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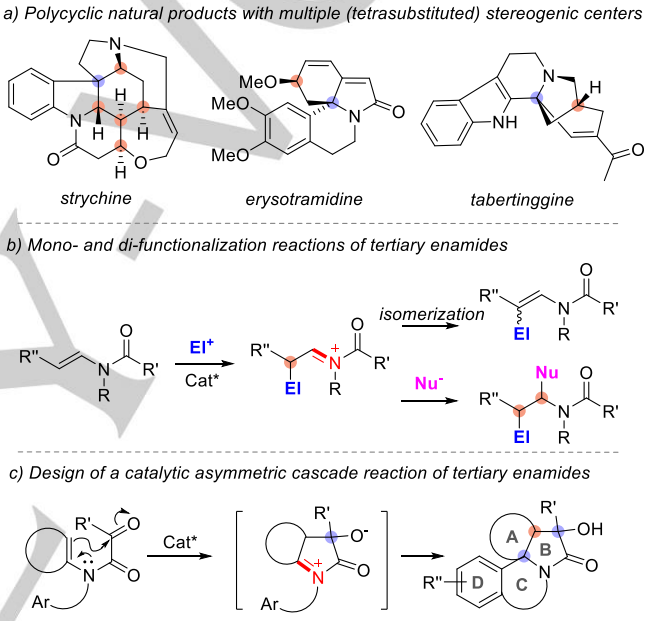
Fused N-Heterocycles with Continuous Stereogenic Centers Accessed by an Asymmetric Catalytic Cascade Reaction of Tertiary Enamides

Li Zhen[a], Shuo Tong*[a], Jieping Zhu[b], Mei-Xiang Wang*[a]

Abstract: *We report in this article a cascade reaction strategy for the expeditious catalytic synthesis of complex N-heterocyclic compounds with continuous and tetrasubstituted stereogenic carbons. Under the sequential catalysis of a chiral binol-Ti complex and BF_3, cyclopentanone-derived tertiary enamides underwent initially an enantioselective enaminic addition to ketonic carbonyls followed by diastereoselective trapping of the resulting acyliminiums by electro-riched aryl moieties to furnish four- and five-ring fused N-heterocyclic products as the sole diastereomers in high yields with up to 99% ee.*

Fused N-heterocyclic structures with multiple (tetrasubstituted) stereogenic centers occur in various natural products (Scheme 1a). They are also privileged core skeletons in the synthesis of complex compounds in drug discovery. Synthesis of these chiral N-heterocyclic compounds in enantiomeric pure form is by no means trivial. Lengthy and tedious multistep reactions are generally required. For example, the early total synthesis of strychnine, one of the most significant landmarks in total synthesis, required 28 steps with a very low overall yield.[1]

Domino reactions or cascade reactions involve two or more chemical bond-forming transformations that take place in time-resolved fashion under the same reaction conditions.[2] In comparison with traditional stepwise synthesis of fused polycyclic structures, domino reactions offer great advantages in terms of synthetic efficiency and practical simplicity. Remarkably, the rational design of reaction substrates and reaction pathways allows the rapid and precise construction of diverse organic compounds that are not readily obtainable by other methods.[3] In a recent synthesis of strychnine, for instance, an anion-induced biscyclization involving a Michael addition/Mannich reaction led to the formation of a key tetracycle skeleton of strychnine, which largely shortened the synthetic steps.[4] Although the power of domino reactions have been demonstrated in literature, the full capacity of the methodology, especially the catalytic asymmetric domino synthesis based on novel synthons and unique reaction sequences remains largely unexplored. [5]



Scheme 1. a) Representative examples of polycyclic natural products with multiple (tetrasubstituted) stereogenic centers; b) reaction modes for the functionalization of tertiary enamides and c) the design of a catalytic asymmetric cascade reaction for the construction of ABCD-ring fused N-heterocyclic structures.

Tertiary enamides are a unique type of synthons in organic synthesis. First of all, there are a number of synthetic methods documented in literature, allowing the preparation of diverse tertiary enamides readily from commodity chemicals and reagents.[6] Secondly, being enamine variants, tertiary enamides show however much higher stability than enamines because of the electronic effect of an electron-withdrawing group on nitrogen atom. In general, no special cautions are necessary to handle these bench stable compounds. In addition, on the contrary to the old notion that tertiary enamides are chemically inert and not useful in synthesis, tertiary enamides have been shown to react smoothly with a large number of electrophilic compounds[7-15] in the presence of catalysts. Furthermore, one of the salient advantages is the nucleophilic reactivity of tertiary enamides is amenable to regulation by the nature of electron-withdrawing substituents on nitrogen atom or the reaction media because these factors tune subtly the cross conjugation system of enamide

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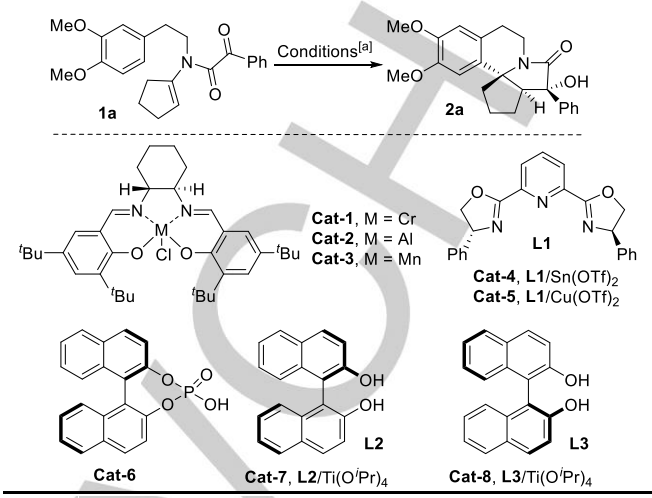
segment (C=C-N-EWG). From their enaminic reactions with electrophiles, tertiary enamides generally produce the corresponding mono-functionalized products. The reactions are believed to proceed through the iminium intermediate followed by iminium-enamine tautomerization (Scheme 1b). We envisioned that if there is another nucleophile in presence and its reaction with the iminium intermediate proceeds faster than the step of isomerization, di-functionalization of tertiary enamides would be accomplished (Scheme 1b). In other words, the domino or cascade reaction comprising enaminic reaction of tertiary enamides followed by the interception of the resulting iminium ions by other nucleophiles would provide a simple, general and unique approach to functionalized organic compounds with very rich structure diversity and complexity. Following the working hypothesis, we have recently developed successfully a chiral Lewis acid-catalyzed intermolecular cascade reaction between tertiary enamides and salicylaldehydes, generating a library of highly enantiomerically pure 4-chromanol derivatives.[11c] We have also demonstrated a catalytic asymmetric intramolecular cascade intermolecular of tertiary enamides to synthesize pyrrolo[2,1-*a*]isoquinoline compounds.[12c] To continue our research to explore the reactions of tertiary enamides and to construct complex small molecular structures of biological and medicinal relevance, we undertook the current study.

Our design of a cascade reaction, which is depicted in Scheme 1c, shows the following features. The use of cyclic ketone-derived tertiary enamides would lead to the formation of ABCD ring-fused N-heterocyclic compounds. During the course of reaction, three continuous stereogenic centers including two tetrasubstituted carbons are generated. The enantioselectivity resulted from the initial chiral catalyst-promoted nucleophilic addition of an enamide to the ketonic carbonyl would dictate the selectivity and stereochemistry of the consecutive cyclization reaction between the resulting acyliminium and aromatic moiety, furnishing most likely a highly enantioselective and diastereoselective catalytic cascade reaction. The heterocyclic compounds obtained are not only densely functionalized amenable to further chemical transformations but resemble the structure of natural products such as erythrina and homoerythrina alkaloids, which have various bioactivities in addition to their well-known curare-like activity.[16]

We began our study with the examination of the cascade reaction of tertiary enamide **1a**, which was prepared conveniently from the condensation between amine and cyclopentanone following by the acylation of the resulting imine with 2-oxo-2-phenylacetyl chloride (Supporting Information). As a prelude to asymmetric catalysis, achiral Lewis acid- and Brønsted acid-catalyzed reactions were tested. A brief survey of catalysts and reaction conditions revealed that $InCl_3$, $BF_3{\cdot}OEt_2$ and *para*-toluenesulfonic acid (*p*-TSA) were the most efficient catalysts to afford the desired tandem reaction within 2 h in DCM. Pleasingly, the reaction afforded an anticipated nitrogen-containing tetracyclic ring product **2a** in 99% yield (Table 1, entries 2-3). It is notable that, although the second cyclization or the interception of iminium by 2,3-dimethoxyphenyl may take place on two sites of the arene ring, no other reigoisomeic product was formed actually. This is mainly attributable to the steric effect. As determined by means of 1H NMR method, the diastereomeric ratio was >19:1,

Table 1. Development of catalytic enantioselective tandem reaction.



Entry	Cat. (0.2 eq)	Additive (0.2 eq)	Solvent	t [h]	d.r.	Yield [%][b]	*ee* [%][c]
1	*p*-TSA	-	DCM	2	>19:1	92	-
2	BF_3	-	DCM	2	>19:1	99	-
3	$InCl_3$	-	DCM	2	>19:1	99	-
4	**Cat-1**	-	DCM	12	>19:1	trace	n.d.[d]
5	**Cat-2**	-	DCM	72	>19:1	47	31
6	**Cat-3**	-	DCM	72	>19:1	0	-
7	**Cat-4**	-	DCM	48	>19:1	82	29
8	**Cat-5**	-	DCM	12	>19:1	45	26
9	**Cat-6**	-	DCM	24	>19:1	46	14
10	**Cat-7**	-	DCM	24	>19:1	50	57
11	**Cat-7**	-	DCE	24	>19:1	42	44
12	**Cat-7**	-	$CHCl_3$	24	>19:1	18	85
13	**Cat-7**	-	CCl_4	48	>19:1	0	-
14	**Cat-7**	-	THF	24	>19:1	47	28
15	**Cat-7**	-	CH_3CN	24	>19:1	72	39
16	**Cat-7**	-	toluene	12	>19:1	18	82
17	**Cat-7**	-	xylenes	24	>19:1	33	94
18[e]	**Cat-7**	*p*-TSA	xylenes	24	>19:1	84	94
19[e]	**Cat-7**[f]	*p*-TSA	xylenes	24	>19:1	95	92
20[g]	**Cat-7**[f]	BF_3	xylenes	24	>19:1	92	98
21[g]	**Cat-7**[h]	BF_3	xylenes	24	>19:1	89	85

[a] Conditions: **1a** (0.2 mmol), catalyst (20 mol%), solvent (6 mL), RT. [b] Yield of isolated product. [c] Measured by chiral-phase HPLC. [d] Not determined. [e] *p*-TSA (20 mol%) was added after 12 h. [f] Used **Cat-7** (15 mol%). [g] $BF_3{\cdot}Et_2O$ (20 mol%) was added after 12 h. [h] Used **Cat-7** (10 mol%).

indicating that the stereochemistry of iminium intermediate dictated excellently diastereoselectivity of second cyclization reaction in the cascade. Encouraged by high reaction efficiency and excellent diastereoselectivity, we then commenced the investigation of asymmetric catalysis to develop enantioselective and diastereoselective synthesis of complexed heterocyclic compounds. A few easy-to-handle privileged chiral catalysts, which structures are depicted in Table 1, were selected in the screening and optimization study. We first looked at the catalytic performance of chiral salen/metal complexes (**Cat-1**,**2**,**3**), which

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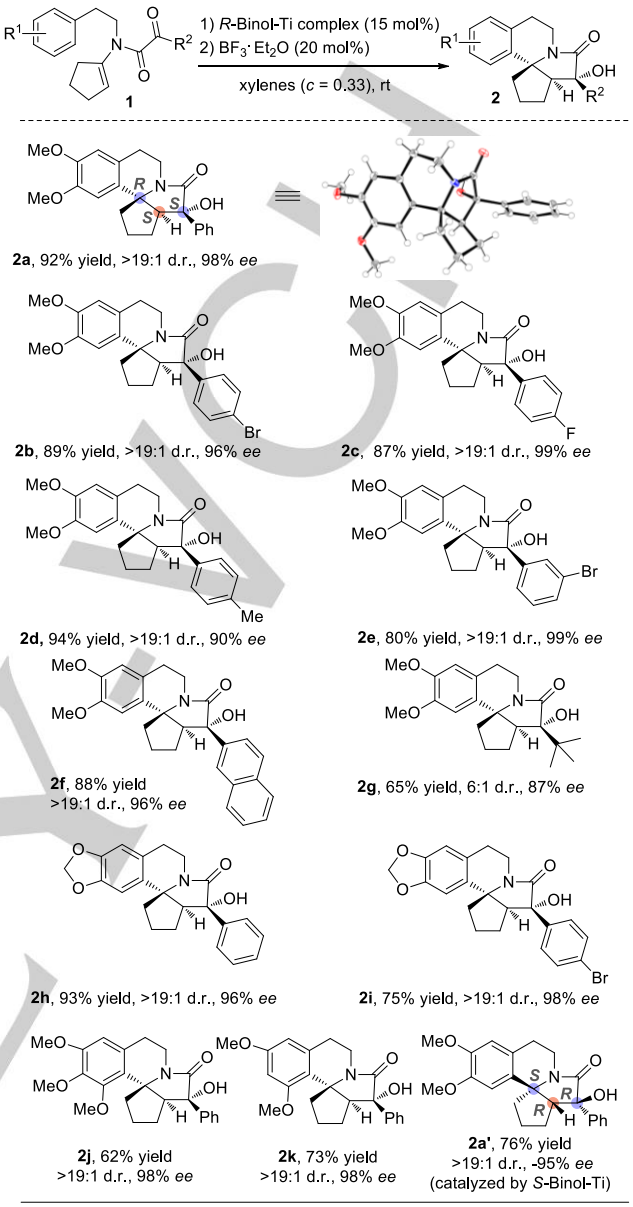
had been validated in catalysing the enantioselective addition of tertiary enamides to ketones. Surprisingly, they either showed virtually no catalytic activity (Table 1, entries 4 and 6) or induced low enantioselectivity (Table 1, entry 5). It was also disappointing that chiral catalysts derived from the complexation of Pybox with tin and copper (**Cat-4**,**5**) gave moderate yields of product with *ee* values below 30% (Table 1, entries 7 and 8). Neither a good yield nor a high ee value was observed from chiral phosphoric acid (**Cat-6**) catalysed reaction (Table 1, entry 9). The complex of *R*-binol with Ti(O^{i}Pr)$_4$ (**Cat-7**) was then examined as the chiral Lewis acid catalyst. Gratifying, the first reaction conducted at room temperature in DCM yielded **2a** in 50% yield with *ee* being 57% (Table 1, entry 10). The promising result promoted us to scrutinize other reaction parameters in order to improve the efficiency and selectivities. As indicated by the results compiled in Table 1 (entries 10-17), reaction media played a crucial role in determining the conversion and stereoselectivity. Switching from DCM to other halogen-containing solvents like DCE, $CHCl_3$, and CCl_4 diminished either reactivity or enantioselectivity (Table 1, entries 11-13 *vs* entry 10). Polar solvents such as THF and CH_3CN also had a detrimental effect on the enantioselective control (entries 14-15). Aromatic solvents toluene and xylenes turned out to be the better choices (entries 16-17). However, although the *ee* value of product **2a** was improved dramatically to 94% when xylenes was employed as the solvent, the chemical yield of **2a** was far from satisfaction. Monitoring the reaction course using TLC revealed the formation of by-products. They were probably generated from reaction pathways other than designed second cyclization of putative iminium intermediate (Scheme 3). To facilitate the second cyclization reaction, an additional Lewis acid or Brønsted acid was added after 12 hours' interaction of **1a** with *R*-binol-Ti(O^{i}Pr)$_4$ complex. To our delight, the addition of either $BF_3{\cdot}OEt_2$ or *p*-TSA (10 - 20 mol%) showed significantly a beneficial effect, leading the formation of highly enantioenriched **2a** in high yields (Table 1, entries 18 - 21). Finally, the reaction of **1a** in xylenes (*c* = 0.33 M) at room temperature in the presence of catalysts **Cat-7** (0.15 eq) and $BF_3{\cdot}OEt_2$ (added after 12 h) was established as the best conditions. Under these optimized conditions, pure nitrogen-containing fused tetracyclic compound **2a** was obtained in 92% yield with excellent enantioselectivity (98% *ee*) and diastereoselectivity (>19 : 1 d.r.) (Table 1, entry 20).

With optimal conditions in hand, we then examined the scope of the cascade reaction for the synthesis **2**. First of all, tertiary enamides having both an electron-withdrawing and electron-donating group on the aromatic ring (**1b**-**1e**) underwent as same efficient and stereoselective cascade reaction as **1a** to afford the corresponding fused tetracyclic products **2b**-**2e** in 87 – 94% yields and 90 – 99% *ee* (Scheme 2). The 2-naphthyl substituted product **2f** was synthesized analogously in a high yield with excellent enantioselectivity and diastereoselectivity. When the aryl group was replaced with an alkyl substitute such as a *t*-butyl, substrate **1g** was transformed similarly into the product **2g**, albeit in a slightly diminished yield and enantioselectivity. The alkyl group seemed to be less powerful than aryl to govern the diastereoselectivity of the reaction to form ring C. In addition to 3,4-dimethoxyphenyl (ring D), other electron-rich aromatic components such as 3,4,5-trimethoxyphenyl,



Scheme 2. Binol-Ti-catalyzed enantioselective synthesis of **2** and X-ray structure of **2a**. Yields are those of the isolated products and the *ee* values were determined by chiral HPLC analysis.

3,5-dimethoxyphenyl, and piperonyl in the reactant **1** were also capable of intercepting the acyliminium intermediate formed from initial *R*-binol-Ti complex-catalyzed nucleophilic addition of enamide to ketonic carbonyl, thus enabling the preparation of the tetracyclic compounds **2j-2k** and even pentacyclic compounds **2h-2i**. All products were obtained with high enantiomeric and diastereomeric purity. As we expected, when the *S*-binol-Ti complex **Cat-8** was applied as a chiral catalyst, the reaction of **1a** gave product **2a'**, the enantiomer of **2a**, in comparable yield and stereoselectivity. The structure of all products were supported by their spectroscopic data (Supporting Information). The absolute configuration of products (*3S*, *4S*, *5R*)-**2** was assigned unambiguously based on the X-ray single crystal and molecular

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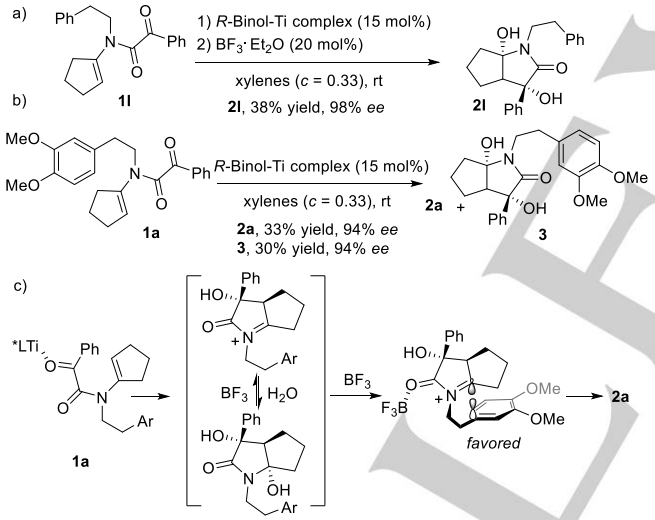
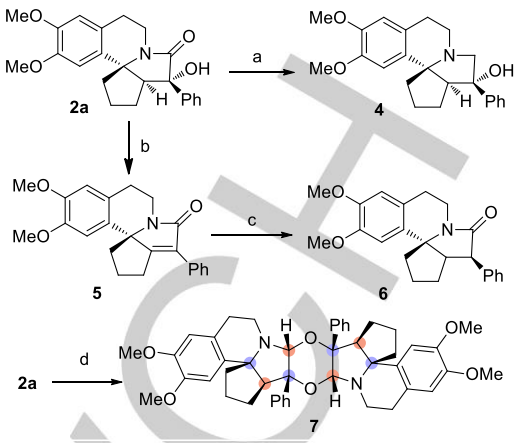
structure of **2a** (Table 1, entry 1 and Supporting Information).[17] The similarity of the core structure and the same stereochemistry of **2a'** to the skeleton of erythrina-type alkaloids are noteworthy.

The excellent stereoselectivities of cascade cyclization reaction of tertiary enamides under the catalysis of chiral binol-Ti(O^iPr)$_4$ and $BF_3{\cdot}OEt_2$ were intriguing. To understand the stereochemical course, we replaced the electron-rich arene moieties by simply a phenyl group. The reaction stopped with the formation of **2l** with ee of 98% (Scheme 3a), indicating the excellent enantioselectivity induced by the chiral catalyst. Moreover, for the reaction of **1a**, when the second catalyst $BF_3{\cdot}Et_2O$ was not added, a monocyclization product **3** was also isolated in 30% yield and 94% *ee* in addition to **2a** (33% yield, d.r. >19:1, 94% ee) (Scheme 3b). Taking all results into account, a reaction pathway was proposed. As depicted in Scheme 3c, *R*-binol-Ti complex activated the ketonic carbonyl trigging a highly enantioselective intramolecular enaminic addition to form the acyliminium, which reacted with water to generate N,O-hemiacetal. Sequentially, the presence of BF_3 accelerated the formation of acyliminium and its interception by the tethered electron-rich aryl moiety from the *Si*-face to afford **2a** in a dominant diastereoselective manner. The *Re*-face trapping was hardly happened because of the steric hindrance of both cyclopentane ring and a bulky aryl substituent.



Scheme 3. Control experiments and a proposed reaction pathway.

The acquired products would constitute a versatile platform for elaboration of diverse N-heterocyclic compounds potentially useful in drug discovery. To illustrate the application of the method, several transformations of **2a** were attempted. As shown in Scheme 4, lactam reduction of **2a** with an excess amount of $LiAlH_4$ in refluxing THF afforded **4** in 64% yield. Dehydration of **2a** afforded the α,β-unsaturated lactam **5** in 96% yield. Further catalytic hydrogenation of **5** in the presence of Pd/C produced **6** in 93% yield with a diastereomeric ratio of >19:1. We also found that reaction of **2a** under milder reduction conditions delivered **7**, a nonacyclic compound in a decent yield.



Scheme 4. Post-transformation of **2a**. a) $LiAlH_4$ (5 equiv), THF, reflux, 8 h, 64%; b) MsCl (3.6 equiv), Et_3N (7 equiv), DCM, RT, 12 h, 96%; c) Pd/C (10% w/w), H_2 (1 atm), MeOH, RT, 12 h, 93%; d) $LiAlH_4$ (3.5 equiv), THF, 60 °C, 4 h, 67%.

In summary, we have developed a novel and asymmetric catalytic cascade reaction of tertiary enamides. The method enabled the rapid synthesis of complex N-heterocyclic compounds with continuous and tetrasubstituted stereogenic centers in high yield and excellent enantioselectivity and diastereoselectivity. We have also shown the synthetic application of the method by transforming the resulting products into four types of different derivatives. The structure of all these products, which are hardly accessible by other synthetic methods, resembled the key structure motif found in many bioactive alkaloids. Currently, synthesis of erythrina-type and iboga-type alkaloids based on this methodology is being actively pursued in this laboratory and results will be reported in due course.

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Keywords: asymmetric catalysis • cascade reactions • tertiary enamides • cyclization reactions • alkaloids analogs

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[17] CCDC 1948733 (**2a**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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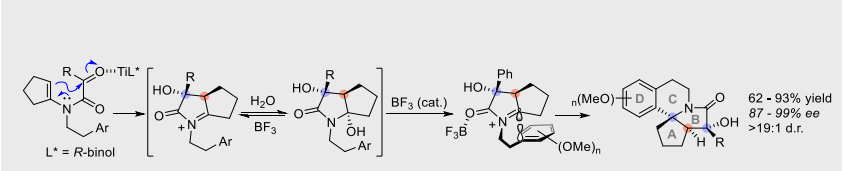

Under the sequential catalysis of a chiral binol-Ti complex and BF_3, cyclopentanone-derived tertiary enamides underwent initially an enantioselective enaminic addition to ketonic carbonyls followed by diastereoselective trapping of the resulting acyliminiums by electro-riched aryl moieties to furnish four- and five-ring fused N-heterocyclic products as the sole diastereomers in high yields with up to 99% ee.

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Fused N-Heterocycles with Continuous Stereogenic Centers Accessed by an Asymmetric Catalytic Cascade Reaction of Tertiary Enamides