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To be cited as: *Chem. Eur. J.* 10.1002/chem.201901860

Link to VoR: http://dx.doi.org/10.1002/chem.201901860

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Chemo- and Regioselective Catalyst-Controlled Carbocyclization of Alkynyl Ketones: Rapid Synthesis of 1-Indanones and 1-Naphthols

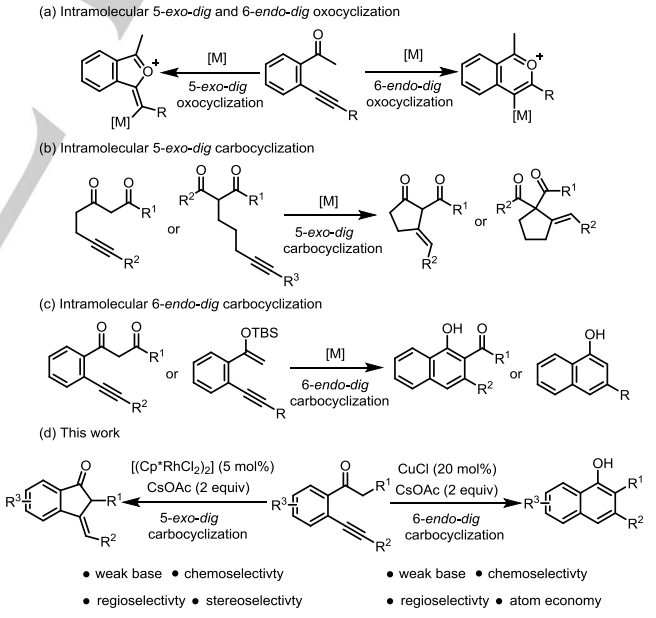
Liangliang Song,[a] Guilong Tian[a] and Erik V. Van der Eycken*[a][b]

Abstract: A catalyst-controlled intramolecular carbocyclization of 2-alkynylarylketones is developed. Under rhodium(III) catalysis, 1-indanones are formed through 5-*exo*-*dig* carbocyclization in exclusive chemo-, regio- and stereoselectivity. When catalyzed by copper(I), 1-naphthols are delivered *via* 6-*endo*-*dig* carbocyclization in exclusive chemo- and regioselectivty.

Site-selective C(sp^3-H) bond functionalization has remained as an attractive and challenging topic in organic chemistry.[1] This approach can avoid the employment of preformed organometallic reagents for conventional cross-couplings, making the synthesis easier and greener.[2] The α-olefination of ketones generally requires strong base-promoted addition of potassium enolates or silyl enol ethers to alkynes.[3] 1-Indanones are important carbocyclic compounds and are present in lots of natural and pharmaceutical products;[4] 1-Naphthols are essential organic compounds that are employed in organic catalysts, organic synthesis and in ligands for transition metal catalysts, and they form the core of numerous natural products and pharmaceuticals.[5]

In the past decades, 2-alkynylarylcarbonyl species have widely been explored as versatile precursors for many important targets with chemical and biomedical potential, because these compounds have multiple reactive sites, allowing them to undergo a variety of transformations, including nucleophilic additions and Diels-Alder reactions.[6] Among the 2-alkynylarylcarbonyl compounds, 2-alkynylarylketones have attracted great attention from lots of organic chemists. The Lewis/Brønsted acid induced intramolecular electrophilic cyclization of 2-alkynylarylketones has been well established as a versatile synthetic method for a variety of biological heterocycles and carbocycles.[7] However, they mainly focus on oxocyclizations. Generally, 5-*exo*-*dig* oxocyclization reactions of 2-alkynylarylketones are performed to undergo nucleophilic additions from isobenzofuranium intermediates (Scheme 1a). Alternately, the similar isobenzopyrylium intermediate derived from 2-alkynylarylketones reacts with alkene or alkyne to achieve [4+2] cycloaddition *via* 6-*endo*-*dig* oxocyclization (Scheme 1a).

Besides the two major reaction pathways, the intramolecular ketone-alkyne cyclization shows a promising approach to access enone derivatives through 5-*exo*-*dig* carbocyclization (Scheme 1b). However, the substrate scope is mainly focused on 1,3-dicarbonyl compounds.[8] To date, only one approach has been reported for the intramolecular 5-*exo*-*dig* carbocyclization of 2-alkynylarylketones.[9a] In 2011, Gevorgyan and co-workers successfully established the Pd-catalyzed regio- and stereoselective 5-*exo*-*dig* carbocyclization of 2-alkynylarylketones. It is also known that 2-alkynylarylketones preferentially undergo 6-*endo*-*dig* carbocyclization to form the useful naphthol (Scheme 1c). However, the substrate scope is limited to 1,3-dicarbonyl compounds and silyl enol ethers.[10] In comparison to 1,3-dicarbonyl compounds, it would be a challenge to realize the catalyst-controlled 5-*exo*-*dig* and 6-*endo*-*dig* carbocyclization selectivity of 2-alkynylarylketones with exclusive chemo- and regioselectivity. Herein, we report a rhodium(III)-catalyzed 5-*exo*-*dig* carbocyclization to synthesize 1-indanones with exclusive chemo-, regio- and stereoselectivity, and a copper(I)-catalyzed 6-*endo*-*dig* carbocyclization to produce 1-naphthols with exclusive chemo- and regioselectivty (Scheme 1d).



Scheme 1. Previous work and this approach.

The investigation commenced by using 2-alkynylarylketone **1a** as a model substrate to optimize the reaction conditions. As revealed by the results in Table 1, treatment of **1a** with $[RhCp^*Cl_2]_2$ (5 mol%) and CsOAc (2 equiv) in DCE at 120 °C enabled the exclusive 5-*exo*-*dig* carbocyclization of **1a**, giving indanone **2a** in 91% yield, as a single chemo-, regio- and stereoisomer with *E*-geometry of the double bond (Table 1, entry 1). Screening of various solvents, such as *t*-AmOH, 1,4-dioxane and toluene, assured that DCE was the most efficient (Table 1,

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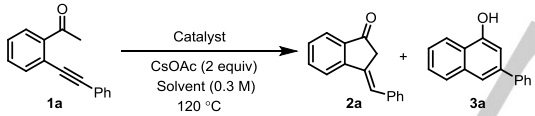
entries 2-4). Without CsOAc, the reaction did not work (Table 1, entry 5). We also evaluated the performance of $Pd(OAc)_2$, resulting in complete decomposition of **1a** (Table 1, entry 6). However, switching to AgOTf as catalyst and 1,4-dioxane as solvent enabled the exclusive 6-*endo*-*dig* carbocyclization of **1a**, giving naphthol **3a** in 30% yield, as a single compound (Table 1, entry 7). $IPrAuNTf_2$ and CuI support the cyclization in a higher yield (Table 1, entries 8-9). CuCl delivered **3a** in 51% yield (Table 1, entry 10). When increasing the loading of CuCl to 20 mol%, **3a** was obtained in 85% yield (Table 1, entry 11). Without CsOAc, the reaction did not work (Table 1, entry 12).

With the optimal conditions in hand, various substrates were studied to evaluate the scope of the rhodium(III)-catalyzed 5-*exo*-*dig* carbocyclization to synthesize 1-indanones (Table 2). The reaction was applicable to 2-alkynylarylketones with various electron-donating or electron-withdrawing groups at the *para* position of the phenylethynyl moiety. The corresponding indanones **2b-f** were obtained in 82-93% yield. Reaction with *meta*-Me- or *ortho*-OMe-substituted 2-alkynylarylketone also smoothly proceeded to give the corresponding indanones with 87% (**2g**) and 76% (**2h**) yields respectively. Additionally, the phenyl group could be replaced by thiophenyl, pyridyl or cyclohexenyl, resulting in the corresponding indanones **2i-k** in 34-84% yield. Furthermore, substrates with a modified acetophenone moiety were well tolerated, leading to the corresponding indanones **2l-p** in 47-90% yield. Notably, the propiophenone substrate turned out to be compatible, offering the corresponding indanone **2q** (53%).

Table 1. Optimization of the carbocyclization conditions[a]

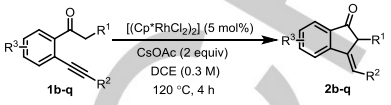


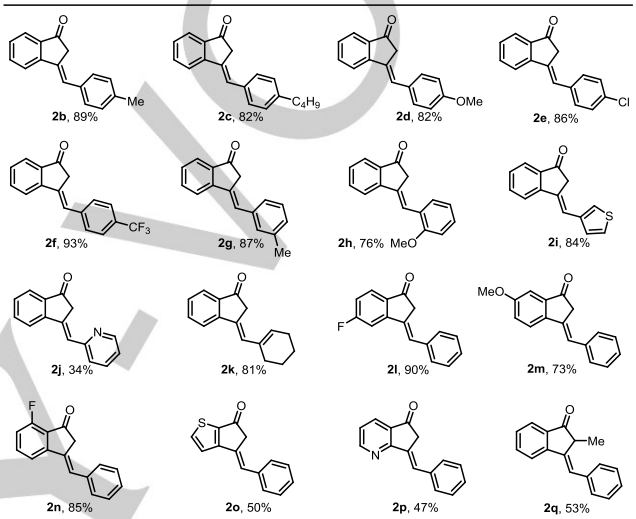
Entry	Catalyst	Solvent	t (h)	**2a**[b] (%)	**3a**[b] (%)
1	**[(Cp*RhCl$_2$)$_2$] (5 mol%)**	**DCE**	**4**	**91**	—
2	[(Cp*RhCl$_2$)$_2$] (5 mol%)	*t*-AmOH	4	23	—
3	[(Cp*RhCl$_2$)$_2$] (5 mol%)	1,4-Dioxane	4	30	—
4	[(Cp*RhCl$_2$)$_2$] (5 mol%)	Toluene	4	11	—
5[c]	[(Cp*RhCl$_2$)$_2$] (5 mol%)	DCE	4	0	—
6	$Pd(OAc)_2$ (5 mol%)	DCE	4	0	—
7	AgOTf (10 mol%)	1,4-Dioxane	12	—	30
8	$IPrAuNTf_2$ (10 mol%)	1,4-Dioxane	12	—	37
9	CuI (10 mol%)	1,4-Dioxane	12	—	42
10	CuCl (10 mol%)	1,4-Dioxane	12	—	51
11	**CuCl (20 mol%)**	**1,4-Dioxane**	**12**	**—**	**85**
12[c]	CuCl (20 mol%)	1,4-Dioxane	12	—	0

[a] Conditions: **1a** (0.3 mmol), catalyst, CsOAc (0.6 mmol), solvent (1.0 mL). [b] Isolated yield. [c] Without CsOAc.

We next focused on the scope of copper(I)-catalyzed 6-*endo*-*dig* carbocyclization to produce 1-naphthols (Table 3). Substrates with diverse electron-donating or electron-withdrawing groups at the *para* position of the phenylethynyl moiety gave the corresponding naphthols **3b-f** in 65-92% yield. Reaction with *meta*-Me 2-alkynylarylketone smoothly afforded the corresponding naphthol in a yield of 82% (**3g**). However, the *ortho*-OMe 2-alkynylarylketone led to recovery of most of the starting material. Moreover, the phenyl group could be replaced by thiophene, pyridine or cyclohexene, leading to the corresponding naphthols **3i-k** in 31-87% yield. Additionally, substrates with various acetophenone moiety were well tolerated, resulting in the corresponding naphthols **3l-o** in 42-79% yield. The propiophenone substrate reacted smoothly under AgOTf catalyst, giving the corresponding indanone **3p** (45%).

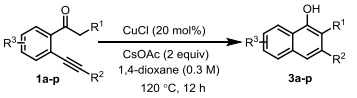
Table 2. Rhodium(III)-catalyzed 5-*exo*-*dig* carbocyclization[a][b]

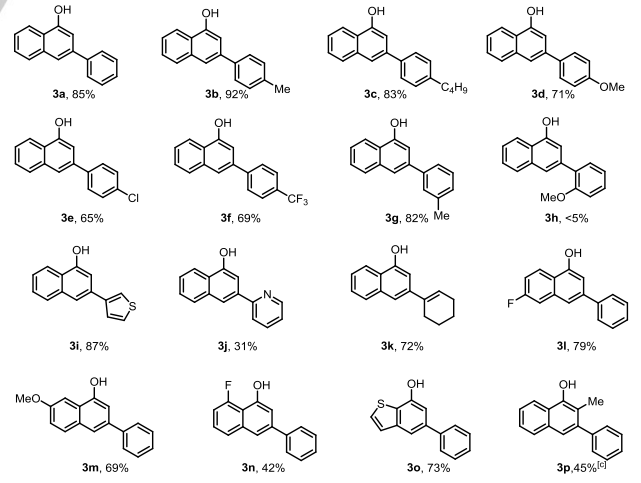




[a] **1** (0.3 mmol), $[RhCp^*Cl_2]_2$ (0.015 mmol), CsOAc (0.6 mmol), DCE (1.0 mL). [b] Isolated yield.

Table 3. Cu-catalyzed 6-*endo*-*dig* carbocyclization[a][b]

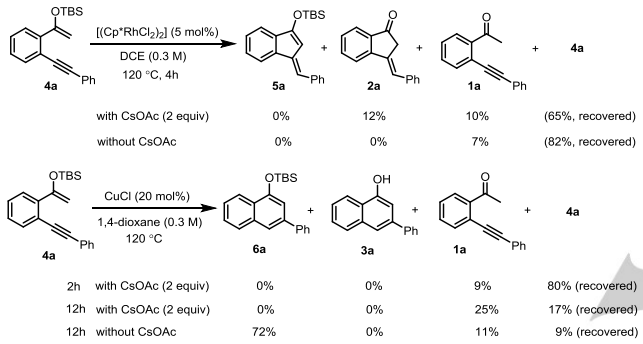




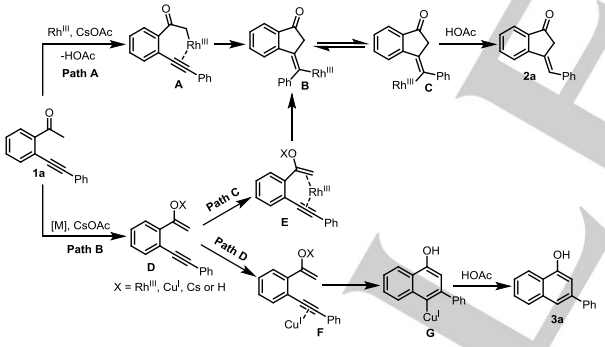
[a] **1** (0.3 mmol), CuCl (0.06 mmol), CsOAc (0.6 mmol), 1,4-dioxane (1.0 mL). [b] Isolated yield. [c] AgOTf (20 mol%) instead of CuCl.

To explore the mechanism of this chemo- and regioselective carbocyclization process, a series of experiments were performed (Scheme 2). When silyl enol ether **4a** was conducted under the standard conditions for the rhodium(III)-catalyzed 5-*exo*-*dig*

carbocyclization, **4a** was recovered in 65% yield, while 2-alkynylarylketone **1a** and indanone **2a** were obtained in yields of 10% and 12% respectively. Without CsOAc, **4a** was recovered in 82% yield, and **1a** was obtained in 7% yield, while there was no **2a** formed, it is because there is no CsOAc to form reactive $Cp^*Rh(OAc)_2$ from $[Cp^*RhCl_2]_2$. These results suggest that two pathways are involved in the construction of **2a** from **1a** and enolate formation of **1a** is only an intermediate of the minor pathway. Then **4a** was treated under standard conditions for the copper(I)-catalyzed 6-*endo-dig* carbocyclization. After 2h, **4a** was recovered in 80% yield, 9% **1a** was isolated. When the reaction was performed under 12h, the starting material partially decomposed, as only 17% of **4a** was recovered, leading to the formation of 25% **1a**. Without CsOAc, **4a** was recovered in 9% yield, while **1a** and TBS-protected naphthol **6a** were obtained in the yields of 11% and 72% respectively. These results indicate that enolate formation of **1a** is the key intermediate in the construction of **3a** from **1a**.



Scheme 2. Control experiments.



Scheme 3. Proposed mechanism.

Based on the above results, plausible pathways are proposed for the formation of **2a** and **3a** from **1a** in Scheme 3. On one hand, rhodium(III)-catalyzed C(sp^3)-H activation of the methyl group of **1a** and subsequent coordination of the triple bond, give intermediate **A** (path A). Intramolecular carborhodation of the triple bond leads to alkenylrhodium(III) intermediate **B**. The subsequent *E-Z* isomerization[9] of the double bond produces isomeric alkenylrhodium(III) intermediate **C**, which undergoes protonation by acetic acid to produce *E* isomer **2a**. On the other hand, enolate formation of **1a** by the transition metal and a base delivers intermediate **D** (path B). For the rhodium(III)-catalyzed 5-*exo-dig* carbocyclization, the coordination of Rh^{III} to the double and the triple bond in intermediate **D** forms intermediate **E** (path C). Subsequent intramolecular 5-*exo-dig* carbocyclization to produce alkenylrhodium(III) intermediate **B** (from path A), gives product **2a**. For the copper(I)-catalyzed 6-*endo-dig* carbocyclization, the coordination of Cu^{I} to the triple bond in intermediate **D** gives intermediate **F** (path D). Subsequent intramolecular 6-*endo-dig* carbocyclization produces intermediate **G**, which undergoes protonation by acetic acid to produce **3a**.

In summary, we have developed a catalyst-controlled intramolecular carbocyclization of 2-alkynylarylketones. Under rhodium(III)-catalyzed 5-*exo-dig* carbocyclization, 1-indanones are obtained in an exclusive chemo-, regio- and stereoselective manner. When employing copper(I)-catalyzed 6-*endo-dig* carbocyclization, 1-naphthols are chemo- and regioselectively produced.

Acknowledgements

Liangliang Song and Guilong Tian appreciate the China Scholarship Council (CSC) for providing a doctoral scholarship. We acknowledge the FWO [Fund for Scientific Research-Flanders (Belgium)] for financial support. We acknowledge the support of RUDN University Program 5-100.

Keywords: carbocyclization • C-H activation • rhodium • copper • enolate

[1] a) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726-11743; b) S.-Y. Zhang, F.-M. Zhang, Y.-Q. Tu, *Chem. Soc. Rev.* **2011**, *40*, 1937-1949; c) G. Qiu, J. Wu, *Org. Chem. Front.* **2015**, *2*, 169-178; d) C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464-3484.

[2] a) T. A. Ramirez, B. Zhao, Y. Shi, *Chem. Soc. Rev.* **2012**, *41*, 931-942; b) B.-J. Li, Z.-J. Shi, *Chem. Soc. Rev.* **2012**, *41*, 5588-5598; c) J. L. Roizen, M. E. Harvey, J. Du Bois, *Acc. Chem. Res.* **2012**, *45*, 911-922.

[3] a) M. Yamaguchi, M. Sehata, A. Hayashi, M. Hirama, *J. Chem. Soc., Chem. Commun.* **1993**, 1708-1709; b) M. Yamaguchi, A. Hayashi, M. Hirama, *J. Am. Chem. Soc.* **1993**, *115*, 3362-3363; c) A. Hayashi, M. Yamaguchi, M. Hirama, *Synlett* **1995**, *1995*, 51-52; d) M. Yamaguchi, T. Tsukagoshi, M. Arisawa, *J. Am. Chem. Soc.* **1999**, *121*, 4074-4075; e) B. A. Trofimov, E. Y. Schmidt, I. A. Ushakov, N. V. Zorina, E. V. Skital'tseva, N. I. Protsuk, A. b. I. Mikhaleva, *Chem. Eur. J.* **2010**, *16*, 8516-8521; f) B. A. Trofimov, E. Y. Schmidt, N. V. Zorina, E. V. Ivanova, I. A. Ushakov, *J. Org. Chem.* **2012**, *77*, 6880-6886; g) F. Mo, H. N. Lim, G. Dong, *J. Am. Chem. Soc.* **2015**, *137*, 15518-15527.

[4] a) T. Ito, T. Tanaka, M. Iinuma, K.-i. Nakaya, Y. Takahashi, R. Sawa, J. Murata, D. Darnaedi, *J. Nat. Prod.* **2004**, *67*, 932-937; b) J. A. Palermo, M. F. Rodríguez Brasco, C. Spagnuolo, A. M. Seldes, *J. Org. Chem.* **2000**, *65*, 4482-4486; c) C. H. Park, X. Siomboing, S. d. Yous, B. Gressier, M. Luyckx, P. Chavatte, *Eur. J. Med. Chem.* **2002**, *37*, 461-468; d) B. V. Ramulu, G. Satyanarayana, *RSC Adv.* **2015**, *5*, 70972-70976.

[5] a) R. Irie, T. Katsuki, *Chem. Rec.* **2004**, *4*, 96-109; b) S. Boonsri, C. Karalai, C. Ponglimanont, S. Chantrapromma, A. Kanjana-opas, *J. Nat. Prod.* **2008**, *71*, 1173-1177; c) J. Sperry, P. Bachu, M. A. Brimble, *Nat. Prod. Rep.* **2008**, *25*, 376-400; d) Y.-S. Cai, Y.-W. Guo, K. Krohn, *Nat. Prod. Rep.* **2010**, *27*, 1840-1870; e) Z. Lou, S. Zhang, C. Chen, X. Pang, M. Li, L. Wen, *Adv. Synth. Catal.* **2014**, *356*, 153-159; f) Y. Guan, Z. Ding, W. D. Wulff, *Chem. Eur. J.* **2013**, *19*, 15565-15571.

[6] a) K. Sekine, A. Takayanagi, S. Kikuchi, T. Yamada, *Chem. Commun.* **2013**, *49*, 11320-11322; b) A. Mukherjee, R.-S. Liu, *Org. Lett.* **2011**, *13*, 660-663; c) K. Saito, Y. Kajiwara, T. Akiyama, *Angew. Chem. Int. Ed.* **2013**, *52*, 13284-13288; d) B. Guo, L. Zheng, L. Yang, R. Hua, *J. Org. Chem.* **2014**, *79*, 4352-4357; e) M. Terada, F. Li, Y. Toda, *Angew. Chem. Int. Ed.* **2014**, *53*, 235-239; f) M. E. Domaradzki, Y. Long, Z. She, X. Liu, G. Zhang, Y. Chen, *J. Org. Chem.* **2015**, *80*, 11360-11368; g) N. Asao, T. Kasahara, Y. Yamamoto, *Angew. Chem.* **2003**, *115*, 3628-3630; h) S. Zhu, Z. Guo, Z. Huang, H. Jiang, *Chem. Eur. J.* **2014**, *20*, 2425-2430; i) S. Bhunia, K.-C. Wang, R.-S. Liu, *Angew. Chem. Int. Ed.* **2008**, *47*, 5063-5066; j) S. Zhu, H. Huang, Z. Zhang,

T. Ma, H. Jiang, *J. Org. Chem.* **2014**, *79*, 6113-6122; k) T. Groß, P. Metz, *Chem. Eur. J.* **2013**, *19*, 14787-14790.

[7] a) J. Sun, J.-K. Qiu, Y.-N. Wu, W.-J. Hao, C. Guo, G. Li, S.-J. Tu, B. Jiang, *Org. Lett.* **2017**, *19*, 754-757; b) B. Guo, Y. Zhou, L. Zhang, R. Hua, *J. Org. Chem.* **2015**, *80*, 7635-7641; c) S.-Y. Yu, H. Zhang, Y. Gao, L. Mo, S. Wang, Z.-J. Yao, *J. Am. Chem. Soc.* **2013**, *135*, 11402-11407; d) D. Wang, S. Liu, X.-C. Lan, A. Paniagua, W.-J. Hao, G. Li, S.-J. Tu, B. Jiang, *Adv. Synth. Catal.* **2017**, *359*, 3186-3193; e) Y.-L. Zhu, A.-F. Wang, J.-Y. Du, B.-R. Leng, S.-J. Tu, D.-C. Wang, P. Wei, W.-J. Hao, B. Jiang, *Chem. Commun.* **2017**, *53*, 6397-6400; f) R.-Y. Yang, J. Sun, Q. Sun, C.-G. Yan, *Org. Biomol. Chem.* **2017**, *15*, 6353-6357.

[8] a) S. Shaw, J. D. White, *J. Am. Chem. Soc.* **2014**, *136*, 13578-13581; b) L. Y. Chan, S. Kim, Y. Park, P. H. Lee, *J. Org. Chem.* **2012**, *77*, 5239-5244; c) Y. Itoh, H. Tsuji, K.-i. Yamagata, K. Endo, I. Tanaka, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 17161-17167; d) A. Matsuzawa, T. Mashiko, N. Kumagai, M. Shibasaki, *Angew. Chem.* **2011**, *123*, 7758-7761; e) S. Montel, D. Bouyssi, G. Balme, *Adv. Synth. Catal.* **2010**, *352*, 2315-2320; f) S. S. K. Boominathan, W.-P. Hu, G. C. Senadi, J.-J. Wang, *Adv. Synth. Catal.* **2013**, *355*, 3570-3574; g) P. W. Davies, C. Detty-Mambo, *Org. Biomol. Chem.* **2010**, *8*, 2918-2922.

[9] a) N. Chernyak, S. I. Gorelsky, V. Gevorgyan, *Angew. Chem.* **2011**, *123*, 2390-2393; b) C. Amatore, S. Bensalem, S. Ghalem, A. Jutand, *J. Organomet. Chem.* **2004**, *689*, 4642-4646.

[10] a) J. W. Dankwardt, *Tetrahedron Lett.* **2001**, *42*, 5809-5812; b) M. A. Ciufolini, T. J. Weiss, *Tetrahedron Lett.* **1994**, *35*, 1127-1130; c) S. P. Shukla, R. Tiwari, A. K. Verma, *Tetrahedron* **2012**, *68*, 9035-9044; d) T. Godet, P. Belmont, *Synlett* **2008**, *2008*, 2513-2517; e) S. Naoe, Y. Suzuki, K. Hirano, Y. Inaba, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2012**, *77*, 4907-4916.

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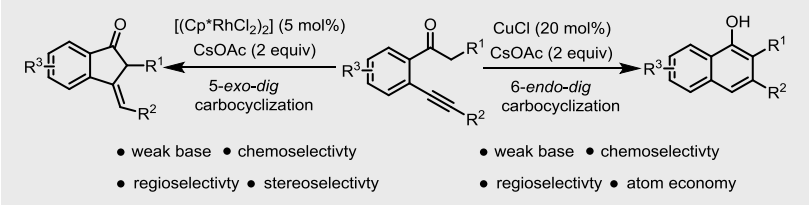

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Chemo- and Regioselective Catalyst-Controlled Carbocyclization of Alkynyl Ketones: Rapid Synthesis of 1-Indanones and 1-Naphthols

A catalyst-controlled 5-*exo-dig* and 6-*endo-dig* carbocyclization of 2-alkynylarylketones for rapid synthesis of 1-indanones and 1-naphthols is developed in exclusive chemo-, regioselectivity.