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Lewis Acid Catalyzed Reaction of Arylvinylidenecyclopropanes with Ethyl (Arylimino)acetates: A Facile Synthetic Protocol for Pyrrolidine and 1,2,3,4-Tetrahydroquinoline Derivatives

Jian-Mei Lu and Min Shi*

State Key Laboratory of Organometallic Chenistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai, China 200032

mshi@mail.sioc.ac.cn

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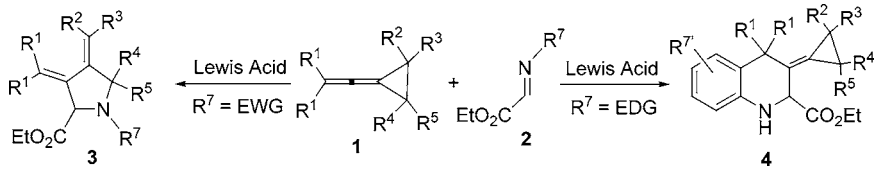
ABSTRACT



A number of pyrrolidine and 1,2,3,4-tetrahydroquinoline derivatives are prepared selectively in moderate to good yields by the reaction of arylvinylidenecyclopropanes 1 with ethyl (arylimino)acetates 2 in the presence of Lewis acid depending on the electronic nature both of 2 and R^1 or R^2 aromatic groups of 1.

Thermal and photochemical skeleton rearrangements of highly strained small rings with multiple bonds and functional groups have attracted much attention from both synthetic and mechanistic viewpoints. At the core of these developments resides the multifaceted reactivity of vinylidenecyclopropanes, for which a wide variety of transformations has been discovered.[1,2] For example, they can easily react with carbon−carbon or carbon−heteroatom multiple bonds to produce [3 + 2] or [2 + 2] cycloaddition products in good yields upon heating or photoirradiation.[3] Recently, we reported the Lewis acid catalyzed reaction of arylvinylidenecyclopropanes with acetals to produce indene derivatives in good yields.[4] Herein, we present a new synthetic protocol for the preparation of pyrrolidine and 1,2,3,4-tetrahydroquinoline derivatives by Lewis acid catalyzed reaction of arylvinylidenecyclopropanes **1** with ethyl (arylimino)acetates **2** where the product is determined by the electronic nature of **2** and the R^1 or R^2 aromatic groups of **1**.

Initial studies were aimed at determining the optimal reaction conditions for the Lewis acid catalyzed reactions. Using diphenylvinylidenecyclopropane **1a** as the substrate, we examined its reaction with ethyl (arylimino)acetate **2a** in the presence of a variety of Lewis acids. The results are summarized in Table 1. Using BF_3•OEt_2 (10 mol %) as the catalyst in 1,2-dichloroethane (DCE) at 60 °C, a [3 + 2] cycloaddition product **3a** was formed in 84% yield (Table

(1) (a) Poutsma, M. L.; Ibarbia, P. A. *J. Am. Chem. Soc.* **1971**, *93*, 440−450. (b) Smadja, W. *Chem. Rev.* **1983**, *83*, 263−320. (c) Hendrick, M. E.; Hardie, J. A.; Jones, M., Jr. *J. Org. Chem.* **1971**, *36*, 3061−3062. (d) Sugita, H.; Mizuno, K.; Saito, T.; Isagawa, K.; Otsuji, Y. *Tetrahedron Lett.* **1992**, *33*, 2539−2542. (e) Mizuno, K.; Sugita, H.; Kamada, T.; Otsuji, Y. *Chem. Lett.* **1994**, 449−452 and references therein. (f) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133−1150.

(2) For synthesis of vinylidenecyclopropanes, see: (a) Isagawa, K.; Mizuno, K.; Sugita, H.; Otsuji, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2283−2285 and references therein. (b) Al-Dulayymi, J. R.; Baird, M. S. *J. Chem. Soc., Perkin Trans 1* **1994**, 1547−1548. Other papers related to vinylidenecyclopropanes: (c) Maeda, H.; Hirai, T.; Sugimoto, A.; Mizuno, K. *J. Org. Chem.* **2003**, *68*, 7700−7706. (d) Pasto, D. J.; Brophy, J. E. *J. Org. Chem.* **1991**, *56*, 4554−4556.

(3) (a) Mizuno, K.; Sugita, H.; Hirai, T.; Maeda, H.; Otsuji, Y.; Yasuda, M.; Hashiguchi, M.; Shima, K. *Tetrahedron Lett.* **2001**, *42*, 3363−3366. (b) Mizuno, K.; Nire, K.; Sugita, H.; Otsuji, Y. *Tetrahedron Lett.* **1993**, *34*, 6563−6566. (c) Sasaki, T.; Eguchi, S.; Ogawa, T. *J. Am. Chem. Soc.* **1975**, *97*, 4413−4414.

(4) Lu, J.-M.; Shi, M. *Org. Lett.* **2006**, *8*, 5317−5320.

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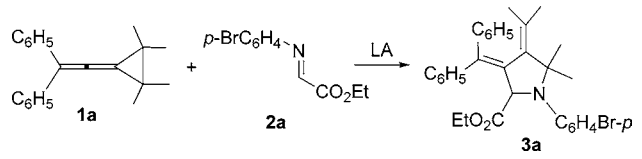
Table 1. Optimization of the Reaction Conditions of **1a** and **2a**

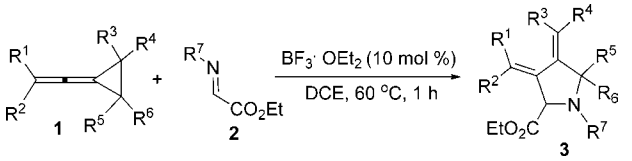


entry[a]	solvent	catalyst	T (°C)	time (h)	yield[b] (%)
1	DCE	$Sc(OTf)_3$	60	1	81
2	DCE	$Yb(OTf)_3$	60	1	75
3	DCE	$SnOTf)_2$	60	1	72
4	DCE		60	12	N.R.
5	DCE	$Zr(OTf)_4$	60	1	76
6	DCE	$In(OTf)_3$	60	1	80
7	DCE	$BF_3{\cdot}OEt_2$	60	1	84
8	DCE	$La(OTf)_3$	60	1	82
9	DCE	TfOH	60	1	78
10	DCE	TMSOTf	60	1	81
11	DCE	$BF_3{\cdot}OEt_2$	rt	1.5	76
12	DCE	$BF_3{\cdot}OEt_2$	80	1	80
13	dioxane	$BF_3{\cdot}OEt_2$	60	19	37[c]
14	CH_3CN	$BF_3{\cdot}OEt_2$	60	1	81
15	Et_2O	$BF_3{\cdot}OEt_2$	35	22	35[d]
16	toluene	$BF_3{\cdot}OEt_2$	60	5	41
17	THF	BF_3-OEt_2	60	19	48[e]
18	EtOH	$BF_3{\cdot}OEt_2$	60	18	11[f]
19	hexane	$BF_3{\cdot}OEt_2$	60	18	54[g]

[a] All of the reactions were carried out using **1a** (0.2 mmol), **2a** (0.3 mmol), and catalyst (10 mol %) in various solvents (2.0 mL). [b] Isolated yield. [c] 31% of **1a** was recovered. [d] 29% of **1a** was recovered. [e] 7% of **1a** was recovered. [f] 64% of **1a** was recovered. [g] 9% of **1a** was recovered.

1, entry 7). The examination of various solvents revealed that DCE is optimal for the reaction (Table 1, entries 13−19).

Table 2. $BF_3{\cdot}OEt_2$-Catalyzed Reaction of Arylvinylidenecyclopropanes **1** with Ethyl (Arylimino)acetates **2**



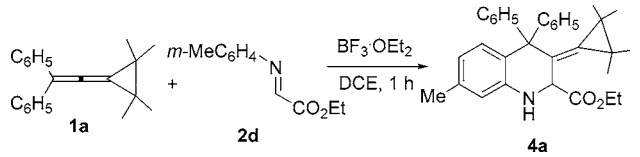
entry[a]	**1** (R^1/R^2)[b]	**2** (R^7)	yield[c] (%)
1	**1b** (p-ClC_6H_4/p-ClC_6H_4)	**2a**	**3b**, 85
2	**1c** (pFC6H4/p-FC_6H_4)	**2a**	**3c**, 79
3	**1d** (C_6H_5/p-ClC_6H_4)	**2a**	**3d** 86 (1:1)[d]
4	**1e** (C_6H_5/p-$CH_3OC_6H_4$)	**2a**	**3e**, 71 (2.6:1)[d]
5	**1f** (C_6H_5/C_6H_5)[e]	**2a**	**3f**, 89
6	**1a** (C_6H_5/C_6H_5)	**2b** (p-ClC_6H_4)	**3h**, 81
7	**1a**	**2c** (o-$CF_3C_6H_4$)	**3h**, 99
8	**1f**[e]	**2b**	**3i**, 82
9	**1g** (C_6H_5/C_6H_5)[f]	**2a**	**3j**, 88

[a] All reactions were carried out using **1** (0.2 mmol), **2** (0.3 mmol), and $BF_3{\cdot}OEt_2$ (10 mol %) in DCE (2.0 mL) at 60 °C. [b] Otherwise specified, $R^3 = R^4 = R^5 = R^6$ = Me. [c] Isolated yields. [d] Ratio of E/Z or Z/E. [e] $R^3 = R^4$ = phenyl, $R^5 = R^6$ = Me. [f] $R^3 = R^4$ = phenyl, $R^5 = R^6$ = H.

With the optimized reaction conditions in hand, we next examined an assortment of starting materials **1** and **2** in order to evaluate the scope of this new [3 + 2] cycloaddition reaction. The results are summarized in Table 2. As can be seen from Table 2, the corresponding pyrrolidine derivatives **3** were obtained in good to high yields within 1 h. For unsymmetrical arylvinylidenecyclopropanes **1d** and **1e**, the corresponding [3 + 2] cycloaddition products **3d** and **3e** were obtained as E/Z mixtures in 86% and 71% yields, respectively (Table 2, entries 3 and 4). Furthermore, similar results were obtained for other ethyl (arylimino)acetates **2b** and **2c** under identical conditions (Table 2, entries 7 and 8). In addition, using **1g** ($R^1 = R^2 = R^3 = R^4$ = phenyl, $R^5 = R^6$ = H) as the substrate, the corresponding [3 + 2] cycloaddition product **3j** was obtained in 88% yield (Table 2, entry 9).

Interestingly, when the reaction was carried out using **1a** with **2d** (in which R^7 was an electron-rich aromatic group) under the optimal reaction conditions, 1,2,3,4-tetrahydroquinoline derivative **4a** was formed in 44% yield, rather than the [3 + 2] cycloaddition product (Table 3, entry 1).[5] Further

Table 3. Optimization of the Reaction Conditions of **1a** and **2d**



entry[a]	$BF_3{\cdot}OEt_2$ (mol %)	T (°C)	yield[b] (%)
1	10	60	44[c]
2	30	60	54[d]
3	50	60	49
4	100	60	45
5	10	rt	49[e]
6	30	rt	58[f]
7	50	rt	61
8	50	0	71
9	50	−20	66[g]

[a] All reactions were carried out using **1a** (0.2 mmol) and **2d** (0.3 mmol) in DCE (2.0 mL). [b] Isolated yields. [c] 9% of **1a** was recovered. [d] 7% of **1a** was recovered. [e] 14% of **1a** was recovered. [f] 15% of **1a** was recovered.[g] The reaction was carried out for 1.5 h.

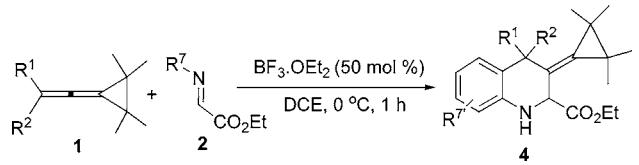
reaction condition screening efforts led to the observation that the best result was obtained using $BF_3{\cdot}OEt_2$ (50 mol %) as the catalyst in DCE at 0 °C to produce **4a** in 71% yield (Table 3, entry 8).

Next, we examined a variety of arylvinylidenecyclopropanes **1** with ethyl (arylimino)acetates **2** (in which R^7 is an electron-rich aromatic group) under these optimal reaction conditions.

The corresponding 1,2,3,4-tetrahydroquinoline derivatives **4** were obtained in moderate yields (Table 4). For unsym-

(5) Previously, Prato and Scorrano's group reported $BF_3{\cdot}OEt_2$-catalyzed cycloaddition reaction of aryliminoacetates and electron-rich olefins to give tetrahydroquinoline derivatives. See: Borrione, E.; Prato, M.; Scorrano, G.; Stivanello, M. *J. Heterocycl. Chem.* **1988**, *25*, 1831−1835.

Table 4. BF_3·OEt_2-Catalyzed Reaction of Arylvinylidenecyclopropanes **1** with Ethyl (Arylimino)acetates **2**



entry[a]	**1** (R^1/R^2)	**2** (R^7)	yield[b] (%)
1	**1b** (*p*-ClC_6H_4/*p*-ClC_6H_4)	**2d** (*m*-MeC_6H_4)	**4b**, 70
2	**1c** (*p*-FC_6H_4/*p*-FC_6H_4)	**2d**	**4c**, 70
3	**1d** (C_6H_5/*p*-ClC_6H_4)	**2d**	**4d**, 68 (1:1)[c]
4	**1h** (*p*-MeC_6H/*p*-MeC_6H_4)	**2d**	**4e**, 70
5	**1i** (*p*-$MeOC_6H_4$/*p*-$MeOC_6H_4$)	**2d**	**4f**, 66
6	**1a** (C_6H_5/C_6H_5)	**2e** (*p*-MeC_6H_4)	**4g**, 75
7	**1a**	**2f** (C_6H_5)	**4h**, 50

[a] All reactions were carried out using **1** (0.2 mmol), **2** (0.3 mmol), and BF_3·OEt_2 (50 mol %) in DCE (2.0 mL) at 0 °C. [b] Isolated yields. [c] Ratio of syn/anti or anti/syn.

metrical **1d**, product **4d** was obtained as a syn/anti mixture in 68% yield (Table 4, entry 3). Similar results were obtained for **2e** and **2f** under identical conditions (Table 4, entries 6 and 7). The structure of **4h** was determined by X-ray diffraction (Figure 1).[6]

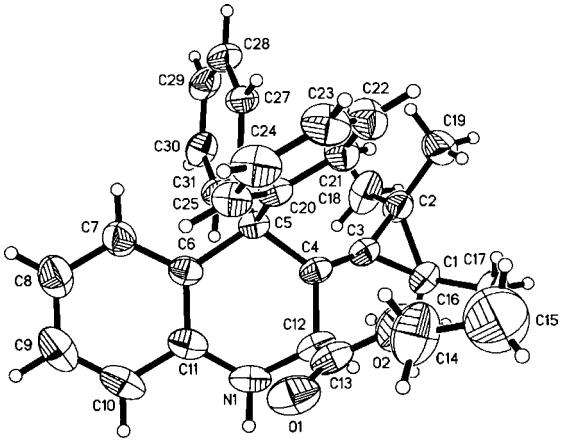
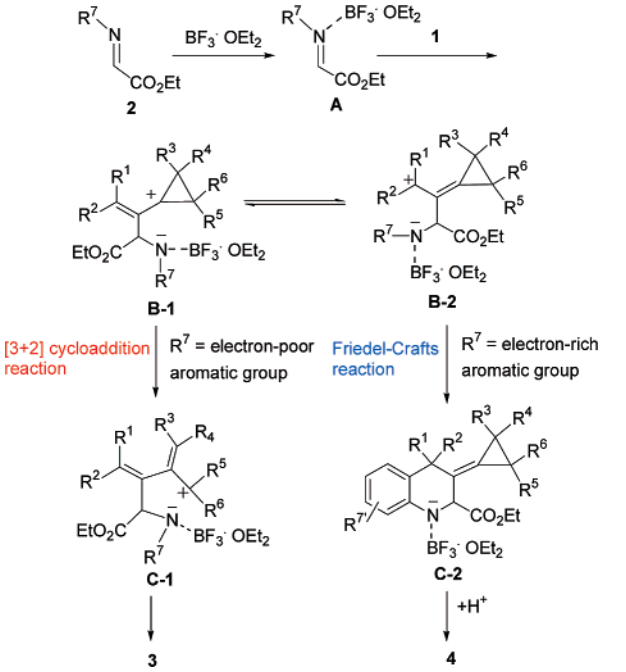


Figure 1. ORTEP drawing of **4h**.

Plausible mechanisms for the formation of pyrrolidines **3** and 1,2,3,4-tetrahydroquinolines **4** are outlined in Scheme 1. First, ethyl (arylimino)acetate **2** is activated by BF_3·OEt_2 to afford intermediate **A**, which is subsequently attacked by the central carbon of **1** to give the corresponding allylic carbocationic intermediates **B-1** and **B-2**.[7] Intermediate **C-1**, derived from **B-1** via a cyclopropyl ring-opening process, undergoes cyclization to give the corresponding [3 + 2] cycloaddition product **3** when R^7 is an electron-poor aromatic group. However, when R^7 is an electron-rich aromatic group, intramolecular Friedel−Crafts reaction takes place from intermediate **B-2** to give intermediate **C-2**,[8] which finally furnishes product **4**.[9]

Scheme 1. Proposed Mechanism for the Formation of **3** and **4**



Further investigation revealed that in the reaction of **1h** ($R^1 = R^2 = p$-MeC_6H_4, $R^3 = R^4 = R^5 = R^6 = Me$) with **2a** ($R^7 = p$-$BrC_6H_4$) in DCE at 60 °C, both [3 + 2] cycloaddition product **3k** and intramolecular Friedel−Crafts reaction product **4i** were obtained in 56% and 36% yields, respectively (Scheme 2). This is probably due to the fact that when R^1 and R^2 are both electron-rich aromatic groups, intermediate **B-2** is more stable, and thus, the intramolecular Friedel−Crafts reaction product can also be formed even when R^7 is an electron-poor aromatic group.

In conclusion, we have developed an effective Lewis acid-catalyzed synthesis of pyrrolidine and 1,2,3,4-tetrahydroquinoline derivatives by the reactions of arylvinylidenecyclopropanes **1** with ethyl (arylimino)acetates **2** under mild

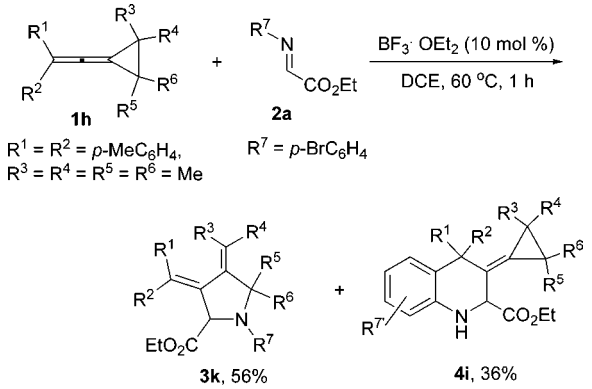
(6) The crystal data of **4h** have been deposited with the CCDC (no. 613268): empirical formula, $C_{31}H_{33}NO_2$; formula weight, 451.58; crystal color, habit, colorless, prismatic; crystal system, monoclinic; lattice type, primitive; lattice parameters, a = 10.881(5) Å, b = 9.452(4) Å, c = 25.882(12) Å, $\alpha = 90°$, $\beta = 97.981(8)°$, $\gamma = 90°$, V = 2636(2) $Å^3$; space group, $P2(1)/c$; $Z = 4$; D_{calc} = 1.138 g/cm^3; F_{000} = 968; diffractometer, Rigaku AFC7R; residuals, R; R_w, 0.0686, 0.1976.

(7) (a) Regas, D.; Afonso, M. M.; Rodriguez, M. L.; Palenzuela, J. A. *J. Org. Chem.* **2003**, *68*, 7845−7852. (b) Xu, B.; Shi, M. *Synlett* **2003**, 1639−1642. (c) Hayashi, Y.; Shibata, T.; Narasaka, K. *Chem. Lett.* **1990**, 1693−1696.

(8) (a) Fleming, I. *Chemtracts: Org. Chem.* **2001**, *14*, 405−406. (b) Chevrier, B.; Weis, R. *Angew. Chem.* **1974**, *86*, 12−21.

(9) Kobayashi has concluded that this type of aza-Diels−Alder reaction proceeded via a stepwise mechanism, see: (a) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195−1202. (b) Shi, M.; Shao, L.-X.; Xu, B. *Org. Lett.* **2003**, *5*, 579−582.

Scheme 2. $BF_3{\cdot}OEt_2$-Catalyzed Reaction of Arylvinylidenecyclopropane **1h** with Ethyl (Arylimino)acetate **2a**



conditions. The reaction is believed to proceed via [3 + 2] cycloaddtion or intramolecular Friedel−Crafts reaction pathways, depending on the electronic nature both of **2** and the R^1 or R^2 aromatic groups of arylvinylidenecyclopropanes **1**. Efforts are in progress to elucidate further mechanistic details of these reactions and to understand their scope and limitations.

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Supporting Information Available: Spectroscopic data of all of the new compounds, detailed descriptions of experimental procedures, and X-ray data for compound **4h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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