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Palladium-Catalyzed Highly Regioselective [3 + 2] Cycloaddition Reactions of Alkylidenecyclopropa[*b*]naphthalenes with Alkenes or Alkynes: An Efficient Synthesis of 1(3)-Alkylidene-2,3-dihydro-1*H*-benzo[*f*]indenes and 1-Alkylidene-1*H*-benzo[*f*]indenes

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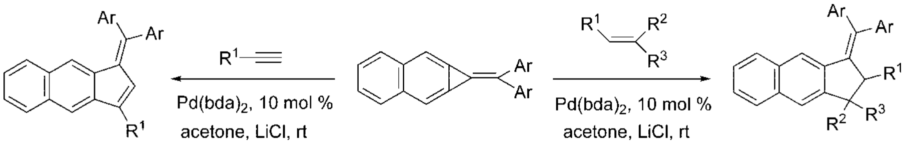
ABSTRACT



The first palladium-catalyzed highly regioselective [3 + 2] cycloaddition reactions of alkylidenecyclopropa[*b*]naphthalenes 1 with alkenes or alkynes is presented, providing an efficient method for the synthesis of 1(3)-alkylidene-2,3-dihydro-1*H*-benzo[*f*]indenes or 1-alkylidene-1*H*-benzo[*f*]indenes under mild conditions.

Naphthalenes fusing a cyclopentyl or cyclopentenyl ring are of marked interest due to their applications as bioactive compounds and synthetic intermediates in organic synthesis.[1] However, there are only limited reports about their synthesis with substituent groups due to a lack of sufficient construction of the annulated naphthalene ring at one time during the five-membered ring closure reaction.[2,3] Thus, there is a need to develop a new method for the efficient synthesis of these compounds with different substituent groups.

The transition-metal-catalyzed [3 + 2] cycloaddition reactions of methylenecyclopropanes (MCPs) with carbon−carbon or carbon−heteroatom multiple bonds are efficient methods for construction of five-membered rings incorporating an exocyclic carbon−carbon double bond.[4] An often troublesome feature of the [3 + 2] cycloaddition reactions

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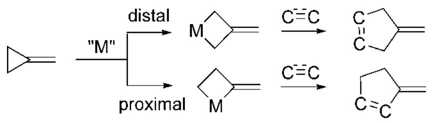
is the multiform reactivities of the three strained bonds in the cyclopropane ring, leading to formation of different products through cleavage of proximal or distal bonds of the three-membered ring (Scheme 1).

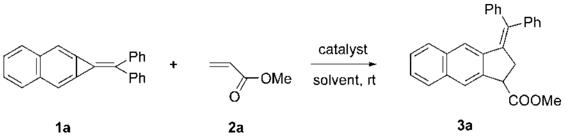
Scheme 1



During our systematic study of MCPs chemistry,[5] we were interested in the chemistry of its analogues, alkylidenecyclopropa[*b*]naphthalenes **1**. Because of the unusual structure of alkylidenecyclopropa[*b*]naphthalenes **1**, incorporating within one molecule a triafulvene, a [3]radialene, and the cycloproparene, they have attracted much attention from physical, theoretical, and synthetic viewpoints.[6] Especially, much attention has been paid to the synthesis of otherwise inaccessible compounds from alkylidenecyclopropa[*b*]naphthalenes. In this paper, we envisioned that the insertion of a Pd(0) species into alkylidenecyclopropa[*b*]naphthalenes could lead to the mild alkenyl metallo-cyclointermediate appending a naphthalene ring, which would be further annulated with a carbon−carbon multiple bond in the subsequent [3 + 2] cycloaddition reaction, thus providing a new efficient method for construction of naphthalenes incorporating a five-membered ring with an exocyclic carbon−carbon double bond. To the best of our knowledge, for transition-metal-mediated reactions, only one example of alkylidenecyclopropa[*b*]naphthalenes **1** with stoichiometric rhodium(I) and platinum(0) reagents has been studied,[7] and no other catalyzed reaction has been reported. Herein, we report the first highly regioselective palladium-catalyzed [3 + 2] cycloaddition reactions of alkylidenecyclopropa[*b*]naphthalenes **1** with alkenes or alkynes under mild conditions and provide an efficient synthesis of 1(3)-alkylidene-2,3-dihydro-1*H*-benzo[*f*]indenes and 1-alkylidene-1*H*-benzo[*f*]indenes.

We initially examined the reaction of the 1-(diphenylmethylene)-1*H*-cyclopropa[*b*]naphthalene **1a**[8] with methyl acrylate under different reaction conditions. The results are summarized in Table 1. The reaction of **1a** with **2a** did not proceed without the palladium catalyst (entry 1, Table 1). $Pd(OAc)_2$ and $Pd(dba)_2$ could catalyze the reaction to afford **3a** in 28% and 41% yield, respectively, within 1 h at room temperature in acetone (entries 2 and 3, Table 1). $Pd(PPh_3)_4$ did not catalyze this reaction under the same conditions (entry 4, Table 1). Using phosphane ligands, such as $P(C_6H_4Me\text{-}o)_3$ and $P(OPr\text{-}i)_3$, did not give better results than $Pd(dba)_2$ (entries 5 and 6, Table 1). However, in the presence of lithium chloride,[9] **3a** was produced in a better yield under $Pd(dba)_2$ catalysis (entry 7, Table 1). Lithium bromide and tetra(*n*-butyl)ammonium chloride were less effective than lithium chloride (entries 9 and 10, Table 1). While the reaction with sodium iodide was totally ineffective due to the precipitation of palladium black (entry 11, Table 1),

Table 1. Optimization of Reaction Conditions for the Pd-Catalyzed [3 + 2] Cycloaddition Reaction of **1a** with Methyl Acrylate **2a**[a]



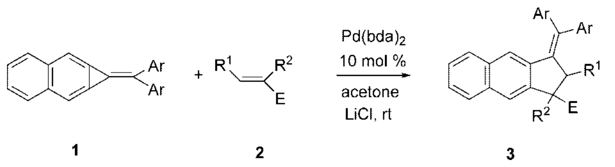
entry	catalyst	additive	solvent	time	yield (%)[b]
1	no	no	CH_3COCH_3	48 h	0
2	$Pd(OAc)_2$	no	CH_3COCH_3	1 h	28
3	$Pd(dba)_2$	no	CH_3COCH_3	1 h	41
4	$Pd(PPh_3)_4$	no	CH_3COCH_3	48 h	0
5	$Pd(dba)_2/P(C_6H_4Me\text{-}o)_3$	no	CH_3COCH_3	0.5 h	19
6	$Pd(dba)_2/P(OPr\text{-}i)_3$	no	CH_3COCH_3	0.5 h	15
7	$\mathbf{Pd(dba)_2}$	**LiCl**	$\mathbf{CH_3COCH_3}$	**0.5 h**	**69**
8	$Pd(dba)_2$[c]	LiCl	CH_3COCH_3	24 h	36[d]
9	$Pd(dba)_2$	LiBr	CH_3COCH_3	1 h	65
10	$Pd(dba)_2$	$n\text{-}Bu_4N^+Cl^-$	CH_3COCH_3	0.5 h	61
11	$Pd(dba)_2$	NaI	CH_3COCH_3	1 h	12[e]
12	$Pd(dba)_2$[f]	LiCl	CH_3COCH_3	0.5 h	63
13	$Pd(dba)_2$[g]	LiCl	CH_3COCH_3	0.5 h	35
14	$Pd(dba)_2$	LiCl	THF	1 h	55
15	$Pd(dba)_2$	LiCl	MeOH	1 h	38
16	$Pd(dba)_2$	LiCl	MeCN	1 h	35
17	$Pd(dba)_2$	LiCl	CH_3COOH	1 h	18

[a] The reaction was carried out at rt using **1a** (0.164 mmol), **2a** (5 equiv), catalyst (10 mol %), and additive (10 equiv) in acetone (2 mL). [b] Isolated yield based on **1a**. Unless otherwise stated, **1a** converted completely. [c] 5 mol % catalyst was used. [d] 38% of **1a** was recovered. [e] 50% of **1a** was recovered. [f] The reaction temperature was 40 °C. [g] 2 equiv of Et_3N was added as the base.

elevated reaction temperature or addition of triethylamine gave a lower yield of **3a** (entries 12 and 13, Table 1). Next, we examined the effect of solvent choice on this reaction (entries 14−17, Table 1). The reaction ran smoothly in THF, CH_3CN, CH_3OH, and CH_3COOH, but the yields of **3a** were not as high as those in acetone.

Using the optimal reaction conditions, we carried out the reaction with various alkylidenecyclopropa[*b*]naphthalenes **1** and alkenes with electron-withdrawing group **2**, and the results are listed in Table 2. From the results in Table 2, we could see that the reaction exhibited an excellent regioselectivity of the double bond of acrylate. We only detected one isomer in the crude product. The regioselectivity of the double bond was determined by a NOESY experiment (**3a**, Figure 1). However, when 2-butenal **2d** was used as the substrate, only a trace amount of the product **3g** was formed, probably due to the steric hindrance of the methyl group in the substrate (entry 7, Table 2).

Table 2. Pd(dba)$_2$-Catalyzed [3 + 2] Cycloaddition Reaction of **1** with Alkenes Containing Electron-Withdrawing Group **2**



entry	Ar	R^1/R^2/E	product	time	yield (%)[a]
1	C_6H_5, **1a**	H/H/COOMe, **2a**	**3a**	0.5 h	70[b]
2	**1a**	H/H/COOEt, **2b**	**3b**	0.5 h	68
3	**1a**	H/Me/COOMe, **2c**	**3c**	6 h	30
4	4-MeC_6H_4, **1b**	**2a**	**3d**	0.5 h	61
5	4-FC_6H_4, **1c**	**2a**	**3e**	0.5 h	58
6	4-ClC_6H_4, **1d**	**2a**	**3f**	0.5 h	63
7	**1a**	Me/H/CHO, **2d**	**3g**	24 h	trace[c]

[a] Isolated yield based on **1**. [b] 1 mmol **1a** was used. [c] Stereochemistry unknown.

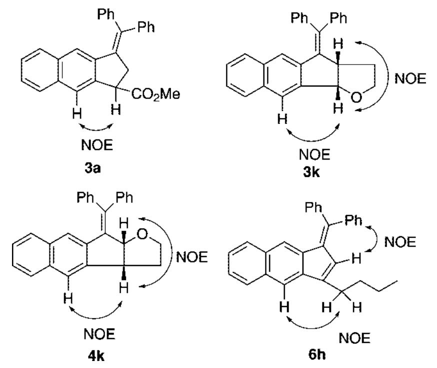
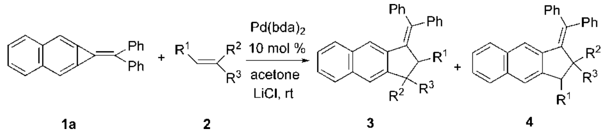


Figure 1. NOE experiment of **3a**, **3k**, **4k**, and **6h**.

As well as acrylate, general alkenes could also be applied to this reaction. Some typical examples are summarized in Table 3. For cyclopentene **2e**, hex-1-ene **2f**, and styrene **2g**, the reactions also proceeded smoothly with high regioselectivity. The regioselectivity of the resulting compounds was confirmed by X-ray single crystal diffractional analysis of **3i** (Figure 2).[10] However, when 2,3-dihydrofuran **2h** was used as the substrate, regioisomers of **3k** and **4k** were obtained with *cis*-configuration (**3k** and **4k**, Figure 1).

Table 3. Pd(dba)$_2$-Catalyzed [3 + 2] Cycloaddition Reaction of **1** with General Alkenes **2**



entry	R^1/R^2/R^3	product	time	yield (%)[a]
1	−$(CH_2)_3$−/H, **2e**	**3h**	0.5 h	64
2	H/H/$(CH_2)_3CH_3$, **2f**	**3i**	0.5 h	75
3	H/H/Ph, **2g**	**3j**	1 h	50
4	−OCH_2CH_2−/H, **2h**	**3k**/**4k**	0.5 h	65 (50:50)[b]

[a] Isolated yield based on **1**. [b] Determined by isolation.

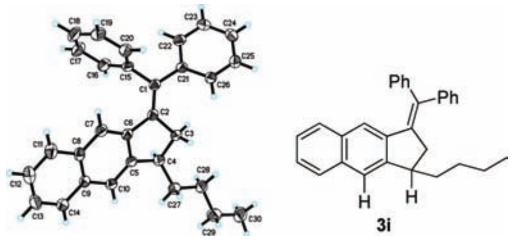


Figure 2. X-ray structure of compound **3i**.

To determine the scope of this transformation, we next examined the reaction of alkylidenecyclopropa[*b*]naphtha-

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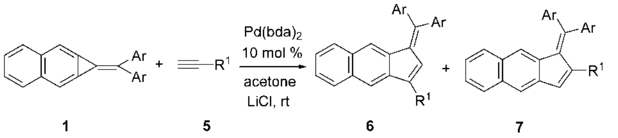
lenes **1** with alkynes **5**. The results are summarized in Table 4. We found alkynes with electron-deficient groups such as ethyl propiolate **5a**, 1-(4-fluorophenyl)prop-2-yn-1-one **5b**, and 1-(4-methylphenyl)-prop-2-yn-1-one **5c**, which were also effective for this reaction, and the corresponding 1-alkylidene-1*H*-benzo[*f*]indenes **6** were obtained in moderate yields with excellent regioselectivity of the acetylene bond (entries 1−5, Table 4). When general alkynes were applied, the reactions proceeded smoothly to give the corresponding products with good regioselectivity (entries 6−10, Table 4) (Figure 1, **6h**). The reactions seem to give much more competitive yields when alkyl-substituted alkynes were used (entries 7−10, Table 4).

Table 4. Pd(dba)$_2$-Catalyzed [3 + 2] Cycloaddition Reaction of **1** with Alkynes **5**[a]

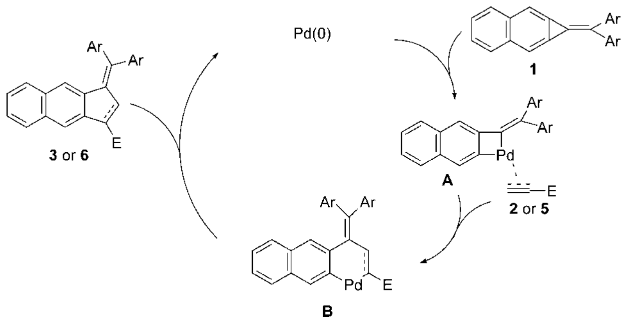


entry	Ar	R^1	product	time	yield (%)[a]
1	**1a**	COOEt, **5a**	**6a**	6 day	46
2	**1b**	**5a**	**6b**	5 day	47
3	**1a**	4-FC$_6$H$_4$CO, **5b**	**6c**	2 day	71
4	**1a**	4-CH$_3$C$_6$H$_4$CO, **5c**	**6d**	3 day	68
5	**1c**	**5c**	**6e**	5 day	52
6	**1a**	C$_6$H$_5$, **5d**	**6f**	13 h	54
7	**1a**	C$_3$H$_5$, **5e**	**6g/7g**	2 h	80 (89:11)[b]
8	**1a**	*n*-C$_4$H$_9$, **5f**	**6h/7h**	1 h	93 (91:9)[b]
9	**1c**	**5f**	**6i/7i**	1 h	88 (90:10)[b]
10	4-MeOC$_6$H$_4$, **1e**	**5f**	**6j/7j**	2 h	84 (86:14)[b]

[a] Isolated yield based on **1**. [b] The ratio was determined by ^{1}H NMR analysis.

On the basis of the above results, previous investigation on Pd-catalyzed [3 + 2] cycloaddition reaction of methylenecyclopropanes[4,11] and the NMR and X-ray single crystal diffractional analysis on the organometallic complexes of alkylidenecyclopropa[*b*]naphthalenes with stoichiometric rhodium(I) and platinum(0) reagents,[7] a possible mechanism for the reaction of alkylidenecyclopropa[*b*]naphthalenes **1** with alkenes or alkynes catalyzed by Pd(dba)$_2$, are shown in Scheme 2. First, oxidative addition of palladium(0) to a highly strained three-membered-ring σ-bond of the alkylidenecyclopropa[*b*]naphthalenes **1** leads to the palladacyclobutene complex **A**. Subsequently, the regioselective insertion reaction of **A** with alkenes **2** or alkynes **5** at the less sterically hindered side gives the palladacyclohexene complex **B**. Then, reductive elimination of palladium(0) gives the [3 + 2] cycloadduct **3** or **6**.

Scheme 2. Proposed Mechanism



In summary, we have disclosed a highly regioselective Pd-catalyzed [3 + 2] cycloaddition reaction of alkylidenecyclopropa[*b*]naphthalenes **1** with alkenes or alkynes, giving the corresponding 1(3)-alkylidene-2,3-dihydro-1*H*-benzo[*f*]indenes or 1-alkylidene-1*H*-benzo[*f*]indenes in moderate to good yields under mild conditions. Further studies into the scope, mechanism, and synthetic applications of this transformation are being carried out in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data of all new compounds (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) At present, the role for the LiCl additive is not clear. We think this may have some salt effect or act as the ligand in the reaction. For selected papers of the LiCl additive, please see: (a) Ma, S.; Zhang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 184. (b) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645. (c) Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 82. (d) Wang, Z.; Zhang, Z.; Lu, X. *Organometallics* **2000**, *19*, 775. (e) Zhang, Z.; Lu, X.; Xu, Z.; Zhang, Q.; Han, X. *Organometallics* **2001**, *20*, 3724.

(10) X-ray crystal data for compound **3i**: $C_{30}H_{28}$; MW = 388.52; Monoclinic, space group $P2(1)/c$; $a = 11.8669(13)$, $b = 9.9929(11)$, $c = 19.656(2)$ Å; $\alpha = 90$, $\beta = 101.360(2)$, $\mu = 90$, $V = 2285.2(4)$ Å^3, $T = 293$ (2) K, $Z = 4$, $\rho_{calcd} = 1.129$ Mg/m^3, $\mu = 0.063$ mm^{-1}, $\mu = 0.71073$ Å; F(000) 832, independent reflections ($R_{int} = 0.0500$), 12 207 reflections collected; refinement method, full-matrix least-squares refinement on F2; goodness-of-fit on F2 = 0.919; final R indices [$I > 2\sigma(I)$] $R1 = 0.0577$, $wR2 = 0.1361$.

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