Simple strategy for synthesis of optically active allylic alcohols and amines by using enantioselective organocatalysis

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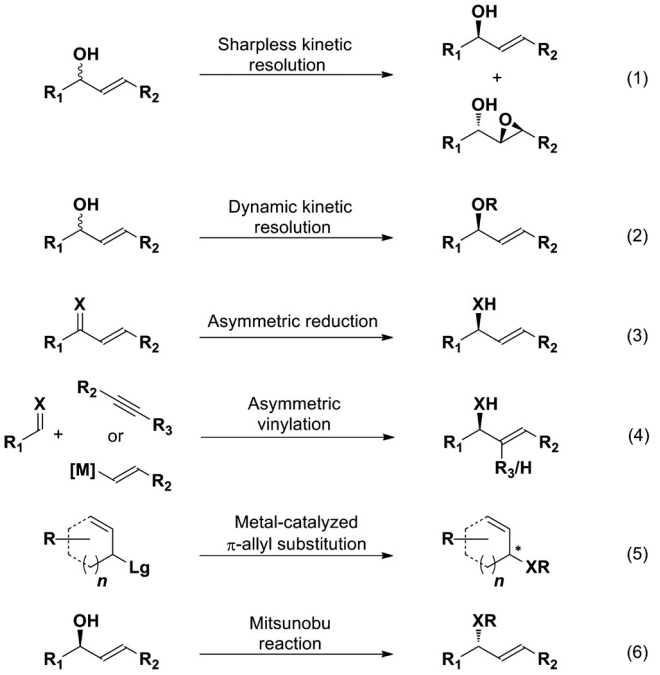
A simple organocatalytic one-pot protocol for the construction of optically active allylic alcohols and amines using readily available reactants and catalyst is presented. The described reaction is enabled by an enantioselective enone epoxidation/aziridination-Wharton-reaction sequence affording two highly privileged and synthetically important classes of compounds in an easy and benign way. The advantages of the described sequence include easy generation of stereogenic allylic centers, also including quaternary stereocenters, with excellent enantio- and diastereomeric-control and high product diversity. Furthermore, using monosubstituted enones as substrates, having moderate enantiomeric excess, the one-pot reaction sequence proceeds with an enantioenrichment of the products and high diastereoselectivity was achieved.

asymmetric catalysis | allylic amines | enantioselectivity

Allylic alcohols and amines represent two of the most abundant and fundamental building blocks in contemporary organic synthesis. The possible transformations of these important compounds are numerous and proceed often with excellent stereoinduction (1–3). Consequently, optically active allylic alcohols and amines have appeared innumerable times as key intermediates in asymmetric total syntheses, showing the need for efficient and benign methods of their formation.

One of the traditional synthetic approaches to optically active allylic alcohols is the catalytic kinetic resolution applying enzymes (4). In addition, Sharpless and coworkers have successfully established an asymmetric titanium-catalyzed resolution of racemic secondary allylic alcohols via the Sharpless-Katsuki epoxidation (5), resulting in a mixture of epoxy-alcohols and optically active allylic alcohols (Scheme 1, expression 1). However, the fact that the resolution method is restricted to a theoretical yield of 50%, makes other direct routes to optically active allylic alcohols highly desirable. With the dynamic kinetic resolution (6), a procedure that allows full conversion of the starting compound to *one* desired product with excellent stereocontrol was established. In this process, a fast and efficient in situ racemization reaction of the undesired enantiomer of the starting material is the key to overcome the 50%-yield limit of the traditional resolution method. However, the scope of this reaction is limited to mainly acyclic substrates and the combined use of transition metal and enzyme is necessary (Scheme 1, expression 2).

As an alternative to the resolution method, several different enantioselective reduction protocols of enones have been developed. Examples are the Corey-Bakshi-Shibata reduction (7), applying a borane-prolinol complex, and the catalytic enantioselective hydrogenation, applying BINAP [2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl]-diamine ruthenium complexes developed by Noyori and coworkers (8) (Scheme 1, expression 3). The needs of bulky functional groups, different substitution patterns at the enone functionality, and inert reaction conditions for obtaining high selectivities are some of the drawbacks of these methods. Another protocol for the enantioselective synthesis of allylic alcohols is the 1,2-addition of vinylic metal species, generated either by transmetallation of boronates or by rhodium- or iridium-catalyzed reductive coupling of acetylenes (9) (Scheme 1, expression 4). While the transmetallation strategy requires the preparation of a "primary organometallic reagent," the reductive coupling of acetylenes is usually performed under high pressure of hydrogen. Foreshadowed by the pioneering work of Trost et al., metal-catalyzed π-allyl substitutions of racemic allylic carbonates or esters have been extensively investigated in the last years (Scheme 1, expression 5). These methods provide straightforward and widely applied synthetic routes to nonterminal allylic alcohols (10–15). Nevertheless, despite the wide applicability, significant challenges remain yet to be solved. Among them is the restriction of π-allyl substitutions to symmetrically disubstituted π-allyl systems, which excludes certain substitution patterns in the allylic products.



Scheme 1. Different methods for synthesis of allylic alcohols and amines; X = O, NH.

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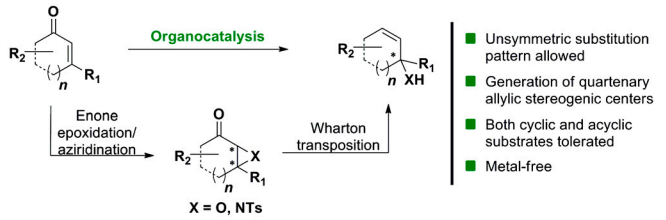
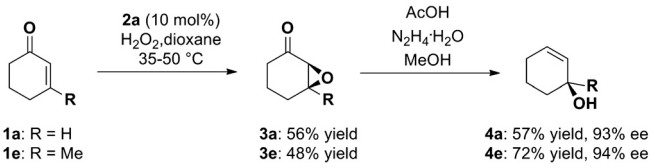


Scheme 2. An organocatalytic approach to allylic alcohols and amines.



Scheme 3. Enantioselective organocatalytic synthesis of allylic alcohols.

Moreover, the formation of quaternary allylic centers is, to the best of our knowledge, not possible using these methods.

Optically active allylic amines have so far been synthesized by almost similar protocols. While the metal-catalyzed π-allyl substitution for the synthesis of allylic amines (Scheme 1, expression 5) is restricted by the same issues mentioned above (16, 17), the 1,2-addition of vinylic metal species to imines (Scheme 1, expression 4) often applies an additional chiral auxiliary attached to the nitrogen atom in order to obtain high stereocontrol (9). An efficient transformation with complete stereoinversion, is the Mitsunobu reaction (Scheme 1, expression 6) which has been applied numerous times for the synthesis of optically active allylic amines (18). However, this process requires optically active allylic alcohols as starting materials and thus provides an indirect route to this important class of compounds.

Despite the achievements published so far for the synthesis of optically active allylic alcohols and amines, there is still need for developments of general, robust, and easy synthetic approaches to these classes of compounds. Incorporation of organocatalytic functionalizations in complex one-pot reactions has recently emerged as an efficient strategy for the formation of many important optically active compounds, otherwise difficult to obtain (19–25). The present work shows the development of an organocatalytic synthetic process, making use of a single amino-catalyst (26–31) in combination with cheap and readily available starting materials, for the formation of allylic alcohols and amines in moderate to good yields and excellent enantioselectivities (Scheme 2). The described reactions are enabled by an enantioselective enone epoxidation/aziridination-Wharton-reaction sequence. While the organocatalytic epoxidation of cyclic and acylic enones has been recently described by List et al. (32, 33) and Deng et al. (34), the organocatalytic aziridination of enones has been mainly limited to acyclic substrates (35, 36). We envisioned that a merger of the catalytic enone functionalizations with the hydrazine mediated 1,3-transposition following the Wharton protocol (37) could allow simple access to a broad spectrum of optically active allylic products under metal-free conditions, and preferably in an one-pot process (Scheme 2).

Results and Discussion

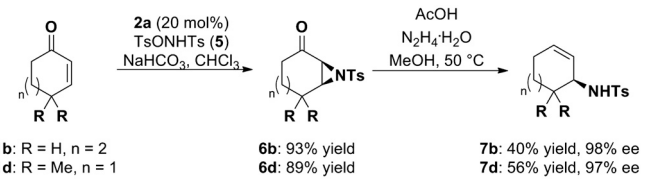
To find the optimal reaction conditions, we started our investigations for the synthesis of optically active allylic alcohols by using cyclohexenone **1a** as a model substrate and performing the envisaged sequence in two separate steps (Scheme 3). Both the epoxidation and Wharton transposition reactions could be achieved providing the desired allylic alcohol **4a** with high enantioselectivity. Comparable results could be attained for 3-methyl cyclohexenone **1e** allowing the formation of the tertiary allylic alcohol **4e**, otherwise difficult to obtain, with excellent enantiomeric excess.

However, the volatility of the optically active epoxy ketones **3a**, **e** and allylic alcohols **4a**, **e** (Scheme 3) makes the development of an one-pot protocol, and therefore a minimization of purification steps, desirable. We have found that sequential addition of hydrazine, methanol, and acetic acid to the reaction mixture of the epoxidation process, after full conversion of the organocatalytic step has been achieved, resulted in higher isolated yields of the corresponding allylic alcohols and maintaining the high enantioselectivity.

A plethora of cyclic enones of various ring-size and substitution patterns were evaluated as substrates in this one-pot sequence and the results are outlined in Table 1. The obtained yields ranged from moderate to good, while the enantiomeric excess remained high in all cases (87–99% ee). Seven-membered allylic alcohols were formed in similar high enantioselectivity, while for the application of cyclopentenone a significant decrease in reactivity was observed, as expected in analogy to previous reports (32). Substitutions at 5-, 4-, and 3-position of the enone were all well tolerated. With respect to use of enones with substitutions at 3- and 4-positions it is noteworthy that they represent substitution patterns difficult to obtain using conventional methods, such as palladium-catalyzed π-allyl substitution or dynamic kinetic resolution. The formation of quaternary allylic stereogenic centers with good enantio-control by nonresolution methods is a highly challenging task (38). Using the present conditions, a variety of allylic alcohols carrying a quaternary allylic center are formed with enantioselectivities up to 99% ee. Finally, it is also demonstrated that acyclic enones (Table 1, entry 9) are valid substrates for this reaction. However, for the acyclic product **4h** an E/Z ratio of 1:1 is observed, which is in accordance with the mechanism of the Wharton rearrangement (39–41).

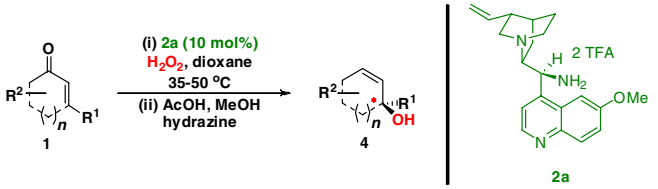
The traditional Wharton reaction is facilitated with a α-carbonyl leaving group, which typically is an epoxy motif as applied in the one-pot reaction sequence for the formation of the optically active allylic alcohols, by which the chirality is set during the first organocatalytic step. Intuitively, we propose that an electron-poor aziridine should be equally effective as the "chiral leaving group," thereby facilitating the formation of the corresponding optically active allylic amines. To the best of our knowledge, such a reaction for this class of compounds has not yet been described. As mentioned previously, the organocatalytic aziridination of cyclic enones has only been rarely described, whereas acyclic enones have been studied more frequently (35, 36). Differently substituted hydroxylamine derivatives were tested as nucleophilic reagents, in which the hydroxy functionality serves as the leaving group and enables therefore the formation of the three-membered heterocycle after the nucleophilic 1,4-addition of the amine moiety. We chose 4-methyl-*N*-(tosyloxy)benzenesulfonamide **5** as a suitable nucleophile, because of its easy and simple access via ditosylation of hydroxylamine and the two-step sequence was initially performed separately (Scheme 4). We were pleased to observe, that the subjection of the synthesized and isolated aziridines to the Wharton transposition conditions led smoothly to the formation of optically active allylic *N*-tosyl amines in good yields and excellent enantioselectivities.

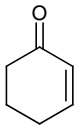
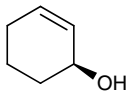
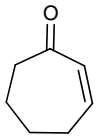
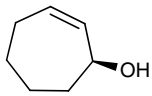
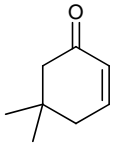
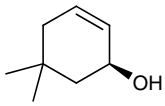
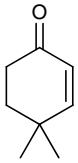
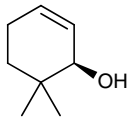
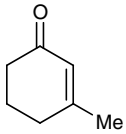
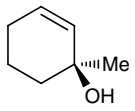
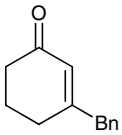
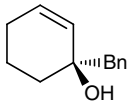
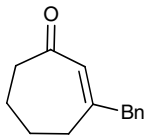
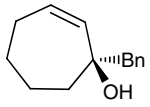
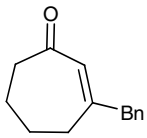
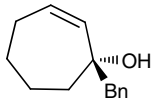
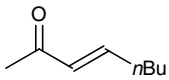
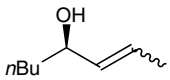
Although the products **7b**, **d** proved to be nonvolatile, an one-pot sequence is highly desirable, reducing purification steps,



Scheme 4. Enantioselective organocatalytic synthesis of allylic amines.

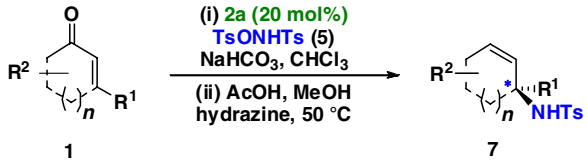
Table 1. One-pot synthesis of allylic alcohols using an organocatalytic epoxidation-Wharton sequence



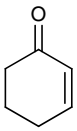
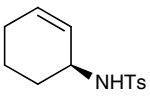
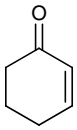
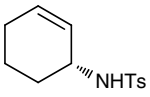
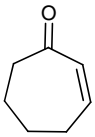
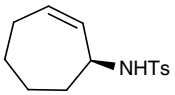
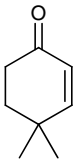
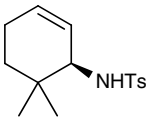
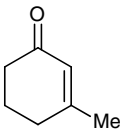
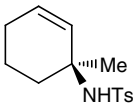
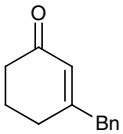
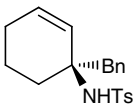
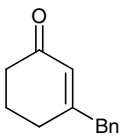
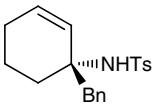
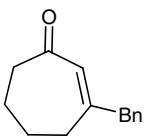
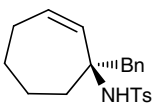
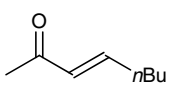
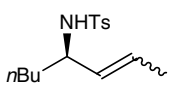
Entry	Enone (**1**)		Product (**4**)		Yield (%)*	ee (%)†
1	**1a**		**4a**		50 (32)§	93 (93)§
2	**1b**		**4b**		45	92
3	**1c**		**4c**		58	87
4	**1d**		**4d**		47	94
5	**1e**		**4e**		40 (35)§	94 (94)§
6	**1f**		**4f**		40	98
7	**1g**		**4g**		45	99
8‡	**1g**		*ent*-**4g**		42	96
9	**1h**		**4h**		54	96

*Yields of isolated products.
†Determined by chiral stationary phase GC or HPLC.
‡The quasienantiomer of the catalyst is used (**2b**, see Scheme 5).
§Results for the sequence performed in two separate steps.

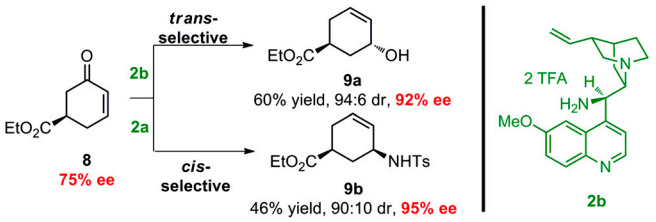
Table 2. One-pot synthesis of allylic amines using an organocatalytic aziridination-Wharton sequence



1 7

Entry	Enone (1)		Product (7)		Yield (%)*	ee (%)†
1	**1a**		**7a**		56	96
2‡	**1a**		*ent*-**7a**		52	95
3	**1b**		**7b**		48 (37)§	98 (98)§
4	**1d**		**7d**		50 (50)§	97 (97)§
5	**1e**		**7e**		57	99
6	**1f**		**7f**		61	99
7‡	**1f**		*ent*-**7f**		69	99
8	**1g**		**7g**		42	94
9	**1h**		**7h**		52	97

*Yields of isolated products.
†Determined by chiral stationary phase HPLC.
‡The quasi-enantiomer of the catalyst was used (**2b**, see Scheme 5).
§Results for the sequence performed in two separate steps.



Scheme 5. Diastereoselective synthesis of allylic alcohols and amines.

material costs, and time. By increasing the amount of acetic acid used in the reductive elimination step, the allylic amines could be synthesized in an one-pot fashion in equally good or higher yields and without affecting the high enantioselectivity (Table 2).

Both six- and seven-membered enones participate in the reaction with satisfactory results and 95–99% ee. As expected, substitution at 4- and 3-position of the enone is tolerated. However, enones bearing substituents in 5-position resulted only in low conversion in the organocatalytic aziridination step. Although the aziridination of 3-substituted cyclic enones has been reported with only moderate enantioselectivity, we accomplished the generation of quaternary allylic centers (**7e**, **f**, **g**) with excellent enantio-control, using the nucleophile **5**. The use of acyclic substrates (entry 9) furnished again the desired product **7h** in high enantiomeric excess (97% ee); however also in this case a 1:1 mixture of *E*/*Z* isomers was obtained.

To further challenge the robustness of the developed reaction sequence, we decided to evaluate the process applying the enantioenriched monosubstituted cyclohexenone **8** (42). As demonstrated in Scheme 5, the synthesis of optically active cyclic allylic alcohol and amine having two stereogenic centers was accomplished with good yields and diastereoselectivities. By employing catalyst **2b**, the *trans*-substituted product **9a** is formed in good yield and diastereomeric ratio, and an enantio-enrichment from 75% to 92% ee is achieved because of double stereoselection. However, by applying catalyst **2a**, the *cis*-product is formed preferably, as demonstrated for compound **9b** formed in 95% ee. A review of literature shows that methods for catalytic asymmetric synthesis of disubstituted cyclic allylic alcohols and amines are limited. Among the simplest and most applied methods is the palladium-catalyzed π-allyl substitution. However, stereo-selective π-allyl substitution is mostly carried out on *cis*-substituted substrates giving retention of the relative stereochemistry of the products, while the corresponding *trans*-product is obtained usually by Mitsunobu inversion (43). Consequently, we believe that the described diastereoselective reaction can serve as a complementary method to the palladium-catalyzed reactions for the formation of both *cis* and *trans*-substituted allylic products.

The mechanistic proposal of the reported one-pot reactions for the formation of optically active allylic alcohols and amines is outlined in Scheme 6. Condensation of the 9-amino-9-deoxyepiquinine ditrifluoroacetic acid salt catalyst **2a** and enone **1** leads to the formation of an activated iminium species **10**, which is subjected to nucleophilic attack of H_2O_2 or TsONHTs (4-Methyl-N-(tosyloxy)benzenesulfonamide) under formation of intermediate **11**. Spontaneous ring closure and hydrolysis provided the optically active epoxy-ketone **3** and aziridine **6** intermediates and liberation of the amino-catalyst. Next, condensation of **3** or **6** with hydrazine under acidic conditions afforded the short-lived iminium species **12**, which upon subsequent ring opening rearrange to intermediate **13**. Final release of volatile N_2 and protonation of the formed vinyl anions provided the desired optically active allylic alcohols **4** and amines **7**. Despite the elevated temperatures and acidic conditions, no racemization was observed, furnishing the products in excellent enantioselectivities.

Conclusion

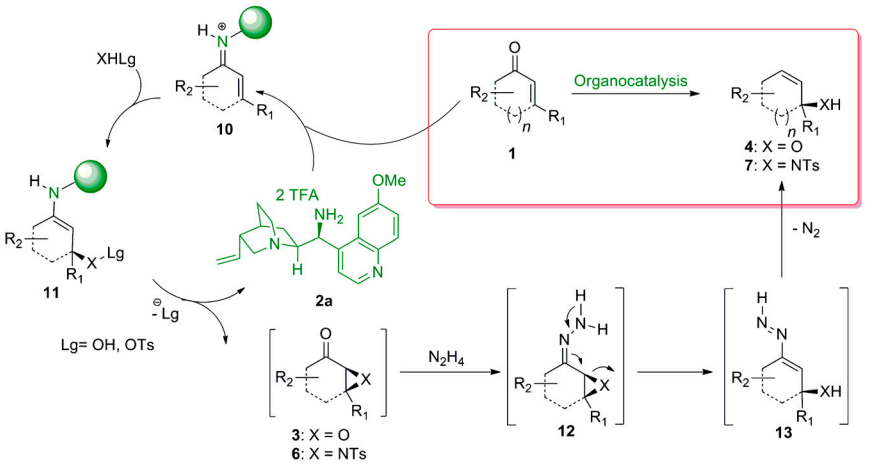
In conclusion, we have developed a simple and metal-free one-pot protocol for construction of optically active allylic alcohols and amines using readily available starting materials. The advantages of the described sequence include easy formation of quaternary allylic centers and expanded product diversity. It should therefore serve as practical complementary to presently available methods.

Materials and Methods

Unless otherwise stated, all commercially available reagents were purchased and used as received without further purification. The amino catalysts **2a**, **b**, enones **1c**, **f**, **g** and **8** were synthesized according to literature procedures (32, 42).

Typical Procedure for One-Pot Synthesis of Allylic Alcohols. An ordinary glass vial equipped with a magnetic stirring bar was charged with the enone **1** (0.25 mmol, 1.0 equivalent), the catalyst **2** (0.025 mmol, 0.1 equivalent), and dioxane (1.0 mL). After 30 min of stirring at room temperature, H_2O (50 wt% in H_2O, 0.30 mmol, 1.2 equivalent) was added. The reaction was heated to 35–50 °C (see individual entries) and kept under vigorous stirring until complete conversion of the enone as monitored by TLC (usually 24–72 h). MeOH (5.0 mL), hydrazine monohydrate (1.25 mmol, 5.0 equivalent), and AcOH (0.63 mmol, 2.5 equivalent) were then added in the described sequence. After an additional 0.5–1 h of stirring at room temperature, the crude reaction mixture was diluted with $NaHCO_3$ (sat.), extracted with CH_2Cl_2 (3 × 10 mL), dried over $MgSO_4$, and most of the excess solvents were carefully removed in vacuo. The remaining volume (*ca.* 1–2 mL) was charged on silica gel and purified by FC (gradient: pentane to pentane/Et_2 2:1).

Typical Procedure for One-Pot Synthesis of Allylic Amines. An ordinary glass vial



Scheme 6. Mechanistic proposal of the formation of allylic alcohols and amines.

equipped with a magnetic stirring bar was charged with TsONHTs **5** (0.38 mmol, 1.5 equivalent), the catalyst **2** (0.05 mmol, 0.2 equivalent), and $CHCl_3$ (1.0 mL). After 10 min of stirring at room temperature, enone **1** (0.25 mmol, 1.0 equivalent) and $NaHCO_3$ (0.5 mmol, 2 equivalent) were added sequentially. The reaction was kept under vigorous stirring until complete conversion of the enone as monitored by TLC (usually 24–72 h). MeOH (5.0 mL), hydrazine (1.25 mmol, 5.0 equivalent), and AcOH (1.13 mmol, 4.5 equivalent) were then added in the described sequence. After an additional 1 h of stirring at 50 °C, the crude reaction mixture was cooled to room temperature, diluted with $NaHCO_3$ (sat.), extracted with CH_2Cl_2 (3×10 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by FC on silica gel (gradient: pentane to pentane/EtOAc 1:1).

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