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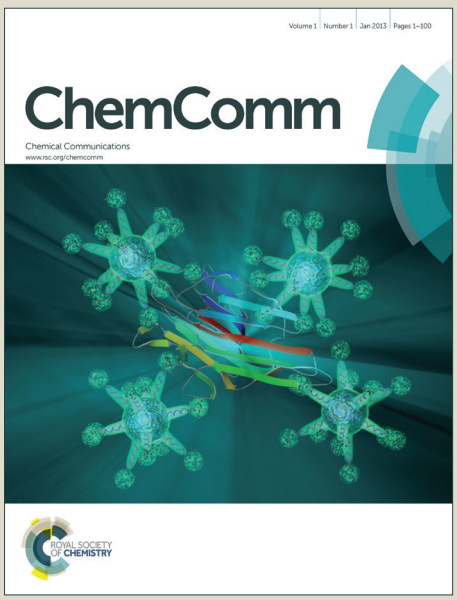

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Exploring Tertiary Enamides as Versatile Synthons in Organic Synthesis

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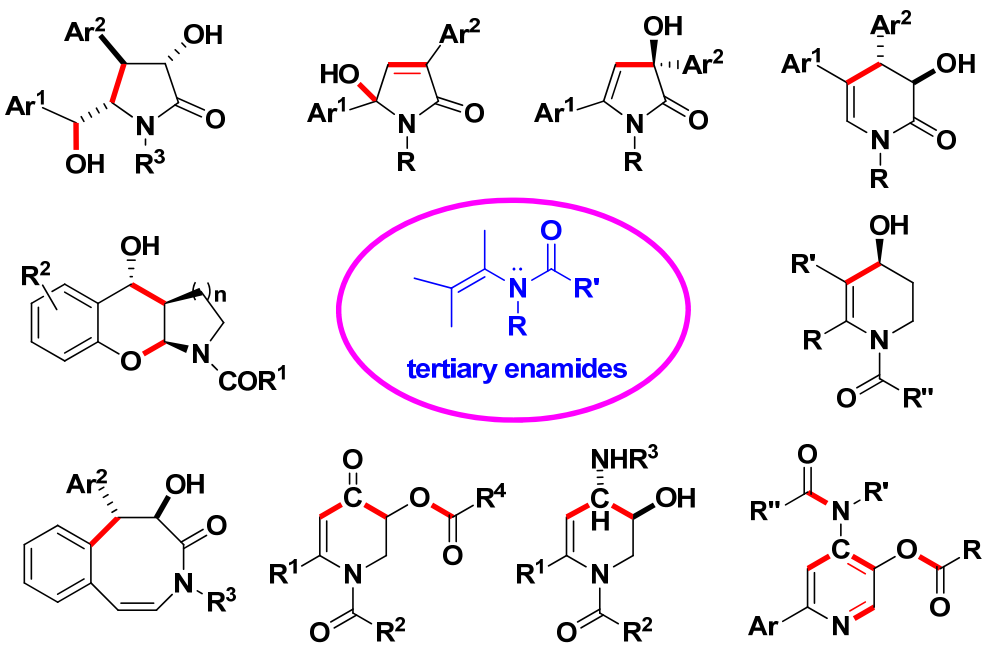

Contrary to general notion, tertiary enamides are reactive and unique synthons for the construction of diverse heterocycles of biological significance.

Abstract: Tertiary enamides had long been known as stable and marginally valuable enamine variants in synthesis. The notion has been challenged however in recent years. Enabled regulation of the cross conjugation system of tertiary enamides has

been shown successfully to enhance delocalization of the nitrogen lone-pair electrons into carbon-carbon double, reinvigorating the enaminic reactivity of tertiary enamides. In this Feature article, I will summarize the recent advances in the exploration of nucleophilic reactions of tertiary enamides and their applications in the synthesis of natural products and heterocyclic compounds of biological and pharmaceutical relevance, with a primary focus on our own work.

Introduction

Enamines are powerful synthetic intermediates and find wide applications in organic synthesis owing to the Stork's milestone works in 1950s.[1,2] The importance of enamine chemistry has been substantiated in recent years by asymmetric enamine catalysis.[3] When one of the *N*-alkyl groups of enamines is replaced by an electron-withdrawing group such as an acyl, tertiary enamides are generated. Further substitution of the other *N*-alkyl by hydrogen leads to the formation of secondary enamides (Figure 1). In comparison to enamines, enamides exhibit much diminished enaminic reactivity because the *N*-electron-withdrawing group alleviates the delocalization of lone-pair electrons of the nitrogen atom into the carbon-carbon double bond.[4] The stability of enamides is well demonstrated by the occurrence of stable enamide structures in natural products.[5] The vast majority of synthetic applications of enamides documented in literature are their asymmetric reduction reactions. Indeed, enamides or dehydroamino acid derivatives are used as a testing ground for the study of efficiency and enantioselectivity of catalytic asymmetric hydrogenation of the carbon-carbon double bond.[6]

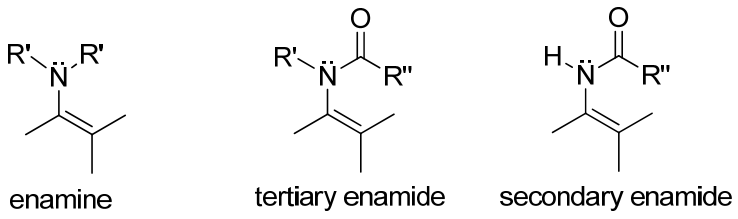

Figure 1. General structures of enamine, tertiary and secondary enamides.

Secondary enamides have been shown recently to be reactive towards highly electron-deficient unsaturated reactants.[7-10] However, these reactions catalyzed by either chiral Lewis acids or Brønsted acids proceed through the typical aza-ene addition reaction pathways in which secondary enamides act actually as the aza-ene components (C=C-N-H). No reactions take place when tertiary enamides are employed instead of secondary enamides under the identical conditions. Only in the case of interacting with powerful electrophiles such as oxonium,[11] iminium[12,13] and acyl halides,[12] do tertiary enamides display enaminic or nucleophilic reactivity. Synthetic applications of tertiary enamides are therefore very limited.

The notion that tertiary enamides are stable, silenced enamines and marginally valuable chemical entities has been challenged. Structural analysis reveals a cross conjugation system within tertiary enamides. Conjugation of the lone-pair electrons of nitrogen with the carbon-carbon double bond and with the carbon-oxygen double bond would favor the charge-separated resonance forms A and B, respectively (Figure 2). We envisioned that the enabled regulation of the cross conjugation system by means of electronic and steric effects of the substituents attached on the enamide segment (C=C-N-CO) would enhance the delocalization of the lone-pair electrons of nitrogen into the carbon-carbon double bond, reviving the nucleophilicity of tertiary enamides. Changing the reaction conditions by varying the polarity of the reaction media for instance would also tune the cross conjugation system to rejuvenate the enaminic reactivity of tertiary enamides. In the past years we have endeavored to explore the nucleophilic reactions and synthetic applications of stable tertiary enamides. We have shown that tertiary enamides are unique shelf stable enamine variants and versatile synthons in synthesis. This feature article will highlight recent advances in the nucleophilic reactions of tertiary enamides and their applications in the synthesis of *N*-heterocyclic compounds, with a primary focus on our own work.

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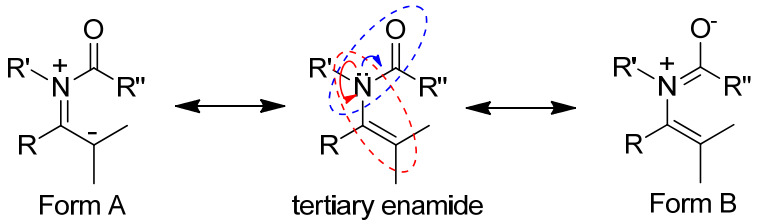
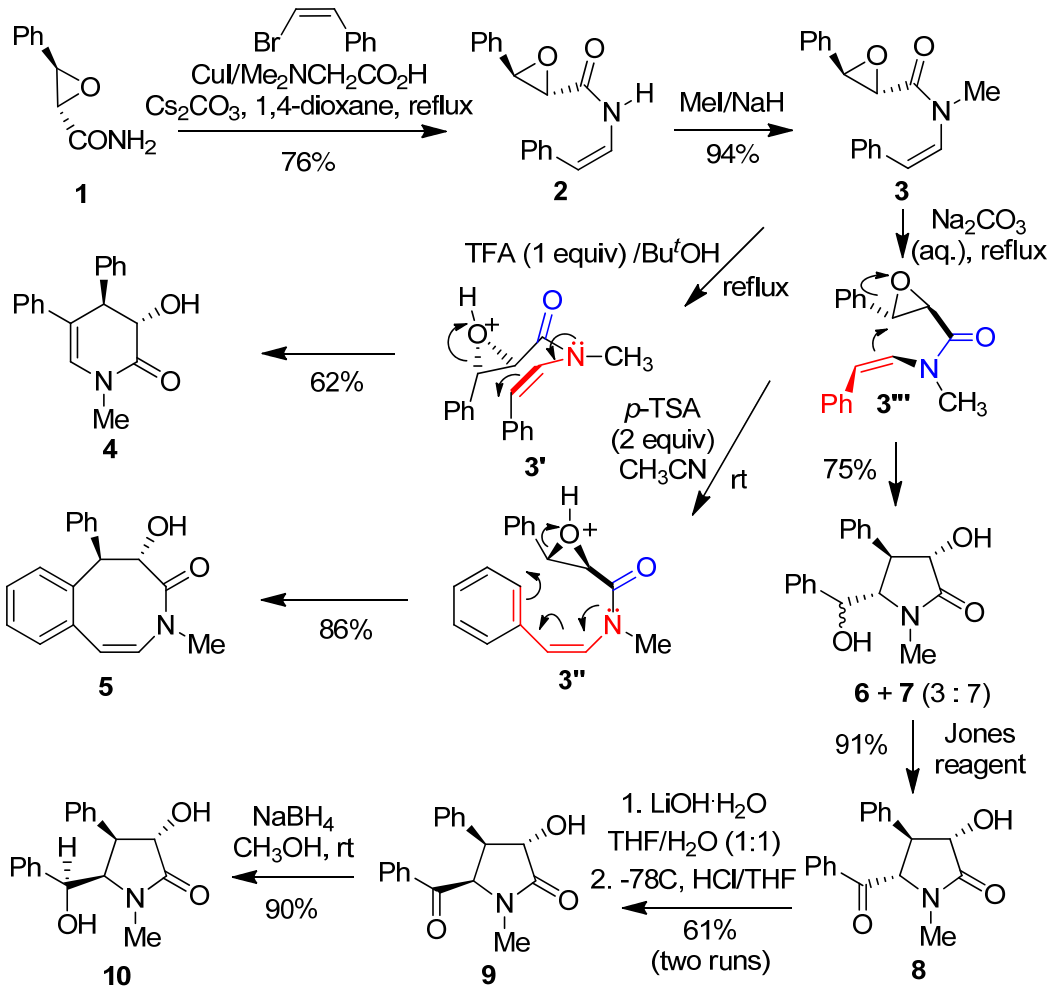


Figure 2. General structure of tertiary enamide and its resonance forms

Nucleophilic reaction with epoxides

Our research project on tertiary enamides embarked with the exploration of synthetic applications of enantiomerically pure 2*R*,3*S*-2-arylglycidamides that were readily prepared from biotransformations of racemic *trans*-2,3-epoxy-3-arylpropanenitriles catalyzed by *Rhodococcus erythropolis* AJ270, a nitrile hydratase and amidase containing microbial whole-cell catalyst.[14] Our attention was initially drawn by the epoxide-bearing tertiary enamide (+)-SB204900 **3**, an alkaloid isolated from a hexane extract of *Clausena lansium* leaves.[15] By means of CuI-catalyzed coupling reaction of 2*S*,3*R*-(+)- and 2*R*,3*S*-(-)-2-phenylglycidamides with (*Z*)-1-phenyl-2-bromoethene followed by exclusive *N*-methylation, we established the first synthesis of both antipodes of SB204900 and assigned the absolute configuration of the naturally occurring enantiomer[16] (Scheme 1). It was the study that stirred our curiosity about other clausena alkaloids such as clausenamide, neoclausenamide, homoclausenamide, and ζ-clausenamide. The alkaloids were isolated from the hot water extract of leaves of Rutaceae Clausena *lansium*, a type of fruit tree widely distributed in southern China.[17] In Chinese folk medicine, the leaves and fruits are used to treat asthma, influenza, gastrointestinal disorders, viral hepatitis and dermatological diseases.[18] Despite the unique structures and intriguing biological activities, we were surprised to find out that the biosynthesis of diverse structures of clausena alkaloids had not been elucidated and their syntheses had remained largely unexplored.[19] Structural scrutiny led us to propose the biosynthetic pathways hypothesizing SB204900 is the key precursor to all other clausena alkaloids through different intramolecular cyclization reactions. To our delight, SB204900 was transformed selectively into the desired natural products following our hypothesis.[20,21] As depicted in Scheme 1, for example,

(+)-SB204900 **3** underwent TFA-mediated 6-*endo-tet* enamine-epoxide cyclization in refluxing Bu^{t}OH to produce (-)-homoclausenamide **4** in 62% yield.[20,21] In acetonitrile at ambient temperature, 8-*endo*-arene-epoxide cyclization of (+)-SB204900 was promoted upon the treatment with 2 equivalents of *p*-toluenesulfonic acid, affording a good yield of (-)-ζ-clausenamide **5**.[19] However, the 5-*endo-tet* alkene-epoxide cyclization reaction of (+)-SB204900 proceeded in a hot aqueous Na_2CO_3 solution to form a mixture of neoclausenamide **6** and its 6-epimer **7** in a 3:7 ratio.[20,21] The Jones oxidation led to (+)-neoclausenamidone **8** which underwent epimerization under kinetic conditions followed by reduction to furnish (-)-clausenamide **10**.[21]



Scheme 1. Synthesis of (+)-SB204900 **3** and its conversion to (-)-homoclausenamide **4**, (-)-ζ-clausenamide **5**, (-)-neoclausenamide **6**, and (-)-clausenamide **10**

The successful biomimetic synthesis of homoclausenamide **4** from SB204900 indicated convincingly that tertiary enamide **3** was capable of acting as an enamine **3'**

to undergo nucleophilic attack at the epoxide moiety. In addition, in a perfectly predisposed conformational structure of **3** in acetonitrile, conjugation of the tertiary enamide was probably extended to the benzene moiety to form a pseudo-dienamide system **3"**, facilitating arene-epoxide cyclization reaction to produce ζ-calusenamide **5**. Furthermore, in pure water, the tertiary enamide adopted most likely a conformation in which the phenylvinyl moiety is perpendicular to the plane of the conjugated carboxamide. The delocalization of the nitrogen lone pair electrons into the carbon-carbon double bond is therefore prohibited. The ostensible tertiary enamide behaved actually as an isolated styrene **3'"**. As a consequence, the alkene-epoxide cyclization reaction was favored energetically. It is especially worth addressing that the reaction pathways are strongly dependent upon the reaction conditions, particularly the nature or the polarity of reaction solvent employed. In other words, different conditions can alter or regulate conformational structures and enhance the conjugational systems, rendering the tertiary enamide as an enamine, a pseudo-dienamine or an alkene species (Scheme 1).

The enaminic reaction of tertiary enamides with epoxides was utilized in the preparation of a number of 4,6-diaryl-3-hydroxy-3,4-dihydropyridin-2(1*H*)-ones, isomers of homoclausenamide **4**.[22] We[16] also successfully applied the strategy of 8-*endo*-*tet* arene-epoxide cyclization of tertiary enamide, accomplishing the first synthesis of (-)-balasubramide (-)-**16**, an indole-fused eight-membered lactam-containing alkaloid isolated from Clausena *indica* which grows in the central montane rainforests in Sri Lanka[23] (Scheme 2).

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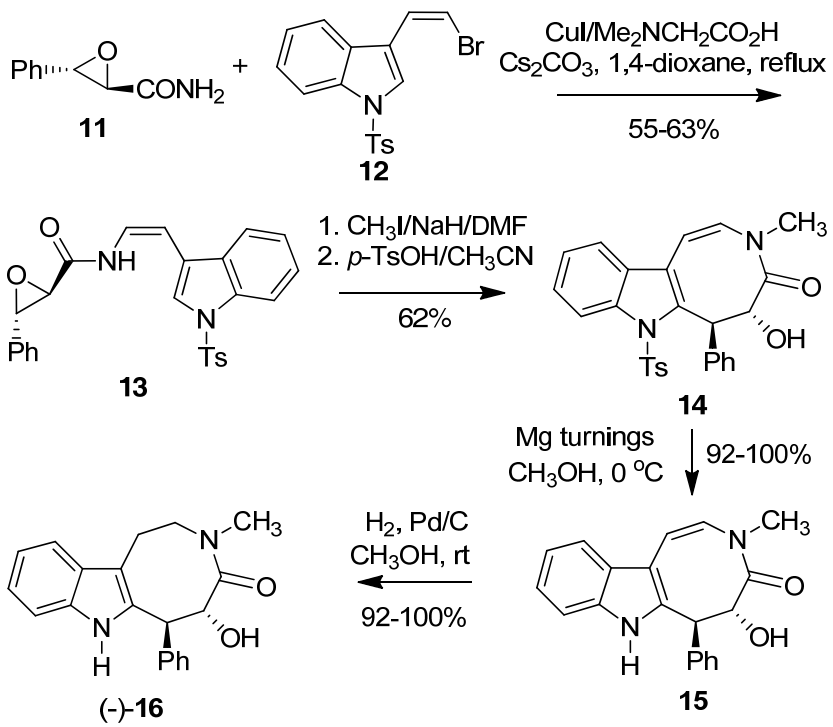
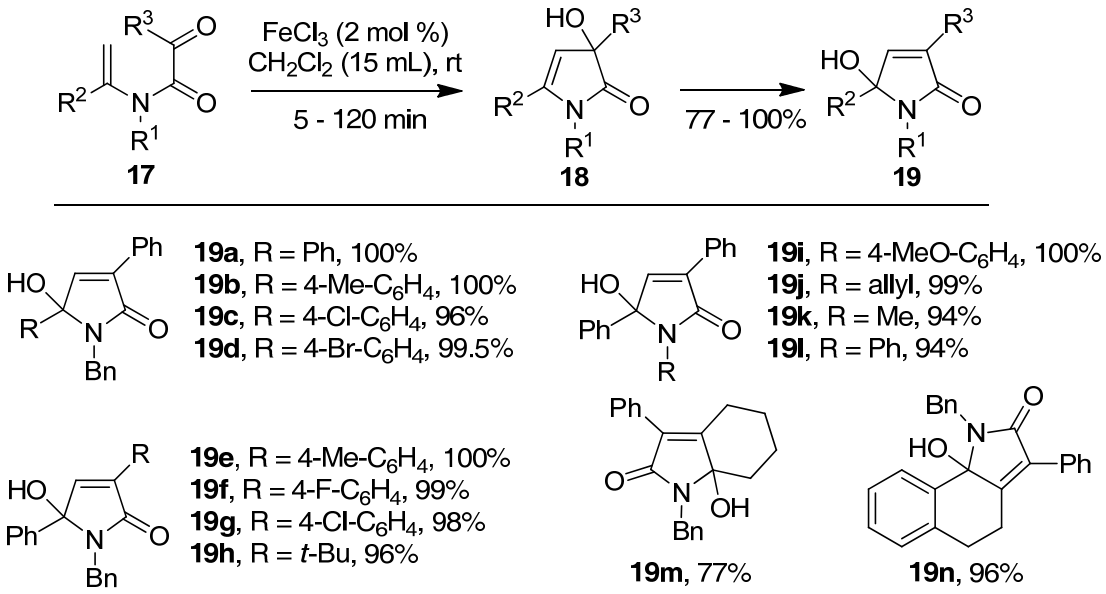


Scheme 2. Synthesis of (-)-balasubramide **16**

Nucleophilic reaction with carbonyls

Encouraged by the enaminic reaction of tertiary enamides with epoxides, we next examined the intramolecular nucleophilic addition of tertiary enamides to ketones. As we expected, tertiary enamides **17** underwent cyclization readily with the activated ketone moieties in the presence of a Lewis acid catalyst. Interestingly, while zinc salt-catalyzed reactions gave a mixture of 3-hydroxy-1*H*-pyrrol-2(3*H*)-ones **18** and their 5-hydroxy-1*H*-pyrrol-2-(5*H*)-one isomers **19**, $FeCl_3$-catalyzed reactions afforded exclusively 5-hydroxy-1*H*-pyrrol-2-(5*H*)-one products under various conditions. It was evident that the 3-hydroxy group resulting from initial attack of enaminic carbon at the ketonic carbonyl underwent spontaneous rearrangement to 5-position. As summarized in Scheme 3, the $FeCl_3$-catalyzed reaction was highly efficient and robust. Irrespective of the nature of substituents, almost all tertiary enamides **17** were transformed into 5-hydroxy-1*H*-pyrrol-2-(5*H*)-one derivatives **19** in nearly quantitative yields.[24] It is noteworthy that the resulting products resemble the structure of naturally occurring oteromycin,[25] a microbial metabolite acting as an antagonist of endothelin receptor. Some 5-hydroxy-1*H*-pyrrol-2-(5*H*)-one analogs have been shown

to possess interesting biological activities[26] and to serve as intermediates in the synthesis of natural products.[27]



Scheme 3. Synthesis of 5-hydroxy-1*H*-pyrrol-2-(5*H*)-one derivatives **19** by means of intramolecular nucleophilic addition of tertiary enamides to ketones

Delineated in Scheme 4 is a most plausible reaction mechanism.[24] The direct enaminic reaction of a tertiary enamide to $FeCl_3$-activated ketonic carbonyl generates a cyclic iminium intermediate **21** which undergoes deprotonation to afford 3-hydroxy-3,5-diaryl-1*H*-pyrrol-2(3*H*)-one product **18**. Dehydration of **18** leads to the formation of 2-oxo-2*H*-pyrrolium intermediate **22** which is trapped by a water molecule to furnish the formation of final 5-hydroxy-3,5-diaryl-1*H*-pyrrol-2(5*H*)-one product **19**. It should be addressed that the activation of the ketone carbonyl occurs most likely in a mono-coordination fashion as **20**. The chelation of the α-oxo amide to iron is not beneficial or responsible for the intramolecular enaminic reaction because the rigid geometry of the chelation structure does not bring proximity of the enaminic carbon to the ketone carbonyl carbon. The involvement of the 2-oxo-2*H*-pyrrolium intermediate **22** was supported by the fact that an enantioenriched (*S*)-1-benzyl-3-hydroxy-3,5-diphenyl-1*H*-pyrrol-2(3*H*)-one (*S*)-**18a** with ee of >99%

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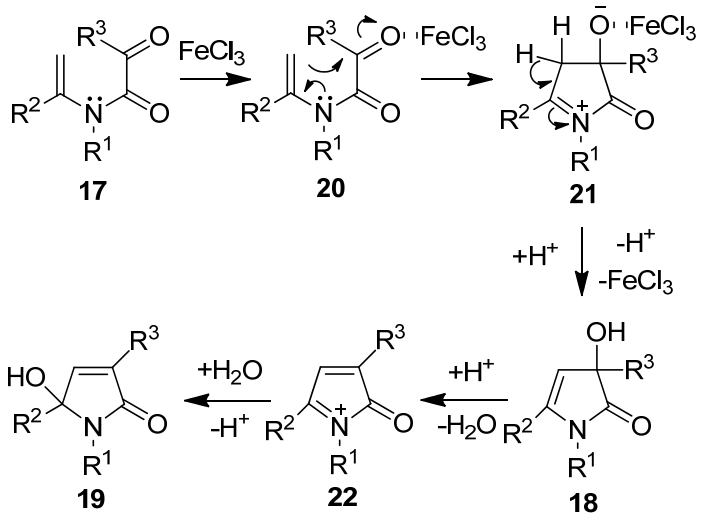
was converted quantitatively into a racemic mixture of 1-benzyl-5-hydroxy-3,5-diphenyl-1*H*-pyrrol-2(5*H*)-one **19a**.



Scheme 4. A plausible reaction mechanism for $FeCl_3$-catalyzed cyclization reaction of tertiary enamides **17**

In the presence of a catalytic amount (5 mol %) of Cr(III)(*R*,*R*-salen)Cl complex, tertiary enamides **17** undergo enantioselective intramolecular nucleophilic addition to ketones to produce (*S*)- or (*R*)-3-hydroxy-1*H*-pyrrol-2(3*H*)-one derivatives **18**[28] (Scheme 5). Other complexes between *R*,*R*-salen ligand and Al^{III}-Cl, Fe^{III}-Cl, Co^{II}-Cl and Mn^{III}-Cl do not catalyze the reaction. The use of Na_2CO_3 helps to inhibit rearrangement of the hydroxy group from 3- to 5-position which is facilitated by an acid, ensuring the high chemical yields of products **18**. The asymmetric catalysis shows remarkable enantioselectivity as high enantiomeric excess values (94% - 99%) are obtained for almost all products **18**. Only in the case of substrates that bear an *N*-methyl or *N*-phenyl, do the reactions of **17k** and **17l** give products **18k** and **18l** with 89% ee and 88% ee, respectively. A fused tricyclic product **18n** of high enantiopurity (94% ee) is also synthesized in 92% yield from the tetralone-derived tertiary enamide albeit a higher catalyst loading (20 mol %) and an elongated reaction time (144 h) are required.

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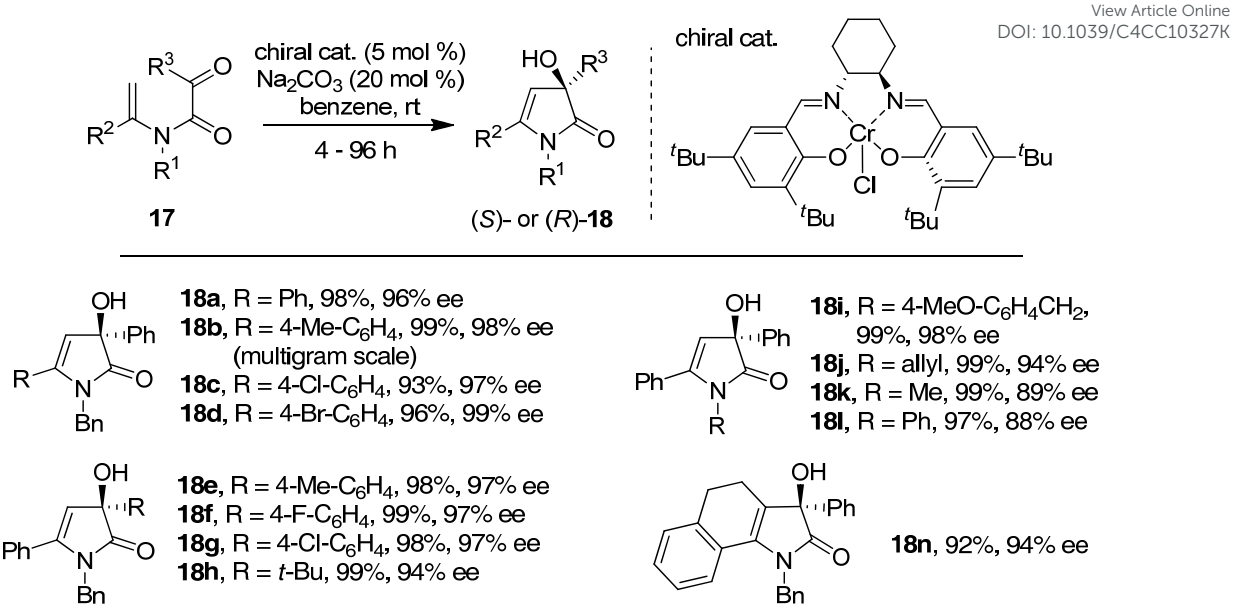

Scheme 5. Catalytic asymmetric addition of tertiary enamides to ketones

The resulting unsaturated γ-lactam compounds that contain a hydroxylated tetrasubstituted stereogenic carbon atom are valuable chiral intermediates. Their synthetic applications have been demonstrated in the practical preparation of (3*S*,5*S*)-3,5-diphenyl-3-pyrrolidinol,[28] whose racemic form has been found to possess various pharmacological properties.[29] As illustrated in Scheme 6, catalytic hydrogenation of **18i** affords quantitatively product **23** as a single diastereomer. The excellent diastereoselectivity results probably from both the directing effect of the hydroxy group and the steric effect of the 3-phenyl group. Treatment of **23** with Ac_2O gives compound **24** with its absolution configuration being determined unambiguously by X-ray crystallography. Deprotection of *N*-PMP by CAN and of acetyl group by hydrolysis leads to the formation of product **26**. Reduction of the lactam by $LiAlH_4$ furnishes the formation of (3*S*,5*S*)-3,5-diphenyl-3-pyrrolidinol **27**. The overall yield of this five-step synthesis of **27** from **18i** is about 80%.

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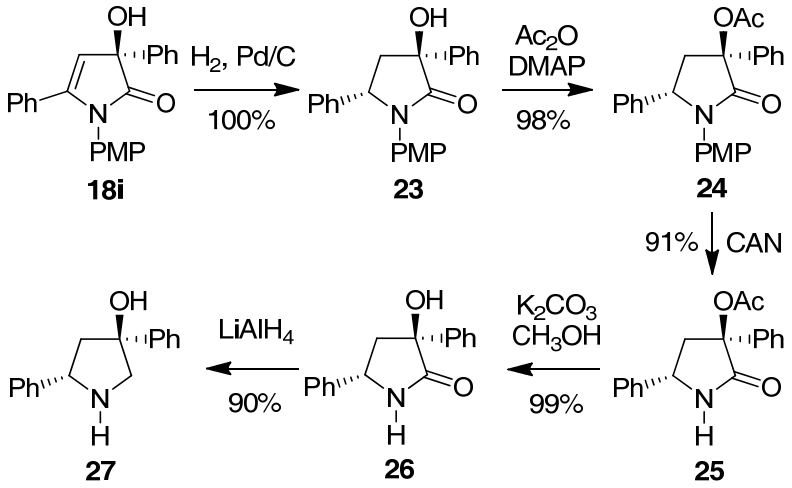

Scheme 6. Synthesis of (3*S*,5*S*)-3,5-diphenyl-3-pyrrolidinol **27**

Following the successful reaction with activated ketones, we[30] tested intramolecular addition of tertiary enamides to aldehydes in the presence of a chiral Lewis acid catalyst. A number of metal-(*R*,*R*-salen) complexes were screened, and they displayed either appallingly low activity or disappointing enantioselectivity. A mixture of *R*-BINOL and $Ti(O^iPr)_4$ (2:1) (5 mol %) was found to be an efficient catalytic system, promoting the transformation of reactants **28** into (*S*)-1,2,3,4-tetrahydropyridin-4-ol derivatives **29** in DCM at -20 ^oC - -35 ^oC. The catalytic asymmetric cyclization reaction shows a broad substrate scope (Scheme 7). When *N*-benzoyl-substituted tertiary enamides **28a-h** are used, all reactions give good to excellent yields of **29** with ee values ranging from 91.4% to >99.5%. Notably, the velocity of the reaction is governed by the nature of the *N*-electron-withdrawing group. Replacement of an *N*-benzoyl by an *N*-benzyloxycarbonyl leads to slow transformation of **28i** at -30 ^oC with product **29i** being isolated in only 69% in 42 h. A higher temperature (-20 ^oC) and an elongated time (50 h) are required to implement the conversion of an *N*-acetyl-substituted substrate **28j** into product **29j** in 82% yield. The reaction also allows the construction of an enantiopure bicyclic product **29k**.

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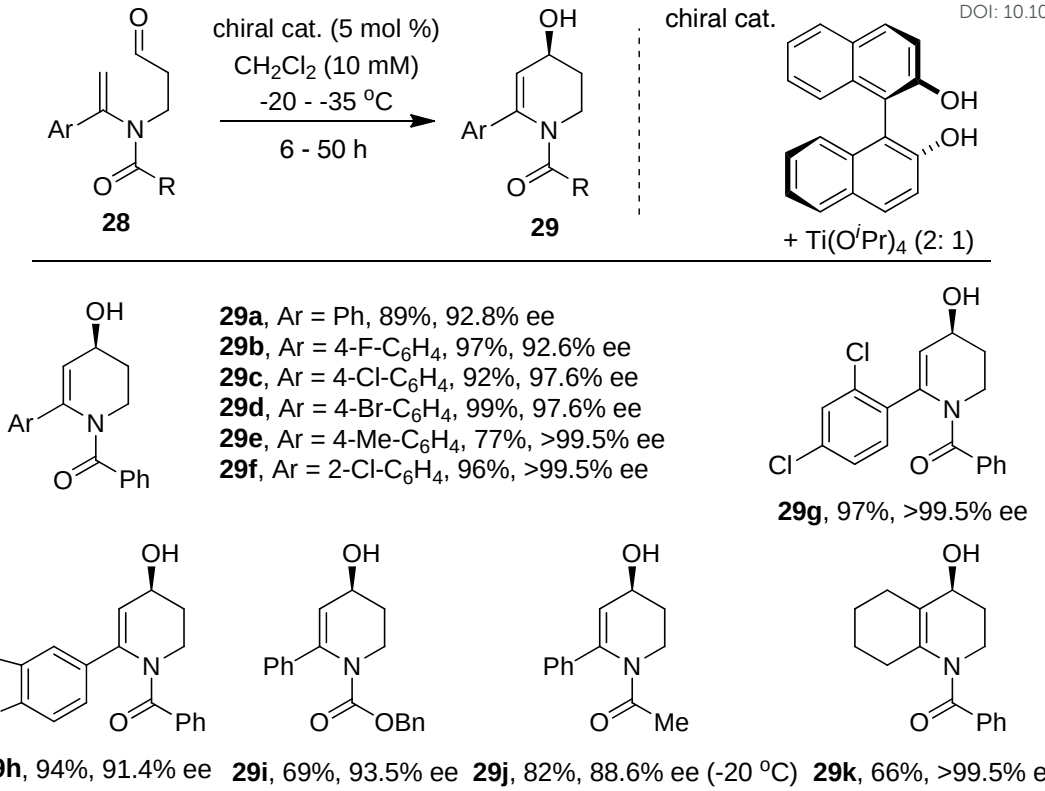


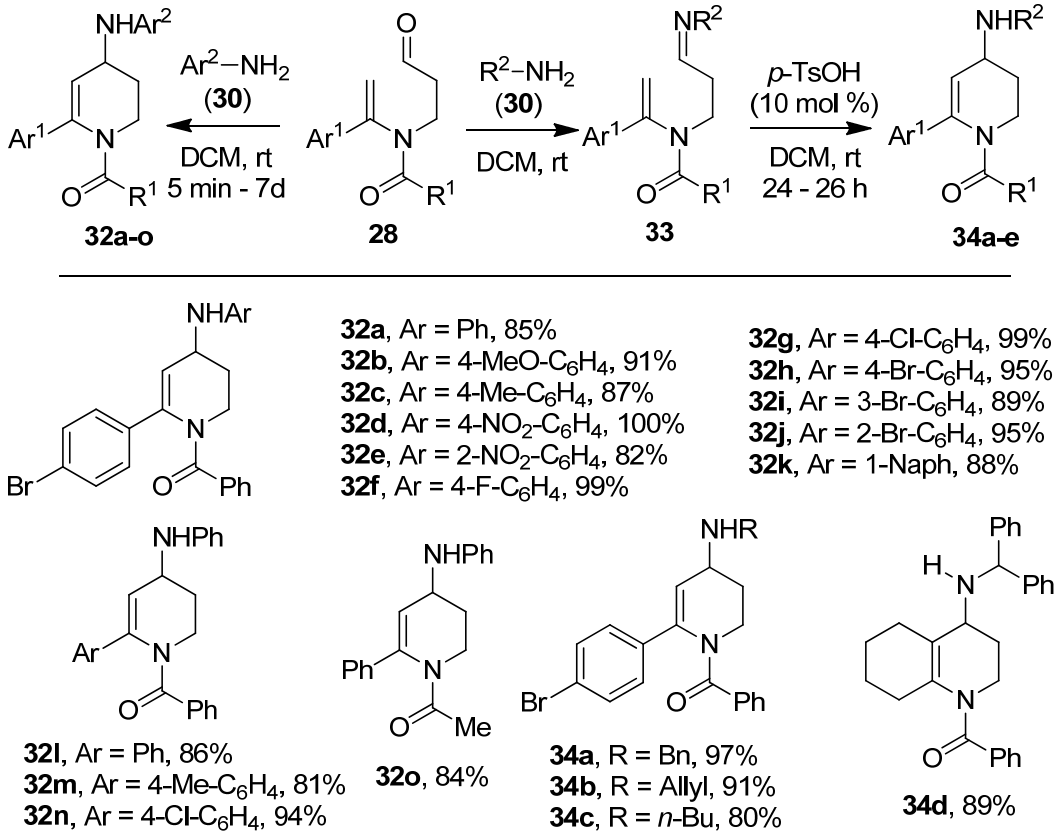
Scheme 7. Catalytic asymmetric addition of tertiary enamides to aldehydes

It is interesting to note that the mechanism of asymmetric catalysis is not trivial. Almost identical positive nonlinear effects are observed with different catalyst concentrations. However, the higher the catalyst loading, the faster the transformation of **28**. These results exclude the monomeric (*R*)-BANOL-Ti(O^iPr)$_4$ as an active species in catalysis. Detailed studies of ^{1}H NMR spectroscopy and diffusion-ordered spectroscopy along with computer simulation have revealed the involvement of [(*R*)-bino-Ti(O^iPr)$_2$]$_3$ as the most probable catalytic species albeit its structure awaits further investigation.[30,31]

Nucleophilic reaction with imines

Tertiary enamides exhibit good enaminic reactivity in addition reactions to aromatic imines under mild conditions. When aldehyde-containing tertiary enamides **28** are treated with anilines **30** in DCM at room temperature, for example, 4-anilino-1,2,3,4-tetrahydropyridine derivatives are formed without the detection of imine intermediates. This indicates convincingly that the speed of nucleophilic

reaction of tertiary enamides to imine exceeds the velocity of condensation reaction between aldehyde and anilines. As summarized in Scheme 8, reaction between **28** and aromatic amines **30** affords products **32a-o** in excellent yields. It is interesting to note that the reaction rate varies dramatically depending on the nature of the substituent on the anilines. It takes less than 0.5 h for electron-rich anilines to finish the cyclization whereas the reaction of halogen-substituted anilines requires 1 to 8 h to go to completion. In the case of 4-nitroaniline and 2-nitroaniline, good yields of products **32d** and **32e** are obtained in 3 and 7 days, respectively. It should be noted, however, that the substituent effect influences only the first reaction step, *viz.* the formation of imine from the condensation between aniline and aldehyde. The electron-deficient anilines appear less reactive towards the aldehyde group. Once aromatic imines are generated, they are attacked by the nucleophilic enamides, leading to the formation of the six-membered heterocyclic ring products efficiently.[32]



Scheme 8. Nucleophilic addition of tertiary enamides to aromatic and aliphatic imines

In contrast to anilines, aliphatic amines react with tertiary enamides to form

aliphatic imine intermediates **33** quantitatively. No nucleophilic reaction between enamides and aliphatic imines occurs under the identical conditions. The clear-cut difference in reactivity of tertiary enamides towards aromatic and aliphatic imines is intriguing, reflecting the requirement of active imine components to react with tertiary enamides. Catalyzed by a Brønsted acid such as *p*-toluenesulfonic acid, intramolecular addition of tertiary enamides to aliphatic imines proceeds effectively to produce 4-amino-1,2,3,4-tetrahydropyridine derivatives **34** in high yields[32] (Scheme 8). The resulting products are analogs of 1-benzoyl-2-benzyl-4-aminopiperidine CGP 49823, an orally and centrally active non-peptide NK1 antagonist.[33]

Nucleophilic reaction with nitriliums

Isonitriles are unique divalent species and are able to undergo α-addition reactions with both electrophiles and nucleophiles at the same carbon atom. The reaction proceeds initially with the addition of isonitriles to electrophiles such as aldehydes to form nitrilium intermediates. The resulting nitrilium intermediates are highly reactive and are readily intercepted by heteroatom nucleophiles.[34] Based on the reactivity of isonitriles, we designed a [5+1] cycloaddition reaction of *N*-formylmethyl-substituted tertiary enamides to isonitriles to construct six-membered *N*-heterocycles. We were pleased to discover that, promoted by $Zn(OTf)_2$, *N*-formylmethyl-substituted tertiary enamides **35** undergo reaction with isonitriles **36** and acyl chlorides **37** under aerobic conditions to produce 2-substituted 4-acylamino-5-acyloxypyridines **38**. The key steps in this reaction cascade involve an unprecedented α-addition of aldehyde and enamide to isonitrile, facile aerobic oxidative aromatization followed by intermolecular acyl transfer from pyridinium nitrogen to 5-hydroxy and acylation of the 4-amino group by an external acyl chloride (Scheme 9). The reaction is very general, accepting all types of tertiary enamides, isonitriles and acyl chlorides as substrates to afford efficiently 2-substituted 4-acylamino-5-acyloxypyridines in good to excellent yields.[35] The resulting diversely substituted pyridines are very useful in medicinal chemistry as their analogs have been shown to possess strong acetylcholinesterase (AChE) inhibitory activity.[36]

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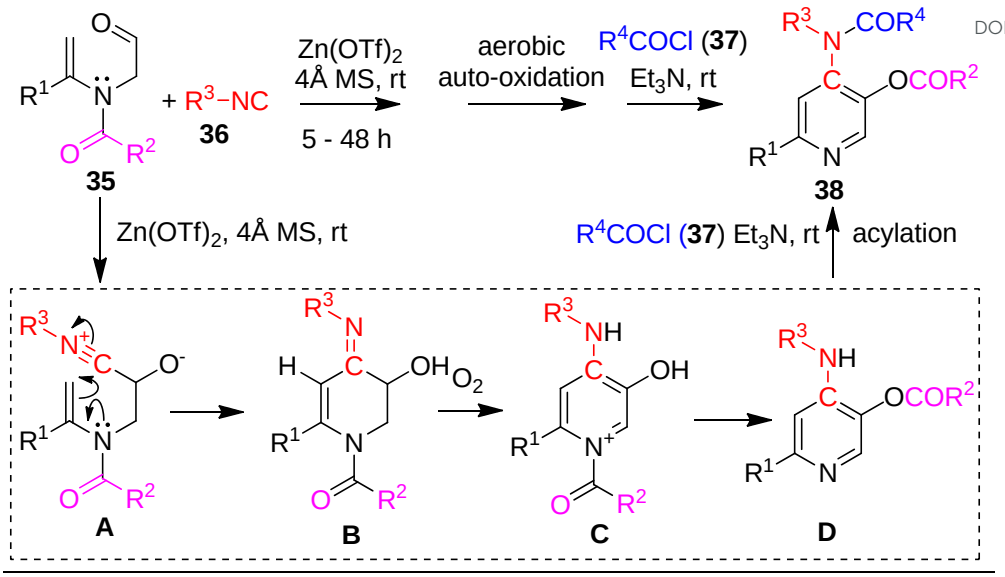
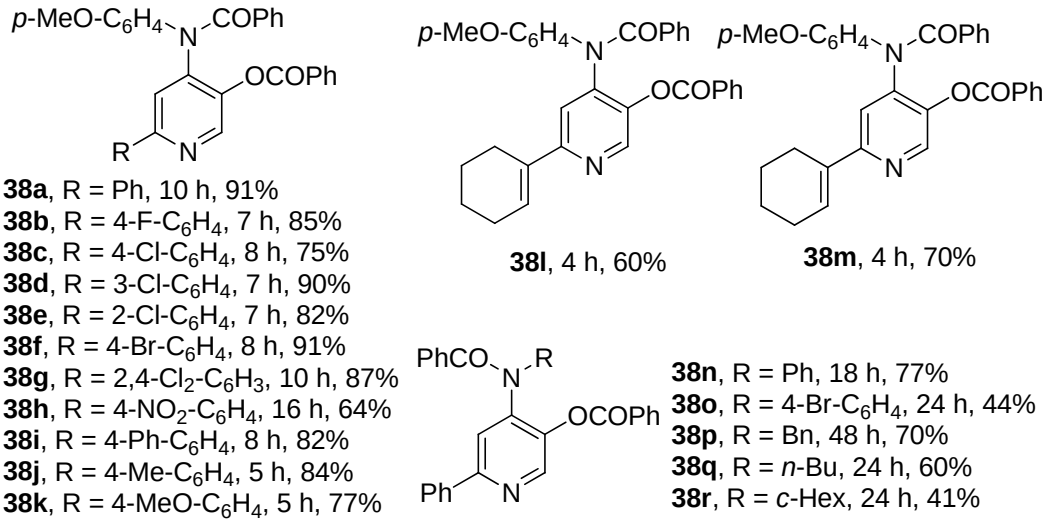
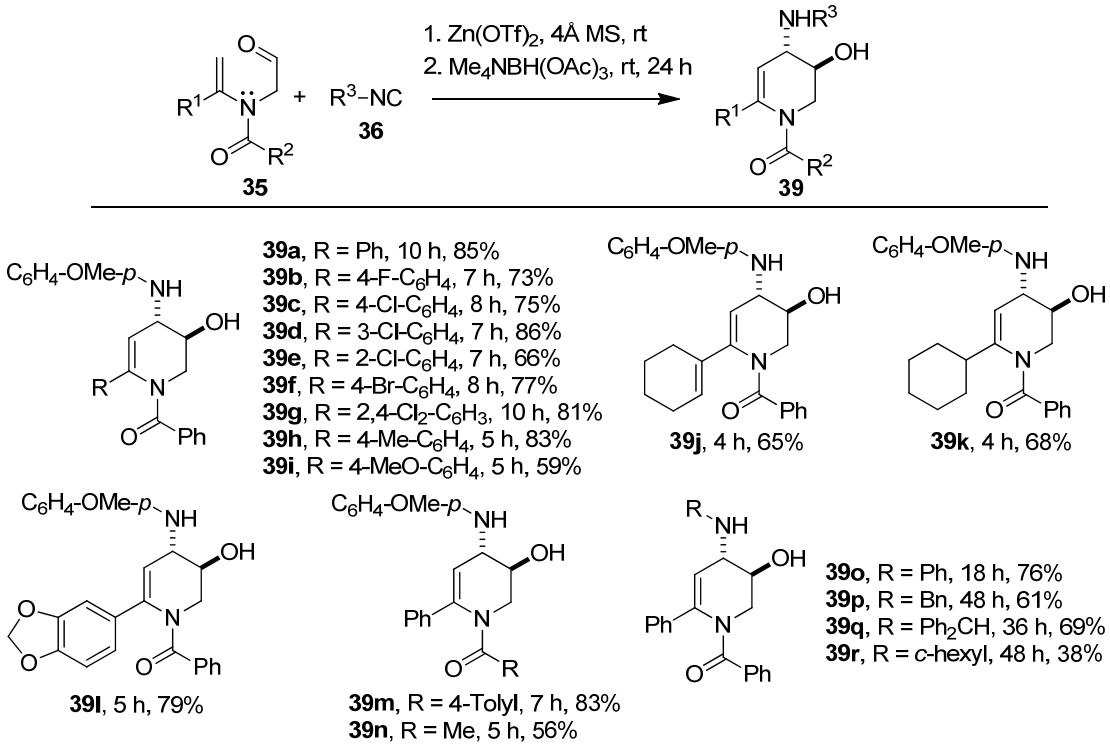




Scheme 9. Synthesis of polysubstituted pyridines from the reaction of *N*-formylmethyl-substituted tertiary enamides with isonitriles and acyl chlorides

Since the cycloaddition reaction between *N*-formylmethyl-substituted tertiary enamides and isonitriles forms initially intermediate B (Scheme 9), termination of sequential reaction by reduction or hydrolysis of the imino moiety of presumed intermediate B prior to its oxidative aromatization would furnish functionalized 1,2,3,4-tetrahydropyridines and 2,3-dihydropyridin-4(1*H*)-ones, respectively. As depicted in Scheme 10, $Zn(OTf)_2$-mediated reaction between isonitriles and *N*-formylmethyl-substituted tertiary enamides followed by reduction with $Me_4NBH(OAc)_3$ at ambient temperature produces 1,6-disubstituted *trans*-3-hydroxy-4-amino-1,2,3,4-tetrahydropyridines **39** in moderate to good yields.[37]

The high stereoselectivity for preferential formation of *trans*-configured product reflects most probably a powerful directing effect of the hydroxy group in the reduction of the imine group of B with $Me_4NBH(OAc)_3$. Trapping of the intermediate B by an acyl chloride followed by hydrolysis under acid conditions before auto-oxidative aromatization leads to the formation of substituted 2,3-dihydropyridin-4(1*H*)-one products **40**[37] (Scheme 11). It is remarkable that the cascade reactions between *N*-formylmethyl-substituted tertiary enamides and isonitriles provide powerful and divergent synthetic routes to pyridine, 1,2,3,4-tetrahydropyridine and 2,3-dihydropyridin-4(1*H*)-one derivatives simply by means of employing different terminating methods.



Scheme 10. Synthesis of *trans*-3-hydroxy-4-amino-1,2,3,4-tetrahydropyridine derivatives.

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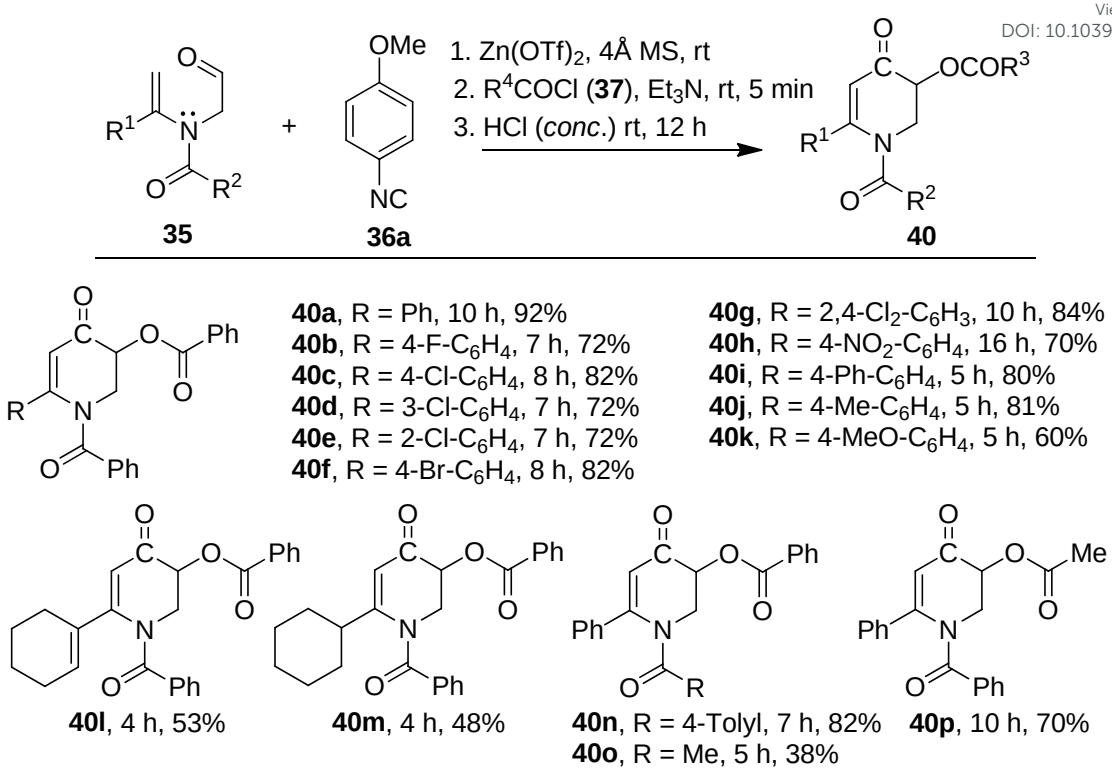

Scheme 11. Synthesis of 2,3-dihydropyridin-4(1*H*)-one derivatives.

We then extended our study to the reaction of *N*-formylmethyl-substituted tertiary enamides with isonitriles and amines, envisaging the formation of 3-aminopyridine, 3,4-diamino-1,2,3,4-tetrahydropyridine or 3-amino-2,3-dihydropyridin-4(1*H*)-one derivatives. Surprisingly, the reaction does not form any of the designed products. Instead, functionalized imidazolinium salts **42** are obtained in good yields.[38] An ^{18}O-labeling experiment reveals an intriguing reaction pathway which comprises the formation and fragmentation of a bridged heterocyclic intermediate (Scheme 12). It is noteworthy that the enamine unit does not participate in the reaction probably due to its lower nucleophilicity in comparison to that of the nitrogen anion of intermediate F. Because the tertiary enamide moiety remains intact in the reaction, synthesis is successfully expanded to various *N*-formylmethyl-substituted tertiary amides. The three component reaction of *N*-formylmethyl-substituted tertiary amides with amines and isonitriles has now been developed into an efficient method for the expedient synthesis of diverse polysubstituted imidazolinium salts.[38]

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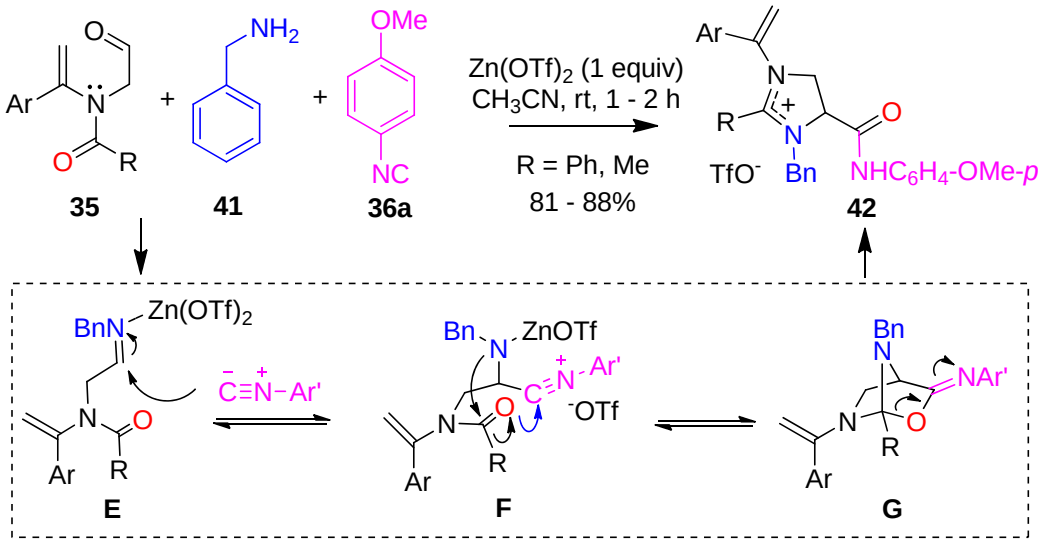
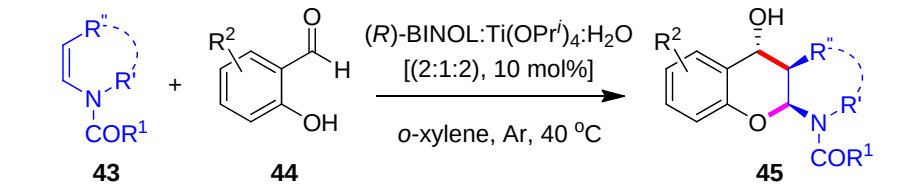


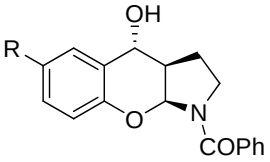
Scheme 12. Synthesis of imidazolinium derivatives.

Difunctionalization of tertiary enamides

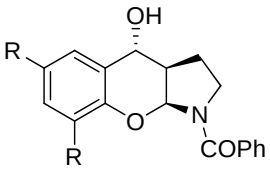
Nnucleophilic reactions of tertiary enamides with electrophiles initially form iminium intermediates. In all aforementioned examples, the iminium intermediates undergo spontaneously deprotonation to afford adducts or mono-functionalized products. Since the resulting iminium intermediates are highly electrophilic, their interception by nucleophilic reagents would generate difunctionalized products of tertiary enamides. To explore the difunctionalization of tertiary enamides, we[39] have studied very recently the intermolecular reaction between tertiary enamides and salicylaldehydes. Catalyzed by the complex between (*R*)-BINOL and Ti(O^{i}Pr)$_4$, both cyclic and acyclic tertiary enamides **43** are able to undergo cyclization with almost all tested salicylaldehydes **44**, affording diverse *cis,trans*-configured 4-chromanols **45** that contain three continuous stereogenic centers in good yields with excellent diastereoselectivity and enantioselectivity. The reaction proceeds through tandem enaminic addition of tertiary enamide to aldehyde followed by the intramolecular trapping of the resulting iminium by the hydroxy group. Oxidation of the resulting *cis,trans*-configured 4-chromanols yielded almost quantitatively chroman-4-one derivatives which are converted diastereospecifically into *cis,cis*-configured

4-chromanols upon reduction with $NaBH_4$. It should be noted that, as the members of dihydrobenzopyran family, 4-chromanol and chroman-4-one derivatives occur as natural and synthetic products with various biological activities.[40] Perinadine A, a complex alkaloid isolated recently from marine-derived fungus Penicillium citrinum, for example, features a pyrrolidine-fused 4-chromanol core structure.[41]

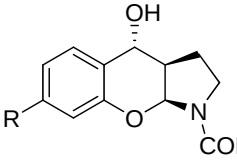




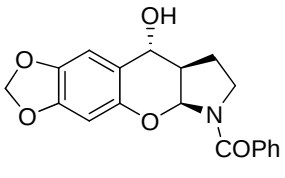
45a, R = H, 17 h, 98%, dr >20:1, 96.5% ee
45b, R = F, 2 h, 91%, dr >20:1, 97.9% ee
45c, R = Cl, 3 h, 86%, dr >20:1, 96.5% ee
45d, R = Br, 3 h, 94%, dr >20:1, 97.8% ee
45e, R = CN, 3 h, 91%, dr >20:1, 96.1% ee
45f, R = CO_2Me, 5 h, 93%, dr >20:1, 97.0% ee
45g, R = Ph, 6 h, 99%, dr >20:1, 98.2% ee
45h, R = Me, 17 h, 92%, dr >20:1, 97.1% ee
45i, R = MeO, 6 h, 78%, dr >20:1, 95.9% ee



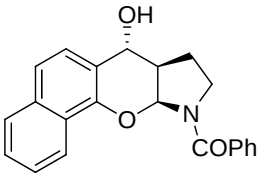
45j, R = Cl, 2 h, 90%, dr >20:1, 96.0% ee
45k, R = Br, 2 h, 89%, dr >20:1, 95.1% ee



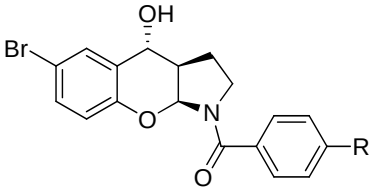
45l, R = Br, 6 h, 99%, dr 15:1, 95.3% ee
45m, R = OMe, 168 h, 39%, dr 9:1, 51.2% ee



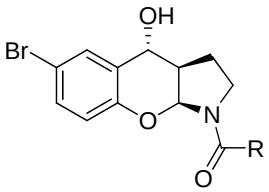
45n, 24 h, 27%, dr >20:1
81.9% ee



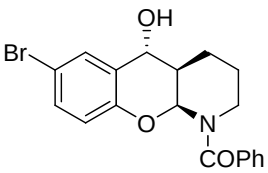
45o, 96 h, 77%, dr >20:1
95.5% (95.8%) ee



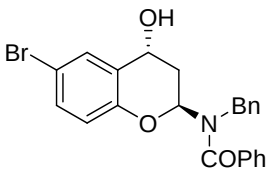
45p, R = Cl, 4 h, 95%, dr >20:1, 99.2% ee
45q, R = MeO, 2 h, 95%, dr >20:1, 98.7% ee



45r, R = Me, 2 h, 69%, dr >20:1, 43.2% ee
45s, R = OBn, 1 h, 67%, dr > 20:1, 80.2% ee



45t, 120 h, 65%
dr 11:1, 95.7% ee



45u, 24 h, 52%, dr 7:1
99.1% ee

Scheme 13. Synthesis of 4-chromanols from catalytic asymmetric di-functionalization of tertiary enamides with salicylaldehydes.

Conclusion and perspective

We have shown that, contrary to general notion, tertiary enamides exhibit good enaminc reactivity towards functional groups such as epoxides, carbonyls, imines and nitriliums. Both intramolecular and intermolecular reactions of tertiary enamides provide efficient methods for the synthesis of diverse heterocycles that are not readily obtained by other means. Furthermore, reactions between tertiary enamides and carbonyls catalyzed by chiral Lewis acids lead to the construction of functionalized heterocyclic compounds of high enantiopurity.

Admittedly, the study of the reactions and applications of tertiary enamides is still in its infancy. Reactivity and synthetic versatility of tertiary enamides await for example extensive and in-depth exploration. Asymmetric catalytic difunctionalizations of tertiary enamides through cascade reactions and multicomponent reactions, which would produce molecules of complexity, are particularly worth pursuing. Synthesis of natural products such as alkaloids using tertiary enamides protocol is a challenging but very attractive goal. It is anticipated that easy availability, tunable stability and versatile reactivity will render tertiary enamides powerful and unique synthons in organic synthesis.

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