ORGANIC LETTERS

2011
Vol. 13, No. 4
640–643

Ni-Catalyzed Intramolecular Cycloaddition of Methylenecyclopropanes to Alkynes

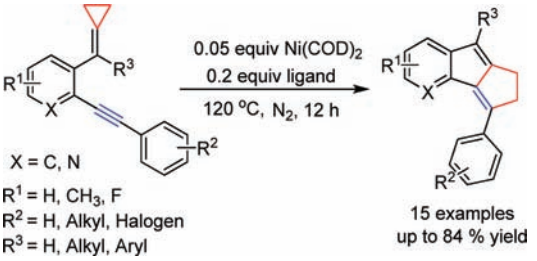
Bangben Yao, Yong Li, Zunjun Liang, and Yuhong Zhang*

Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. China

yhzhang@zju.edu.cn

Received November 30, 2010

ABSTRACT



Ni-catalyzed intramolecular cycloaddition of methylenecyclopropanes (MCPs) to arkylalkynes via proximal bond cleavage is reported. The reaction provides a facile route for the preparation of cyclopenta[*a*]indene derivatives.

Transition-metal-catalyzed organic reactions involving the activation of C−C σ bonds have recently aroused considerable interest because of their great importance in organic synthesis and as a fundamental challenge in organic chemistry.[1] Among the substrates utilized in C−C activation reactions, methylenecyclopropanes (MCPs) occupy a privileged position because of their ready accessibility and high reactivity.[2] In the past decades, numerous promising transition-metal systems for accessing complex polycyclic frameworks by cycloaddition of MCPs have been reported.[3] Two typical oxidative cleavages in cycloaddition reactions of MCPs have been observed: distal-bond (Scheme 1, I) and proximal-bond cleavage.[4−8] However, few examples of intramolecular cycloaddition of MCPs via proximal-bond cleavage are available.[9] Herein, we report a unique Ni-catalyzed intramolecular cycloaddition of MCPs with arylalkynes via the cleavage of proximal bonds (Scheme 1, II). For the first time, an aryl ring moiety was employed as the linker of MCPs and alkynes, which led to the formation of

(1) For reviews, see: (a) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (b) van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759. (c) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610. (d) Horino, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 2144. (e) Park, Y.-J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (f) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2452. (g) Winter, C.; Krause, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 2460.

(2) Selected reviews: (a) Henry, N. C.; Wong, M. Y.; Chun, W. T.; Yu, C. Y. *Chem. Rev.* **1989**, *89*, 165. (b) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867. (c) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. (d) de Meijere, A.; Kozhushkov, S. I.; Khlebnikov, A. F. *Top. Curr. Chem.* **2000**, *207*, 89. (e) Shao, L.-X.; Shi, M. *Curr. Org. Chem.* **2007**, *11*, 1135.

(3) (a) Trost, B. M. *Angew. Chem., Int. Ed.* **1986**, *25*, 1. (b) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (c) Lautens, M.; Klute, W.; Tam, W. *Chem, Rev.* **1996**, *96*, 49. (d) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (e) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (f) Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306. (g) Aïssa, C.; Fürstner, A. *J. Am. Chem. Soc.* **2007**, *129*, 14836.

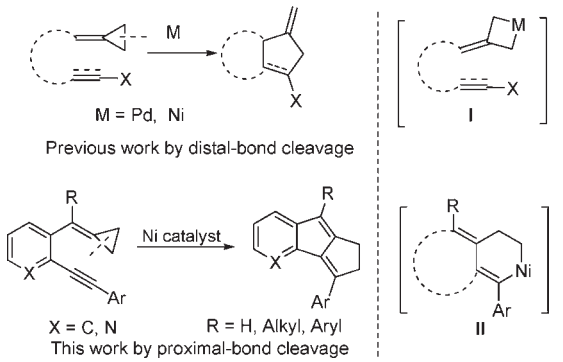
(4) Intermolecular [3 + 2] cycloadditions of MCPs via distal bond cleavage, see: (a) Binger, P.; Schuchardt, U. *Chem. Ber.* **1981**, *114*, 3313. (b) Binger, P.; Doyle, M.; Benn, R. *Chem. Ber.* **1983**, *116*, 1. (c) Nakamura, I.; Oh, B.-H.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1298. (d) Oh, B.-H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6203. (e) Siriwardana, A. I.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 3202. (f) Thormeier, S.; Carboni, B.; Kaufmann, D. E. *J. Organomet. Chem.* **2002**, *657*, 136.

(5) Intermolecular cycloadditions of MCPs via proximal bond cleavage: (a) Noyori, R.; Odagi, T.; Takaya, H. *J. Am. Chem. Soc.* **1970**, *92*, 5780. (b) Noroyi, R.; Kumagai, Y.; Umeda, I.; Takaya, H. *J. Am. Chem. Soc.* **1972**, *94*, 4018. (c) de Meijere, A.; Kurahashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 7881. (d) Kawasaki, T.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 4911. (e) Murakami, M.; Ishida, N.; Miura, T. *Chem. Commun.* **2006**, 643. (f) Binger, P.; Wedemann, P. *Tetrahedron Lett.* **1985**, *26*, 1045.

(6) Intermolecular [3 + 2 + 2] cycloadditions of MCPs via proximal bond cleavage: (a) Saito, S.; Masuda, M.; Komagawa, S. *J. Am. Chem. Soc.* **2004**, *126*, 10540. (b) Komagawa, S.; Saito, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2446. (c) Saito, S.; Komagawa, S.; Azumaya, I.; Masuda, M. *J. Org. Chem.* **2007**, *72*, 9114. (d) Yamasaki, R.; Terashima, N.; Sotome, I.; Komagawa, S.; Saito, S. *J. Org. Chem.* **2010**, *75*, 480. (e) Zhao, L.-G.; de Meijere, A. *Adv. Synth. Catal.* **2006**, *348*, 2484.

10.1021/ol1028628
Published on Web 01/18/2011

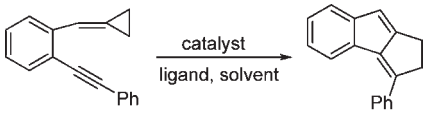
Scheme 1



valuable 5,5-fused polycyclic systems. The transformation provides a facile accessment for cyclopenta[*a*]indene derivatives.[10]

The viability of the approach was tested on substrate **3a**, which is easily assembled by Sonogashira coupling of 2-bromobenzaldehyde with phenyl acetylene and a subsequent Wittig reaction (see the Supporting Information). As shown in Table 1, rhodium catalyst, which was utilized in the cyclization of MCPs,[3f] failed to promote the attempted cycloaddition reaction (Table 1, entry 1). Treatment of **3a** in xylene with 10 mol % of $Pd(PPh_3)_4$ and 20 mol % of PPh_3 at 140 °C for 48 h provided the desired cycloadduct **4a**, albeit in rather low yield (Table 1, entry 2). To our delight, the use of nickel catalyst considerably increased the efficiency of the reaction to give **4a** in 64% yield in DMSO at 120 °C for 12 h (Table 1, entry 2). Other nickel species, such as $NiCl_2 \cdot 2H_2O$, $NiCl_2(PPh_3)_2$, $NiCl_2(PCy_3)_2$, $NiBr_2$(diglyme), and $Ni(acac)_2$, were completely ineffective (Table1, entries 4−8). The use of

Table 1. Optimization of Reaction Condition Studies [a]



3a **4a**

entry	catalyst	ligand	solvent	yield[b] (%)
1	$Rh(PPh_3)_3Cl$		THF	0 [c]
2	$Pd(PPh_3)_4$	PPh_3	xylene	38 [d]
3	$Ni(COD)_2$	PPh_3	DMSO	64
4	$NiCl_2 \cdot 2H_2O$	PPh_3	DMSO	0
5	$NiCl_2(PPh_3)_2$	PPh_3	DMSO	0
6	$NiCl_2(PCy_3)_2$	PPh_3	DMSO	0
7	$NiBr_2$(diglyme)	PPh_3	DMSO	0
8	$Ni(acac)_2$	PPh_3	DMSO	0
9	$Ni(COD)_2$	P(Bu-*n*)$_3$	DMSO	51
10	$Ni(COD)_2$	dppe	DMSO	58
11	$Ni(COD)_2$	dppp	DMSO	62
12	$Ni(COD)_2$	dppb	DMSO	59
13		PPh_3	DMSO	0
14	$Ni(COD)_2$		DMSO	0
15	$Ni(COD)_2$	PPh_3	DMF	40
16	$Ni(COD)_2$	PPh_3	dioxane	trace
17	$Ni(COD)_2$	PPh_3	toluene	trace
18	$Ni(COD)_2$	PPh_3	CH_3CN	trace
19	$Ni(COD)_2$	PPh_3	xylene/DMSO	71 [e]

[a] Reaction conditions: **3a** (0.3 mmol), Ni catalyst (0.015 mmol), ligand (0.06 mmol), solvent (5 mL), 120 °C, N_2, 12 h. [b] Isolated yields. [c] $Rh(PPh_3)_3Cl$ (0.015 mmol), $AgSbF_6$ (0.0225 mmol), THF (5 mL). [d] $Pd(PPh_3)_4$ (0.03 mmol), 140 °C, 48 h. [e] Xylene/DMSO = 0.5:4.5 mL.

phosphine ligands was crucial to the reaction (Table 1, entries 9−12). Both alkyl- and arylphosphines showed effects on the transformation (Table 1, entries 3 and 9). Bidentate phosphine ligands, such as dppe, dppp, and dppb, improved the cyclization process as well (Table 1, entries 10−12). No reaction took place without catalyst or ligand (Table 1, entries 13 and 14). We screened different solvents, and the most suitable media for this cyclization transformation is the combination of DMSO and xylene (Table 1, entries 15−19). Thus, the reaction efficiently proceeded when 5 mol % of $Ni(COD)_2$ and 20 mol % of PPh_3 were used in the combination of DMSO and xylene at 120 °C for 12 h.

With the optimal reaction conditions in hand, we next studied the scope and generality of the reaction (Table 2). A variety of arylalkynes could be used in the cyclization reaction. For example, para-substituted ethynylarenes provided the corresponding cyclopenta[*a*]indene products in moderate yields (Table 2, entries 2 and 3). It is important to note that the chloride group tolerated in the reaction thus made it possible for further assembly through the cross-coupling reactions (Table 2, entry 4). Ethynylarenes with an ortho substitutent delivered the corresponding product **4e** in lower yield (Table 2, entry 5), illustrating that the steric hindrance played the role to the reaction. Meta-substituted ethynylarenes such as **3f** and **3g** were more efficient compared with their para or ortho analogues and afforded slightly higher yields (Table 2, entries 6

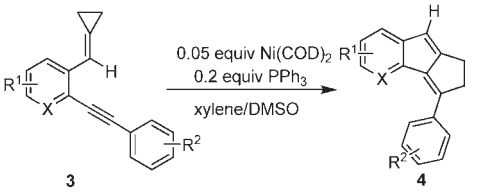
(7) Intramolecular cycloadditions of MCPs via distal bond cleavage: (a) Yamago, S.; Nakamura, E. *J. Chem. Soc., Chem. Commun.* **1988**, 1112. (b) Lewis, R. T.; Motherwell, W. B.; Shipman, M. *J. Chem. Soc., Chem. Commun.* **1988**, 948. (c) Stolle, A.; Becker, H.; Salaün, J.; de Meijere, A. *Tetrahedron Lett.* **1994**, *35*, 3517. (d) Corlay, H.; Lewis, R. T.; Motherwell, W. B.; Shipman, M. *Tetrahedron* **1995**, *51*, 3303. (e) Bräse, S.; Schömenauer, S.; McGaffin, G.; Stolle, A.; de Meijere, A. *Chem.—Eur. J.* **1996**, *2*, 545. (f) Corlay, H.; Motherwell, W. B.; Pennell, A. M. K.; Shipman, M.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1996**, *52*, 4883. (g) Lautens, M.; Ren, Y.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8821. (h) Lautens, M.; Ren, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9597. (i) Lautens, M.; Ren, Y. *J. Am. Chem. Soc.* **1996**, *118*, 10668. (j) Corlay, H.; Fouquet, E.; Magnier, E.; Motherwell, W. B. *Chem. Commun.* **1999**, 183.

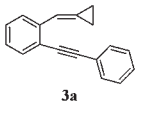
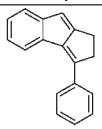
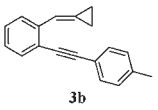
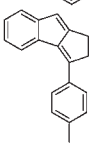
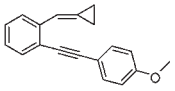
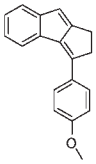
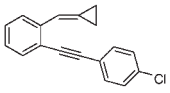
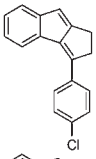
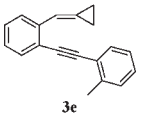
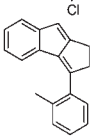
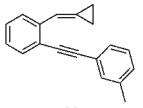
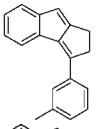
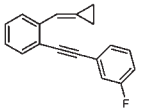
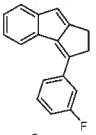
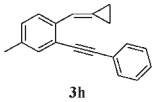
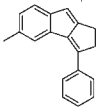
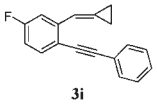
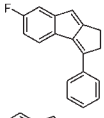
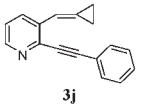
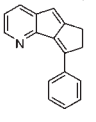
(8) Recent works of intramolecular cycloadditions of MCPs via distal bond cleavage: (a) Delgado, A.; Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9282. (b) Evans, P. A.; Inglesby, P. A. *J. Am. Chem. Soc.* **2008**, *130*, 12838. (c) Durán, J.; Gulías, M.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2005**, *7*, 5693. (d) Trillo, B.; Gulías, M.; Castedo, L.; Mascareñas, J. L. *Adv. Synth. Catal.* **2006**, *348*, 2381. (e) Gulías, M.; García, R.; Delgado, A.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 384. (f) Gulías, M.; Durán, J.; López, F.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2007**, *129*, 11026. (g) Bhargava, G.; Trillo, B.; Araya, M.; López, F.; Castedo, L.; Mascareñas, J. L. *Chem. Commun.* **2010**, *46*, 270. (h) López, F.; Delgado, A.; Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 10262.

(9) Bapuji, S. A.; Motherwell, W. B.; Shipman, M. *Tetrahedron Lett.* **1989**, *30*, 7107.

(10) (a) Baker, Wilson; Glockling, F.; McOmie, J. F. W. *J. Chem. Soc.* **1951**, 3357. (b) Oh, D.-C.; Williams, P. G.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2006**, *8*, 1021.

Table 2. Scope of the Substrates[a]



entry	3	4	yield [b] (%)
1	 3a		71 (4a)
2	 3b		52 (4b)
3	 3c		58 (4c)
4	 3d		43 (4d)
5	 3e		32 (4e)
6	 3f		74 (4f)
7	 3g		68 (4g)
8	 3h		62 (4h)
9	 3i		73 (4i)
10	 3j		53 (4j)

[a] Reaction conditions: **3** (0.3 mmol), $Ni(COD)_2$ (0.05 equiv), PPh_3 (0.2 equiv), xylene/DMSO = 0.5:4.5 mL, 120 °C, N_2, 12 h. [b] Isolated yields.

and 7). The substrates formed from both electron-donating and electro-withdrawing substituted 2-bromobenzaldehyde performed well under the cycloaddition reactions (Table 2, entries 8 and 9). Gratifyingly, the use of pyridine

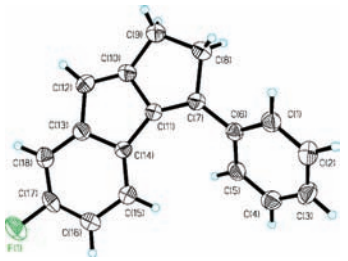
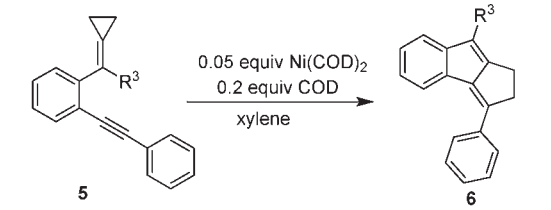


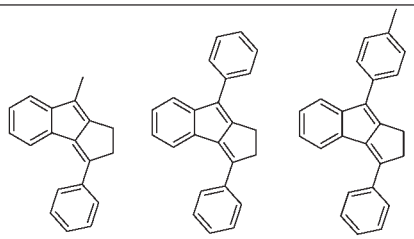
Figure 1. ORTEP drawing of compound **4i**.

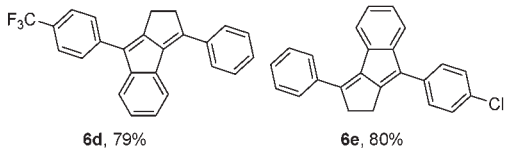
substrate derived from 2-bromopyridine-3-carbaldehyde also tolerated and provided the cyclization product **4j** in 53% yield, which provided an alternative route for fused heterocyclic molecules (Table 2, entry 10). Alkyl alkynes did not participate in this cyclization reaction. The structure of the product was further confirmed by X-ray single-crystal diffraction of **4i** (Figure 1).

Encouraged by the successful cyclization of monosubstituted methylenecyclopropane, we next extended our reaction to disubstituted MCPs at the cyclopropyl alkene carbon. To our delight, the disubstituted MCPs also participated in the cyclization under the reaction conditions. In these cases, however, COD presented better effect than that of phosphine ligands. As can be seen from Table 3, both methyl and aryl substituents of substrates **5** participated in the reaction in xylene when the ligand was changed to

Table 3. Substrates with Substitution at the Exocyclic Methylene Carbon[a]

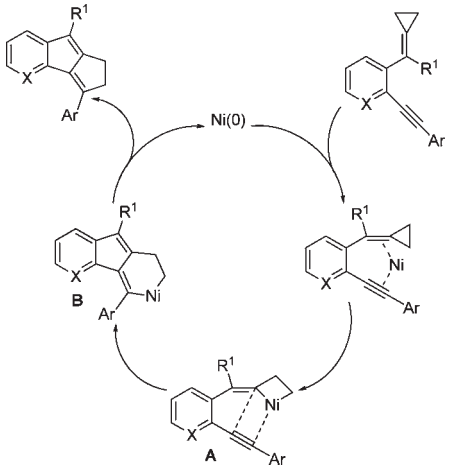






[a] Reaction conditions: **5** (0.3 mmol), $Ni(COD)_2$ (0.015 mmol), COD (0.06 mmol), xylene (5.0 mL), 120 °C, N_2, 12 h.

Scheme 2. Plausible Mechanism



1,5-cyclooctadiene (COD). Diarylidenecyclopropanes were even more reactive to afford the corresponding cycloadducts in higher yields regardless of the electronic properties of substituent on the aromatic rings.

In search of a possible [3 + 2 + 2] annulation process, we performed the reaction of **3a** with various activated alkenes such as ethyl acrylate, acrolein, and styrene. However, the desired [3 + 2 + 2] cycloadducts were not detected. During our preparation of this manuscript, Mascareñas and co-workers described an elegant example of [3 + 2 + 2] cycloaddition involving MCP proximal bond cleavage.[11]

(11) Saya, L.; Bhargava, G.; Vavarro, M. A.; Gulías, M.; López, F.; Fernández, I.; Castedo, L.; Mascareñas, J. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9886.

In their experiments, the reductive elimination of intermediate **B** is difficult to give 6,5-fused bicyclic systems (Scheme 2). On the basis of previous studies[5,6,11] and our experimental results, a plausible mechanism of the reaction is proposed as shown in Scheme 2. Oxidative addition of nickel(0) to the proximal C−C σ bond of cyclopropyl alkene leads to the nickelacyclobutane species **A**. The subsequent intramolecular addition of intermediates **A** into C−C triple bond generates the six-membered nickel cycle **B**, which undergoes the reductive elimination to liberate the cyclopenta[*a*]indenes with the regenerate of the Ni(0). According to previous DFT caculations and experimental data for the reactions of alkylidenecyclopropanes, the reductive elimination of intermediate **B** is not easy.[11] In our system, the formation of larger conjugation system might make the reductive elimination of intermediate **B** easier.

In summary, we have developed a new nickel-catalyzed intramolecular cycloaddition of MCPs with arylalkynes by the cleavage of proximal C−C bond. Both monosubstituted and disubstituted MCPs underwent the reaction smoothly. The procedure provided a general and efficient method for the synthesis of cyclopenta[*a*]indenes.

Acknowledgment. Funding from Natural Science Foundation of China (Nos. 21072169 and 20872126) and Fundamental Research Funds for the Central Universities (2010QNA3011) is acknowledged.

Supporting Information Available. Experimental procedure, X-ray data for **4i** (CIF), and spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS) for the products. This material is available free of charge via the Internet at http://pubs.acs.org.