

The Michael Addition–Elimination of Ylides to α,β -Unsaturated Imines. Highly Stereoselective Synthesis of Vinylcyclopropanecarbaldehydes and Vinylcyclopropylaziridines

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Much attention has been paid to the construction of multisubstituted cyclopropanes, the basic structural elements in a wide range of biologically active compounds as well as important intermediates in organic synthesis.¹ The tandem Michael addition–elimination of ylides to electron-deficient alkenes provides easy access to functionalized cyclopropanes.² However, few examples were reported on the preparation of cyclopropanecarbaldehydes³ via ylide cyclopropanation of α,β -unsaturated aldehydes, except those related to stabilized ylides,^{2c,4} due to the difficulty associated with the control of the chemoselectivity (C=C versus C=O). Our group described a method for the one-step enantioselective synthesis of 1,3-disubstituted-2-vinylcyclopropanes^{3,5} with high diastereoselectivity from α,β -unsaturated esters, amides, ketones, and nitriles via a sulfur or tellurium ylide.⁶ However, switching the substrate to α,β -unsaturated aldehyde gave epoxide in lieu of the desired cyclopropanecarbaldehyde.⁷ We recently sought a solution to this problem and developed the first example of ylide cyclopropanation of α,β -unsaturated imines, leading to a highly stereoselective synthesis of vinylcyclopropanecarbaldehydes and vinylcyclopropylaziridines. In this communication, we wish to report the preliminary results.

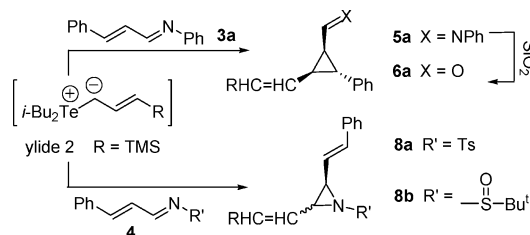
The reactions of ylides with α,β -unsaturated imines were well-studied and documented to afford aziridines as the products via a 1,2-addition.⁸ To the best of our knowledge, no example of ylide cyclopropanation of α,β -unsaturated imines via a 1,4-addition has been described in the literature. Fortunately, we found that telluronium salt **1**, after deprotonation by NaHMDS, could react with imine **3a** in a 1,4-addition manner to afford cyclopropanecarbaldehyde⁹ **6a** and **7a** with excellent chemoselectivity and diastereoselectivity (**6a/7a** > 99/1) in 85% yield (entry 1, Table 1). Further studies showed that the *N*-substituents strongly affected the chemoselectivity. When *N*-sulfonyl or *N*-sulfinyl imine was selected as a substrate instead of the *N*-phenyl imine, only aziridine was obtained. Therefore, the chemoselectivity of the reaction of the ylide with α,β -unsaturated imine could be controlled by a reasonable choice of the *N*-substituents (Scheme 1).

Having established the feasibility of and optimal conditions for the cyclopropanation, we surveyed the scope of the α,β -unsaturated imines. As shown in Table 1, β -aryl and β -heteroaryl α,β -unsaturated imines were good substrates to afford the desired products with high diastereoselectivities (up to >99/1) in good yields (entries 1–7, Table 1), providing easy access to vinylcyclopropanecarbaldehydes that could not be prepared by a direct reaction of α,β -unsaturated aldehydes with allylic ylides due to the problem of the chemoselectivity. Substitution on the aryl ring with both electron-withdrawing and electron-donating groups proved to be well-tolerated, notably, with an ester group attached to the aromatic substituent.

Table 1. Selective Cyclopropanation between Unsaturated Imines and Telluronium Ylide⁷

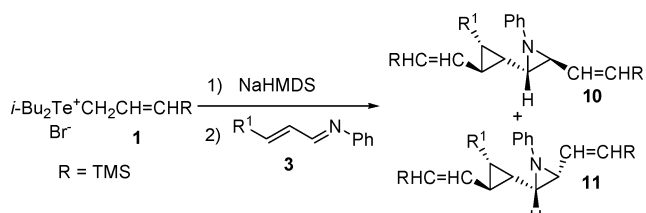
entry	salt	3 (R ¹)	6/7 ^a	yield (%) ^b	ee (%) ^c
1	1	3a (C ₆ H ₅)	>99/1	85	—
2	1	3b (4-ClC ₆ H ₄)	>99/1	75	—
3	1	3c (4-CF ₃ C ₆ H ₄)	>99/1	85	—
4	1	3d (4-MeOC ₆ H ₄)	>99/1	68	—
5	1	3e (4-MeO ₂ C ₆ H ₄)	>99/1	80	—
6	1	3f (2-furanyl)	>99/1	68	—
7	1	3g (2,4-Cl ₂ C ₆ H ₃)	>32/1	88	—
8	9	3a (C ₆ H ₅)	>60/1	85	99
9	9	3b (4-ClC ₆ H ₄)	>60/1	73	95
10	9	3c (4-CF ₃ C ₆ H ₄)	>36/1	83	95
11	9	3d (4-MeOC ₆ H ₄)	>99/1	68	95
12	9	3f (2-furanyl)	>99/1	61	95

^a Determined by 300 M ¹H NMR. ^b Isolated yield. ^c Determined by chiral HPLC for compound **6** when salt **9** was used.

Scheme 1

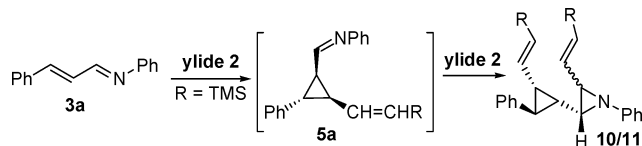
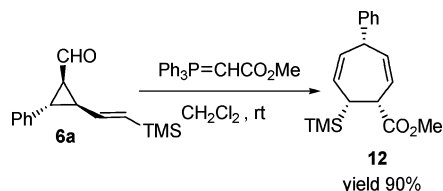
In a previous study,^{6a} it was demonstrated that chiral telluronium salt **9** was good for the highly enantioselective synthesis of vinylcyclopropane derivatives. For both β -aryl and β -heteroaryl α,β -unsaturated imines, the reaction with chiral salt **9** instead of salt **1** gave the desired cyclopropanes with both excellent diastereoselectivity and enantioselectivity in good yields (entries 8–12, Table 1), providing a new method for the preparation of optically active vinylcyclopropanecarbaldehydes in one-pot.

It was a great surprise to us that vinylcyclopropylaziridines **10a** and **11a** were isolated in 82% overall yield when increasing the equivalent ratio between telluronium salt **1** and imine **3a** to 3 to 1, because aliphatic *N*-phenylaldimines were found to be inert to ylide **2** in our previous study.¹⁰ This experimental result also demonstrated the formation of intermediate **5a**, suggesting that the cyclopropyl-

Table 2. One-Pot Synthesis of Cyclopropylaziridines⁷


Entry	3	10/11 ^a	Yield(%) ^b
1	3a	Ph-CH=CH-N-Ph	13/1 82
2	3b	4-ClC ₆ H ₄ -CH=CH-N-Ph	13/1 80
3	3c	4-CF ₃ C ₆ H ₄ -CH=CH-N-Ph	13/1 81
4	3d	4-MeOC ₆ H ₄ -CH=CH-N-Ph	8/1 63 ^c
5	3e	4-MeO ₂ CC ₆ H ₄ -CH=CH-N-Ph	15/1 82
6	3g	2,4-Cl ₂ C ₆ H ₃ -CH=CH-N-Ph	13/1 86

^a Determined by 300 M ¹H NMR. ^b Isolated yield. ^c Products are not very stable on silica gel, and 4 equiv of salt **1** was used. When **3f** was selected as a substrate, the products were completely decomposed on column.

Scheme 2**Scheme 3.** Tandem Reaction from Vinylcyclopropanecarbaldehyde **6a** to Cycloheptadiene **12**⁷

aziridines were produced via a Michael addition–elimination, followed with an aziridination reaction by a second ylide attack (Scheme 2).

By employing 3–4 equiv of salt **1** relative to imine **3**, we found that the desired product with cumulated three-membered rings could be synthesized with good diastereoselectivity (up to 15/1) in reasonable yields (Table 2). Again, β -aryl and β -heteroaryl α,β -unsaturated imines worked well in the sequential cyclopropanation–aziridination. Entry 5 is noteworthy, indicating that the ester group is compatible with the reaction.

In summary, we have developed a new protocol for the preparation of vinylcyclopropanecarbaldehydes as well as cyclopropylaziridines via allylic ylides using readily available α,β -

unsaturated imines as starting materials. The high diastereoselectivity, excellent enantioselectivity, and in particular the unique chemoselectivity make this reaction potentially useful. For example, the aldehyde **6a** was easily transformed into a seven-membered ring compound **12** through a Wittig reaction, followed by a [3,3] σ -rearrangement (Scheme 3).

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Supporting Information Available: Synthesis and characterization of key compounds, chiral HPLC data of **6** (PDF, CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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