## Highly efficient [2 + 2] intramolecular cyclizations of allenynes under microwave irradiation: construction of fused bicyclic compounds<sup>†</sup>

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A palladium [2 + 2] cycloaddition of 1,6- and 1,7- allenyne carboxylates and microwave-mediated [2 + 2] cycloaddition of various 1,*n*-allenynes were developed and, particularly, the microwave irradiated [2 + 2] cycloaddition of allenynes can provide a simple, general and eco-friendly synthetic method to fused bicyclo[*m*,2,0]alkadienes.

Bicyclic compounds fused with a cyclobutene ring have gained much interest in recent years, because of their importance in theoretical and photochemical studies.<sup>1</sup> These compounds have been mostly prepared from intramolecular [2 + 2] cycloaddition of 1,*n*-envnes by photo-irradiation. Since such fused compounds are prone to facile thermal isomerizations to the corresponding acyclic compounds, few synthetic studies have been reported before Trost reported the formation of fused bicyclo[3,2,0]heptenes from the Pd-catalyzed cyclization of 1,6-enynes.<sup>2</sup> Since then, there were a few reports dealing with intramolecular metal-mediated [2 + 2]cycloadditions,<sup>3</sup> none of which involved direct cycloadditions of allenynes in synthetic points. Allenynes have witnessed tremendous developments on their use for diverse synthetic applications as well as for precursors for searching new reactions of unsaturated systems.<sup>4</sup> We envisioned that a [2 + 2] cycloaddition of 1,n-allenynes could provide an easy access to bicyclo[m,2,0]alkadienes as shown in Fig. 1.

Recently, 1,*n*-allenynes have been shown to exhibit two different mechanistic pathways depending on the amount of Mo(CO)<sub>6</sub> used. When using a stoichiometric amount of Mo(CO)<sub>6</sub>, 1,7-allenynes underwent Pauson–Khand reactions.<sup>5</sup> However, Hammond reported that a catalytic amount of Mo(CO)<sub>6</sub> could catalyze the [2 + 2] cycloaddition of 1,7-allenynes to bicyclo[3,2,0]octadienes *via* metallocyclopentene intermediates (eqn (1)).<sup>6</sup> Hammond postulated that the electron-withdrawing *gem*-difluoro substituent of allenynes would be expected to favor reductive elimination of the molybdenum metallocycle rather than a CO insertion.



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We have demonstrated that 1,7-allenynes have three different cyclization modes with different palladium catalysts. Cycloreduction occurred at the triple bond to give alkenyl-palladium species that underwent carbopalladation to give sixmembered cycles.<sup>7</sup> Arylative cyclization occurred at the allene functionality to form a  $\pi$ -allylpalladium intermediate which underwent carbocyclization to give the corresponding fivemembered rings. In continuing our research on allenyne cyclization, we describe a highly economical as well as environmentally benign microwave-irradiated [2 + 2] cycloaddition in comparison with Pd-catalyzed [2 + 2] cycloaddition of 1,*n*-allenynes.<sup>8</sup>

Microwaves have become a new energy source that is powerful enough to complete reactions in minutes rather than hours or even days.<sup>9</sup> This may be because of the so-called "microwave effect" generated within the medium.<sup>10</sup> In fact, there are many reports concerning improvement of stereo-, regio- or chemoselectivity and of chemical efficacy when microwaves were used instead of conventional heating. However, allenyne reactions in the absence of metal catalysts have not been reported in the literature. Upon optimization of the [2 + 2] cycloaddition of a model substrate **1a**, we found that the use of a catalytic amount of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> in toluene, or microwave irradiation afforded the corresponding fused bicycle **2a** in good to excellent yields (eqn (2) and Table 1).

At first, using Hammond's conditions on 1a resulted in decomposition at 110 °C, but gave the [2 + 2]-cyclization product in 40% yield at 85 °C (entry 1). This [2 + 2] cycloaddition was generally catalyzed by various transition metal catalysts such as Ni(PPh<sub>3</sub>)<sub>4</sub>, RuPhCl<sub>2</sub> dimer, RhCl(PPh<sub>3</sub>)<sub>3</sub> or PtCl<sub>2</sub> in varying yields (entries 2-5). Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd(OAc)<sub>2</sub>, or π-allylpalladium chloride dimer, however, resulted in decomposition of allenyne 1a (entries 6-8). In a sharp contrast, PdCl<sub>2</sub>, Pd(dppe)Cl<sub>2</sub> and  $Pd(PPh_3)_2Cl_2$  catalyzed this [2 + 2]-cycloaddition smoothly to give 2a in 47, 61 and 76% yields, respectively (entries 9-11). Being gratified by the good catalyst in hand, we then surveyed reaction solvents such as dichloroethane, THF, p-dioxane, acetonitrile and DMF (entries 12-16). The optimal conditions for this reaction were found to be a use of a mixture of  $Pd(PPh_3)_2Cl_2$  (5 mol%) in refluxing toluene, where the allenyne 1a underwent smooth [2 + 2]cycloaddition to give 2a in 76% yield without forming any other side products (entry 11). To our surprise, this allenyne 1a thermally underwent [2 + 2]-cyclization to give the product in 64% yield after a prolonged heating for 20 h (entry 17). In view of

 Table 1
 [2 + 2] cycloaddition of allenyne 1a

	p-Ts_N_CO2E	t conditions p-Ts.		⊃₂Et
	1a		2a	
No	Catalysts (mol%) or conditions	Solvent	$T(^{\circ}\mathrm{C})/t(\mathrm{h})$	Yield (%)
1	Mo(CO) <sub>6</sub> (5)	DMSO-toluene	85/7	40
2	$Ni(PPh_3)_4(5)$	Toluene	110/5	50
3	$(RuPhCl_2)_2$ (5)	Toluene	110/5	60
4	$RhCl(PPh_3)_3$ (5)	Toluene	110/6	85
5	$PtCl_2(5)$	Toluene	110/4	31
6	$Pd(PPh_3)_4$ (5)	Toluene	50/2	Decomp.
7	$Pd(OAc)_2$ (5)	Toluene	50/2	Decomp.
8	$(\pi-allyl)PdCl/PPh_3$ (5)	Toluene	110/6	Decomp.
9	PdCl <sub>2</sub> (10)	Toluene	110/6	47
10	$Pd(dppe)Cl_2(5)$	Toluene	110/7	61
11	$Pd(PPh_3)_2Cl_2$ (5)	Toluene	110/6	76
12	$Pd(PPh_3)_2Cl_2$ (5)	EDC	80/16	Trace
13	$Pd(PPh_3)_2Cl_2$ (5)	THF	85/5	20
14	$Pd(PPh_3)_2Cl_2$ (5)	p-Dioxane	110/5	60
15	$Pd(PPh_3)_2Cl_2$ (5)	CH <sub>3</sub> CN	85/5	28
16	$Pd(PPh_3)_2Cl_2$ (5)	DMF	110/5	23
17	No catalyst	Toluene	110/20	64
18	Microwave	Neat	110/0.15	55
19	Microwave	Toluene	110/0.15	89

environmental factors, we turned to microwave irradiation by anticipating a more rapid reaction completion. We performed a set of the reactions neat as well as in toluene (entries 18 and 19). Under both conditions, the reactions were completed within only 10 min to give 2a as the sole product. The microwave reaction in toluene was the most efficient in terms of chemical yield.<sup>11</sup>

Next, we attempted to measure the scope of this microwave protocol, using various 1,*n*-allenynes **1b**-j comparing with the Pdcatalyzed cyclization conditions in entry 12 in Table 2. Our [2 + 2]cycloaddition results are summarized in Table 2. Several features are to be noted. Overall, the microwave protocol turned out to be superior to the Pd-catalyzed method in terms of reaction efficiency. Pd-catalyzed [2 + 2] cycloadditions worked well for 1,7-allenyne carboxylates 1b-f and 1,6-allenyne carboxylates 1g-h to give bicyclo[4,2,0]octadienes 2b-f and bicyclo[3,2,0]heptadienes 2g-h, respectively. Phenyl-substituted allenyne 1h and 1,8-allenyne carboxylate 1i-j, however, did not undergo these cycloadditions under the given conditions. Second, all allenynes 1b-j were successfully cyclized under microwave irradiation to give the corresponding bicyclo[m,2,0]alkadienes **2b-j** (Table 2).<sup>12</sup> Even phenyl-substituted allenyne 1h was cyclized albeit over a little longer time (20 min) to give the product 2h in 75% isolated yield. Third, cycloaddition of 1,8-allenyne carboxylates 1i-j under various conditions with or without metal catalysts did not occur, but turned out to be successful by using microwave irradiation for 45 min to afford the bicyclo[5,2,0]nonadiene derivatives 2i-j in 79 and 78% yields, respectively. Finally, it is worthwhile to note that all these fused bicyclic products obtained from this study were stable during silica gel chromatography and a prolonged storage at room temperature.

The stability of these fused compounds can be understood by noting that thermal conrotatory electrocyclic reactions are inhibited due to the fused ring contribution (eqn (4)). Table 2 Intramolecular  $\left[2+2\right]\text{-cycloaddition of all$ enynes under conditions A and B

R .	Cond. A or Cond. B	R		
1b-j (allenynes)		2b-j		
Conditions <sup>a</sup>				

yield (%) 89 75 95
89 75 95
75 95
95
82
01
71
/0
93
81
94
91
97
87
75
61
79
NR
78
NR

<sup>*a*</sup> Conditions: A: toluene solution under microwave irradiation, B: 5 mol% PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> catalyst in toluene.

$$\begin{array}{c} & & \\ & &$$

Mechanistically, we believed that Pd(II) first forms a  $\pi$ -complex with both a triple bond and a double bond of substrate 1. Such  $\pi$ -complexes are known to undergo migratory C–C coupling to give palladacyclopentene **A**. Reductive elimination of intermediate **A** could produce the product 2 and regenerate Pd(II) for the next cycle (Scheme 1). The mechanism of the microwave-irradiated cycloadditions, however, is unclear. One possible explanation is that the microwave heating of the substrates might break one unsaturated bond to form a transient diradical such as **B** that could undergo rapid cyclization to give the product 2.

In conclusion, we have shown a Pd-catalyzed [2 + 2] cycloaddition of 1,6- and 1,7-allenyne carboxylates and also a



Scheme 1

very simple and eco-friendly microwave-mediated [2 + 2] cycloaddition of various 1,*n*-allenynes. Particularly, the microwave-irradiated [2 + 2] cycloaddition of allenyns can provide a general synthetic method to fused bicyclo[*m*,2,0]alkadienes from the corresponding allenynes. We are currently seeking the application of this methodology to the library generation of fused bicyclic ring systems for the construction of natural as well as pharmaceutical products.

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