Heterocycles Hot Paper

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Access to Oxoquinoline Heterocycles by N-Heterocyclic Carbene Catalyzed Ester Activation for Selective Reaction with an Enone**

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Abstract: *Organocatalytic ester activation is developed for a highly selective cascade reaction between saturated esters and amino enones. The reaction involves activation of the β-carbon atom of the ester as a key step. This method allows a single-step access to multicyclic oxoquinoline-type heterocycles with high enantiomeric ratios.*

Nitrogen-containing heterocycles are widely used as bioactive compounds and functional materials. Among these heterocycles, the multicyclic cyclopenta[c]quinolin-4-one (oxoquinoline-type heterocycle) is often presented as a core structural scaffold. These oxoquinoline-type cores are found in natural products (such as meloscine, scandine, and epimeloscine)[1] and in synthetic molecules exhibiting antitumor,[2] anti-inflammation,[3] anti-viral,[4] anti-mycobacterial,[5] and anti-schizophrenia[6] activities (Figure 1a). Previous methods for this class of molecules require multiple synthetic steps and afford only racemic products.[7] Therefore the development of single-step, efficient, chemo- and stereoselective domino methods using simple starting materials and catalysts is needed. In recent years, organocatalytic domino reactions have emerged as an effective strategy to assemble relatively sophisticated molecules. Studies in this direction mainly involve primary and secondary amine catalysts (enamine/iminium catalysis cascade).[8] Cascade reactions using more than one type of organic catalysts (such as N-heterocyclic carbene and amine organic catalysts) have also been reported by the groups of Enders, Rovis, Jørgensen, Chen, and others.[9,10]

Our laboratory is interested in organocatalytic activation of esters.[11] Esters are stable substrates with tunable reactivities. The controllable reactivities can therefore allow highly chemoselective reactions to be developed. This feature makes our organocatalytic ester activation strategy a potentially attractive choice[12] for the development of effective domino reactions to quickly assemble relatively sophisticated molecules. We recently reported N-heterocyclic carbene (NHC) catalyzed activation of the saturated β sp^3-carbon atom of an ester as a nucleophilic center.[11j] We next set out to selectively control the reactivities of the β, α, and carbonyl carbon atoms of an ester (chemoselectivity issues). One objective is to develop protocols for the synthesis of structurally diverse products by starting from identical substrates.[13] Another aim is to realize a domino cascade process for rapid access to complex molecules. Herein we report a highly effective domino process for the enantioselective access to multicyclic oxoquinoline-type heterocycles (Figure 1b). The reaction involves NHC-catalyzed activaton of

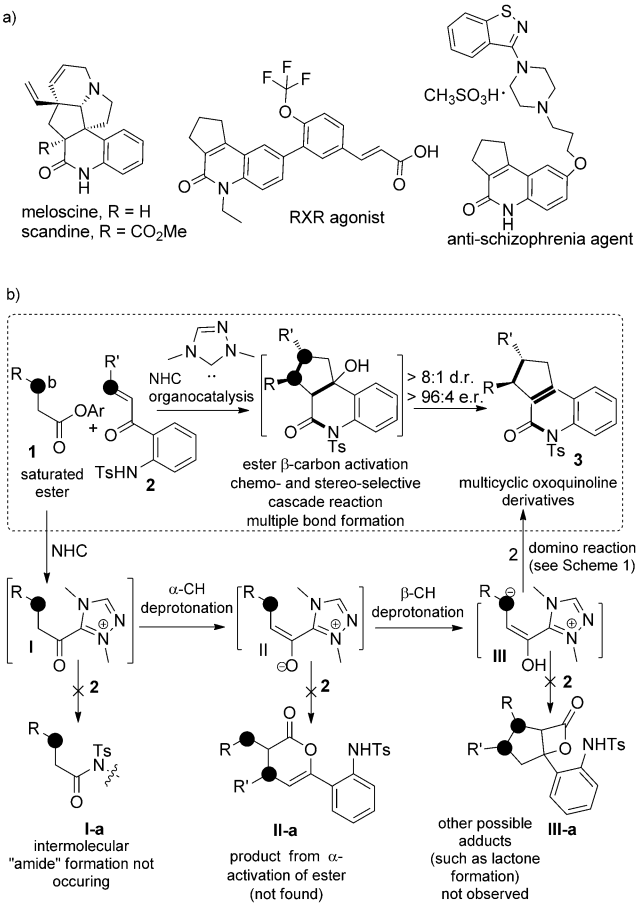

Figure 1. Rapid access to oxoquinoline-type heterocycles. a) Examples of natural products and bioactive molecules. b) Organocatalytic access to oxoquinoline heterocycles by activation of the inert β-sp^3-carbon atom of esters and selective reaction with enones (this work). Ts = 4-toluenesulfonyl.

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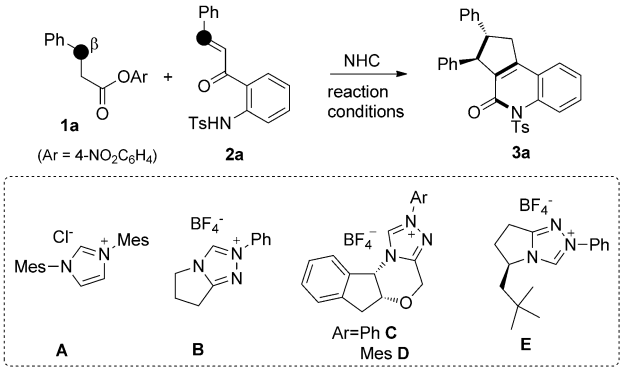
the β sp^3-carbon atom of an ester as the crucial step. Key to the success of this reaction cascade is the suppression of several possible side reactions, including amide formation of the NHC-bound ester intermediate **I**, reaction of the α-carbon atom of the enolate intermediate **II**, and undesired cascade reaction of the intermediate **III**. Specifically, the decreased nucleophilicity of the tosyl-protected amine in the *o*-tosylamino enone **2** was predicted to suppress the possible intermolecular amide (**I-a**) formation between the amino group of **2** and **I**. The use of a strong base (DBU) could promote deprotonation at the β-carbon atom and suppress reaction at the α-carbon atom (to form **II-a**). And the formation of a six-membered lactam (**3**) is more favorable than that of the four-membered lactone **III-a**.

Key results of our initial study and optimization of the reaction conditions using **1a** as a model ester substrate are summarized in Table 1. The enone substrate **2a**, bearing an arylamino moiety, was chosen as the other model reactant and the tosyl moiety was identified as a suitable protecting group. An imidazolium carbene pre-catalyst (**A**) was not effective for this reaction (Table 1, entry 1). When the achiral triazolium NHC pre-catalyst **B** was used with DBU as a base in THF, the desired cascade product **3a** was obtained with 90% yield and 20:1 d.r. (entry 2). Possible side products such as those illustrated in Figure 1b (e.g., amide formation or reaction at the α-carbon atom) were nearly undetectable. Notably, the protecting group on the amine moiety was important for the success of this reaction. For example, the free amino enone could not provide the desired cascade product, and no clear side products were identified. A benzoylamino enone gave less than 10% yield of the desired cascade product, and the major side-product was **III-a** (isolated from formation of cyclopentene after decarboxylation of **III-a**; Figure 1). We next evaluated chiral triazolium NHC catalysts. The aminoindanol-derived triazolium pre-catalysts **C** and **D**, which are excellent carbene catalysts in asymmetric reactions of aldehydes, were not effective for our ester activation (entry 3). Lastly, the triazolium salt **E**, derived from L-neopentylglycine and having a bulky *tert*-butyl substituent, was found to be effective in this cascade reaction, thus affording **3a** in 80% yield, 15:1 d.r., and 96:4 e.r. (entry 4). The use of toluene as solvent (entry 5) gave similar results (83% yield, 10:1 d.r., 97:3 e.r.). Other common organic solvents (e.g., CH_3CN, CH_2Cl_2, 1,4-dioxane, and ethyl acetate) also worked fine for this reaction (see the Supporting Information).

Table 1: Screening of reaction conditions for the reaction of **1a** with **2a**.[a]



Entry	NHC	Solvent	Yield [%][b]	d.r.[c]	e.r.[d]
1	**A**	THF	0	–	–
2	**B**	THF	90	20:1	–
3	**C** or **D**	THF	trace	–	–
4	**E**	THF	80	15:1	96:4
5	**E**	toluene	83	10:1	97:3

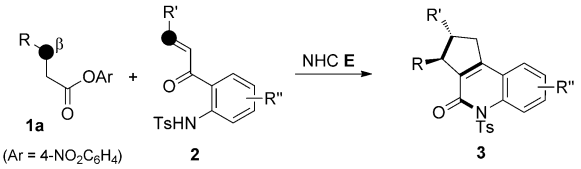
[a] Standard reaction conditions: NHC precursor (20 mol%), **1a** (2.0 equiv), **2a** (0.2 mmol), DBU (1.5 equiv), solvent (0.5 mL), 4 Å M.S., RT, 24 h. [b] Yield of products after column chromatography. [c] Diastereomeric ratio of **3a**, determined by ^{1}H NMR analysis of unpurified reaction mixtures. Absolute configuration of product was determined by X-ray analysis of **3m** (Table 2). [d] Determined by HPLC analysis using a chiral stationary phase. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Mes = 2,4,6-trimethylphenyl, THF = tetrahydrofuran.

With acceptable reaction conditions in hand (Table 1, entry 5), we next evaluated the scope with respect to the saturated ester substrates by using **2a** (Table 2, **3a**–**j**). When esters with a β-aryl substituent were used, both electron-rich and electron-deficient moieties were tolerated on the aryl group (**3b**–**f**). Esters bearing a β-naphthyl (**3g**) or hetero(aryl) (**3h**) substituent worked effectively as well. Remarkably, esters with a β-alkyl substituent (**3i** and **3j**) reacted with **2a** to afford the corresponding cascade products with excellent d.r. and e.r. values, albeit with moderate yields. The scope of the *o*-tosylamino enones **2** was then studied by using **1a** as a model ester substrate (**3k**–**v**). When chalcone-type *o*-tosylamino enone substrates [e.g., R′ = (hetero)aryl group in **3k**–**t**] were used, all the reactions gave the corresponding products with good to excellent yields, and excellent d.r. and e.r. values (**3k**–**t**). The *o*-tosylamino enone substrate with R′ as an alkenyl unit was also tolerated, thus affording **3u** in 93% yield, 14:1 d.r., and 96:4 e.r. In our reaction sequence, the use of an enone with an alkyl unit (R′ as a propyl group) afforded the desired product with 40% yield and excellent d.r. and e.r. values (**3v**). In this case, the major side reaction (accounting for about 40% consumption of the amino enone substrate) was an intramolecular Michael addition of the amine to the enone. The cascade products were nearly undetectable when R or R′ = H. The cascade reactions can be readily scaled up without obvious loss in yield and selectivity. For example, gram-scale preparation (1.03 gram scale) of **3a** was achieved with similar yield and e.r. value as obtained from the small-scale reaction presented in Tables 1 and 2.

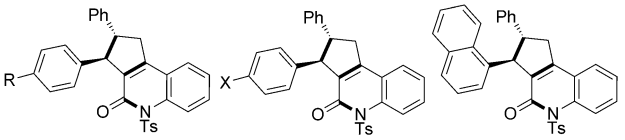
The proposed pathway for the formation of the cascade product **3** is further illustrated in Scheme 1. Addition of the NHC to the ester **1** could give the NHC-bounded ester intermediate **I**, which undergoes α-CH deprotonation to form the ester enolate intermediate **II**. β-CH deprotonation of **II** affords **III** which bears a nucleophilic β-carbon atom. A formal Michael addition of the nucleophilic β-carbon atom of **III** to **2** generates the intermediate **IV**. Subsequent proton transfer followed by intramolecular aldol reaction and lactam formation leads to **VIII**, which undergoes dehydration[14] to form **3**.

Lastly, we demonstrated additional synthetic transformations of the multicyclic domino reaction products by using **3a**

Table 2: Scope with respect to the ester **1** and the *o*-tosylamino enone **2**.[a]



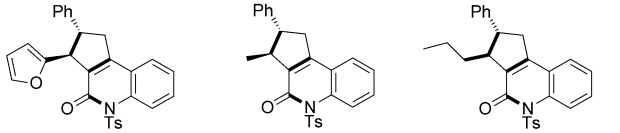
Examples of an ester (**1**), with **2a** as the model electrophile:



R=H, **3a**; 83% yield
10:1 d.r.; 97:3 e.r.
R=OMe, **3b**; 91% yield;
16:1 d.r.; 97:3 e.r.
R=Me, **3c;** 79% yield
15:1 d.r., 97:3 e.r.

X=Cl, **3d;** 85% yield
13:1 d.r., 97:3 e.r.
X=Br, **3e;** 90% yield
12:1 d.r., 97:3 e.r.
X=F, **3f;** 77% yield
11:1 d.r., 97:3 e.r.

3g; 64% yield
20:1 d.r., 97:3 e.r.

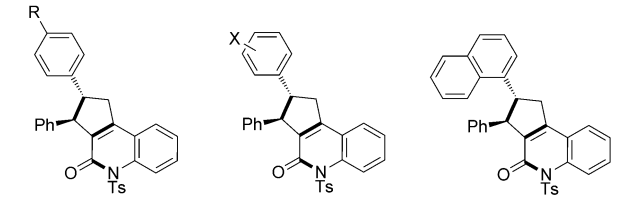


3h; 71% yield
8:1 d.r., 96:4 e.r.

3i; 63% yield[b]
20:1 d.r., 97:3 e.r.

3j; 51% yield[b]
20:1 d.r., 96:4 e.r.

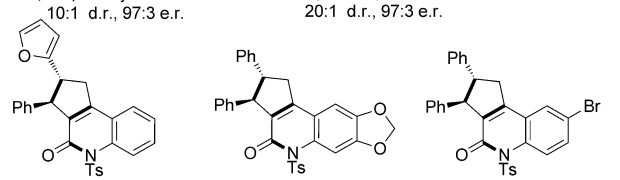
Examples of an *o*-tosylamino enone (**2**), with **1a** as the model ester:



R=OMe, **3k;** 93% yield
12:1 d.r., 97:3 e.r.
R=Me, **3l;** 77% yield
15:1 d.r., 97:3 e.r.
R=Cl, **3m;** 85% yield
10:1 d.r., 97:3 e.r.

X=*p*-Br, **3n;** 72% yield
12:1 d.r., 97:3 e.r.
X=*m*-Br, **3o;** 74% yield
13:1 d.r., 97:3 e.r.
X=*o*-Br, **3p;** 72% yield
20:1 d.r., 97:3 e.r.

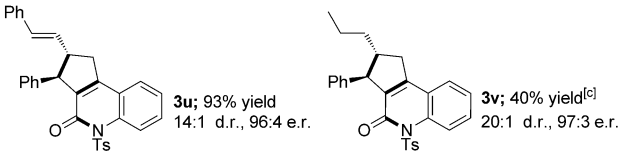
3q; 70% yield
15:1 d.r., 96:4 e.r.



3r; 70% yield
14:1 d.r., 96:4 e.r.

3s; 90% yield
9:1 d.r., 96:4 e.r.

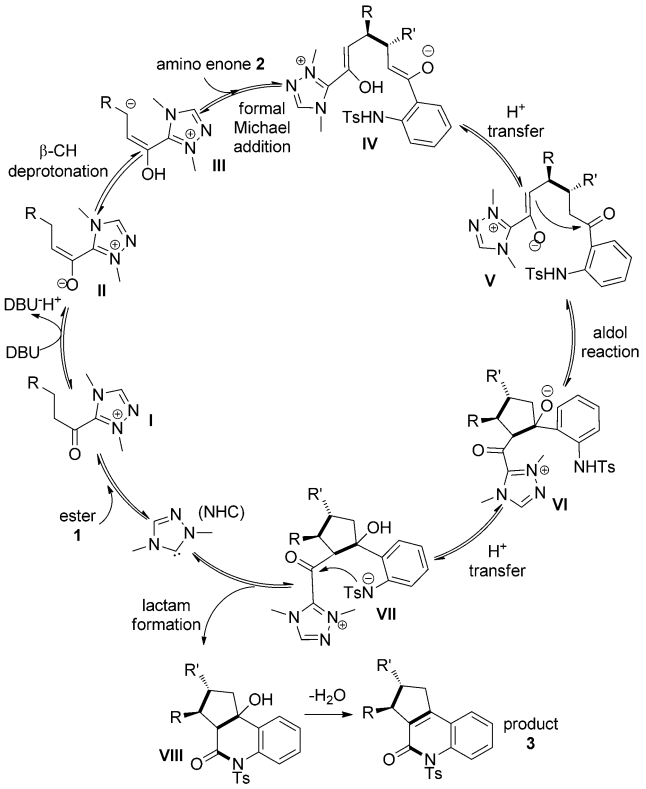
3t; 62% yield
9:1 d.r., 97:3 e.r.



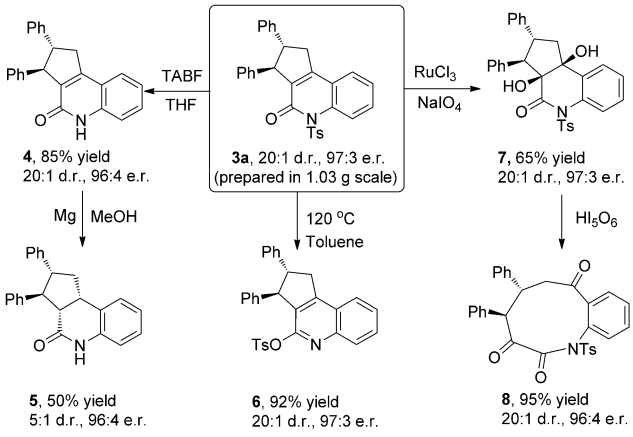
3u; 93% yield
14:1 d.r., 96:4 e.r.

3v; 40% yield[c]
20:1 d.r., 97:3 e.r.

[a] Reaction conditions as in Table 1, entry 5; yields (after SiO_2 chromatography purification) are based on the *o*-tosylamino enone **2**. [b] Reactions run with 3.0 equivalents of ester, 200 mol% DBU, and 0.25 mL toluene for 48 h at room temperature. [c] The *o*-tosylamino enone was added in three portions.



Scheme 1. Proposed mechanism.



Scheme 2. Synthetic transformations of the cascade product **3a.** TBAF = tetra-*n*-butylammonium fluoride.

as a model (Scheme 2). The Ts group of **3a** could be readily removed by TBAF at room temperature to give lactam-type adduct **4** in 85% yield with 20:1 d.r. and 96:4 e.r.[11l,15] The carbon–carbon double bond reduction of **4** was realized stereoselectively by using magnesium in methanol to afford the compound **5**.[7c,16,17] Notably, the tricylic skeleton of **5** is a common moiety found in natural products (such as meloscine, scandine, and epimeloscine)[1] and biologically active compounds[7c,d] (such as fluorinated dihydroquinolines and dihydroquinolines with amine-containing side chains). N to O sulfonyl migration of **3a** at elevated temperature in toluene afforded the quinoline derivative **6**.[11o,18] The OTs group is amenable to further coupling reactions based on literature procedures.[19] Alkene dihydroxylation of **3a** using

$RuCl_3$ and $NaIO_4$ effectively afford the compound **7** with 65% yield and excellent diastereo- and enantioselectivity.[20,21] Oxidative carbon–carbon cleavage of the diol in **7** with HI_5O_6 afforded the nine-memebered lactam **8** bearing two ketone functionalities and two stereogenic centers.[22] Notably, in all these transformations the original stereogenic centers were not affected and the new stereogenic centers were formed with high selectivities.

In summary, we have developed a single-step, chemo-, stereo-, and enantioselective domino method for synthesis of multicyclic oxoquinoline-type heterocycles. This reaction involves NHC-catalyzed activaton of the β sp^3-carbon atom of an ester as a crucial step. Because of the unique reactivity patterns of carboxylic esters (e.g., in comparison with aldehydes or ketones), we expect that previously challenging cascade processes can be made possible through further development of organocatalytic activation of esters.

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