Enantioselective NiH-Catalyzed Syn-Hydrometalative Cyclization of Alkyne-tethered Ketoamides to α-Hydroxy-γ-Lactams

Hai-Xiang Zeng†, Xiao-Wen Zhang†, Qi-Yang Li, and Wen-Bo Liu*

†These authors contributed equally
*Corresponding authors (email: wenboliu@whu.edu.cn)

Sauvage Center for Molecular Sciences, Engineering Research Center of Organosilicon Compounds & Materials (Ministry of Education), College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, 430072 (China)

Abstract: An enantioselective NiH-catalyzed syn-hydrometalation of alkyne-tethered ketoamides for the synthesis of α-hydroxy-γ-lactams is reported. Using Ni(OTs)₂•6H₂O/(S,S)-Me-Duphos as a precatalyst and (EtO)₂MeSiH as a hydride source, a broad range of enantioenriched γ-lactams with a fully substituted stereogenic center are obtained in 32–84% yields with 89.5:10.5–96.5:3.5 er. Synthetic utilities, including scale-up reaction and product derivatization, are also demonstrated. This research represents a ligand-enabled regioselective functionalization of alkynes and provides an efficient strategy to access functional group-enriched chiral heterocycles.

γ-Lactams represent a privileged class of heterocycles in synthetic chemistry and pharmaceutical research, often associated with their biological activities [1,2]. Consequently, a plethora of methods have been developed for the synthesis of γ-lactam derivatives. Of particular interest are α-functionalized γ-lactams, for instance, α-hydroxy-γ-lactams [3,4], which are embodied as a core architecture in a variety of bioactive molecules (Scheme 1a). Recently established protocols demonstrated the enabling capability of asymmetric catalysis in advancing the assembly of α-hydroxy-γ-lactams. Representative intramolecular examples including Cu-catalyzed annihilation of tertiary enamides [5–7] and Ni-catalyzed cyclization of allene-tethered ketoamides [8] were reported by the groups of Wang and Lam, respectively. Intermolecular approaches such as direct α-hydroxylation of presynthesized lactams [9,10], organocatalyzedaza-Michael/aldol cascade reaction of α-ketoamides with α,β-unsaturated aldehydes [11], and Ir-catalyzed [3+2] annulation of α-ketoamides with 1,3-dienes [12] were also disclosed. Despite these advances, in view of the diversity of the γ-lactams, development of alternative synthetic methods empowering the incorporation of functional groups is still appealing.

Scheme 1. The Occurrence of γ-Lactams in Natural Products (a) and Ni-catalyzed Asymmetric Hydrometalization of Alkyne-tethered Carbonyl Electrophiles (b–e).
Non-enantioselective nickel-catalyzed hydrocyclization of alkyne-tethered electrophiles represents a promising strategy for accessing heterocycles [13–18]. Although a handful of solutions recently emerged, its enantioselective variants are still underdeveloped and suffering from challenges with respect to regioselectivity, enantioselectivity, and substrate scope. The groups of Tang [19,20] and Liu [21] successfully realized a Ni(0)-catalyzed enantioselective coupling of O- and N-tethered alkynes in exo- and syn-selectivity guided by an oxidative cyclization mechanism (Scheme 1b), but access to γ-lactams was impeded. Recently, we have reported an endo- and anti-selective hydrocyclization of alkynes catalyzed by a nickel complex derived from hexaaquonickel bis(p-toluenesulfonate) and InPhox L1 (Scheme 1c) [22]. This approach provides a new reaction pattern in terms of mechanism and selectivity for hydrofunctionalization of alkynes. Under the optimized conditions, a syn-hydrometallative cyclization was also observed as a minor pathway. Notably, our further exploration led to ligand-dependent regio- and stereo-selectivity tuning, that is, InPhox ligand (L1) provides a six-membered tertiary alcohol B through an anti-hydrocyclization process, while a bidentate phosphate ligand, Me-Duphos (L2), delivers a five-membered product C via a syn-hydrometallation and cyclization manner. These results prompted us to further explore the complement selectivity of this catalytic system in the assembly of valuable but challenging-synthesized heterocycles. We envisaged that if syn-hydrometallation of alkyne-tethered ketoamides followed by an intramolecular nuclophic addition onto the ketone moiety occurred, γ-lactams, prominent structures in pharmaceutical agents, could be readily accessed (Scheme 1e). Here we report our study of this nickel-catalyzed syn-hydrometallative cyclization for the synthesis of α-hydroxy-γ-lactams. In this reaction, a tertiary chiral center and a stereo-defined β-exo-cyclic olefin were concurrently introduced in high enantio- and regio-selectivities. These functional groups provide opportunities for downstream derivatization.

Table 1. Selected Results of Condition Optimizations

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>yield (%)</th>
<th>er (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>71</td>
<td>90:10</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>21</td>
<td>81.5:18.5</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>34</td>
<td>15:85</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>29</td>
<td>78:22</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>42</td>
<td>85.5:14.5</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>&lt;5</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>1b</td>
<td>57</td>
<td>94.5:5.5</td>
</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>77 (73)</td>
<td>94.5:5.5</td>
</tr>
</tbody>
</table>

*Conducted with Ni(OTs)2•6H2O (10 mol %), L1 (12 mol %), (EtO)2MeSiH (2.0 equiv), and L1 (0.1 mmol) in DME (1.0 mL, 0.1 M) at 90 °C for 24 h. Determined by 1H NMR using 1,3,5-trimethoxybenzene as an internal standard and isolated yield listed in the parentheses. Determined by HPLC analysis (Chiralpak IB). Conducted using 10 mol % of L2 at 40 °C in 2-MeTHF (1.0 mL, 0.1 M). With 50 mol % of NaH2PO4 as an additive.

At the outset of this study, N-Ts-protected α-ketoamide 1a was chosen as a model substrate to investigate the reaction conditions (Table 1 and Tables S1–S9 in SI). With a nickel complex in situ formed from Ni(OTs)2•6H2O and Me-Duphos (L2) as the precatalyst and (EtO)2MeSiH as the hydride source, we were pleased to obtain the desired γ-lactam 2a in 71% yield with 90:10 er (entry 1). The steric bulkiness of the ligands has a profound influence on the reaction, and the use of Et-Duphos (L3) resulted in a significantly decreased yield (entry 2). Likewise, the reaction with bulkier tert-butyl substituted biphosphines, including QuinoxP (L4), BenzP (L5), and DuanPhos (L6), behaved with low reactivity (29–42% yields, entries 3–5). However, BINAP (L7) as the ligand showed a complete lack of reactivity (entry 6). The protecting group on the tethered nitrogen was found to be crucial for reactivity and enantioselectivity (Table S5). To our delight, switching from Ts (1a) to PO(OPh)2 (1b) led to an increased yield and enantioselectivity of the corresponding γ-lactam 2b (entry 7). Upon further screening of solvents, temperature, and additives, we found that with 50 mol % dihydrogen phosphate sodium as an additive, the reaction was conducted in 2-MeTHF at 40 °C providing 73% yield and 94.5:5.5 er (entry 8), which was identified as the optimal conditions. The absolute configuration of 2b (>99.5:0.5 er after recrystallization) was determined by single-crystal X-ray diffraction analysis (see SI).

With these conditions optimized, we began the scope of the reaction. The compatibility of substituents on the alkyne moiety was first examined (Table 2). Substrates with various substituents including electron-rich and electron-deficient aromatics (2c–2g) afforded the corresponding products in 32–67% yields with 89.5:10.5–96.5:3.5 er. Acetyl and ester functionalities were also tolerated by this reduction reaction conditions (2f and 2g). Substrates with an ortho-methyl group provided lactam 2d in 75% yield and 92.5:7.5 er. The reaction with thiethyl (2h) and 6-OMe-naphthyl (2i) resulted in increased...
Scheme 2. Substrate Scope.

*Conducted on a 0.1 mmol scale under the standard conditions (entry 8, Table 1). Enantioselectivity ratio (er) determined by HPLC. *0.2 mmol scale.
Next, we turned our attention to understanding the reaction mechanism. In the presence of a hydrosilane, the nickel(II) precatalyst might form a nickel(II) hydride species or be reduced to a nickel(0) species [23,24]. Accordingly, two possible mechanisms can be pictured, namely, a Ni(0)-initiated oxidative cyclometalation/σ-metathesis/reductive elimination cycle (Scheme 3a) and a Ni(II)—H-initiated alkynyl migratory insertion/carbonyl addition pathway (Scheme 3b). The precedent studies by Montgomery, Jamison, and Tang revealed that a Ni(0)/Ni(II) mechanism is operational (Scheme 3a) with Ni(cod); and electron-rich phosphine as the precatalyst and Et$_3$SiH as the hydride source [17,19]. Our previously mechanistic insights indicate that Ni(II)—H species is capable of alkynyl hydrofunctionalization following the cycle of Scheme 3b [22]. In order to determine which mechanism is favored, further investigations were carried out (Scheme 3c).

A control experiment by replacing Ni(OTs)$_2$·6H$_2$O with Ni(cod)$_2$ led to a sluggish reaction delivering 2b in only 7% yield. We also applied Tang’s conditions [19] to the reaction with substrate 1b, but only a trace amount of the desired product was observed. Taking these results together, the Ni(0)/Ni(II) cycle that depicted in Scheme 3a is less likely involved. The regioselectivity of the alkyne insertion step was briefly studied. Amide is a widely used directing group in transition metal catalysis [25,26]. Regioselective functionalization of alkynes using directing groups has also been documented in the literature [27,28]. One probability for the regioselectivity of our reaction is that the amide part of the ketoamide serves as a directing group to control the insertion of the alkyne into the nickel-hydrogen bond. To investigate this possibility, substrate 3 was synthesized and subjected to the standard reaction conditions, and five-membered product 4 was obtained exclusively, which ruled out the influence of the substrate and indicates that the regioselectivity is controlled by the ligand.

Finally, synthetic applications based on a representative γ-lactam 2b were showcased in Scheme 4. A scale-up reaction delivered 1.10 g of the desired product 2b in a slightly diminished yield (65%) with maintained er. Treatment of 2b with m-CPBA produced an epoxide 6 in 88% yield with perfect diastereoselectivity (>20:1 dr) [29]. Aziridination reaction of 2b led to the formation of product 7 in 87% yield [30]. Hydrogenation of the double bond in 2b catalyzed by Pd/C formed compound 8 quantitatively, albeit with moderate diastereoselectivity (3:1 dr) [20]. Semi-reduction of the amide of 2b using LiAlH$_4$ generated pinacol 9 in 68% yield with perfect diastereoselectivity [10].

Conditions: (a) m-CPBA (1.5 equiv), NaHCO$_3$ (2.5 equiv), DCM, 0 °C to rt; (b) Phl(OAc)$_2$ (3.0 equiv), PhthNH$_2$ (2.8 equiv), K$_2$CO$_3$ (3.5 equiv), DCM, 0 °C to rt; (c) Pd/C (10 mol %), H$_2$ (1 atm), EA, rt; (d) LiAlH$_4$ (3.0 equiv), THF, –78 °C. See SI for details.

In conclusion, a regio- and enantio-selective NiH-catalyzed syn-hydrocyclization of alkyne-tethered α-ketoamides was developed. A range of enantioenriched γ-lactams with an α-tertiary alcohol unit was efficiently synthesized in good yields and enantioselectivities. With a nickel(II)/Duphos precatalyst combined with (EtO)$_2$MeSiH as a hydride source, the reaction operates through syn-hydrometalation of alkynes to form an alkenyl nickel species and then engages in an intramolecular nucleophilic 1,2-addition. This ligand-enabled regioselectivity provides a valuable mode for alkyne functionalization.

Acknowledgments We thank National Key R&D Program of China (2022YFA1502900), NSFC (22222111 and 21971198), Large-scale Instrument and Equipment Sharing Foundation of Wuhan University, and the Natural Science Foundation of Hubei Province (Grant No. 2020CFA036) for financial support. Dr. Hengjiang Cong is thanked for X-ray crystallographic analysis. We acknowledge the Core Research Facilities of CCMS (WHU) for access to analytic equipment.

Conflict of interest The authors declare no conflict of interest.

References
Table of Contents graphic