Synthetic Methods

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A Soft Vinyl Enolization Approach to α-Acylvinyl Anions: Direct Aldol/Aldol Condensation Reactions of (*E*)-β-Chlorovinyl Ketones[**]

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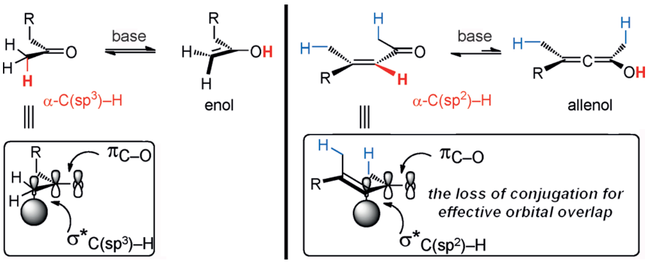
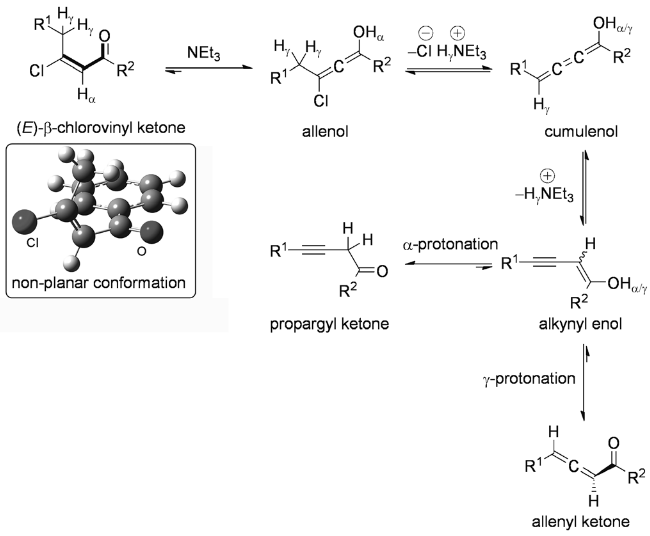
Keto–enol tautomerization is one of the fundamental chemical phenomena that empowers our ability to modulate the reactivity of carbonyl compounds. The enol and metal enolate forms of carbonyl compounds constitute one of the most widely used nucleophiles in the C–C bond forming strategies that readily accommodate various electrophiles as reaction partners.[1] Whereas regio- and stereoselective enol(ate) formation of carbonyl compounds with α-C(sp^3)–H bonds has been achieved with an increasing degree of sophistication,[2] the generation of corresponding enol and enolate forms of carbonyl compounds with α-C(sp^2)–H bonds (such as allenol and allenolates) has been limited to a few exceptional cases of α,β-unsaturated carbonyl compounds (Scheme 1).[3]



Scheme 1. Molecular orbital overlap requirement for α-deprotonation.

The unfavorable orbital overlap between the π_{C-O} bonding orbital and the $\sigma^*_{\alpha\text{-}C-H}$ anti-bonding orbital in a conjugate system makes the α-vinyl deprotonation extremely challenging under mild reaction conditions.[4] Moreover, the presence of other C(sp^2/sp^3)–H bonds in conjugated carbonyl compounds under strong basic conditions adds more complexity to the degree of chemocontrol.[5] Although alternative synthetic methods to form allenolates from alkynyl carbonyl compounds have been developed to avoid such regio- and chemoselectivity issues,[6–9] new methods for the direct generation of allenol/allenolates from α,β-unsaturated carbonyl compounds are highly desirable for the development of α-acylvinyl nucleophile equivalents.

During our investigation of the elimination pathway of β-halovinyl ketones,[10] we observed a facile α-vinyl enolization of (*E*)-β-chlorovinyl ketones by the action of a weak base, NEt$_3$. The non-planar conformational preference of (*E*)-β-chlorovinyl ketones, as opposed to the planar conformational preference of (*Z*)-β-chlorovinyl ketones, was believed to result in better orbital overlap between the π_{C-O} bonding orbital and the $\sigma^*_{\alpha\text{-}C-H}$ anti-bonding orbital, thus allowing for a mild α-vinyl enolization of (*E*)-β-chlorovinyl ketones (Scheme 2). Motivated by our earlier studies combined with the lack of access to α-vinyl nucleophilic synthons from α,β-unsaturated carbonyl compounds under mild reaction conditions,[5] we examined the α-vinyl enolization of (*E*)-β-chlorovinyl ketones for intermolecular C–C bond formations. Herein, we describe the realization of such direct and mild C–C bond formations in the context of aldol and aldol condensation reactions through a facile vinyl enolization method.



Scheme 2. Proposed mechanism for mild α-vinyl enolization of (*E*)-β-chlorovinyl ketones.

To examine the aldol reaction of enol intermediates from the elimination of (*E*)-β-chlorovinyl ketones, we subjected equimolar amounts of (*E*)-β-chlorovinyl ketone **1a** and 2-nitrobenzaldehyde **2a** to mild basic conditions (NEt$_3$; see the Supporting Information for details). To our delight, we observed the formation of a 1:1 diastereomeric mixture of

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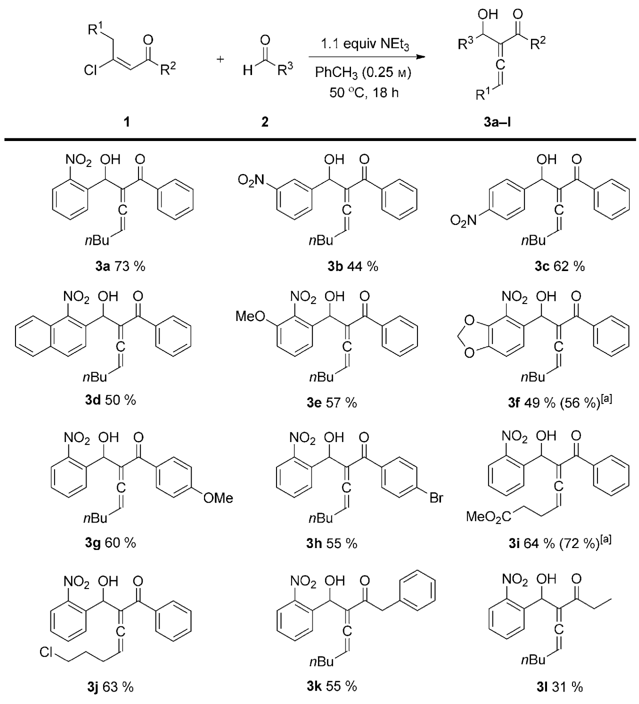
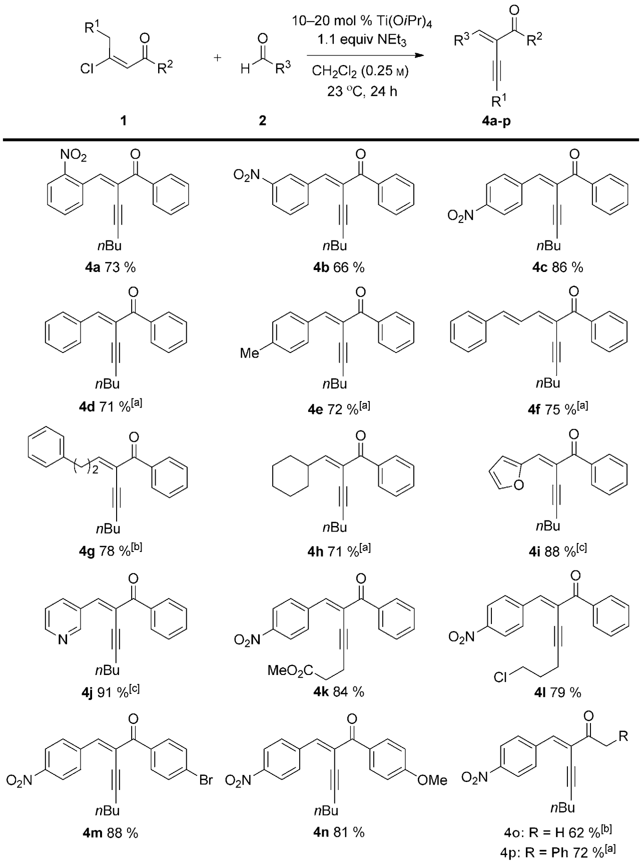


Scheme 3. Scope of the direct aldol reaction of (*E*)-β-chlorovinyl ketones. Yields shown are of isolated product **3**. [a] Reactions at 23 °C in CH_2Cl_2.

aldol products **3** (Scheme 3). This simple and direct reaction procedure provided aldol product **3a** in 73 % yield within 18 h of reaction time. To investigate the substrate scope, we employed a number of aryl aldehydes in the aldol reaction. In general, electron-deficient aryl aldehydes underwent aldol reaction (**3a**–**3f**), whereas other aryl aldehydes failed to undergo aldol reaction and instead exclusively formed the elimination products.[11] Although more studies are needed to expand the scope of the electrophiles, a salient feature of the current mild α-vinyl enolization of (*E*)-β-chlorovinyl ketones was well demonstrated upon the aldol reactions of diversely functionalized/substituted (*E*)-β-chlorovinyl ketones (**3g**–**3l**).[12] The access to such functionalized allenyl ketone derivatives is not currently possible by other "hard enolization" methods such as the direct lithiation of α-allenyl ketones[13] and strong base-promoted isomerization of alkynyl esters.[9] In particular, the employment of aliphatic (*E*)-β-chlorovinyl ketones in our mild α-vinyl enolization approach highlights the unusual chemoselectivity in which α-vinyl enolization was preferentially performed over α-alkyl enolization (**3k**–**3l**). Our results herein are the first α-vinyl enolization of α,β-unsaturated carbonyl systems under mild conditions.

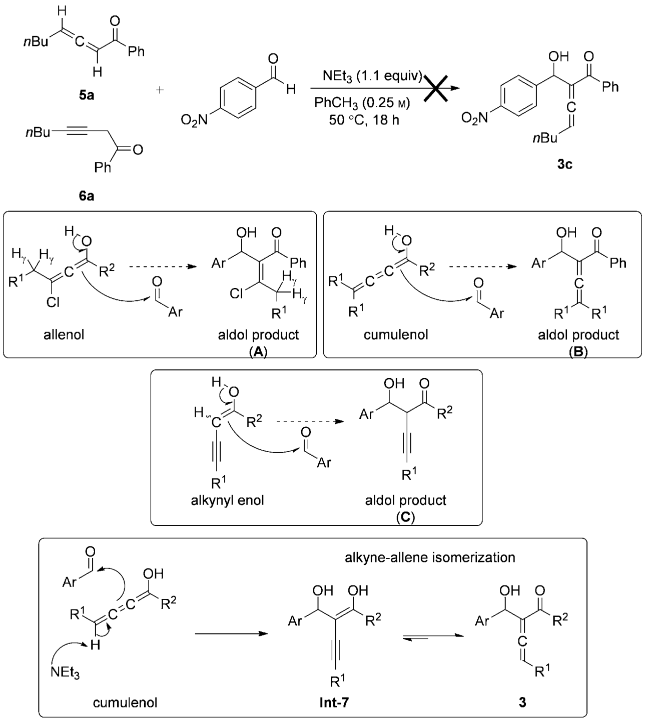
Our observation of the facile formation of an allenol under the action of a mild base prompted us to investigate the feasibility of generating metal allenolates in the presence of a Lewis acid and a weak base, a process termed "soft enolization".[14] Thus, we briefly screened different Lewis acids to broaden the scope of our aldol reaction. Among the Lewis acids we screened, $Ti(OiPr)_4$ was identified as the Lewis acid that promotes aldol condensation reactions (see the Supporting Information for details). Although the soft α-alkyl enolization generally requires stoichiometric amounts of a metal, we found that a catalytic amount of the hard Lewis acid $Ti(OiPr)_4$[15] was sufficient to induce an aldol condensation, providing synthetically versatile 2-(1-alkynyl)-2-alken-1-ones **4** (Scheme 4). It is worth noting that whereas enyne derivatives **4** have been widely utilized in various transition-metal-catalyzed synthetic transformations,[16] the preparation of **4** has not been trivial owing to their functional-group-rich nature, which routinely requires four to five linear steps.[16a] Our aldol condensation reaction provides a facile synthetic route to a range of acyclic enynes **4** in a two-step reaction sequence: the $AlCl_3$-catalyzed (*E*)-selective Friedel–Crafts acylation of alkyne and the $Ti(OiPr)_4$-catalyzed aldol condensation of (*E*)-β-chlorovinyl ketones. Not only aryl aldehydes with different electronic and steric characters (**4a**–**4e**), but also an α,β-unsaturated aldehyde such as cinnamaldehyde (**4f**) and aliphatic aldehydes such as cyclohexanecarboxaldehyde (**4h**), were effective electrophiles. The reaction of heteroaryl aldehydes also afforded enynes (**4i** and **4j**), although a stoichiometric amount of $Ti(OiPr)_4$ was necessary in these cases.[17] A distinctive feature of our aldol condensation of (*E*)-β-chlorovinyl ketones was that a diverse array of functional groups, such as esters and halides, were tolerated



Scheme 4. Scope of aldol condensation by soft α-vinyl enolization. Yields shown are of isolated product **4**. [a] 20 mol % of $Ti(OiPr)_4$. [b] 50 mol % of $Ti(OiPr)_4$. [c] 100 mol % of $Ti(OiPr)_4$.

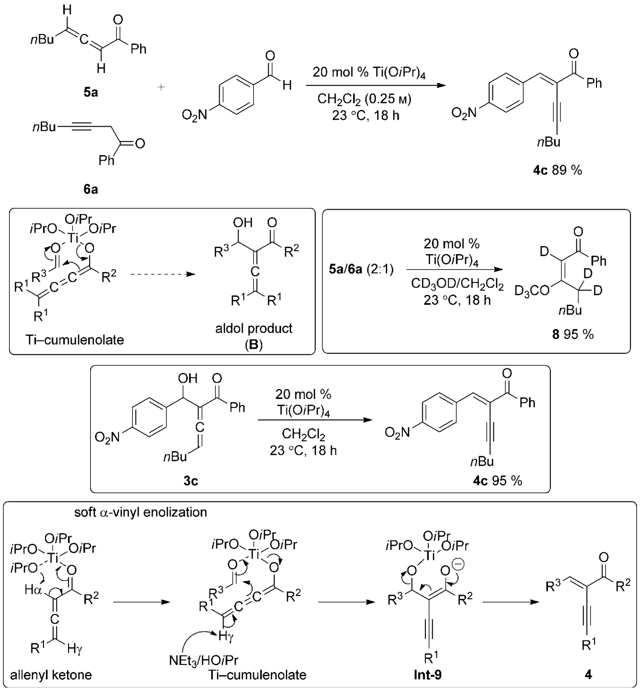
and led to the formation of functionalized enynes (**4k**–**4n**). One particular note regarding the reaction outcome is that the aldol condensation of (*E*)-β-chlorovinyl ketones with α′-hydrogen atoms also led to the exclusive formation of enynes (**4o** and **4p**), although such α′-hydrogen atoms are expected to have lower pKa values than α-vinyl hydrogen atoms.[18]

Examples of the NEt_3-promoted aldol reaction typically required the use of electron-deficient aldehydes to effectively compete against the protic source that promoted the elimination pathway to allenyl and propargyl ketones. In contrast, the $Ti(OiPr)_4$-catalyzed aldol condensation reaction worked well with various aldehydes with different electronic and steric features. Thus, it is possible to speculate that there are different intermediate species between the aldol and aldol condensation reactions. For the NEt_3-promoted aldol reaction, we did not observe the formation of aldol products when a 2:1 mixture of allenyl ketone **5a** and propargyl ketone **6a** was treated with 4-nitrobenzaldehyde under our aldol reaction conditions (Scheme 5). Further studies also showed the following: 1) the absence of aldol products **A** from β-chlorovinyl ketone (a possible aldol pathway of allenol); 2) no aldol reaction product **B** using γ,γ-disubstituted-β-chlorovinyl ketones (a possible aldol pathway of cumulenol); 3) the absence of aldol products **C** from propargyl ketone (a possible aldol pathway of alkynyl enol). On the basis of the above considerations, we propose an aldol reaction mechanism involving the NEt_3-promoted vinylogous aldol-type reaction, which leads to the observed aldol products after alkyne–allene isomerization. The lack of diastereoselectivity in our aldol products suggests that the stereogenic center created by the aldol reaction exerts little effect on the alkyne-allene isomerization.[19]



Scheme 5. Proposed reaction mechanism for the NEt_3-promoted aldol reaction.

As for the $Ti(OiPr)_4$-catalyzed aldol condensation reaction, whereas no reaction was observed using (*Z*)-β-chlorovinyl ketones, we found that a facile aldol condensation reaction between **5a** and **6a** (in a 2:1 mixture) readily occurred in the absence of NEt_3 when a catalytic amount of $Ti(OiPr)_4$ was used (Scheme 6). Several observations regarding the $Ti(OiPr)_4$-catalyzed aldol condensation are noteworthy: 1) no aldol condensation product **B** was observed using γ,γ-disubstituted allenyl ketones (a possible aldol pathway of Ti–cumulenolate); 2) the formation of α,γ-deuterium-exchanged product **8**[10] was observed from allenyl and alkynyl ketones under $Ti(OiPr)_4/CD_3OD$ conditions (a possible isomerization of alkynyl ketones to allenyl ketones); 3) a catalytic amount of $Ti(OiPr)_4$ readily induced the dehydration of aldol product **3c**. Although our previous study established that the conformation of (*E*)-β-chlorovinyl ketones changes in the presence of hard and soft Lewis acids,[10] it appears that $Ti(OiPr)_4$ does not strongly interact with the carbonyl group of (*E*)-β-chlorovinyl ketones to cause the conformational change, this is possibly due to the less Lewis basic nature of the carbonyl group, as well as the less Lewis acidic nature of $Ti(OiPr)_4$ relative to TMSOTf. Instead, the more Lewis basic carbonyl groups of allenyl and propargyl ketones preferentially interact with $Ti(OiPr)_4$ and acidify the α-hydrogen for deprotonation by a proximal alkoxide.[20] Based on our experimental observations, we propose a mechanism for the $Ti(OiPr)_4$-catalyzed aldol condensation reaction that involves a vinylogous aldol-type reaction of the Ti–cumulenolate



Scheme 6. Proposed reaction mechanism for the $Ti(OiPr)_4$-catalyzed aldol condensation reaction.

followed by Ti-promoted dehydration, as shown in Scheme 6.[21] This interpretation is consistent with the fact that $TiCl_4$ does not promote aldol condensation reaction of allenyl and alkynyl ketones.

In summary, we have synthesized a new class of vinyl anion synthons from (*E*)-β-chlorovinyl ketones under mild basic conditions. The synthetic utility of these synthons has been demonstrated in intermolecular aldol and aldol condensation reactions, which lead to functional-group-rich allenyl ketones and enyne derivatives. Although further mechanistic studies remain to be conducted, our preliminary findings suggest the base-promoted vinylogous aldol-type reaction of cummulenol(ate)s as a possible reaction pathway. Given the widespread applicability of enols and metal enolates in stereoselective C–C bond forming reactions,[2] we anticipate that the synthetic scope of cummulenol(ate)s can be further expanded. Accordingly, our current efforts are directed towards addressing the low diastereoselectivity issue by using stereoselective isomerization under Brønsted base catalysis, and further broadening the synthetic utility of cummulenol(ate)s in other C–C bond forming reactions.

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[21] Whereas the Ti-catalyzed aldol reaction is a redox neutral process, and thus capable of regenerating Ti^{IV} complexes with isopropoxide ligands as an active catalyst species, the subsequent dehydration reaction potentially alters the ligand environment of Ti^{IV} complexes. The real reason for how a catalytic amount of $Ti(OiPr)_4$ induces the adol condensation is not clear at the present time. However, the fact that Ti^{IV} complexes, especially the alkoxides, typically aggregate through metathetic ligand exchange, it is our current interpretation that the aggregation of Ti^{IV} complexes may happen in the presence of a small amount of water during the dehydration reaction, where water molecules are loosely coordinated to the Ti^{IV} aggregates. This process potentially preserves most of isopropoxide ligands on the metal center, which can be recycled to induce the Ti-catalyzed aldol reaction. We thank one of the referees for pointing out this catalytic aspect of Ti^{IV} complexes.