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LDA-Mediated Selective Addition Reaction of Vinylidenecyclopropanes with Aldehydes, Ketones, and Enones: Facile Synthesis of Vinylcyclopropenes, Allenols, and 1,3-Enynes

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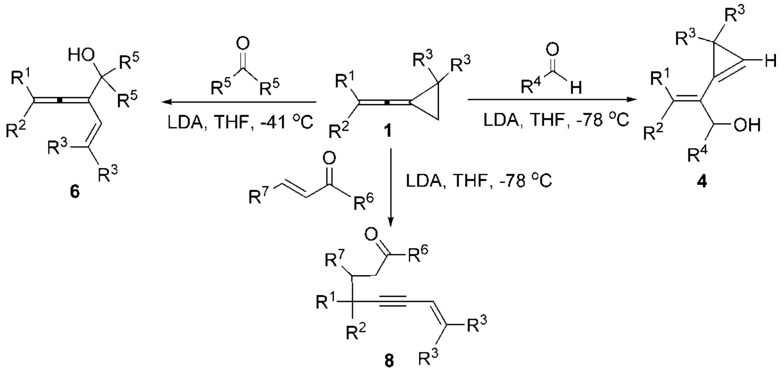
ABSTRACT



Highly selective addition reaction of vinylidenecyclopropanes 1 was realized by treatment with LDA in THF and quenching with aldehydes, ketones, and enones. A number of vinylcyclopropenes, allenols, and 1,3-enynes were obtained selectively in moderate to good yields depending on the nature of different electrophiles.

Vinylidenecyclopropanes **1**[1] are one of the most remarkable known organic compounds. They have an allene moiety connected by a cyclopropane ring, and yet they are thermally stable and reactive substances in organic synthesis. Thermal and photochemical skeletal conversions of vinylidenecyclopropanes **1** have attracted much attention from mechanistic and synthetic viewpoints since the cyclopropanes can gain additional driving force by the relief of angular strain.[2] Recently, numerous palladium-catalyzed[3] as well as Lewis acid or Brønsted acid catalyzed/mediated[4] reactions of vinylidenecyclopropanes **1** have also been disclosed. However, the Lewis base or Brønsted base catalyzed/mediated reactions of vinylidenecyclopropanes **1** are rare. Previously,

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(1) For the synthesis of vinylidenecyclopropanes, please see: (a) Isagawa, K.; Mizuno, K.; Sugita, H.; Otsuji, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, *228*, 3–2285. (b) Al-Dulayymi, J. R.; Baird, M. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, *154*, 7–1548. For some other papers related to vinylidenecyclopropanes, see: (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. For a recent review, see: (e) Maeda, H.; Mizuno, K. *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 1014–1025.

(2) (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. *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**, *44*, 9–452. (f) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133–1150. (g) Mizuno, K.; Sugita, H.; Hirai, T.; Maeda, H.; Otsuji, Y.; Yasuda, M.; Hashiguchi, M.; Shima, K. *Tetrahedron Lett.* **2001**, *42*, 3363–3366. (h) Mizuno, K.; Nire, K.; Sugita, H.; Otsuji, Y. *Tetrahedron Lett.* **1993**, *34*, 6563–6566. (i) Sasaki, T.; Eguchi, S.; Ogawa, T. *J. Am. Chem. Soc.* **1975**, *97*, 4413–4414.

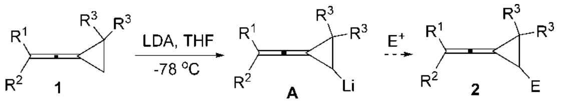
(3) (a) Lu, J.-M.; Shi, M. *Tetrahedron* **2006**, *62*, 9115–9122. (b) Fall, Y.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2007**, *48*, 3579–3581.

10.1021/ol800463k CCC: $40.75

we reported the reaction of *gem*-aryl-disubstituted methylenecyclopropanes with BuLi in tetrahydrofuran (THF) to give the corresponding addition products in good yields by quenching with various electrophiles.[5,6] In this paper, we wish to report the addition reaction of vinylidenecyclopropanes **1** by treatment with lithium diisopropylamide (LDA) in THF to give the corresponding vinylcyclopropenes **4**, allenols **6**, and 1,3-enynes **8** in moderate to good yields selectively by quenching with aldehydes, ketones, and enones.

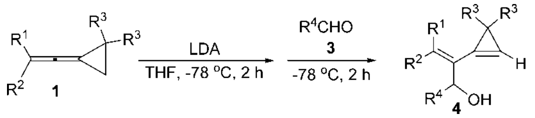
In the case of vinylidenecyclopropanes **1**, since it is anticipated that lithiation of the cyclopropane ring could easily take place to give the corresponding lithiated intermediate **A** by treatment with LDA at low temperature, the subsequent quenching with electrophile E^+ would similarly produce the corresponding product **2** (Scheme 1).

Scheme 1. Proposal on the Lithiation of Vinylidenecyclopropanes **1**



We first carried out the lithiation reaction of vinylidenecyclopropane **1a** by using LDA (2.0 equiv) in THF at −78 °C, and the reaction was subsequently quenched by addition of *p*-bromobenzaldehyde **3a** (1.5 equiv) in a one-pot manner. Interestingly, we found that vinylcyclopropene **4a** was obtained in 86% yield rather than the expected product **2** (Table 1, entry 1). Its structure was determined by ^1H and ^{13}C NMR spectroscopic data and HRMS (see the Supporting Information). Other lithiation reagents such as *n*-butyllithium (BuLi) and lithium bis(dimethylsilyl)amide (LHMDS) were also examined, but the results were not as good as those using LDA. We next examined an assortment of starting materials **1** and aldehydes **3** in order to evaluate the scope and limitations of this addition reaction. As can be seen from Table 1, the corresponding vinylcyclopropenes **4** were obtained in moderate to good yields (Table 1). In the reactions with arylaldehydes, the corresponding products **4a**−**4l** were obtained in good yields (Table 1, entries 1−12). In the reactions with aliphatic aldehydes **3h** and **3i**, the corresponding products **4n** and **4o** were obtained in 67 and 79% yields, respectively (Table 1, entries 14 and 15). As for 2-furaldehyde **3g**, the corresponding vinylcyclopropene **4m** was obtained in 64% yield (Table 1, entry 13). For α,*β*-unsaturated aldehyde **3j**, the corresponding 1,2-addition product **4p** was formed similarly as the sole product in 43% yield (Table 1, entry 16).

Table 1. Reaction of Various Aldehydes **3** with Carbanion Derived from Vinylidenecyclopropanes **1** and LDA



entry[a]	**1** (R^1/R^2/R^3)	**3** (R^4)	yield (%)[b]
1	**1a** (C_6H_5/C_6H_5/C_6H_5)	**3a** (*p*-BrC_6H_4)	**4a**, 86
2	**1a**	**3b** (*p*-ClC_6H_4)	**4b**, 82
3	**1b** (C_6H_5/C_6H_5/*p*-ClC_6H_4)	**3c** (C_6H_5)	**4c**, 62
4	**1c** (C_6H_5/C_6H_5/*p*-MeC_6H_4)	**3c**	**4d**, 84
5	**1d** (*p*-FC_6H_4/*p*-FC_6H_4/C_6H_5)	**3c**	**4e**, 84
6	**1d**	**3a**	**4f**, 77
7	**1d**	**3b**	**4g**, 64
8	**1d**	**3d** (*p*-MeC_6H_4)	**4h**, 80
9	**1d**	**3e** (*m*-FC_6H_4)	**4i**, 68
10	**1e** (*p*-FC_6H_4/*p*-FC_6H_4/*p*-MeC_6H_4)	**3a**	**4j**, 76
11	**1f** (*p*-ClC_6H_4/*p*-ClC_6H_4/C_6H_5)	**3c**	**4k**, 88
12	**1d**	**3f** (1-naphthaldehyde)	**4l**, 76
13	**1d**	**3g** (2-furaldehyde)	**4m**, 64
14	**1d**	**3h** ($C_6H_5CH_2CH_2$)	**4n**, 67
15	**1d**	**3i** ($CH_3CH_2CH_2$)	**4o**, 79
16	**1a**	**3j** (***E*-$C_6H_5CH{=}CH$**)	**4p**, 43

[a] After vinylidenecyclopropanes **1** (0.2 mmol) were lithiated by LDA (0.4 mmol) at −78 °C for 2 h, aldehydes **3** (0.3 mmol) were added. Then the reactions were quenched by addition of the aqueous solution of ammonium chloride after 2 h. [b] Isolated yields.

More interestingly, when the reaction was carried out using benzophenone **5a** as an electrophile under identical conditions, the allenol derivative **6a** was formed in variable yields ranging from 42 to 83% along with the corresponding cyclopropene product[7] obtained in different ratios with **6a** ranging from 1:4 to 1:50 (Table 2, entry 1). The structure of **6a** was unambiguously determined by an X-ray diffraction.[8] When the lithiation time was prolonged to 5 h at −78 °C under identical conditions, **6a** was obtained in 77% yield along with 5% yield of the corresponding cyclopropene product (Table 2, entry 2). Adding anhydrous cerium(III) chloride as an additive into the reaction system afforded **6a** in 62% yield (Table 2, entry 3).[9] If the temperature of lithiation was increased to −41 °C, **6a** could be obtained in 85% yield under the similar conditions. In addition, when the reaction temperature was increased to −20 °C, **6a** could also be obtained in 60% yield. Moreover, in both cases, the corresponding cyclopropene product was obtained in less than 1% yield on the basis of ^1H NMR spectroscopic data (Table 2, entries 4 and 5). These results suggest that the formation of the corresponding cyclopropene product was facilitated at lower temperature and the subtle change of the

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(4) (a) Lu, J.-M.; Shi, M. *Tetrahedron* **2007**, *63*, 7545–7549. (b) Zhang, Y.-P.; Lu, J.-M.; Xu, G.-X.; Shi, M. *J. Org. Chem.* **2007**, *72*, 509–516. (c) Shao, L.-X.; Zhang, Y.-P.; Qi, M.-H.; Shi, M. *Org. Lett.* **2007**, *9*, 117–120. (d) Xu, G.-C.; Liu, L.-P.; Lu, J.-M.; Shi, M. *J. Am. Chem. Soc.* **2005**, *127*, 14552–14553. (e) Xu, G.-C.; Ma, M.; Liu, L.-P.; Shi, M. *Synlett* **2005**, *1869*, 1872. (f) Lu, J.-M.; Shi, M. *Org. Lett.* **2006**, *8*, 5317–5320. (g) Lu, J.-M.; Shi, M *Org. Lett.* **2007**, *9*, 1805–1808. (h) Stepakov, A. V.; Larina, A. G.; Molchanov, A. P.; Stepakova, L. V.; Starova, G. L.; Kostikov, R. R.; Russ, J. *Org. Chem.* **2007**, *43*, 41–49.

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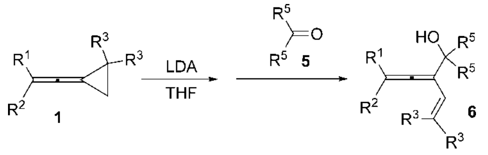
(6) Huang, J.-W.; Shi, M. *Org. Biomol. Chem.* **2005**, *3*, 399–400.

(7) The structure of this cyclopropene product is similar to the vinylcyclopropane **4**.

(8) The crystal data of **6a** have been deposited in CCDC with number 656880 (also see the Supporting Information).

(9) (a) Ahn, Y.; Cohen, T. *Tetrahedron Lett.* **1994**, *35*, 203–206. (b) Imamoto, T.; Kusumoto, T.; Yokoyama, M. *Tetrahedron Lett.* **1983**, *24*, 5233–5236.

Table 2. Reaction of Various Ketones **5** with Carbanion Derived from Vinylidenecyclopropanes **1** and LDA



entry[a]	$R^1/R^2/R^3$	R^5	temp (°C)	yield (%)[b,c]
1	**1a** ($C_6H_5/C_6H_5/C_6H_5$)	**5a** (C_6H_5)	−78	**6a** (42−83)[d]
2	**1a**	**5a**	−78	**6a** (77)[e]
3	**1a**	**5a**	−78	**6a** (62)[f]
4	**1a**	**5a**	−41	**6a** (85)
5	**1a**	**5a**	−20	**6a** (60)
6	**1a**	**5b** (p-MeC_6H_4)	−41	**6b** (73)
7	**1a**	**5c** (p-ClC_6H_4)	−41	**6c** (77)
8	**1a**	**5d** (Bu)	−41	**6d** (64)
9	**1b** ($C_6H_5/C_6H_5/p$-ClC_6H_4)	**5a**	−41	**6e** (85)
10	**1c** ($C_6H_5/C_6H_5/p$-MeC_6H_4)	**5a**	−41	**6f** (76)[g]
11	**1e** (p-FC_6H_4/p-FC_6H_4/p-MeC_6H_4)	**5a**	−41	**6g** (84)
12	**1f** (p-ClC_6H_4/p-ClC_6H_4/C_6H_5)	**5a**	−41	**6h** (53)[h]
13	**1g** (p-MeC_6H_4/p-MeC_6H_4/C_6H_5)	**5a**	−41	**6i** (85)
14	**1h** (C_6H_5/Me/C_6H_5)	**5a**	−41	**6j** (83)[i]
15	**1i** (Bu/Bu/C_6H_5)	**5a**	rt	**6k** (77)[j]

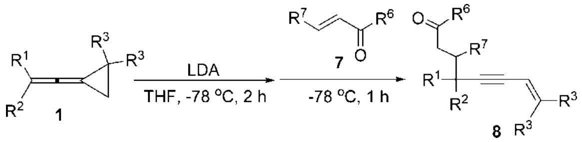
[a] After vinylidenecyclopropanes **1** (0.2 mmol) were lithiated by LDA (0.4 mmol) for 3 h at the listed temperature, ketone **5** (0.3 mmol) were added. Reactions were quenched by addition of the aqueous solution of ammonium chloride after 2 h. [b] Isolated yields. [c] Unless otherwise specified, the ratios of **6** and the cyclopropene were >100:1. [d] Lithiation time was 2 h. [e] Lithiation time was 5 h, and 5% of cyclopropene product was obtained. [f] Cerium(III) chloride (0.4 mmol) was added. [g] 5% of cyclopropene product was obtained. [h] 3% of cyclopropene product was obtained. [i] Only one isomer was obtained. [j] 14% of **1i** was recovered.

reaction temperature can significantly effect the ratios of **6** and the cyclopropene.

Under these optimized reaction conditions, we next examined an assortment of vinylidenecyclopropanes **1** and ketones **5** in order to evaluate the scope of this reaction. For most cases in which R^1, R^2, R^3, and R^5 = aromatic groups, the corresponding allenol derivatives **6** can be obtained in good yields (Table 2, entries 4, 6, 7, 9, 11, and 13). As for dialkylvinylidenecyclopropane **1i**, the corresponding allenol derivative **6k** was obtained in 77% yield at room temperature (Table 2, entry 15). When 5-nonanone **5d** (aliphatic ketone) was used as an electrophile, **6d** was formed in 64% yield (Table 2, entry 8). As for vinylidenecyclopropanes **1c** (R^1, R^2 = C_6H_5, R^3 = p-MeC_6H_4) and **1f** (R^1, R^2 = p-ClC_6H_4, R^3 = C_6H_5), the corresponding allenol derivatives **6f** and **6h** were obtained in 76 and 53% yields along with 5 and 3% yields of the corresponding cyclopropene products, respectively (Table 2, entries 10 and 12). For unsymmetrical vinylidenecyclopropane **1h** (R^1 = C_6H_5, R^2 = Me), **6j** was obtained as a sole product in 83% yield (Table 2, entry 14). Moreover, on the basis of above results, we can conclude that the aromatic R^1 and R^2 groups bearing electron-withdrawing groups or the aromatic R^3 group bearing electron-donating groups will generally result in lower selectivity in this reaction which can be found in the cases of substrates **1c** (R^3 = p-MeC_6H_4) and **1f** (R^1, R^2 = p-ClC_6H_4) (Table 2, entries 10 and 12).

When the addition reaction was carried out using enones instead of aldehydes and ketones as electrophiles, the corresponding 1,3-enyne derivatives **8** were obtained rather than vinylcyclopropene and allenol derivatives. As can been seen from Table 3, for almost all cases in which R^1, R^2, and R^3 = aromatic groups, the lithiation with LDA and quenching with methyl vinyl ketone **7a** could proceed smoothly to give 1,3-enyne derivatives **8** in good yields (Table 3, entries 1−6). As for unsymmetrical vinylidenecyclopropane **1h** (R^1 = C_6H_5, R^2 = Me), 1,3-enyne derivative **8g** was obtained in 75% yield as isomeric mixtures (Table 3, entry 7). As for ethyl vinyl ketone **7b** and phenyl vinyl ketone **7c**, the corresponding 1,3-enynes were obtained in 64 and 31% yields, respectively (Table 3, entries 8 and 9). When 2-cyclopenten-1-one **7d** and 2-cyclohexen-1-one **7e** were used as the electrophiles, the corresponding 1,3-enyne derivatives **8j** and **8k** were formed in 83 and 95% yields, respectively (Table 3, entries 10 and 11). The structure of **8j** was further determined by an X-ray diffraction.[10] For β-methyl-substituted enone **7f**, this addition reaction could also proceed smoothly to afford the corresponding product **8l** in 80% yield (Table 3, entry 12). Surprisingly, no reaction occurred when dialkylvinylidenecyclopropane **1i** was used as the substrate. Adding anhydrous cerium(III) chloride or copper salts such as CuI, CuBr, CuCl, and CuCN into the addition reaction system did not improve the yield of 1,3-enyne under the standard conditions.

Table 3. Reaction of Various Enones **7** with Carbanion Derived from Vinylidenecyclopropanes **1** and LDA



entry[a]	$R^1/R^2/R^3$	R^6/R^7	yield (%)[b]
1	**1a** ($C_6H_5/C_6H_5/C_6H_5$)	**7a** (Me/H)	**8a**, 72
2	**1b** ($C_6H_5/C_6H_5/p$-ClC_6H_4)	**7a**	**8b**, 71
3	**1c** ($C_6H_5/C_6H_5/p$-MeC_6H_4)	**7a**	**8c**, 75
4	**1e** (p-FC_6H_4/p-FC_6H_4/p-MeC_6H_4)	**7a**	**8d**, 72
5	**1f** (p-ClC_6H_4/p-ClC_6H_4/C_6H_5)	**7a**	**8e**, 33
6	**1g** (p-MeC_6H_4/p-MeC_6H_4/C_6H_5)	**7a**	**8f**, 57
7	**1h** (C_6H_5/Me/C_6H_5)	**7a**	**8g**, 75[c]
8	**1a**	**7b** (Et/H)	**8h**, 64
9	**1a**	**7c** (C_6H_5/H)	**8i**, 31
10	**1a**	**7d** [$-(CH_2)_2-$]	**8j**, 83
11	**1a**	**7e** [$-(CH_2)_3-$]	**8k**, 95
12	**1a**	**7f** (Me/Me)	**8l**, 80

[a] After vinylidenecyclopropanes **1** (0.2 mmol) were lithiated by LDA (0.4 mmol) at −78 °C for 2 h, enones **7** (0.3 mmol) were added. Then the reactions were quenched by addition of the aqueous solution of ammonium chloride after 1 h. [b] Isolated yields. [c] syn:anti or anti:syn = 14:1.

A plausible mechanism for the formation of **4**, **6**, and **8** is outlined in Scheme 2. Initially, the lithiation of the cyclo-

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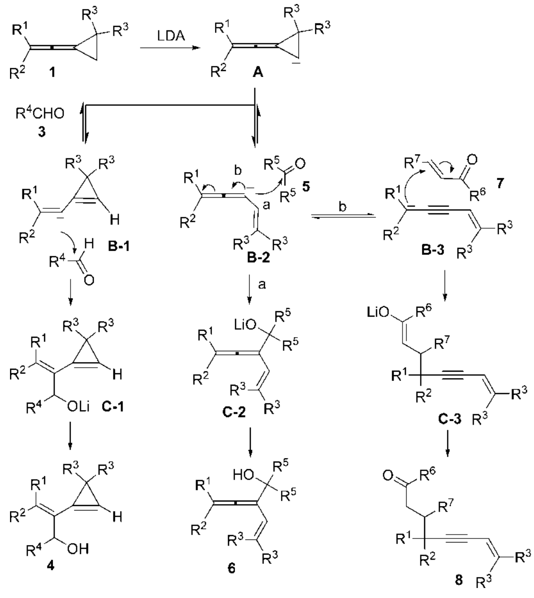
(10) The crystal data of **8j** have been deposited in CCDC with number 670799 (also see the Supporting Information).

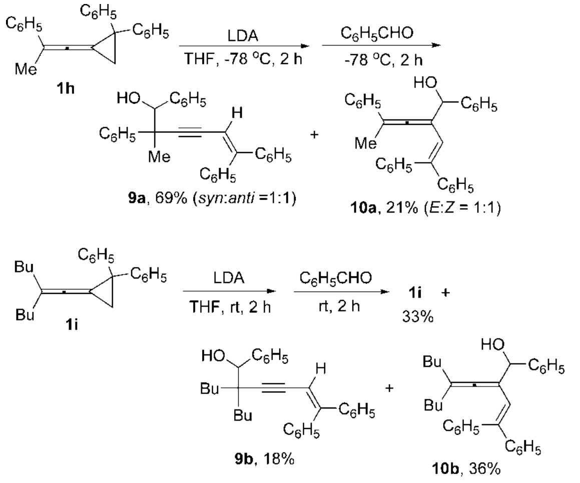
Scheme 2. Proposed Mechanism for the Formation of **4**, **6**, and **8**



propyl ring of vinylidenecyclopropane **1** gives the corresponding cyclopropyl carbanion intermediate **A** by treatment with LDA.[6] When aldehyde **3** is used as an electrophile (E^+), anionic intermediate **B-1** is formed through 1,3-shift[11] via carbanion **A**, which reacts with **3** to give intermediate **C-1** and subsequently to furnish product **4**. Intermediate **A** can also undergo a ring-opening reaction to produce allenic carbanion **B-2**.[12]When ketone **5** is used as an electrophile (E^+), allenol **6** is obtained by the reaction of **B-2** with **5** through intermediate **C-2** (Scheme 2, path a). Furthermore, intermediate **B-2** can also undergo rearrangement to form propargylic carbanion **B-3**.[13] When enone **7** is used as an electrophile (E^+), intermediate **C-3** is formed through 1,4-addition of **B-3** to enone (Scheme 2, path b). Protonation of intermediate **C-3** produces the corresponding 1,3-enyne **8**. This highly selective synthesis of vinylcyclopropenes **4**, allenols **6**, and 1,3-enynes **8** by the addition reaction of lithiated vinylidenecyclopropanes **1** with aldehydes, ketones, and enones in THF may be due to the electronic nature of the employed electrophiles as well as the steric effect between the electrophiles and intermediates **A**, **B-1**, **B-2**, and **B-3**. In addition, the reaction temperature may also affect the stability of intermediates **A**, **B-1**, **B-2**, and **B-3**. Further work regarding this interesting selectivity is underway. Since selective synthesis has been a formidable challenge in organic chemistry, this work provides an interesting example on the controlled highly selective synthesis of vinylcyclopropenes, allenols, and 1,3-enynes beginning from the same starting materials.

As a control experiment, we found that if the reaction was carried out between vinylidenecyclopropanes **1h** ($R^1 = C_6H_5$, R^2 = Me) and **1i** (R^1, R^2 = Bu) with benzaldehyde **3c** product mixtures of 1,3-enynes and allenols were both obtained in good total yields, suggesting that the electronic nature and steric effect of the employed vinylidenecyclopropane **1** also could significantly effect the product outcome (Scheme 3).

Scheme 3. Reaction between **1h** and **1i** with Benzaldehyde **3c**



In conclusion, we have developed a highly selective addition reaction of vinylidenecyclopropanes **1** with LDA in THF to give vinylcyclopropenes **4**, allenols **6**, and 1,3-enynes **8** in moderate to good yields by quenching with aldehydes, ketones, and enones. 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 the new compounds, the detailed descriptions of experimental procedures, and X-ray diffraction data for compounds **6a** and **8j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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