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

Bo Zhu, Richmond Lee, Jiangtao Li, Xinyi Ye, San-Ni Hong, Shuai Qiu, Michelle L. Coote,* and Zhiyong Jiang*

Abstract: We report a synthetic strategy for chemoselective switch and diastere-divergent approach to asymmetric reaction between 5H-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 enanti- 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 chemodivergence have been acknowledged as one of the most promising developments in organic and medicinal chemistry.[1,2] However, such examples are few,[3] 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 5H-oxazol-4-ones has grown significantly in the past decade.[4] The challenge remains for the asymmetric tandem conjugate addition–protonation[5] of 5H-oxazol-4-ones providing molecules bearing 1,3,3-tertiary–hetero–quaternary stereocenters.[3a-b] And only recently one such example was reported,[4a] probably owing to difficulties in the stereo-control of protonation process. The 5H-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 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 5H-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 cycloaddition products to give corresponding diastereoisomers, enabling diastereo-divergent creation of 1,3-tertiary–hetero-quaternary stereocenters. Enantiodivergence 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 5H-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.[9] 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 stereo-selectivity was seen with 3,5-dimethoxystyryl 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

---

[a] Bo Zhu,[b] Jiangtao Li,[b] San-Ni Hong, Shuai Qiu, Prof. Dr. Z. Jiang
Key Laboratory of Natural Medicine and Immuno-Engineering of Henan Province, Henan University
Jinming Campus, Kaifeng, Henan, 475004, P. R. China
E-mail: chmjzy@henu.edu.cn
[b] R. Lee,[b] Prof. Dr. M. L. Coote
ARC Centre of Excellence for Electromaterials Science Research School of Chemistry
Australian National University
Canberra ACT 2601, Australia
E-mail: michelle.coote@anu.edu.au
[c] X. Ye
Division of Chemistry and Biological Chemistry
Nanyang Technological University
21 Nanyang Link, 637371, Singapore

† These authors contributed equally to this work.

Supporting information for this article is given via a link at the end of the document.
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.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Solv./T [°C]</th>
<th>t [h]</th>
<th>3a-4a[^a]</th>
<th>Yield [%[^b]]</th>
<th>ee [%[^c],d]</th>
<th>dr[^e]</th>
<th>Yield [%[^f]]</th>
<th>ee [%[^g],d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>DCM/25</td>
<td>60</td>
<td>&gt;99:1</td>
<td>82</td>
<td>82</td>
<td>3:1</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>2</td>
<td>II</td>
<td>DCM/25</td>
<td>12</td>
<td>&gt;99:1</td>
<td>93</td>
<td>93</td>
<td>5:1</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>3</td>
<td>III</td>
<td>DCM/25</td>
<td>12</td>
<td>&gt;99:1</td>
<td>95</td>
<td>95</td>
<td>6:1</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>4</td>
<td>III</td>
<td>DCM/5</td>
<td>36</td>
<td>&gt;99:1</td>
<td>96</td>
<td>96</td>
<td>7:1</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>5[^f]</td>
<td>III</td>
<td>DCM/5</td>
<td>72</td>
<td>&gt;99:1</td>
<td>96</td>
<td>96</td>
<td>9:1</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>6</td>
<td>IV</td>
<td>EtO/25</td>
<td>2</td>
<td>1.2:4</td>
<td>98</td>
<td>3:1</td>
<td>56:9</td>
<td>1:1</td>
<td>56:9</td>
</tr>
<tr>
<td>7</td>
<td>IV</td>
<td>EtO/25</td>
<td>16</td>
<td>1.3:2</td>
<td>94</td>
<td>1:1</td>
<td>56:9</td>
<td>1:1</td>
<td>56:9</td>
</tr>
<tr>
<td>8</td>
<td>IV</td>
<td>CHF$_3$/5</td>
<td>12</td>
<td>2:1:1</td>
<td>93</td>
<td>1:1</td>
<td>65:8</td>
<td>1:1</td>
<td>65:8</td>
</tr>
<tr>
<td>9</td>
<td>IV</td>
<td>CHF$_3$/5</td>
<td>16</td>
<td>1.5:1</td>
<td>99:99</td>
<td>1:1</td>
<td>68:92</td>
<td>1:1</td>
<td>68:92</td>
</tr>
</tbody>
</table>

[^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 4 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. 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 EtO at lower temperature the enantioselectivity stayed the same (5°C, Table 1, entry 8), so other low polarity solvents were screened. Pentalfluorobenzene (CF$_3$H$_2$) as solvent at 5°C gave 28% yield of 4a and higher ee at 83% (Table 1, entry 9). Performing the reaction in CF$_3$H$_2$ 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[^9] (10 mol% of catalyst III, CH$_2$Cl$_2$, 5°C), substrate screening of various N-substituted N-itaconimides 2 and 5H-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–1 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 5H-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[^4].**

[^4] Reaction conditions: 1 (0.2 mmol), 2 (0.3 mmol), III (0.02 mmol), CH$_2$Cl$_2$ (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$_2$Cl$_2$ 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 CF$_3$H$_2$ as solvent at −5°C, and a series of products 4a–u were obtained in 68–92% yield with 90–99% ee. These results show that the reaction is applicable to a wide range of 5H-oxazol-4-ones containing different substituents on C2 and C5 positions and N-aryl, 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$_2$Cl$_2$ as solvent at 5°C (Table 3.2), and the corresponding tandem conjugate addition–protonation products 3b and 3j–l were obtained with similarly high ee values but slightly depressed drs 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.
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 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 Gibbs’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,Re-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 elucidate 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 pathway (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 pathway (Δ$\Delta G = +15.9$ kcal/mol). TS structures optimized with Si,Re-Re,Re- or Si,Re-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.

Figure 2. TS for Michael addition process. Values are Gibbs’s free energy (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 cyloaddition product 4h with 0.5 equiv of LiOH in CH2Cl2 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 NaHCO3 and Na2CO3, 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 CH2Cl2 at 5 °C, a series of 3 were obtained from the corresponding cycloaddition products (4s-u, 4h and 4q-p) 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 drs (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 NaHCO3 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]
In summary, we have successfully developed expedient and practical routes for realizing a novel asymmetric and chemoselective switch strategy between 5H-oxazol-4-ones and N-taconimides. 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] cycladdition 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 the electrocyclic C2 atom of 5H-oxazol-4-ones in asymmetric catalysis. For the diastereo-divergent route we devised a novel basic silica gel reagent promote the conversion of the cycladdition 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.

Acknowledgements

We are grateful for the grants from NSFC (21072044), NCET-11-0938 and the Program for Innovative Research Team from the University of Henan Province (14IRTSTHN006). MLC gratefully acknowledges Dr Xiaohe Miao (KAUST) for supplementary computing time.

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


[10] See the Electronic Supporting Information (E.S.I.) for details. For DFT, all reported Gibb’s free energies or enthalpies are relative to free starting materials 1a, 2a and IV.


[12] No reaction was observed when 3a was in the presence of [4+2] cycloaddition conditions.

[13] CCDC-1054275 (3h), CCDC-1058188 (4h), CCDC-1058217 (3a*) and CCDC-1418364 (6) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


A Switchable Chemoselectivity: The first asymmetric reaction of 5H-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–heteroquaternary stereocenters. DFT calculations provide a plausible mechanistic understanding to stereochemistry and the nature of chemoselective switch.