Organocatalysis

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Chemoselective Switch in the Asymmetric Organocatalysis of 5*H*-Oxazol-4-ones and *N*-Itaconimides: Addition–Protonation or [4+2] Cycloaddition

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Abstract: *We report a synthetic strategy for a chemoselective switch and a diastereo-divergent approach for the asymmetric reaction of 5H-oxazol-4-ones and N-itaconimides catalyzed by* L*-tert-leucine-derived tertiary amine–urea compounds. The reaction was modulated to harness either tandem conjugate addition–protonation or [4+2] cycloaddition as major product with excellent enantio- and diastereoselectivities. Subjecting the enantio-enriched cycloaddition products to a basic silica gel reagent yields the diastereomer vis-à-vis the product directly obtained under 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 chemodivergence 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 chemoselectivity.

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. 5*H*-Oxazol-4-one possesses 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 site and deprotonated the C5 enolate, similar to 2-azadienes,[6] to perform [4+2] cycloaddition with suitable dienophiles, thus making a polycyclic nitrogen heterocycle.[7]

This work endeavours to identify reaction conditions that facilitate chemoselective switching in the asymmetric reaction between 5*H*-oxazol-4-ones and *N*-itaconimides catalyzed by L-*tert*-leucine-derived tertiary amine–urea compounds (Figure 1). The judicious choice of solvent, temperature, and catalyst should ultimately yield highly enantio-enriched [4+2] products after cycloaddition or tandem conjugate addition–protonation. As a corollary, we employed a 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.

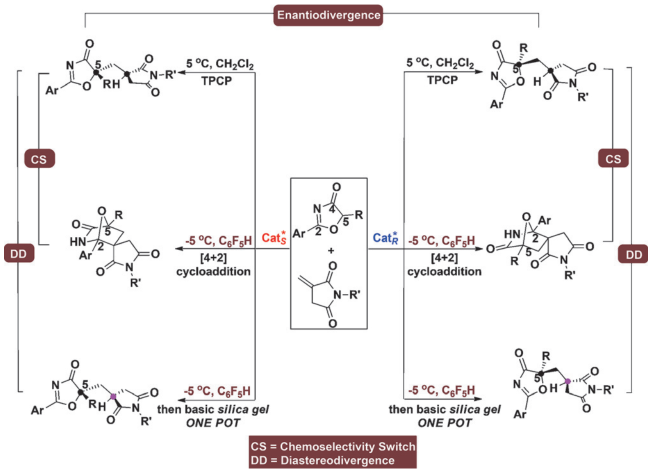

Figure 1. Organocatalytic asymmetric reaction between 5*H*-oxazol-4-ones and *N*-itaconimides. Tandem conjugate addition–protonation = T-CAP.

We initiated our study by testing the feasibility of tandem conjugate addition–protonation of 5*H*-oxazol-4-one **1a**, and

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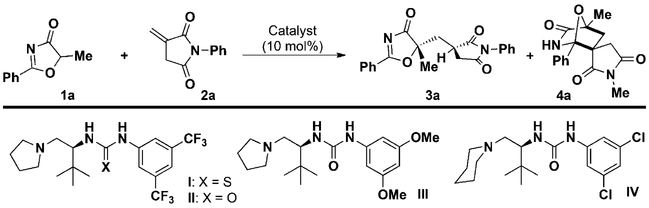
Table 1: Optimization of reaction conditions.[a]



Entry	Cat.	Solv./*T* [°C]	*t* [h]	**3a**:**4a**[b]	**3a**			**4a**	
					Yield [%][c]	*ee* [%][d]	d.r.[b]	Yield [%][c]	*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

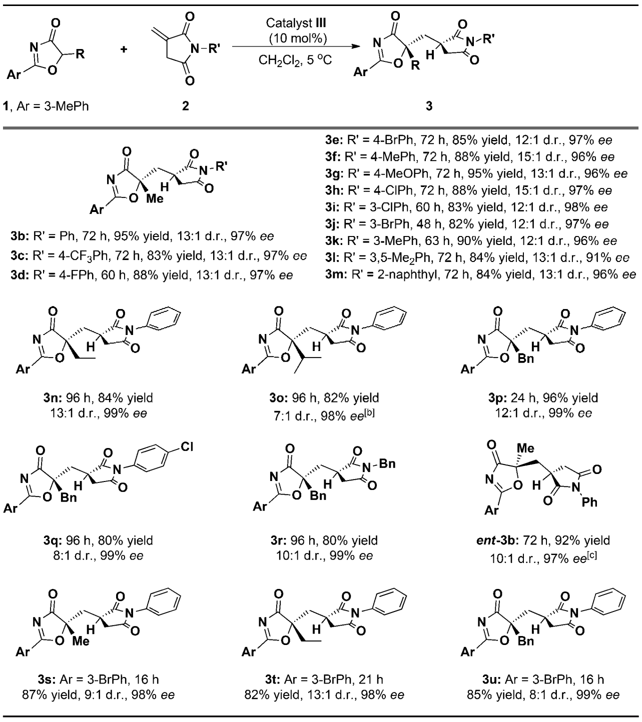
[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.075 mmol), solvent (0.5 mL). [b] The ratio of **3a**:**4a** and d.r. were determined by crude ^{1}H NMR. The dr of **4a** >19:1. [c] The yield was isolated by flash column. [d] The *ee* was determined by HPLC. [e] 2.5 mL solvent was used. [f] 5 mol%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

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 used 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**, the efficacy of which 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 °C produced **3a** in 96% *ee* and 7:1 d.r. (Table 1, entry 4); and the d.r. value was further increased to 9:1 when the concentration was diluted five times (Table 1, entry 5).

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 analog 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]



3b: R' = Ph, 72 h, 95% yield, 13:1 d.r., 97% *ee*
3c: R' = 4-CF_3Ph, 72 h, 83% yield, 13:1 d.r., 97% *ee*
3d: R' = 4-FPh, 60 h, 88% yield, 13:1 d.r., 97% *ee*
3e: R' = 4-BrPh, 72 h, 85% yield, 12:1 d.r., 97% *ee*
3f: R' = 4-MePh, 72 h, 88% yield, 15:1 d.r., 96% *ee*
3g: R' = 4-MeOPh, 72 h, 95% yield, 13:1 d.r., 96% *ee*
3h: R' = 4-ClPh, 72 h, 88% yield, 15:1 d.r., 97% *ee*
3i: R' = 3-ClPh, 60 h, 83% yield, 12:1 d.r., 98% *ee*
3j: R' = 3-BrPh, 48 h, 82% yield, 12:1 d.r., 97% *ee*
3k: R' = 3-MePh, 63 h, 90% yield, 12:1 d.r., 96% *ee*
3l: R' = 3,5-Me_2Ph, 72 h, 84% yield, 13:1 d.r., 91% *ee*
3m: R' = 2-naphthyl, 72 h, 84% yield, 13:1 d.r., 96% *ee*

3n: 96 h, 84% yield
13:1 d.r., 99% *ee*

3o: 96 h, 82% yield
7:1 d.r., 98% *ee*[b]

3p: 24 h, 96% yield
12:1 d.r., 99% *ee*

3q: 96 h, 80% yield
8:1 d.r., 99% *ee*

3r: 96 h, 80% yield
10:1 d.r., 99% *ee*

***ent*-3b:** 72 h, 92% yield
10:1 d.r., 97% *ee*[c]

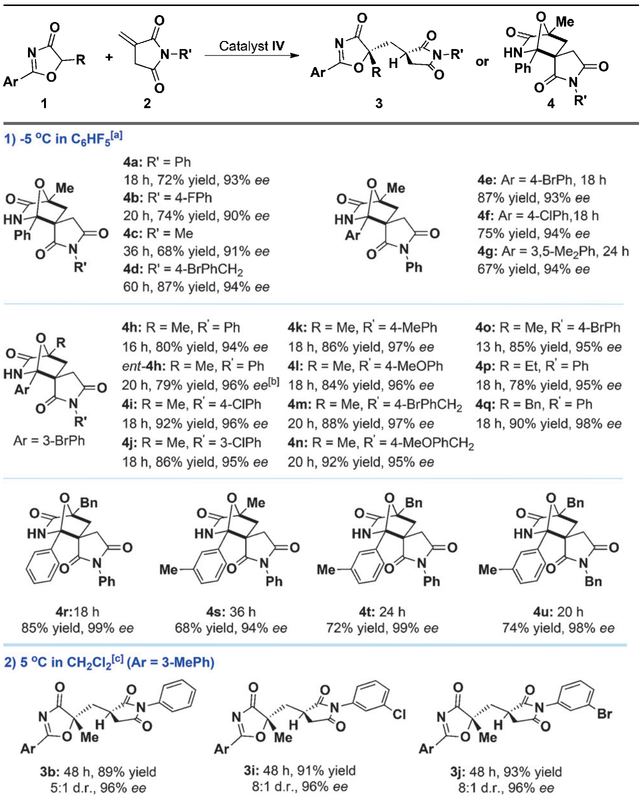
3s: Ar = 3-BrPh, 16 h
87% yield, 9:1 d.r., 98% *ee*

3t: Ar = 3-BrPh, 21 h
82% yield, 13:1 d.r., 98% *ee*

3u: Ar = 3-BrPh, 16 h
85% yield, 8:1 d.r., 99% *ee*

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

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



4a: R' = Ph
18 h, 72% yield, 93% *ee*
4b: R' = 4-FPh
20 h, 74% yield, 90% *ee*
4c: R' = Me
36 h, 68% yield, 91% *ee*
4d: R' = 4-BrPhCH$_2$
60 h, 87% yield, 94% *ee*

4e: Ar = 4-BrPh, 18 h
87% yield, 93% *ee*
4f: Ar = 4-ClPh,18 h
75% yield, 94% *ee*
4g: Ar = 3,5-Me$_2$Ph, 24 h
67% yield, 94% *ee*

4h: R = Me, R' = Ph
16 h, 80% yield, 94% *ee*
ent-**4h:** R = Me, R' = Ph
20 h, 79% yield, 96% *ee*[b]
4i: R = Me, R' = 4-ClPh
18 h, 92% yield, 96% *ee*
4j: R = Me, R' = 3-ClPh
18 h, 86% yield, 95% *ee*

4k: R = Me, R' = 4-MePh
18 h, 86% yield, 97% *ee*
4l: R = Me, R' = 4-MeOPh
18 h, 84% yield, 96% *ee*
4m: R = Me, R' = 4-BrPhCH$_2$
20 h, 88% yield, 97% *ee*
4n: R = Me, R' = 4-MeOPhCH$_2$
20 h, 92% yield, 95% *ee*

4o: R = Me, R' = 4-BrPh
13 h, 85% yield, 95% *ee*
4p: R = Et, R' = Ph
18 h, 78% yield, 95% *ee*
4q: R = Bn, R' = Ph
18 h, 90% yield, 98% *ee*

4r:18 h
85% yield, 99% *ee*

4s: 36 h
68% yield, 94% *ee*

4t: 24 h
72% yield, 99% *ee*

4u: 20 h
74% yield, 98% *ee*

3b: 48 h, 89% yield
5:1 d.r., 96% *ee*

3i: 48 h, 91% yield
8:1 d.r., 96% *ee*

3j: 48 h, 93% yield
8:1 d.r., 96% *ee*

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), **IV** (0.01 mmol), C_6HF_5 (4.0 mL), −5 °C. The yield was isolated by flash column. The *ee* was determined by HPLC. The dr was determined by crude ^{1}H NMR spectroscopy. All dr values >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. The yield was isolated by flash column. The *ee* was determined by HPLC. The dr was determined by crude ^{1}H NMR spectroscopy.

Next we turned our attention to generating other derivatives of **4a** (Table 3 part 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 part 2), and the corresponding tandem conjugate addition–protonation products **3b** and **3i**–**j** were obtained with similarly high *ee* values but slightly depressed dr values (dr = diastereomeric ratio) as compared to **III** as the catalyst (Table 2). These results indicate that a strategy for a chemoselectivity switch could be realized by conveniently tuning solvent and temperature.

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 the eclipsed approach is more stable than the staggered one by as much as 2.7 kcal mol^{-1} because of secondary π–π* orbital interactions[9e] and based on this eclipsed approach, there are four possible stereo-outcomes (see Figures S1 and S2 in the Supporting Information). Comparison of all of the relative Gibbs free activation energies of the TS of these four 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]**, $\Delta G^{\neq} = +15.9$ kcal mol^{-1}). 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 ($\Delta G^{\neq} = +18.0$ to $+20.0$ kcal mol^{-1}) and thus likely to be less competitive kinetically.

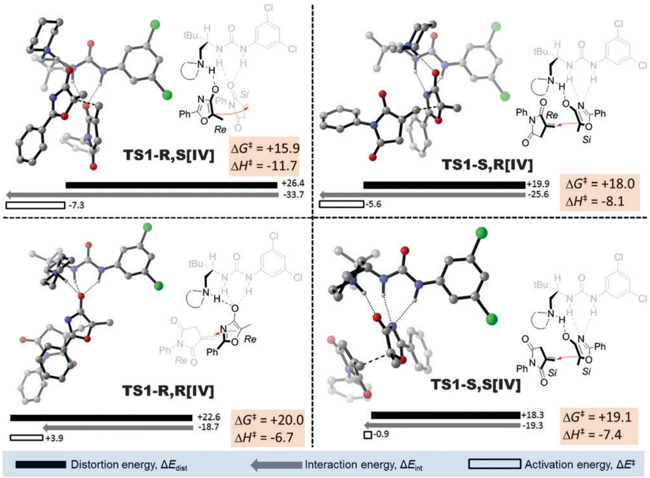
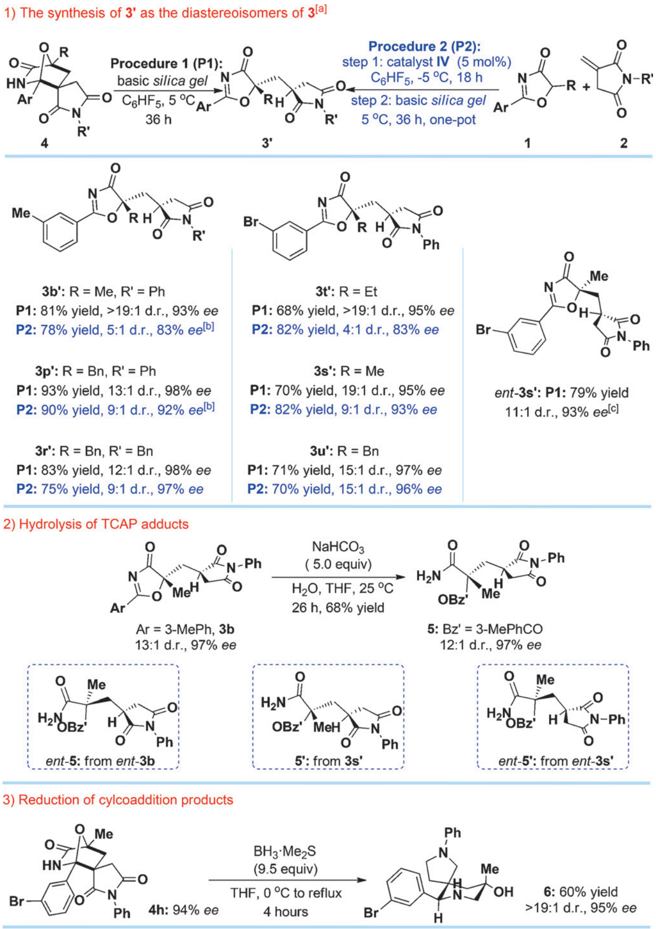


Figure 2. TS for the Michael addition process. Values are Gibbs free energy and enthalpy (kcal mol^{-1}) of dichloromethane (DCM) optimized transition-state electronic structures relative to free starting materials **1a**, **2a**, and **IV**.

The distortion/interaction model was employed to further analyze the reactivity of the first enantio-discriminating TSs,[11] with **TS1-R**,**S[IV]** revealing the strongest interaction energy and consequently lowest activation energy (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 ($\Delta G = -7.9$ kcal mol^{-1}) is not the most thermodynamically stable product formed. Instead, addition–protonation products **3a** and its diastereomer **3a''**, $\Delta G = -9.1$ kcal mol^{-1} and −12.6 kcal mol^{-1}, respectively, are more stable and could be transformed from **4a** with elevation in reaction temperature (see the Supporting Infromation for full explanation).

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 d.r. of 2:1. 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/10 g), 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 values (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]



Scheme 1. Synthetic routes used in this work. [a] Reaction on a 0.2 mmol scale. 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 steps. [b] Step 1 was performed for 36 hours. [c] From *ent*-**4h**. Yield was isolated by flash column. The *ee* was determined by HPLC. The dr was determined by crude ^1H NMR spectroscopy.

Hydroxylation of **3b** was then performed with 5.0 equiv of $NaHCO_3$ in THF at 25 °C (Scheme 1 part 2). Amide **5** with a benzoyl-protected α-tertiary alcohol was obtained in 68 % yield after 26 hours without compromising *ee* value and d.r. 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 part 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 part 3).[15]

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 diastereo-divergent 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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