A highly efficient cycloaddition of vinylarenes with electron-deficient alkynes affording 1,2-disubstituted-3,4-dihydronaphthalenes catalysed by *N*,*N*-dimethylformamide dimethyl acetal†

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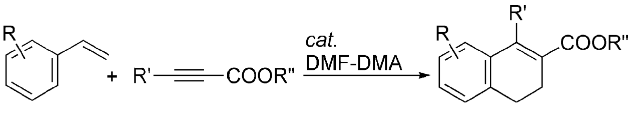
1,2-Disubstituted-3,4-dihydronaphthalenes could be conveniently synthesized with high yields by the cycloaddition reactions of easily available vinylarenes with electron-deficient alkynes such as dimethyl, or diethyl acetylenedicarboxylate, methyl phenylpropiolate in the presence of DMF·DMA (*N*,*N*-dimethylformamide dimethyl acetal) as organocatalyst.

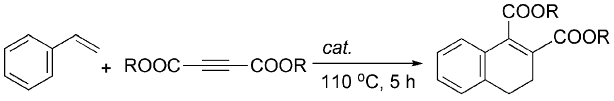
The catalytic cycloaddition reaction is one of the most important and efficient synthetic protocols for the one-step construction of cyclic compounds.[1] In recent years, organocatalysis reactions employing metal-free organic molecules as catalysts have received unprecedented attention.[2] Remarkable advantages of organocatalytic reactions are that the catalytic reactions can be carried out under air and the catalysts are usually inexpensive and stable. In our attempts to develop an efficient organocatalyst system for the addition reaction of alkynes to alkenes, we have found that in the presence of *N*,*N*-dimethylformamide dimethyl acetal (DMF·DMA), the addition reaction of vinylarenes with electron-deficient alkynes proceeded smoothly to give the adducts of 1,2-disubstituted 3,4-dihydronaphthalenes (Scheme 1). It is well known that some functionalized dihydronaphthalenes not only exhibit physiological and biological activities, but they are also valuable intermediates for the synthesis of numerous biologically natural products and pharmaceuticals. Therefore, the design and development of efficient synthesis methods are an attractive and interesting research topic in synthetic chemistry.[3] In this communication, we wish to report the results of the cycloaddition reaction of vinylarenes with electron-deficient alkynes catalyzed by DMF·DMA. To the best of our knowledge, this is the first example of an efficient synthesis of functionalized dihydronaphthalenes from the one-step catalytic cycloaddition of easily available vinylarenes and alkynes.[4]



Scheme 1

When a mixture of styrene **1a** (1.0 mmol), an equimolar amount of diethyl acetylenedicarboxylate **2a** and DMF·DMA (0.2 mmol) in toluene (1.0 mL) under air was heated at 110 °C for 5 h, GC and GC-MS analyses of the resulting reaction mixture revealed the formation of an adduct **3aa** from the intermolecular addition of **1a** with **2a**. **3aa** could be isolated in 9% yield, and its structure was characterized as diethyl 3,4-dihydro-1,2-naphthalate by its spectral data (Table 1, entry 1).†

Table 1 Reaction of styrene with acetylenedicarboxylate[a]



1a R = C_2H_5, **2a**; CH_3, **2b** **3**

Entry	Alkyne	Catalyst	**1a**–**2** (in molar)		Yield (%)[b]
1[c]	**2a**	$(CH_3)_2NCH(OCH_3)_2$ [d]	1 : 1	**3aa**	(9)
2[c]	**2a**	$(CH_3)_2NCH(OCH_3)_2$	2 : 1	**3aa**	40
3[c]	**2a**	$(CH_3)_2NCH(OCH_3)_2$	4.3 (0.5 mL) : 1	**3aa**	62
4	**2a**	$(CH_3)_2NCH(OCH_3)_2$	8.6 (1 mL) : 1	**3aa**	93 (82)
5	**2b**	$(CH_3)_2NCH(OCH_2CH_2O)$ [e]	8.6 (1 mL) : 1	**3ab**	95 (87)
6	**2a**	DMF	8.6 (1 mL) : 1	**3aa**	16

[a] Reactions were carried out using 1.0 mmol of **2**, 0.2 mmol of catalyst at 110 °C for 5 h. [b] Yield according to GC based on the amount of alkyne used. Numbers in parentheses are isolated yields. [c] Toluene (1.0 mL) was used as solvent. [d] *N*,*N*-Dimethylformamide dimethyl acetal (DMF-DMA). [e] *N*,*N*-Dimethylformamide ethylene acetal.

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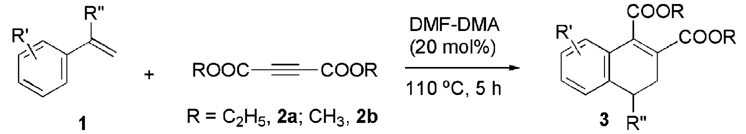
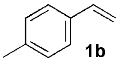
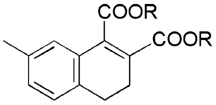
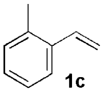
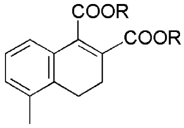
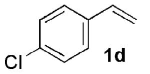
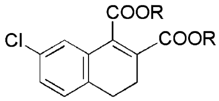
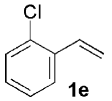
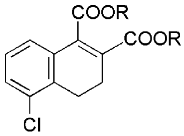
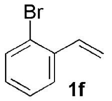
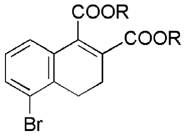
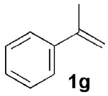
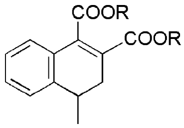
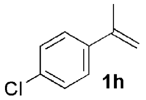
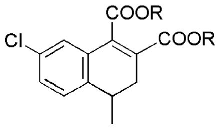
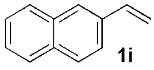
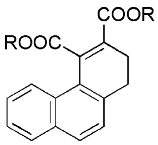
† Electronic supplementary information (ESI) available: Experimental general method, characterization data of product **3**, and copies of ^1H NMR and ^{13}C NMR spectra for **3**. See DOI: 10.1039/b706768b

Table 2 DMF-DMA-catalysed cyclic addition of vinylarenes with acetylenedicarboxylate[a]



Entry	Styrene **1**	Adduct **3**			Yield (%)[b]
1	 **1b**		$R = C_2H_5$	**3ba**	77 (89)
2	 **1c**		$R = C_2H_5$	**3ca**	78 (85)
3	 **1d**		$R = C_2H_5$	**3da**	86 (91)
4	 **1e**		$R = C_2H_5$	**3ea**	85 (89)
5[c]	 **1f**		$R = C_2H_5$	**3fa**	36 (42)
6	 **1g**		$R = C_2H_5$ $R = CH_3$	**3ga** **3gb**	82 (90) 85 (92)
7	 **1h**		$R = C_2H_5$	**3ha**	63 (84)
8	 **1i**		$R = C_2H_5$	**3ia**	83 (86)

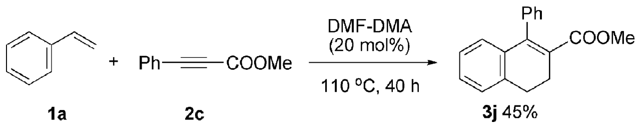
[a] Reactions were carried out using 1.0 mmol of **2** and 0.2 mmol of catalyst in 1.0 mL of 1 at 110 °C for 5 h. [b] Isolated yield (GC yield) based on the amount of **2** used. [c] Reaction was carried out using 1.0 mmol of **1f**, 1.0 mmol of **2a** in toluene (1.0 mL) at 110 °C for 6 h.

To optimize this organocatalyst-catalysed cycloaddition reaction, the influence of reaction conditions on the yield of **3aa** has been examined. As shown in Table 1, the yield of **3aa** depends strongly on the catalysts and the ratio of **1a** and **2a** employed. In toluene, an excess amount of **1a** could accelerate this cycloaddition reaction; the yield of **3aa** was increased with an increase in the ratio of **1a**–**2a** (Table 1, entries 2–3). A satisfactory yield of **3aa** (93% GC yield) could be achieved when a large excess amount of **1a** (8.6 equivalents) was used (Table 1, entry 4). Under conditions identical to those of entry 4, instead of DMF·DMA, *N*,*N*-dimethylformamide ethylene acetal also displayed high catalytic activity to afford **3aa** in high yield (Table 1, entry 5). When DMF was used, the yield of **3aa** was only 16% (Table 1, entry 6). Again, if the DMF-catalyzed reaction was performed in toluene, **3aa** was formed in a small amount (<5%). In addition, it should be noted that when trialkylamines such as Et_3N and Bu_3N were used as catalysts, or in the absence of catalyst, the formation of **3aa** was not detectable by GC.

To examine the generality of the present cycloaddition system, under the optimized reaction conditions (as indicated in entry 4 of Table 1), the cycloaddition reactions of various vinylarenes with **2a** or dimethyl acetylenedicarboxylate (**2b**) were examined, and the results are summarized in Table 2. The electronic nature of vinylarenes does not seem to affect the reactivity; vinylarenes bearing either electron-donating or electron-withdrawing groups in the *para* or *ortho* position of the phenyl ring underwent the cycloaddition reaction smoothly to generate the corresponding adducts in good yields (entries 1–4). When using an equivalent of **1f** and **2a** in toluene, the corresponding desired product **3fa** was isolated in a moderate yield (entry 5). Furthermore, α-methyl substituted vinylarenes, such as α-methylstyrene (**1g**) and 4-chloro-α-methylstyrene (**1h**) also underwent the cycloaddition reaction smoothly to give the expected products in good yields (entries 6–7).

In addition, the present catalyst system could be applied to the synthesis of substituted dihydrophenanthrene. For example, the reaction of 2-vinylnaphthalene (**1i**) with **2a** took place to generate 1,2-diethoxycarbonyl-3,4-dihydrophenanthrene (**3ia**) in high yield (entry 8).

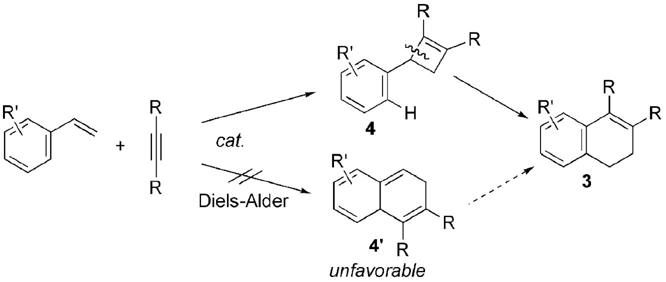
On the other hand, under the same reaction conditions, the reaction of another electron-deficient alkyne, methyl phenylpropiolate (**2c**) with styrene was very sluggish. At 110 °C for 40 h, the cycloadduct **3j** was isolated in only moderate yield (Scheme 2). In this case, it should be noted that the reaction proceeded with complete regioselectivity, and only **3j** was determined in the reaction mixture by GC and GC-MS.



Scheme 2

The mechanism for the present DMF·DMA-catalysed cycloaddition of vinylarenes with acetylenedicarboxylate is not clear; the promoting role of DMF·DMA in this reaction is not understood at this time. Concerted formation of cyclobutene **4** as the intermediate is the simplest hypothesis (Scheme 3). The formation of **4** by [2 + 2] cycloaddition of alkenes with electron-deficient alkynes without a catalyst,[5] or with the use of transition metal complexes as catalysts, has been reported.[6] The unstable **4** is proposed to selectively rearrange to afford the more stable six-membered ring of **3**, forming the product *via* a ring-extending reaction, similar to the thermal rearrangements of 4-arylcyclobutenones.[7]

The other possible pathway for the present reaction is the DMF·DMA-catalyzed Diels–Alder cycloaddition of vinylarene with acetylenedicarboxylate to furnish intermediate **4′**, which undergoes aromatization by hydrogen shift to give **3**. However, to the best of our knowledge, *there is no successful Diels–Alder reaction in which vinylarene acts as a diene, therefore the formation of **3*** via *the Diels–Alder reaction pathway seems to be very unfavourable*.



Scheme 3 Proposed mechanism for cycloaddition reaction.

In summary, vinylarenes and electron-deficient alkynes undergo cycloaddition reactions in the presence of DMF·DMA to afford 1,2-disubstituted 3,4-dihydronaphthalenes in good to excellent yields. The presented procedure is novel because (1) it has provided an attractive and economic strategy for synthesizing the functionalized dihydronaphthalenes, (2) it presents a new organocatalyzed cyclization. This method exhibits the advantages of substrate versatility and mild reaction conditions. Further study for the generalization of this type of cycloaddition reaction is underway in our laboratory.

Acknowledgements

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Notes and references

1 For examples of reviews, see: (*a*) M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, **96**, 49–92; (*b*) K. V. Gothelf and K. A. Jorgensen, *Chem. Rev.*, 1998, **98**, 863–910; (*c*) K. M. Brummond and J. L. Kent, *Tetrahedron*, 2000, **56**, 3263–3283; (*d*) R. E. Sammelson and M. J. Kurth, *Chem. Rev.*, 2001, **101**, 137–202; (*e*) M. Harmata, *Acc. Chem. Res.*, 2001, **34**, 595–605; (*f*) J. A. Varela and C. Saa, *Chem. Rev.*, 2003, **103**, 3787–3802; (*g*) M. Harmata and P. Rashatasakhon, *Tetrahedron*, 2003, **59**, 2371–2395; (*h*) I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765–2810.

2 For examples of recent reviews, see: (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2001, **40**, 3726–3748; (*b*) M. Benaglia, A. Puglisi and F. Cozzi, *Chem. Rev.*, 2003, **103**, 3401–3429; (*c*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138–5175; (*d*) Y. Shi, *Acc. Chem. Res.*, 2004, **37**, 488–496; (*e*) M. J. O'Donnell, *Acc. Chem. Res.*, 2004, **37**, 506–517; (*f*) T. Ooi and K. Maruoka, *Acc. Chem. Res.*, 2004, **37**, 526–533; (*g*) D. Enders and T. Balensiefer, *Acc. Chem. Res.*, 2004, **37**, 534–541; (*h*) W. Notz, F. Tanaka and C. F. Barbas, III, *Acc. Chem. Res.*, 2004, **37**, 580–591; (*i*) J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719–724; (*j*) G. Guillena and D. J. Ramon, *Tetrahedron: Asymmetry*, 2006, **17**, 1465–1492; (*k*) T. Akiyama, J. Itoh and K. Fuchibe, *Adv. Synth. Catal.*, 2006, **348**, 999–1010.

3 The traditional method for synthesis of dihydronaphthalene derivatives is the dearomatization of naphthalene derivatives by the nucleophilic addition of organometallic reagents mediated by transition metal complexes. For a review, see: (*a*) A. R. Pape, K. P. Kaliappan and E. P. Kundig, *Chem. Rev.*, 2000, **100**, 2917–2940; (*b*) For examples of recent reports on the synthesis of dihydronaphthalene derivatives, see: T. Hamura, M. Miyamoto, K. Imura, T. Matsumoto and K. Suzuki, *Org. Lett.*, 2002, **4**, 1675–1678; (*c*) H. Inoue, N. Chatani and S. Murai, *J. Org. Chem.*, 2002, **67**, 1414; (*d*) D. C. Harrowven and M. J. Tyte, *Tetrahedron Lett.*, 2002, **43**, 5971–5972; (*e*) N. Asao, T. Kasahara and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2003, **42**, 3504–3506; (*f*) S. GowriSankar, C. G. Lee and J. N. Kim, *Tetrahedron Lett.*, 2004, **45**, 6949–6953; (*g*) D. Sil and V. J. Ram, *Tetrahedron Lett.*, 2005, **46**, 5013–5015.

4 The reaction of α-alkoxy-substituted styrenes with dimethyl acetylenedicarboxylate to produce a mixture of the 1 : 1 Diels–Alder adducts (substituted 1,2-naphthalenedicarboxylates) and the 1 : 2 Diels–Alder ene adducts has been reported, see: H. Kotsuki, T. Yamaguchi, K. Ohno, Y. Ichikawa and M. Ochi, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 599–602.

5 (*a*) T. Takao, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 3871–3876; (*b*) G. M. Liliana, L. M. Rosaria and C. Flavio, *Synthesis*, 1994, 149–151.

6 For examples of the transition metal-catalyzed [2 + 2] cycloaddition of alkenes to alkynes, see: (*a*) C. S. Yi, D. W. Lee and Y. Chen, *Organometallics*, 1999, **18**, 2043–2045; (*b*) D.-J. Huang, D. K. Rayabarapu, L.-P. Li, T. Sambaiah and C.-H. Cheng, *Chem.–Eur. J.*, 2000, **6**, 3706–3713; (*c*) R. W. Jordan, K. Villeneuve and W. Tam, *J. Org. Chem.*, 2006, **71**, 5830–5833 and references therein.

7 R. Tiedemann, P. Turnbull and H. W. Moore, *J. Org. Chem.*, 1999, **64**, 4030–4041.