Turning Chemoselective Switch in Asymmetric Organocatalysis of 5*H*-oxazol-4-ones and *N*-Itaconimides towards Tandem Conjugate Addition−Protonation or [4+2] Cycloaddition

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Abstract: We report a synthetic strategy for chemoselective switch and diastereo-divergent approach to asymmetric reaction between 5*H*-oxazol-4-ones and *N*-itaconimides catalysed by *L-tert*-leucine-derived tertiary amine−ureas. The reaction could be modulated to harness either tandem conjugate addition−protonation or [4+2] cycloaddition as major product with excellent enantio- and diastereoselectivities. Subjecting enantio-enriched cycloaddition product with basic *silica gel* reagent yields the diastereomer vis-à-vis the product directly obtained by conditions for addition−protonation, thus opening a diastereo-divergent route for creating 1,3-tertiary−hetero-quaternary stereocenters. Quantum chemical studies further provide stereochemical analysis for the [4+2] process and a plausible mechanism for this chemoselective switch is proposed.

Reactions featuring switchable chemoselectivity enable the same set of starting substrates to generate distinct products under controlled experimental conditions, effectively expanding molecular diversity and scope. As a result, reaction strategies allowing chemo-divergence have been acknowledged as one of the most promising developments in organic and medicinal chemistry.[1,2] However, such examples are few,[2] highlighting difficulties in precisely tuning reaction conditions for desired chemo-selection.

As α-alkyl-α-hydroxy carboxylic acid derivatives are key chiral structural motifs in biologically relevant molecules,[3] interest in asymmetric reactions of 5*H*-oxazol-4-ones has grown significantly in the past decade.[4] The challenge remains for the asymmetric tandem conjugate addition−protonation[5] of 5*H*-oxazol-4-ones providing molecules bearing 1,3-tertiary−hetero-quaternary stereocenters.[3a-b] And only recently one such example was reported,[4m] probably owing to difficulties in the stereo-control of protonation process. The 5*H*-oxazol-4-one possess three reactive sites: C2, C4, and C5, but all literature surveyed to date focused on C-C bond formation at C5. We could theoretically exploit the electrophilic C2 and deprotonated C5 enolate, similar to 2-azadienes,[6] to perform [4+2] cycloaddition with suitable dienophiles, thus making a polycyclic nitrogen heterocycle.[7]

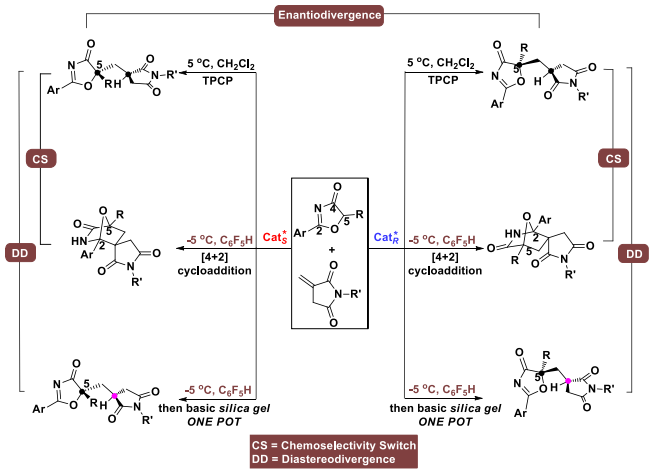

Figure 1. Organocatalytic asymmetric reaction between 5H-oxazol-4-ones and N-itaconimides. Tandem conjugate addition−protonation = TCAP.

This work endeavours to identify reaction conditions that facilitate chemoselective switching in the asymmetric reaction between 5*H*-oxazol-4-ones and *N*-itaconimides catalysed by *L-tert*-leucine-derived tertiary amine−ureas (Figure 1). The judicious choice of solvent, temperature and catalyst should ultimately yield highly enantio-enriched [4+2] cycloaddition or tandem conjugate addition−protonation products. As a corollary, we employed basic *silica gel* reagent for the work-up of cylcoaddition products to give corresponding diastereoisomers, enabling diastereo-divergent creation of 1,3-tertiary−hetero-quaternary stereocenters. Enantio-divergence could be realized simply by using the enantiomer of the organocatalyst.

We initiated our study by testing the feasibility of tandem conjugate addition−protonation of 5*H*-oxazol-4-one **1a**, and *N*-phenyl itaconimide **2a** as an acceptor (Table 1).[8] The class of electrophile chosen, *N*-itaconimides, which contains an activated exocyclic alkene, have been utilized previously as the electrophile in catalytic asymmetric protonation to assemble chiral succinimides with biological targets.[8] However, employing them in tandem conjugate addition−protonation to construct two nonadjacent stereocenters is a first. *L-tert*-Leucine derived tertiary amine−thiourea bifunctional catalyst **I**, whose efficacy has been demonstrated by us and others,[9] was first put to the test. The addition−protonation adduct **3a** was obtained in 82% yield with 82% *ee* and 3:1 d.r. within 60 hours (Table 1, entry 1). Both enantio- and diastereoselectivity were improved by using another variant, catalyst **II** (93% *ee*, 5:1 d.r., Table 1, entry 2). Even better stereoselectivity was seen with 3,5-dimethyloxyphenyl catalyst **III** in which **3a** was obtained with 95% *ee* and 6:1 d.r. (Table 1, entry 3). The reaction performed at 5 ºC produced **3a** in 96% *ee* and 7:1

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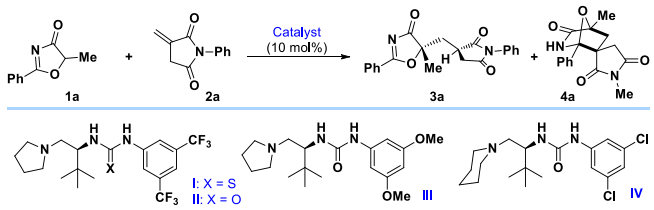
d.r. (Table 1, entry 4); and the *dr* value was further increased to 9:1 when the concentration was diluted five times (Table 1, entry 5).

Table 1: Optimization of reaction conditions.[a]



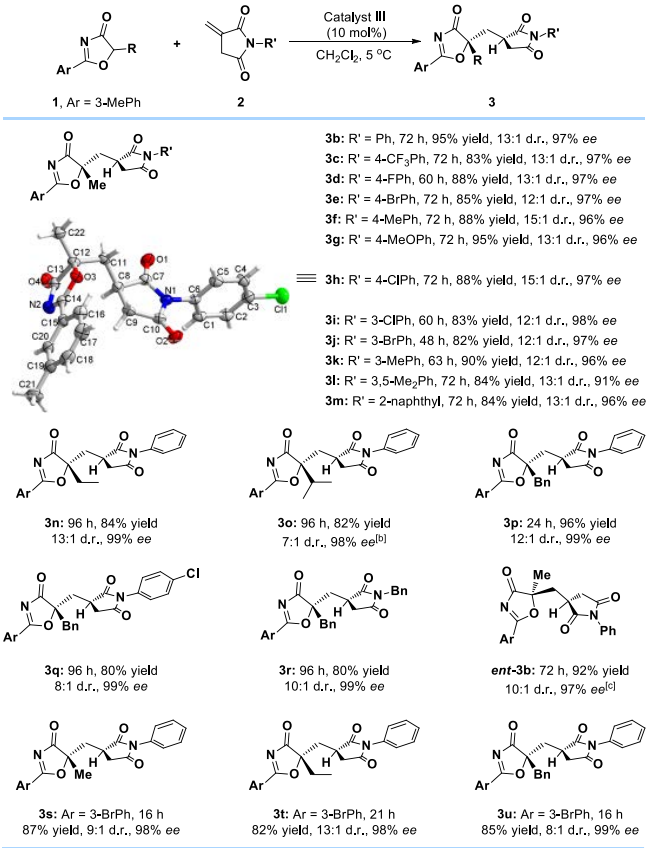
Entry	Cat.	Solv./ T [°C]	*t* [h]	**3a:4a**[b]	**3a** Yield [%][c]	**3a** *ee* [%][d]	*dr*[b]	**4a** Yield [%][c]	**4a** *ee* [%][d]
1	**I**	DCM /25	60	>99:1	82	82	3:1	N.A.	N.A.
2,	**II**	DCM /25	12	>99:1	87	93	5:1	N.A.	N.A.
3	**III**	DCM /25	12	>99:1	90	95	6:1	N.A.	N.A.
4	**III**	DCM /5	36	>99:1	88	96	7:1	N.A.	N.A.
5[e]	**III**	DCM /5	72	>99:1	87	96	9:1	N.A.	N.A.
6	**III**	Et_2O /25	2	1:2.4	24	98	3:1	56	59
7	**IV**	Et_2O /25	4	1:3	15	96	1:1	56	71
8	**IV**	Et_2O /5	16	1:3	20	94	1:1	65	68
9	**IV**	C_6HF_5 /5	12	2:1	65	98/93	1:1	28	83
10[f]	**IV**	C_6HF_5 /−5	16	1:5	16	99/99	1:1	68	92

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.075 mmol), solvent (0.5 mL). [b] The ratio of **3a**:**4a** and *dr* were determined by crude ^{1}H NMR. Dr of **4a** >19:1. [c] Yield was isolated by flash column. [d] Ee was determined by HPLC. [e] 2.5 mL solvent was used. [f] 5 mol% of catalyst **IV**.

By enlisting the reaction conditions in entry 6 of Table 1, we were intrigued to be able to isolate the [4+2] cycloaddition adduct **4a** as the major product.[10] This discovery prompted us to screen reaction conditions, so as to synthesize **4a** with improved yield and stereoselectivity. It was found that catalyst **IV**, an analogue of catalyst **III**, is a more suitable catalyst candidate to produce **4a** (Table 1, entry 7). Unfortunately for Et_2O at lower temperature the enantioselectivity stayed the same (5 °C, Table 1, entry 8), so other low polarity solvents were screened.[10] Pentafluorobenzene (C_6HF_5) as solvent at 5 °C gave 28% yield of **4a** and higher *ee* at 83% (Table 1, entry 9). Performing the reaction in C_6HF_5 at −5 °C with lower catalyst loading of 5.0 mol% **IV** afforded **4a** in 68% yield with 92% *ee* (Table 1, entry 10).

With the optimal conditions established earlier for tandem conjugate addition−protonation[10] (10 mol% of catalyt **III**, CH_2Cl_2, 5 °C), substrate screening of various *N*-substituted *N*-itaconimides **2** and 5*H*-oxazol-4-ones **1** bearing 3-methylphenyl on C2 position and different substituents on C5 position was carried out (Table 2). All screened reactions proceeded smoothly and completed within 24−96 hours, giving adducts **3b-r** in 80−96% yield with 91−99% *ee* and 7:1 to 15:1 d.r.. Employing 10 mol% of *ent*-**III** as catalyst gave *ent*-**3b** in 92% yield with 97% *ee* and 10:1 d.r. after 72 hours (footnote c). The addition−protonation process was also effective with 5*H*-oxazol-4-ones bearing 3-bromophenyl on C2 position, affording adducts **3s-u** in 82−87% yield with 98−99% *ee* and 8:1 to 13:1 d.r.. The stereochemistry of the tandem conjugate addition-protonation products were assigned based on the structure of **3h**, as solved by single crystal X-ray diffraction.[12]

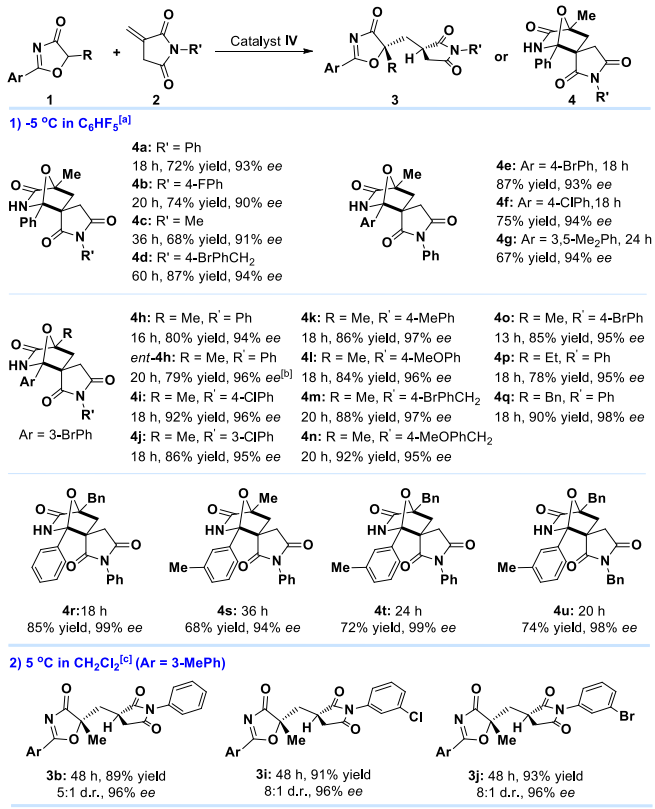
Table 2: Tandem conjugate addition−protonation of **1** and **2** catalyzed by **III**.[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), **III** (0.02 mmol), CH_2Cl_2 (10 mL), 5 °C. Yield was isolated by flash column. *Ee* was determined by HPLC. *Dr* was determined by crude ^{1}H NMR. [b] 10 °C and 4 mL CH_2Cl_2 was used. [c] 10 mol% of *ent*-**III** was used.

Next we turned our attention to generating other derivatives of **4a** (Table 3.1). The reactions were performed in the presence of 5 mol% of **IV** in C_6HF_5 as solvent at −5 °C, and a series of products **4a-4u** were obtained in 68−92% yield with 90−99% *ee*. These results show that the reaction is applicable to a wide range of 5*H*-oxazol-4-ones containing different substituents on C2 and C5 positions and *N*-phenyl, benzyl and alkyl-substituted itaconimides. The absolute configuration of cycloaddition products were assigned based on X-ray crystallographic analysis of **4h**.[11] We also carried out several reactions by employing enantiomeric *ent*-**IV** catalyst in CH_2Cl_2 as solvent at 5 °C (Table 3.2), and the corresponding tandem conjugate addition−protonation products **3b** and **3i-j** were obtained with similarly high *ee* values but slightly depressed *dr*s as compared to **III** as the catalyst (Table 2). These results indicate that a strategy for chemoselectivity switch could be realized by conveniently tuning the solvent and temperature.

Table 3: The reaction of **1** and **2** catalyzed by **IV**.



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), **IV** (0.01 mmol), C_6HF_5 (4.0 mL), −5 °C. Yield was isolated by flash column. *Ee* was determined by HPLC. *Dr* was determined by crude ^{1}H NMR. All *dr*s > 19:1. [b] *ent*-**IV** was catalyst. [c] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), **IV** (0.02 mmol), CH_2Cl_2 (10 mL), 5 °C. Yield was isolated by flash column. *Ee* was determined by HPLC. *Dr* was determined by crude ^{1}H NMR.

In order to guide our understanding of the mechanism and observed stereochemical outcomes, dispersion corrected density functional theory (DFT) calculations at the M06-2X(D3)/def2-TZVP/SMD//B3LYP/6-31G(d,p)/SMD level of theory were carried out to model the reactions of substrates **1a**, **2a**, and catalyst **IV**.[10] First, the electrophile **2a** could approach the bound zwitterionic catalyst-nucleophile complex **IV-1a** in either an eclipsed or staggered fashion. The transition state (TS) for *eclipsed* approach is more stable than the *staggered* by as much as 2.7 kcal/mol due to secondary π-π* orbital interactions [9e] and based on this *eclipsed* approach, there are 4 possible stereo-outcomes (see E.S.I. figure S1 and S2). Comparison of all of the relative Gibb's free activation energies of the TS of these 4 stereo-outcomes in the first Michael addition (Figure 2) reveal that the TS is most stable when the substrates are fused in a *Re,Si* fashion (**TS1-R,S[IV]**, $\Delta G^{\ddagger}$ = +15.9 kcal/mol). TS structures optimized with *Si,Re- Re,Re-* or *Si,Si*-facing substrates (**TS1-S,R[IV]**, **TS1-R,R[IV]** and **TS1-S,S[IV]** respectively) were calculated to be less stable ($\Delta G^{\ddagger}$ = +18.0 to +20.0 kcal/mol) and thus likely to be less competitive kinetically.

The distortion/interaction model was employed to further analyze the reactivity of the first enantio-discriminating TS, [11] with **TS1-R,S[IV]** revealing interaction energy greatly contributing to stability (Figure 2). The subsequent steps following the *Re,Si* pathway were fully modeled to provide a plausible understanding for the observed chemoselective switch. We propose in essence, the first isolable [4+2] cycloaddition product **4a** via *Re,Si* pathway (ΔG = −7.9 kcal/mol) is not the most thermodynamically stable product formed. Instead, addition-protonation products **3a** and its diastereomer **3a'**, ΔG = −9.1 kcal/mol and −12.6 kcal/mol respectively, are more stable and could be transformed from **4a** with elevation in reaction temperature or formed directly from **1a** and **2a** (see E.S.I. for full explanation).

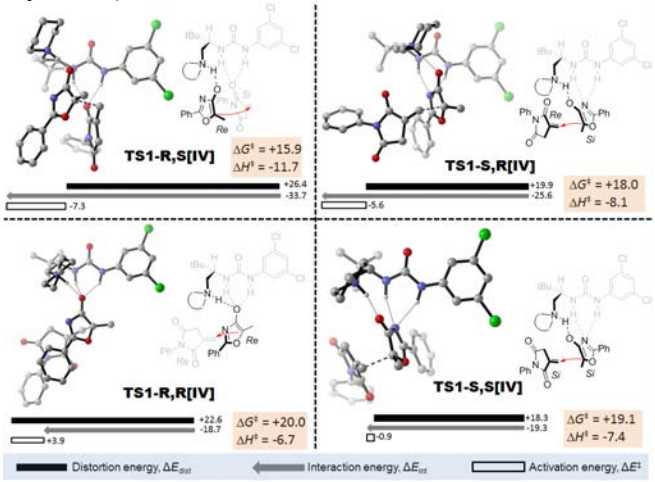
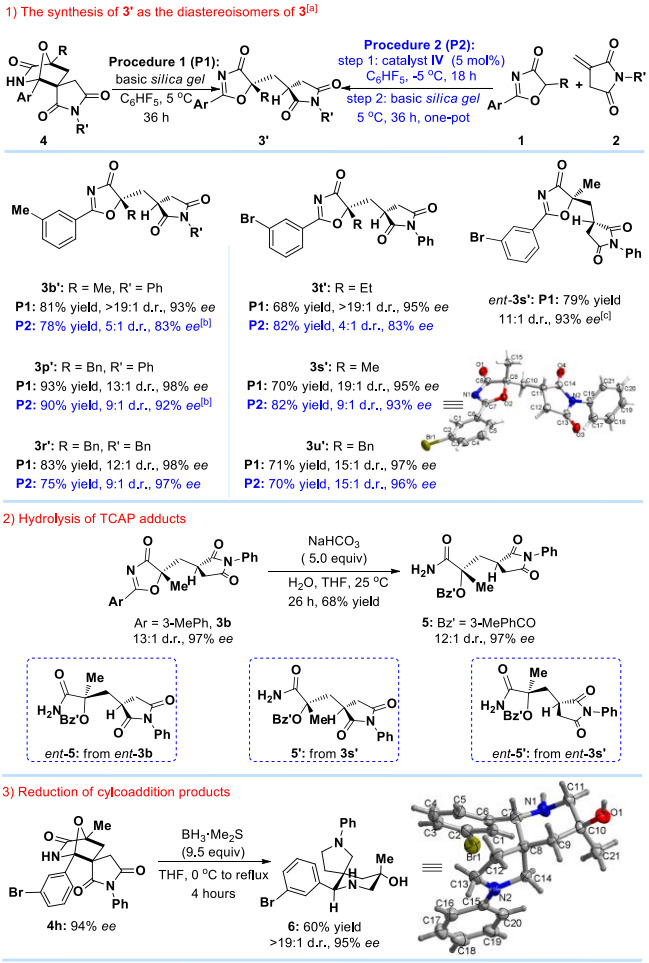


Figure 2. TS for Michael addition process. Values are Gibbs's free energy and enthalpy (kcal/mol) of dichloromethane (DCM) optimized transition state electronic structures relative to free starting materials **1a**, **2a** and **IV**.

Finally, the synthetic utility of this work is demonstrated here. Treatment of cylcoaddition product **4h** with 0.5 equiv of LiOH in CH_2Cl_2 at −10 °C led to 1:1 ratio of **3s** and its diastereoisomer **3s'** without compromising *ee* value.[10] Different inorganic bases were also examined and NaOH was found to give **3s'** with 2:1 d.r.. No reaction was observed when weaker bases, such as $NaHCO_3$ and Na_2CO_3, were used. Interestingly, a more efficient reagent is obtained by treating *silica gel* with base (NaOH/*silica gel* = 40 mg/10g), which promoted this transformation with satisfactory diastereoselectivity. In the presence of basic *silica gel* reagent in C_6HF_5 at 5 °C, a series of **3'** were obtained from the corresponding cycloaddition products (**4s-u**, **4h** and **4p-q**) in 68−93% yield with 12:1 to >19:1 d.r. and high *ee* (Scheme 1.1). Furthermore, a tandem one-pot strategy through combining [4+2] cycloaddition and transformation by directly employing **1** and **2** as starting substrates was explored. Various **3'** were achieved in satisfactory yields with a slightly lower *ee* values and *dr*s (70−90% yield of two steps, 83−96% *ee* and 5:1 to 15:1 d.r.). The absolute configuration of **3'** products were confirmed based on single-crystal X-ray crystallographic analysis of **3s'**.[13] To the best of our knowledge, this is one of the few examples reported to date of a diastereo-divergent[5a-b,14] method for the asymmetric creation of two nonadjacent stereocenters.[5a-b]

Hydroxylation of **3b** was then performed with 5.0 equiv of $NaHCO_3$ in THF at 25 °C (Scheme 1.2). Amide **5** with a benzoyl−protected α-tertiary alcohol was obtained in 68% yield after 26 hours without compromising *ee* value and *dr*. In the same light, the enantiomer and a pair of enantiomeric diastereoisomers of **5** could be conveniently achieved from *ent*-**3b** (Table 2), **3s'** and *ent*-**3s'** (Scheme 1.1) through this methodology. Reduction of **4h** with a borane dimethyl sulfide complex afforded a highly interesting spiro-piperidine−pyrrolidine derivative **6**, which is important in pharmaceuticals (Scheme 1.3).[15]



Scheme 1. Synthetic utilities of this work. [a] 0.2 mmol scale and 4.0 g of basic *silica gel* (NaOH/*silica gel* = 40 mg : 10 g) was used. For **P1**: yield of one step; for **P2**: yield of two step. [b] The **step 1** was performed for 36 hours. [c] From *ent*-**4h**. Yield was isolated by flash column. *Ee* was determined by HPLC. *Dr* was determined by crude ^{1}H NMR.

In summary, we have successfully developed expedient and practical routes for realizing a novel asymmetric and chemoselective switch strategy between 5*H*-oxazol-4-ones and *N*-itaconimides. The *L*-*tert*-leucine-derived tertiary amine–urea catalyst under established protocols (reaction media and temperature) worked efficiently to selectively produce tandem conjugate addition–protonation and [4+2] cycloaddition products with excellent enantio- and diastereoselectivities. Furthermore, the diastereoselectivity of tandem conjugate addition–protonation could be improved by tuning the electronic properties of catalyst. This study is also the first synthetic demonstration to take advantage of electrophilic C2 atom of 5*H*-oxazol-4-ones in asymmetric catalysis. For the diastereo-divergent route we devised a novel basic *silica gel* reagent promote the conversion of the cycloaddition adducts to the corresponding diastereoisomers of addition–protonation adducts with good results, thus furnishing the enantio- and diastereodivergent creation of 1,3-tertiary–hetero-quaternary stereocenters. Future investigations, involving kinetic studies and computations will be detailed to fully understand the mechanistic underpinnings of the chemoselectivity switch.

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Keywords: Asymmetric Organocatalysis • Chemoselectivity Switch • Diastereo-divergence • Enantio-divergence • 5*H*-Oxo-4-ones

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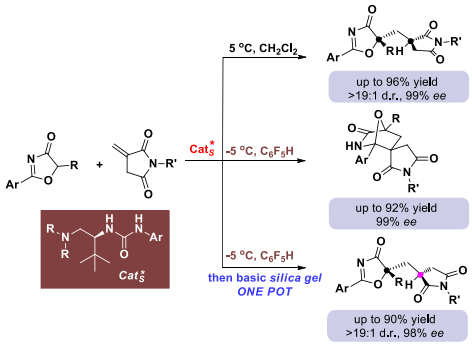

B. Zhu, R. Lee, J. Li, X. Ye, S.-N. Hong, S. Qiu, M. L. Coote, Z. Jiang**

Turning Chemoselective Switch in Asymmetric Organocatalysis of 5*H*-Oxazol-4-ones with *N*-Itaconimides towards Tandem Conjugate Addition–Protonation or [4+2] Cycloaddition

A Switchable Chemoselectivity: The first asymmetric reaction of 5*H*-oxazol-4-ones with itaconimides was successfully developed by employing a chiral amino acid-derived tertiary amine–urea catalyst. The substrates can go through either tandem conjugate addition–protonation or the unprecedented [4+2] cycloaddition with excellent enantio- and diastereoselectivities by judiciously regulating the reaction conditions. A basic *silica gel* reagent was devised to accomplish enantio- and diastereodivergent creation of 1,3-tertiary–hetero-quaternary stereocenters. DFT calculations provide a plausible mechanistic understanding to stereochemistry and the nature of chemoselective switch.