1982**, *96*, 199935u]; c) K. Samula, B. Cichy, *Acta Pol. Pharm.* **1985**, *42*, 256 [*Chem. Abstr.* **1986**, *105*, 171931v].

[2] a) L. S. Liebeskind, J. R. Gasdaska, J. S. MaCallum, S. J. Tremont, *J. Org. Chem.* **1989**, *54*, 669; b) R. C. Cambie, M. R. Metzler, P. S. Rutledge, P. D. Woodgate, *J. Organomet. Chem.* **1990**, *381*,

C26; c) R. C. Cambie, M. R. Metzler, P. S. Rutledge, P. D. Woodgate, *J. Organomet. Chem.* **1990**, *398*, C22; d) N. P. Robinson, L. Main, B. K. Nicholson, *J. Organomet. Chem.* **1989**, *364*, C37.

[3] a) J. Vicente, J.-A. Abad, J. G. Rubio, *Organometallics* **1996**, *15*, 3509; b) J. Vicente, J. A. Abad, B. Lopez-Pelages, E. Martinez-Puente, *Organometallics* **2002**, *21*, 58.

[4] a) L. G. Quan, V. Gevorgyan, Y. Yamamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3545; b) L. G. Quan, V. Gevorgyan, Y. Yamamoto, *J. Am. Chem. Soc.* **1999**, *121*, 9485; c) V. Gevorgyan, L. G. Quan, Y. Yamamoto, *Tetrahedron Lett.* **1999**, *40*, 4089.

[5] a) D. K. Rayabarapu, C.-H. Cheng, *Chem. Commun.* **2002**, 942; b) D. K. Rayabarapu, C.-H. Yang, C.-H. Cheng, *J. Org. Chem.* **2003**, *68*, 6726; c) K.-J. Chang, D. K. Rayabarapu, C.-H. Cheng, *J. Org. Chem.* **2004**, *69*, 4781.

[6] T. Matsuda, M. Makino, M. Murakami, *Chem. Lett.* **2005**, *34*, 1416.

[7] Metal-catalyzed carbocyclization: a) D. B. Grotjahn in *Comprehensive Organometallic Chemistry II*, *Vol. 12* (Ed.: L. S. Hegedus), Pergamon/Elsevier Science, Kidlington, **1995**, pp. 703, 741; b) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49; c) I. Ojima, M. Tzamarioudaki, Z. R. Li, J. Donovan, *Chem. Rev.* **1996**, *96*, 635; d) H. W. Frühauf, *Chem. Rev.* **1997**, *97*, 523.

[8] a) F. Kakiuchi, T. Sato, F. Kakiuchi, N. Chatani, S. Murai, *J. Mol. Catal. A* **2002**, *181–183*, 511; b) F. Kakiuchi, Y. Yamamoto, N. Chatani, S. Murai, *Chem. Lett.* **1995**, 681; c) K. Tsuchikama, M. Kasagawa, Y.-K. Hashimoto, K. Endo, T. Shibata, *J. Organomet. Chem.* **2008**, *693*, 3939; d) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529; e) R. Martinez, R. Chevalier, S. Darses, J. P. Genet. *Angew. Chem.* **2006**, *118, 8412; Angew. Chem. Int. Ed.* **2006**, 45, 8232; *Angew. Chem. Int. Ed.* **2006**, *45*, 8232; f) Y. Ishii, N. Chatani, F. Kakiuchi, S. Murai, *Tetrahedron Lett.* **1997**, *38*, 7565; g) P. W. R. Harris, C. E. F. Rickard, P. D. Woodgate, *J. Organomet. Chem.* **1999**, *589*, 168; h) K. Tsuchikama, M. Kasagawa, K. Endo, T. Shibata, *Synlett* **2010**, 97.

[9] a) K. Parthasarathy, M. Jeganmohan, C.-H. Cheng, *Org. Lett.* **2008**, *10*, 325; b) K. Parthasarathy, C.-H. Cheng, *J. Org. Chem.* **2009**, *74*, 9359; c) V. S. Thirunavukkarasu, K. Parthasarathy, C.-H. Cheng, *Angew. Chem.* **2008**, *120*, 9604; *Angew. Chem. Int. Ed.* **2008**, *47*, 9462; d) V. S. Thirunavukkarasu, K. Parthasarathy, C.-H. Cheng, *Chem. Eur. J.* **2010**, *16*, 1436; e) P. Gandeepan, K. Parthasarathy, C.-H. Cheng, *J. Am. Chem. Soc.* **2010**, *132*, 8569.

[10] a) N. Umeda, H. Tsurugi, T. Satoh, M. Miura, *Angew. Chem.* **2008**, *120*, 4083; *Angew. Chem. Int. Ed.* **2008**, *47*, 4019; b) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050; c) T. Fukutani, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Commun.* **2009**, 5141; d) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908; e) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565; f) S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585; g) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326; h) M. P. Huestis, L. Chan, D. R. Stuart, K. Fagnou, *Angew. Chem.* **2011**, *123*, 1374; *Angew. Chem. Int. Ed.* **2011**, *50*, 1338; i) F. W. Patureau, T. Besset, N. Kuhl, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2154; j) Z.-M. Sun, S.-P. Chen, P. Zhao, *Chem. Eur. J.* **2010**, *16*, 2619; k) D. N. Tran, N. Cramer, *Angew. Chem.* **2010**, *122*, 8357; *Angew. Chem. Int. Ed.* **2010**, *49*, 8181.

[11] For the optimization studies and the effect of the $AgSbF_6$ salt on the yield of the reaction, see the Supporting Information.

[12] a) C.-H. Jun, C. W. Moon, D.-Y. Lee, *Chem. Eur. J.* **2002**, *8*, 2422; b) Y. J. Park, C.-H. Jun, *Bull. Korean Chem. Soc.* **2005**, *26*, 877; c) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; e) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212.

