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# *N*-Heterocyclic Carbene Catalyzed Transformations of 3-Halopropenals to the Equivalents of β-Acylvinyl Anions

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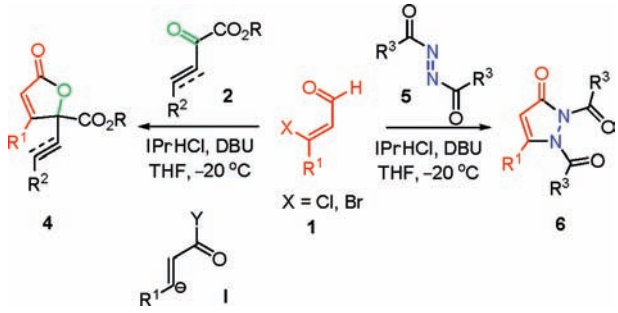
## ABSTRACT




**3-Halopropenals 1 can behave as an alternative equivalent of β-acylvinyl anions (I) in the presence of *N*-heterocyclic carbene precursor (IPr·HCl) and DBU to afford cyclic α,β-unsaturated carbonyl derivatives, butenolides 4 and pyrazolone 6, after cyclization with 2 and 5, respectively.**

Umpolung reactivity of functional groups allows chemists the opportunity to view bond disconnections in nontraditional ways.[1] In this context, β-acylvinyl anions (**I**) can be considered as $sp^2$-hybridized unpoled $d^3$ synthons and are appropriate intermediates to provide a β-bonded α,β-unsaturated functionality.[2] Traditional methodology toward **I** or their equivalents relies on the stoichiometric generation of stabilized carbanions and is hence hampered by some limitations such as harsh reaction conditions and tedious manipulations. Therefore, vinylboronate and vinylstannane compounds have been employed as altenative precursors of **I** upon treatment with transition-metal catalysts.[3] Whereas significant progress has been made by these protocols, few organocatalyzed routes to β-acylvinyl anions or equivalents for subsequent β-functionaliztion exist to date.[4]

*N*-Heterocyclic carbene (NHC)-catalyzed redox transformations of aldehydes constitute an important class of organocatalysis and have found a broad range of applications in synthetic organic chemistry.[5] Remarkably, the proposed NHC-bound homoenolate intermediates, generated from α,β-unsaturated aldehydes by NHCs, can react with various electrophiles resulting in a variety of cyclic compounds.[6,7] Intriguingly, these annulations only made use of β-monosubstituted substrates, presumably due to the instability of

(1) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239.
(2) For a review, see: Chinchilla, R.; Nájera, C. *Chem. Rev.* **2000**, *100*, 1891.
(3) For a transition-metal-catalyzed coupling reaction, see: (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diedrich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(4) For organocatalyzed β-protonation of propargylic aldehydes, proposed via allenol or β-acylvinyl anion intermediates, leading to the synthesis of α,β-unsaturated esters, see: (a) Zeitler, K. *Org. Lett.* **2006**, *8*, 637. (b) Maki, B. E.; Chan, A.; Scheidt, K. A. *Synthesis* **2008**, 1306.
(5) For reviews on NHCs as organocatalysts, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (b) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. Minireviews: (c) Rovis, T. *Chem. Lett.* **2008**, 2. (d) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. Highlights: (e) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632. (f) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506. Perspective: (g) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857.

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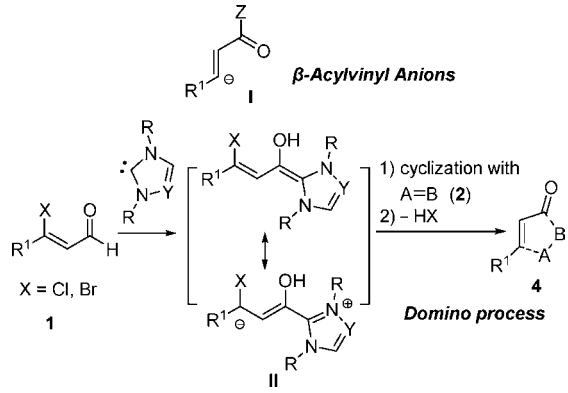
related homoenolate intermediates or inherent steric hindrance.[8] We therefore envisioned that if 3-halo-2-propenals **1** (bearing a electronegative and small halogen atom at the $\beta$-position) can be attacked by NHCs, we may access to zwitterions **II**, which should produce cyclic $\alpha,\beta$-unsaturated carbonyl derivatives **4** via a tandem cyclization/elimination process (Scheme 1).[9] In conjunction with our efforts on

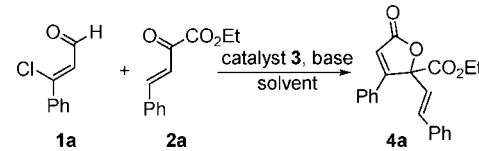
**Scheme 1.** NHC-Catalyzed Reactions to the Equivents of $\beta$-Acylvinyl Anions **I**




extending the reactivity of NHCs,[10] herein we report a novel reaction that converts substituted 3-halo-2-propenals (**1**) into an alternative equivalent of $\beta$-acylvinyl anionic synthons by NHCs under mild conditions.

We initiated our investigation by reacting 3-chloro-3-phenyl-2-propenal **1a** with benzaldehyde in the presence of carbene precursor **3a** (10 mol %) and DBU (12 mol %) in THF. Disappointingly, no expected cross-coupling products were observed, even with an excess amount of DBU (150 mol %). In contrast, while switching the electrophile to $\beta,\gamma$-unsaturated α-keto ester **2a** instead, to our delight, butenolide **4a** was obtained in 35% yield (Table 1, entry 1).[11,12] An initial experiment revealed that at least 150 mol % of base was required to complete the conversion (Table 1, entries 2 vs 5). Of the two common classes of azolium salts, imidazolium **3a** and **3b** proved to be effective, whereas

**Table 1.** Optimization of the Reaction of **1a** and **2a**[a]




| entry | 3 | base | solvent | time (h) | yield[e] (%) |
|---|---|---|---|---|---|
| 1 | **3a** | DBU | THF | 5 | 35 |
| 2 | **3b** | DBU | THF | 2 | 75 |
| 3 | **3c** | DBU | THF | 12 | 18 |
| 4 | **3d** | DBU | THF | 12 | trace |
| 5[b] | **3b** | DBU | THF | 12 | 46 |
| 6[c] | **3b** | $Cs_2CO_3$ | THF | 12 | 31 |
| 7 | **3b** | DIPEA | THF | 12 | 23 |
| 8[d] | **3b** | DBU | THF | 2 | 56 |
| 9 | **3b** | DBU | toluene | 6 | 17 |
| 10 | **3b** | DBU | $CH_2Cl_2$ | 12 | 7 |
| 11 | **3b** | DBU | EtOAc | 3 | 25 |
| 12 | **3b** | DBU | THF−$t$BuOH (10:1) | 2 | 62 |

[a] Reaction conditions: a mixture of **1a** (0.75 mmol), **2a** (0.5 mmol), **3** (10 mol %), solvent (8 mL), and base (0.75 mmol) in 2 mL of solvent was added slowly at −20 °C with stirring over 2 h and the mixture reacted for indicated time. [b] 0.5 mmol of DBU. [c] $Cs_2CO_3$ was added in one pot. [d] At 25 °C. [e] Yield of isolated product. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

triazolium **3c** and **3d** gave only low yield or trace of product, respectively (Figure 1 and Table 1, entries 1−4). Among

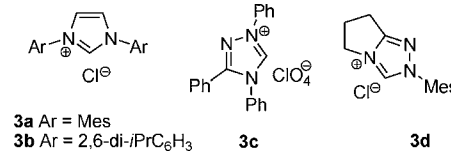



**Figure 1.** Structures of azolium salts **3**.

those tested azolium precursors, sterically more demanding imidazolium salt **3b** was found to be the most efficient catalyst. A brief solvent screen revealed THF to be optimal, providing the desired product in 75% yield at −20 °C after 2 h (Table 1, entry 2).

Under the optimized conditions, the scope of the NHC-catalyzed cyclization/elimination reaction was examined, and the results are presented in Table 2. This process tolerated a variety of enones **2**, including both electron-rich and electron-deficient aryl derivatives (Table 2, entries 2, 3, and 7), as well as heterocyclic and aliphatic examples (Table 2, entries 8 and 9). Additionally, other unsaturated α-keto esters bearing an extended dienylic system and an alkyne also underwent the annulation to provide **4d** and **4l**, respectively (Table 2, entry 4, and Scheme 2). Moreover, variation in the aromatic moiety of $\beta$-haloenals was possible, and the necessary substrates **1** were easily accessible from the corresponding ketones with Vilsmeier−Haack reagent.[13] As expected, $\beta$-bromo-substituted enal **1b** could perform the

(6) For seminal studies, see: (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (b) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205.

(7) For recent reviews on NHC-bound homoenolate, see: (a) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (b) Johnson, J. S. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 691.

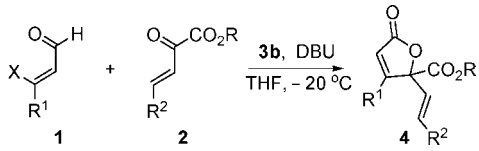
(8) For recent examples, see: (a) Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 17266. (b) Chiang, P.-C.; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 8714. (c) Maki, B. E.; Patterson, E. V.; Cramer, C. J.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 3942.

(9) For conversion of α-haloaldehyde into acylating agent, see: (a) Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518. (b) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406.

(10) (a) Ding, H.; Ma, C.; Yang, Y.; Wang, Y. *Org. Lett.* **2005**, *7*, 2125. (b) Ma, C.; Ding, H.; Zhang, Y.; Bian, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7793. (c) Ma, C.; Ding, H.; Wu, G.; Yang, Y. *J. Org. Chem.* **2005**, *70*, 8919. (d) Ding, H.; Zhang, Y.; Bian, M.; Yao, W.; Ma, C. *J. Org. Chem.* **2008**, *73*, 578.

(11) For reviews of butenolides, see: (a) Carter, N. B.; Nadany, A. E.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2324. (b) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. (c) Bellina, F.; Rossi, R. *Curr. Org. Chem.* **2004**, *8*, 1089.

**Table 2.** NHC-Catalyzed Reactions of **1** and **2**[a]

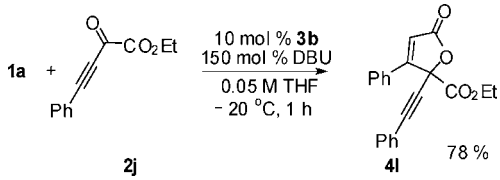



1 2 4

| entry | 1, $R^1$, X | 2, $R^2$, R | time (h) | yield[c] (%) |
|---|---|---|---|---|
| 1 | **1a**, Ph, Cl | **2a**, Ph, Et | 2 | **4a**, 75 |
| 2 | **1a**, Ph, Cl | **2b**, 4-$FC_6H_4$, Me | 2 | **4b**, 63 |
| 3 | **1a**, Ph, Cl | **2c**, 4-$ClC_6H_4$, Et | 2 | **4c**, 58 |
| 4[b] | **1a**, Ph, Cl | **2d**, styryl, Et | 12 | **4d**, 53 |
| 5 | **1b**, Ph, Br | **2a**, Ph, Et | 2 | **4a**, 61 |
| 6 | **1c**, 4-$BrC_6H_4$, Cl | **2e**, 2-$MeC_6H_4$, Et | 3 | **4e**, 81 |
| 7 | **1c**, 4-$BrC_6H_4$, Cl | **2f**, 4-$MeOC_6H_4$, Et | 8 | **4f**, 42 |
| 8 | **1c**, 4-$BrC_6H_4$, Cl | **2g**, 2-fury, Et | 5 | **4g**, 45 |
| 9 | **1c**, 4-$BrC_6H_4$, Cl | **2h**, *n*Pr, Et | 4 | **4h**, 32 |
| 10 | **1d**,4-$MeOC_6H_4$,Cl | **2e**, 2-$MeC_6H_4$, Et | 8 | **4i**, 83 |
| 11 | **1e**, 4-$NO_2C_6H_4$, Cl | **2a**, Ph, Et | 3 | **4j**, 21 |
| 12 | **1f**, styryl, Cl | **2i**, Ph, Me | 8 | **4k**, 36 |
| 13 | **1g**, 1-naphthyl, Cl | **2a**, Ph, Et | 12 | N.R. |

[a] Reaction conditions: **1** (0.75 mmol), **2** (0.5 mmol), and **3b** (10 mol %) in 8 mL of THF and DBU (0.75 mmol) in 2 mL of THF were added slowly over 2 h at −20 °C and the mixture eacted for indicated time. [b] 20 mol % of **3b**. [c] Yield of isolated product.

**Scheme 2.** Cross-Coupling of **1a** and **2j**

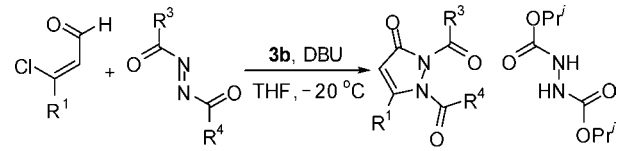



**1a** + **2j** → **4l**

similar conversion, albeit in a reduced yield (Table 2, entry 5). Interestingly, it occurs smoothly with a dienal **1f** also, rendering **4k** selectively in 36% yield (Table 2, entry 12). However, the placement of 1-naphthyl in the $\beta$-position, **1g**, provided none of the desired butenolide (Table 2, entry 13). This result indicated that the steric nature in the aromatic tether of **1** conducted dramatic effects on this conversion.

The incongruity between the substrate scope of the current butenolide-forming cyclizations and that of the usual cinnamaldehyde lactonization[6,14] invited further exploration on their unique reactivity of $\beta$-chloroenals in the prescence of NHCs. Thus, **1a** and different activated diazenes **5** were reacted to explore the possibility of a direct elctrophilic amination in the presence of **3b**.[15] Not surprisingly, while azodicarboxylate **5a** proved to be unsuitable nitrogen-containing electrophile for cinnamaldehyde amination,[15a] it readily cyclized with **1a** to afford pyrazolone **6a** in the presence of imidazolium salt **3b** and DBU (Table 3, entry 1). By using 3 equiv of diazenes, the reaction scope accommodated various $\beta$-aryl chloroenals **1** as well as a set of azodicarboxylates **5a**−**c** (Table 3, entries 1−6). However,

**Table 3.** NHC-Catalyzed Directly Amination of **1** and **5**[a]




1 5 6 7

| entry | 1, $R^1$ | $R^3$ | $R^4$ | 5 | time (h) | yield [b] (%) |
|---|---|---|---|---|---|---|
| 1 | **1a**, Ph | EtO | EtO | **5a** | 12 | **6a**, 54 |
| 2 | **1a**, Ph | *i*-PrO | *i*-PrO | **5b** | 12 | **6b**, 73 |
| 3 | **1a**, Ph | BnO | BnO | **5c** | 12 | **6c**, 68 |
| 4 | **1c**, 4-$BrC_6H_4$ | *i*-PrO | *i*-PrO | **5b** | 12 | **6d**, 61 |
| 5 | **1i**, 4-$MeC_6H_4$ | *i*-PrO | *i*-PrO | **5b** | 18 | **6e**, 42 |
| 6 | **1d**, 4-$MeOC_6H_4$ | *i*-PrO | *i*-PrO | **5b** | 24 | **6f**, 22 |
| 7 | **1a**, Ph | Ph | Ph | **5d** | 12 | trace |
| 8 | **1a**, Ph | Ph | MeO | **5e** | 12 | N.R. |

[a] Reaction conditions: **1** (0.5 mmol), **5** (1.5 mmol), and **3b** (10 mol %) in 8 mL of THF and DBU (1.25 mmol) in 2 mL of THF were added slowly over 2 h at −20 °C and the mixture reacted for the indicated time. [b] Yield of isolated product.

electron-rich enal **1d** conducted this reaction sluggishly and rendered the corresponding product **6f** in reduced yield, accompanying by the formation of hydrazine **7** (Table 3, entry 6).[16] Moreover, the electronic property of diazenes played a critical role in the cyclization reaction; currently, *N*,*N*′-dibenzoyldiazene **5d** and azocarboxylate **5e** yielded no desired products.

A postulated catalytic cycle for the NHCs-catalyzed tandem cross-cyclization/elimination reaction is depicted in Scheme 3. Thus, 3-chloroenal **1** is first attacked by the in situ formed imidazolium carbene **I** to afford $\beta$-chloro-conjugated Breslow intermediate **II**,[17] which could be stabilized by resonance to homoenolate **III**. This in turn attacks activated diazene **5**, followed by tautomerization to produce zwitterion **IV**. The latter intermediate undergoes intramolecular acylation to furnish lactam **V** with the

(12) For previous condensation of enals and enones via homoenolate, see: (a) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736. (b) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098. (c) Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520. (d) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107. (e) Nair, V.; Babu, B. P.; Vellalath, S.; Varghese, V.; Raveendran, A. E.; Suresh, E. *Org. Lett.* **2009**, *11*, 2507. (f) Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2009**, *11*, 677.

(13) Arnold, Z.; Holý, A. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3059. (b) Robertson, I. R.; Sharp, J. T. *Tetrahedron* **1984**, *40*, 3095. (c) Lilienkampf, A.; Johansson, M. P.; Wahala, K. *Org. Lett.* **2003**, *5*, 3387, and references cited therein.

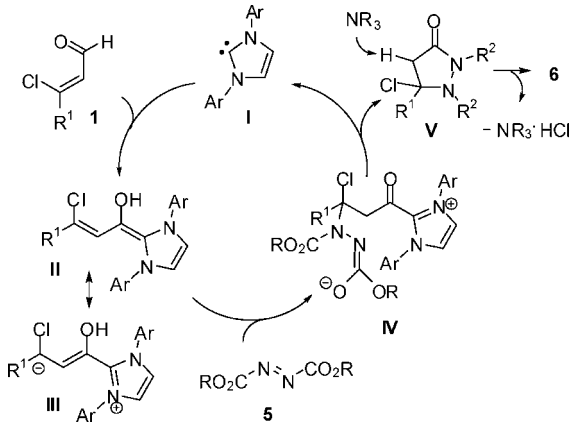
(14) (a) Hirano, K.; Piel, I.; Glorius, F. *Adv. Synth. Catal.* **2008**, *350*, 984. (b) Li, Y.; Zhao, Z.-A.; He, H.; You, S.-L. *Adv. Synth. Catal.* **2008**, *350*, 1885.

(15) For previous NHCs catalyzed elctrophilic C−N bond formation, see: (a) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2740. (b) Huang, X.-L.; He, L.; Shao, P.-L.; Ye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 192. (c) Seayad, J.; Patra, P. K.; Zhang, Y.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 953. (d) Yang, L.; Tan, B.; Wang, F.; Zhong, G. F. *J. Org. Chem.* **2009**, *74*, 1744.

(16) Similar results were observed in the reaction of acylaryldiazene with cinnamaldehyde, which presumably due to the related concomitant hydride transfer, which consumed the homoenolate and thus decreased the yield of **6f**; see ref 15a.

(17) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

**Scheme 3.** Plausible Mechanism of the Reaction of **1** and **5** ($NR_3$ = DBU; Ar = 2,6-di-*i*Pr$C_6H_3$)




regeneration of the carbene catalyst. Finally, $\beta$-elimination ensues, assisted by DBU, yielding pyrazolone **6**.

In summary, we have presented a novel *N*-heterocyclic carbene-catalyzed umpolung reaction which converts 3-halopropenals into the equivalent of $\beta$-acylvinyl anionic synthons for the direct synthesis of cyclic $\alpha,\beta$-unsaturated carbonyl derivatives, butenolides **4** and pyrazolone **6**, in the presence of DBU. Efforts to utilize this reactivity in other transformation as well as asymmetric variants are currently underway.

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**Supporting Information Available:** Experimental procedures and $^{13}C$ and $^{1}H$ NMR and HRMS data for experimental procedures and characterization of the products **4**, **6**, **7** and X-ray crystallographic data (CIF) for **4b** and **6d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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