Organic LETTERS

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Catalytic Asymmetric Difunctionalization of Stable Tertiary Enamides with Salicylaldehydes: Highly Efficient, Enantioselective, and Diastereoselective Synthesis of Diverse 4-Chromanol Derivatives

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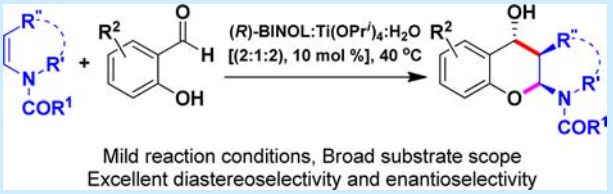
Supporting Information

ABSTRACT: Catalyzed by a chiral BINOL−Ti(O*i*Pr)$_4$ complex, various stable tertiary enamides reacted with salicylaldehydes to afford diverse *cis,trans*-configured 4-chromanols that contain three continuous stereogenic centers in good yields with excellent diastereoselectivity and enantioselectivity. The reaction proceeded through the addition of enamide to aldehyde followed by the intramolecular interception of the resulting iminium by the hydroxy group. Oxidation of the resulting 4-chromanols yielded almost quantitatively chroman-4-one derivatives which underwent diastereospecific reduction with $NaBH_4$ to produce *cis,cis*-configured 4-chromanols.



As the members of the dihydrobenzopyran family, 4-chromanol and chroman-4-one derivatives occur as natural and synthetic products of various biological activities.[1] Perinadine A, a complex alkaloid isolated recently from marine-derived fungus *Penicillium citrinum*, for example, features a pyrrolidine-fused 4-chromanol core structure.[2] Although the syntheses of 4-chromanols and chroman-4-ones are well documented,[1,3] de novo synthesis of enantiopure 4-chromanol and chroman-4-one derivatives under asymmetric catalysis is exceedingly rare. It is challenging and desirable to develop a diversity-orientated synthesis of functionalized 4-chromanols and chroman-4-ones that assemble the core structure of natural products.

Enamines[4] have found wide applications in organic synthesis owing to Stork's landmark work in the 1950s.[5] When one of the *N*-alkyl groups of enamines is replaced by an electron-withdrawing group such as acyl, tertiary enamides are generated. Further substitution of the other *N*-alkyl by hydrogen gives rise to the formation of secondary enamides (Figure 1). While secondary enamides are active aza-ene components,[6] tertiary enamides exhibit diminished nucleophilicity because the *N*-electron-withdrawing group alleviates the delocalization of lone-pair electrons of the nitrogen atom into the carbon−carbon double bond.[7−9] This has been exemplified by a plethora of examples using enamides as a testing ground for the study of asymmetric hydrogenation of the carbon−carbon double bond.[8] Only when reacted with highly electrophilic reagents such as iminium,[10,11] acyl chloride,[10] and oxonium,[12] tertiary enamides behave as nucleophiles.

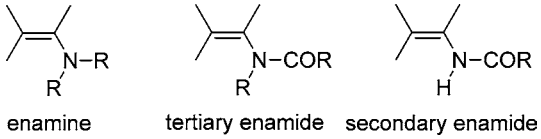


Figure 1. Enamine and tertiary and secondary enamides.

However, the notion that tertiary enamides are stable, silent enamines and marginally valuable chemical entities has been challenged recently.[13−17] We proposed several years ago that the enabled regulation of a cross conjugation system of an enamide moiety by means of the electronic and steric effects of the substituents attached on enamide segment C═C−N−CO and the reaction conditions would rejuvenate the nucleophilicity of a tertiary enamide. This strategy has guided us to accomplish the intramolecular nucleophilic reactions of tertiary enamides with some electrophiles,[13−17] providing novel methods for the synthesis of *N*-heterocyclic compounds. However, almost all synthetic applications of tertiary enamides reported to date are monofunctionalizations via deprotonation of the putative acylated iminium intermediates which are generated from the initial nucleophilic reaction of enamides[11−17] (Figure 2, previous works). We envisaged that interception of the iminiums by a nucleophile would afford difunctionalized products. Various ring structures would be constructed from difunctionalizations if amphiphilic reagents were used (Figure 2, this work). To continue our studies on the exploration of new chemistry for stable tertiary enamides, we designed an unprecedented tandem reaction strategy for the construction of the 4-chromanol framework. The key steps comprise an intermolecular

Received: October 12, 2014
Published: October 30, 2014

   dx.doi.org/10.1021/ol5029964 | *Org. Lett.* 2014, 16, 5972−5975

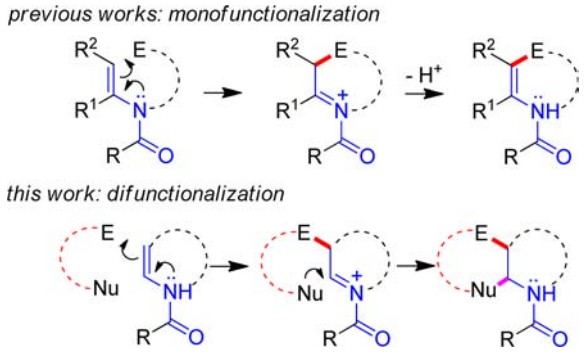


Figure 2. Strategic designs based on reactivity of tertiary enamides.

nucleophilic addition of a tertiary enamide to benzaldehyde followed by an intramolecular trap for the iminiun by the phenol group. We were pleased to discover that, in the presence of chiral BINOL and $Ti(OiPr)_4$, the reaction between tertiary enamides and salicylaldehydes indeed provides a highly enantio- and diastereoselective synthesis of diverse 4-chromanol derivatives which contain three continuous stereogenic centers.

As a prelude of asymmetric catalysis, we first tested an achiral Lewis acid catalyzed reaction of tertiary enamide **1a** with salicyladehyde **2a**. After screening and optimization, $SnCl_2$ was found to catalyze the reaction efficiently under mild conditions, affording a mixture of *cis,trans*- and *cis,cis*-configured pyyrolidine-fused 4-chromanols **3a** and **4a** with a dr (**3a**:**4ab**) of 15 to 1 (Tables S1 and S2). The $SnCl_2$-catalyzed reaction was extended to other tertiary enamides and salicylaldehydes, producing racemic products **3** diastereoselectively in good yields (Table S3).

The outcomes of the $SnCl_2$-catalyzed reaction encouraged us to attempt asymmetric catalysis with the focus on chiral Pybox-SnX_2 complexes **C1** to **C4** (Figure 3). Unfortunately, although

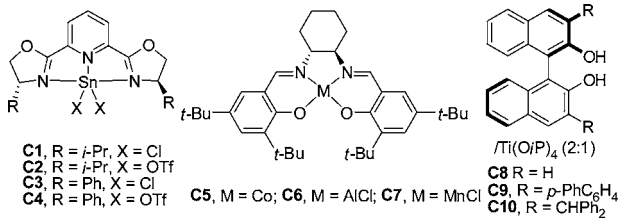


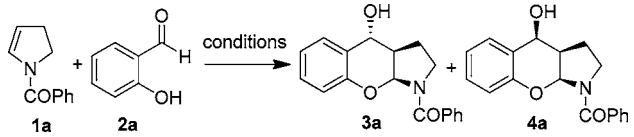
Figure 3. Chiral catalysts used in the study.

these metal complexes were able to effect diastereoselective reaction of **1a** with **2a**, the enantioselectivity was appallingly low with product ee's being 0−31% (entries 1−4, Table S4, Supporting Information). The chiral salen−metal complexes **C5**−**C7**, efficient catalysts for catalyzing the enantioselective addition of tertiary enamides to ketones,[14a] were found to be entirely inactive for the intermolecular reaction between **1a** and **2a** (entries 5−7, Table S4, Supporting Information).

We then turned our attention to the catalytic systems derived from chiral BINOL and $Ti(OiPr)_4$.[18] Based on a previous study,[15] a mixture of chiral BINOL and $Ti(OiPr)_4$ (2:1) with a 10 mol % loading was first tested as catalyst **C8** under anhydrous conditions. As tabulated in Table 1, the reaction at ambient temperature in DCM showed high diastereoselectivity, but moderate efficiency and enantioselectively were observed (entry 1, Table 1). Catalysts **C9** and **C10** which were prepared from modified BINOL derivatives (Figure 3) exhibited disappointingly deteriorated catalytic activity and enantioselectivity (entries 8−9, Table S4, Supporting Information). To improve the catalytic performance of **C8**, the solvent effect was examined. While polar solvents such as THF and CH_3CN were not favorable (entries 2 and 3, Table 1), employment of nonpolar solvents including benzene, toluene, and xylene appeared beneficial, increasing the yield and enantioselectivity (entries 4 to 6, Table 1). Astonishingly, when moistened *o*-xylene was used accidentally, the reaction proceeded rapidly to give **3a** with 85.2% ee (entry 7, Table 1).

Scrutiny of water effect[19] as summarized in entries 11 to 16, Table 1, revealed that addition of water in a range of 5 to 100 mol % led to a dramatic improvement in enantioselectivity, with the

Table 1. Optimization of the Chiral BINOL−Ti Complex C8-Catalyzed Reaction of 1a with 2a[a]



entry	catalyst[b]	solvent	temp (°C)	time (h)	3a+4a (%)[c]	3a:4a[d]	3a (ee) (%)[e]
1	**C8**	DCM	rt	111	52	>20:1	57.7
2	**C8**	THF	rt	86	30	11:1	28.5
3	**C8**	MeCN	rt	86	59	10:1	24.3
4	**C8**	C_6H_6	rt	110	72	>20:1	72.1
5	**C8**	PhMe	rt	86	50	>20:1	56.8
6	**C8**	*o*-xylene	rt	70	59	>20:1	50.8
7	**C8**	*o*-xylene[f]	rt	48	74	>20:1	85.2
8	**C8**	*p*-xylene	rt	70	66	>20:1	60.8
9	**C8**	*p*-xylene[f]	rt	94	76	>20:1	81.1
10	**C8**	*m*-xylene[f]	rt	110	80	>20:1	76.7
11	**C8**:H_2O (5)	*o*-xylene	rt	120	67	>20:1	87.2
12	**C8**:H_2O (10)	*o*-xylene	rt	24	65	>20:1	93.7
13	**C8**:H_2O (20)	*o*-xylene	rt	24	67	>20:1	97.3
14	**C8**:H_2O (40)	*o*-xylene	rt	24	67	>20:1	97.6
15	**C8**:H_2O (80)	*o*-xylene	rt	24	59	>20:1	97.9
16	**C8**:H_2O (100)	*o*-xylene	rt	24	53	>20:1	98.3
17	**C8**:H_2O (20)	*o*-xylene	−5	64	55	>20:1	95.2
18	**C8**:H_2O (20)	*o*-xylene	30	17	66	>20:1	97.3
19	**C8**:H_2O **(20)**	***o*-xylene**	**40**	**17**	**98**	**>20:1**	**96.5**
20	**C8**:H_2O (20)	*o*-xylene	50	17	93	>20:1	96.0
21	**C8**:H_2O (20)	*o*-xylene	60	17	76	>20:1	84.4
22	**C8**:H_2O (20)[g]	*o*-xylene	40	24	89	>20:1	95.6
23	**C8**:H_2O (20)[h]	*o*-xylene	40	48	84	>20:1	96.5
24	**C8**:H_2O (20)[i]	*o*-xylene	40	17	90	>20:1	−96.8[j]

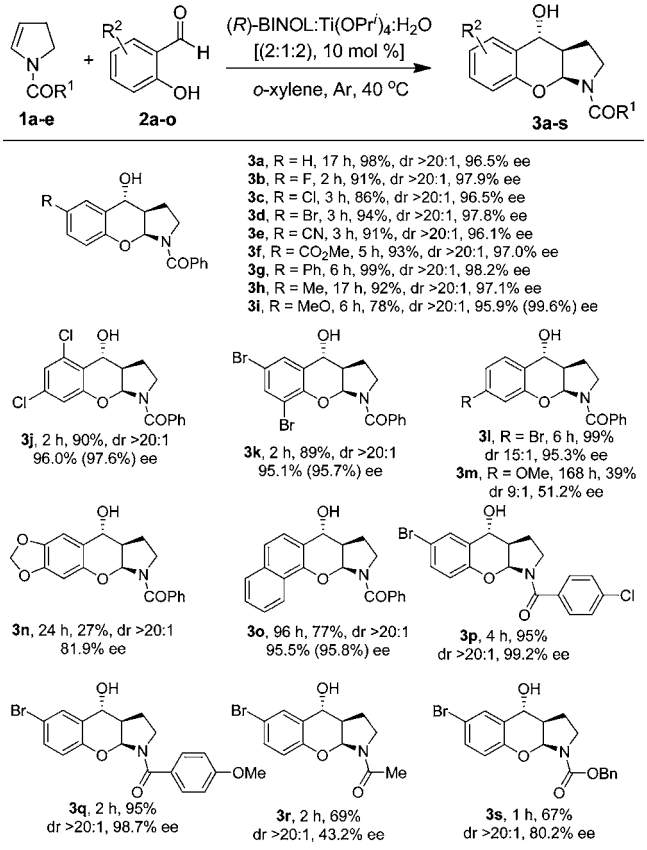
[a] **1a** (0.5 mmol), **2a** (1 mmol), and Ti-complex (10 mol %) were used. [b] H_2O (*x* mol % relative to **1a**) was used. [c] Isolated yield. [d] Determined by ^1H NMR. [e] Determined by chiral HPLC analysis. [f] Solvent was used without drying with sodium. [g] Catalyst loading was 5 mol %. [h] Catalyst loading was 1 mol %. [i] (*S*)-BINOL was used. [j] *Ent*-**3a** was obtained.

dx.doi.org/10.1021/ol5029964 | *Org. Lett.* 2014, 16, 5972−5975

ee of **3a** increasing from 87.2% to 98.3%. It should be noted that the chemical yield of **3a** was slightly corroded if water exceeded 80 mol % in the reaction (entries 15 and 16, Table 1). The reaction was expectedly facilitated at elevated temperatures. When the reaction was performed at 40−50 °C, product **3a** was isolated almost quantitatively with ee's up to 96.5% (entries 19 and 20, Table 1). Higher temperature caused a decrease of enantioselectivity (entry 21, Table 1) whereas lower temperature resulted in a slow reaction (entry 17, Table 1). The catalytic asymmetric reaction could also proceed effectively when the titanium loading was lowered to 1−5 mol %, albeit an elongated reaction period was required (entries 22 and 23, Table 1). The use of (*S*)-BINOL as a chiral ligand gave rise to the formation of *ent*-**3a** in 90% yield and 96.8% ee (entry 24, Table 1).

With the optimized conditions in hand, we then tested the scope and limitations of the catalytic asymmetric synthesis of 4-chromanol derivatives. The outcomes compiled in Scheme 1

Scheme 1. Catalytic Asymmetric Synthesis of 3[a]



[a]Ee values in parentheses are obtained after recrystallization.

show that all salicyladehydes **2a−o** underwent an asymmetric reaction with enamide **1a**. When 5-substituted salicyladehydes **2b−i** were employed, irrespective of the nature of the 5-substituents, the reaction proceeded efficiently to yield products **3b−i** in high yields with excellent enantio- and diastereoselectivity. Functional groups including cyano, ester, and carbon−halogen bonds were well tolerated. Disubstituted reactants such as 4,6-dichloro- and 3,5-dibromo-salicyladehydes reacted equally well to afford **3j** and **3k**. Product **3o** of high enantiomeric purity was synthesized from 1-hydroxy-2-naphthaldehyde **2o**. While the catalytic reaction of 4-bromo-salicyladehyde **2l** with **1a** showed the same level of efficiency and enantio- and diastereoselectivities, 4-methoxy-salicyladehyde **2m** reacted very sluggishly to form product **3m** in 39% yield with poor diastereo- and enantioselectivity. A diminished reaction rate and enantioselectivity were also observed from the reaction of hydroxylated piperonaldehyde **2n**, which gave product **3n** in 27% yield and 81.9% ee. Consistent with the $SnCl_2$-catalyzed reaction, a slow rate observed for substrates **2m** and **2n** in the asymmetric catalysis reflecting the strong substituent effect of the electron-donating alkoxy which reduces the reactivity of aldehyde. It was observed that the 4-alkoxy group on salicyladehyde decreased selectivity in the asymmetric catalysis (Scheme 1).

Enamides **1** bearing other *N*-substituents were also able to undergo a catalytic asymmetric reaction with salicyladehydes. The catalytic efficiency, enantioselectivity, and diastereoselectivity of the reaction were, however, dependent upon the nature of the *N*-substituents. All *N*-aroyl-substituted enamides **1a** (R^1 = Ph), **1b** (R^1 = 4-ClC_6H_4), and **1c** (4-MeOC_6H_4), irrespective of the presence of an electron-withdrawing or -donating group on the benzene ring, reacted efficiently with **2d** to yield the corresponding products **3a**, **3p**, and **3q** with a high level of enantio- and diastereo-selections. It is worth noting that when the *N*-aroyl group (**1a−c**) was replaced by an *N*-Ac or *N*-Cbz substituent, substrates **1d** and **1e** led to the highly efficient and diastereoselective reaction albeit the enantioselectivity was drastically decreased. Obviously, *N*-aroyl substituents on tertiary enamides displayed salient advantages over other groups in enantiocontrol.

The catalytic asymmetric reaction was readily expanded to other heterocyclic and acyclic enamides. Figure 4 shows for

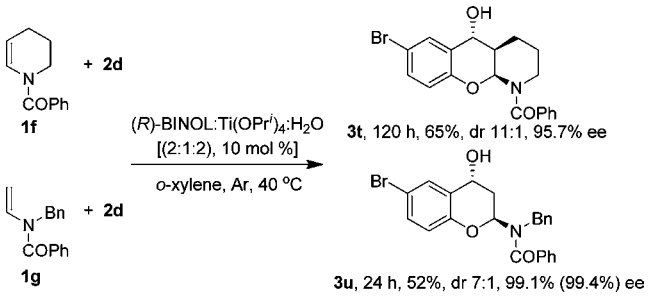


Figure 4. Catalytic asymmetric synthesis of **3s** and **3t**.

example the synthesis of piperidine-fused 4-chromanol **3s** in 65% yield with 95.7% ee from a six-membered heterocyclic tertiary enamide **1f**. A longer reaction time was required owing most likely to the lower nucleophilicity of **1f** in comparison to **1a**. Acyclic tertiary enamide **1g** reacted analogously with **2d** to produce 2-benzamidochroman-4-ol **3t** in 52% yield with 99.1% ee. The decreased diastereoselectivity (dr 11:1 and dr 7:1 respectively) in these cases was probably due to the steric difference of these enamides from the five-membered heterocyclic ones. It was notable that, under the reaction conditions, 2-benzamidochroman-4-ol **3u** was stable and it did not undergo a deamination reaction to form the 4*H*-chromen-4-ol compound.

The catalytic asymmetric reaction was scalable. This was evidenced for instance by the high-yielding reaction of **1a** (5 mmol) with salicylaldehydes **2a**, **2d**, and **2h** which afforded the gram-scale products **3a** (1.33 g, 96.7% ee), **3d** (1.51 g, 95.7% ee), and **3h** (1.29 g, 95.1% ee), respectively, without decreases in enantio- and diastereoselectivity (Figure 5). To demonstrate the synthetic potential of the method, synthesis of chroman-4-one derivatives **5** and their subsequent conversion into compounds **4**,

dx.doi.org/10.1021/ol5029964 | *Org. Lett.* 2014, 16, 5972−5975

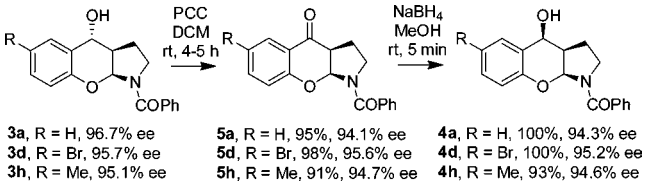


Figure 5. Synthesis of **5** and their conversion to **4**.

which are diastereomers of **3**, were implemented. As shown in Figure 5, oxidation of pyrrolidine-fused 4-chromanols **3a**, **3d**, and **3h** with PCC in DCM at rt gave the corresponding chroman-4-ones **5** in excellent yields. Governed by the steric effect of the *cis*-fused pyrrolidine ring, facile reduction of the carbonyl group of **5** with $NaBH_4$ yielded almost quantitatively *cis,cis*-configured 4-chromanols **4** (Figure 6) as the sole diastereomers. The slightly

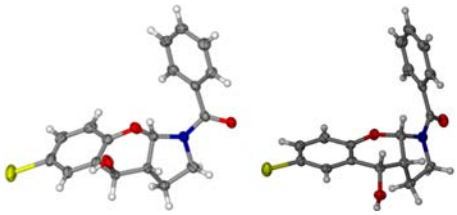


Figure 6. X-ray structure of (3a*R*, 4*R*, 9a*S*)-**3d** (left) and (3a*R*, 4*S*, 9a*S*)-**4d** (right).

lower ee values of chroman-4-ones **5** compared to that of the reactants **3** were attributed to the use of starting materials that contain a tiny amount of minor diastereomer **4** of a lower ee. The enantiomeric purity of the final products **4** was further improved to 95.5%−98.3% after recrystallization (see Supporting Information).

In summary, we have established a general and efficient chiral BINOL-Ti(O*i*Pr)$_4$-catalyzed reaction of tertiary enamides with salicylaldehydes under mild conditions. The reaction proceeds through the enaminic addition of enamide to aldehyde and the interception of the resulting iminium by the phenolic hydroxy group to afford diverse 4-chromanol derivatives in high yields with excellent enantio- and diastereoselectivity. The synthetic potential of the method has been demonstrated by facile transformation of *cis,trans*-configured pyrrolidine-fused 4-chromanols into chroman-4-ones upon oxidation and then to *cis,cis*-configured 4-chromanol diastereomers after diastereoselective reduction. The present study opens a new avenue to the divergent synthesis of functional molecules based on difunctionalizations of unique tertiary enamide synthons. The catalytic mechanism is being actively perused in this laboratory, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Characterization and spectroscopic data, X-ray structures (cif files). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge NNSFC (21320102002) for financial support.

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