Asymmetric Alkenyl C-H Functionalization by $\text{Cp}^*\text{Rh}^{\text{III}}$ forms 2*H*-Pyrrol-2-ones by [4+1]-Annulation of Acryl Amides and Allenes

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Abstract: An efficient $\text{Cp}^*\text{Rh}^{\text{III}}$ -catalyzed enantioselective alkenyl C-H functionalization/[4+1] annulation of acryl amides and allenes is reported. The described transformation provides straightforward access to enantioenriched α,β -unsaturated- γ -lactams bearing a quaternary stereocenter. The reaction operates under mild conditions, displays a broad functional group tolerance and provides 2*H*-pyrrol-2-ones in excellent selectivity of up to 97:3 er. Such scaffolds are frequently found in natural products and synthetic bioactive compounds and are of significant synthetic value. It is noteworthy that the allene serves as a one-carbon unit in the [4+1]-annulation.

Asymmetric catalysis using chiral cyclopentadienyl (Cp^*) rhodium(III) complexes emerged as powerful strategy for enantioselective C–H bond functionalization.^[1,2] Among the broad range of reported transformations with the Cp^*Rh fragment, readily available alkenes served as almost exclusively as components reacting with their π -bond.^[3] In stark contrast to $\text{Cp}^*\text{Rh}^{\text{III}}$ -catalyzed enantioselective transformations involving the activation of *aryl* C–H bonds,^[4] related asymmetric functionalizations of *alkenyl* C–H bonds are very scarce and remain a long-standing and important challenge.^[5] This comes surprising as related achiral reactions with $\text{Cp}^*\text{Rh}^{\text{III}}$ catalyst are established.^[6] It may be traced to the nature of the used directing groups (frequently containing carbonyl or imine functionalities) that electronically activate the connected olefin towards competing side reactions like conjugate additions or polymerizations.^[7] We reported a $\text{Cp}^*\text{Rh}^{\text{III}}$ -catalyzed enantioselective alkenyl C–H activation/ring-opening process of α,β -unsaturated oxime ether substrates and diazabicyclic olefins,^[8] as well as enol-ether functionalization giving access to chiral cyclopropanes.^[9] McNaughton and Rovis developed a streptavidin mutant / Rh^{III} artificial metalloenzyme to synthesize chiral α,β -unsaturated- δ -lactams *via* alkenyl C–H activation/[4+2] annulation sequence.^[10] Despite this progress, efficient enantioselective transformations for alkenyl C–H functionalization remain limited and further advances are highly sought after.

Optically active 2*H*-pyrrol-2-ones and their derivatives are cores of numerous natural products and active compounds with diverse biological activities (Figure 1).^[11,12] In light of the biological relevance and wide-ranging structural diversity of

chiral 2*H*-pyrrol-2-one structures, the development of enantioselective synthetic strategies for their constructing of this framework has attracted the attention.^[13]

Figure 1. Representative natural products and bioactive compounds containing the 2*H*-pyrrol-2-one scaffold.

Inspired by Cp -metal complex catalysed C–H annulations involving allenes,^[14,15] we envisioned a catalytic asymmetric alkenyl C–H activation protocol for atom- and step-economic approach to functionalized α,β -unsaturated- γ -lactams (Scheme 1). In 2016, Liu and Lu reported a Rh^{III} -catalyzed C–H functionalization of vinylic amides with α -allenols for the construction of γ -lactams, in which the hydroxyl group is crucial for the reactivity and selectivity of this transformation.^[15b] Highly complementary to the [4+2]-annulation reactivity of styrenes recently disclosed by McNaughton and Rovis,^[10] we report a chiral $\text{Cp}^*\text{Rh}^{\text{III}}$ -catalyzed enantioselective alkenyl C–H activation/[4+1] annulation of acrylamides and allenes to construct enantioenriched functionalized α,β -unsaturated- γ -lactams with quaternary stereogenic center. The allene serves as a one-carbon unit in the [4+1]-annulation.^[15]

Scheme 1. $\text{Cp}^*\text{Rh}^{\text{III}}$ -catalyzed enantioselective alkenyl C–H activation of acrylamides enable access to functionalized γ -lactams.

The development of the envisaged alkenyl C–H activation / asymmetric [4+1] cyclization sequence was performed with 2-phenyl-*N*-tosyl acryl amide (**1a**) and benzyl allene (**2a**) (Table 1). We first explored the [4+1] annulation reaction in the presence of 2.5 mol% of $(\text{Cp}^*\text{RhCl}_2)_2$ with $\text{Cu}(\text{OAc})_2$ as oxidant, obtaining product **3aa** moderate 46 % yield. Then, standard chiral

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Cp^xRh^{III}(cod) precatalyst (*R*)-**Rh1**^[4a] in combination with benzoyl peroxide as activating additive was employed as first asymmetric trial. The vinylic C-H functionalization proceeded in toluene with AgOAc as oxidant at 80 °C giving target product **3aa** in low yield and modest enantiomeric ratio (entry 2). A brief solvent screen showed that MeCN performed much better and **3aa** was obtained in 50 % yield and 79.5:20.5 er (entry 4). The oxidant influenced the reactivity and the enantioselectivity. For instance with Cu(OAc)₂ provided higher levels reactivity and of enantiocontrol (70 % yield and 85:15 er, entry 5). *p*-Quinone was a competent but provided **3aa** in moderate yield and enantioselectivity (46 % yield, 77.5:22.5 er, entry 7). Different chiral cyclopentadienyl ligands were surveyed. Catalyst (*R*)-**Rh2** with bulkier *O**i*Pr groups^[16] showed almost the same selectivity as (*R*)-**Rh1** (entry 8), while TMS-containing trisubstituted complex (*R*)-**Rh3** was less selective (entry 9).^[17] Notably, *i*Pr-bearing trisubstituted Cp^xRh^{III} (*R*)-**Rh4**^[4k] significantly improved in combination with AgOAc the yield as well as asymmetric induction, delivering **3aa** in 74 % yield and 91.5:8.5 er (entry 10). Notably, the external oxidant proved essential for the catalytic turnover, without adding the oxidant, the desired product was generated with less than 5 % yield. Lowering the reaction temperature to 50 °C and increasing the reaction time increased the enantioselectivity to 93:7 er (entry 12). Replacing copper acetate by copper benzoate as oxidant further improved the selectivity to 96:4 er, although lowering the yield to 61 % (entry 13). The use of PhCN as solvent improved significantly the reactivity, enabling synthesis of lactam **3aa** in 74 % yield and, 96.5:3.5 er (entry 14). The absolute configuration of **3aa** was determined to be *S*, based on single crystal X-ray diffraction analysis (see SI).^[18]

Table 1. Optimization of the enantioselective acryl amide C-H functionalization/cyclization.^[a]

entry	Rh	additive	solvent	oxidant	% yield ^[b]	er ^[c]
1 ^[d]	(Cp ^x RhCl ₂) ₂	AgOAc	MeCN	Cu(OAc) ₂	46	--
2	Rh1	(BzO) ₂	toluene	AgOAc	17	65.5:34.5
3	Rh1	(BzO) ₂	DCE	AgOAc	33	56:44
4	Rh1	(BzO) ₂	MeCN	AgOAc	50	79.5:20.5
5	Rh1	(BzO) ₂	MeCN	Cu(OAc) ₂	70	85:15
6	Rh1	(BzO) ₂	MeCN	Cu(OPiv) ₂	86	83.5:16.5
7	Rh1	(BzO) ₂	MeCN	<i>p</i> -quinone ^[e]	46	77.5:22.5
8	Rh2	(BzO) ₂	MeCN	Cu(OAc) ₂	62	83.5:16.5

9	Rh3	(BzO) ₂	MeCN	Cu(OAc) ₂	57	73.5:26.5
10 ^[d]	Rh4	AgOAc	MeCN	Cu(OAc) ₂	74	91.5:8.5
11 ^[d]	Rh4	AgOAc	MeCN	--	<5	--
12 ^[d,f,g]	Rh4	AgOAc	MeCN	Cu(OAc) ₂	82	93:7
13 ^[d,f,g]	Rh4	AgOAc	MeCN	Cu(OBz) ₂	61	96:4
14 ^[d,f,h]	Rh4	AgOAc	PhCN	Cu(OBz) ₂	74	96.5:3.5

[a] 50 μmol **1a**, 100 μmol **2a**, 5 mol% **Rh**, 5 mol% (BzO)₂ or 10 mol% AgOAc, 105 μmol oxidant, 0.1 M in Solvent at 80 °C for 16 h; [b] isolated yield of **3aa**; [c] determined by chiral HPLC; [d] 50 μmol **1a**, 100 μmol **2a**, 2.5 mol% **Rh**; [e] 50 μmol of oxidant was used; [f] at 50 °C; [g] 64 h; [h] 72 h.

We next evaluated the scope of this protocol with respect to the acryl amides **1** (Scheme 2). The electronic and steric influence of the aromatic substituents at the α-position of the acryl amides (**R**¹) were investigated first. In general, aryl units with electron-donating or electron-withdrawing substituents were accommodated, forming cyclized products **3aa-3ga** in moderate to good yields and high levels of enantioselectivity (51–79 % yield, and 93:7–96.5:3.5 er). Notably, sterically more-demanding aryl moieties like 1-naphthyl (**1h**, 69 % yield, 95:5 er) and *o*-tolyl group (**1i**, 62 % yield, 95.5:4.5 er) had little influence on the reaction performance. In addition, different sulfonyl activating groups **R**² on the nitrogen atom (**1k** and **1l**) were suitable for the [4+1] annulation. Alkyl or benzyl group can replace the aryl unit as substituent **R**¹, furnishing desired lactams **3ma** and **3na** in very good yields albeit slightly reduced enantioselectivity. Moreover, very challenging cyclic 2,3-disubstituted acrylamide **3o** was converted tricyclic lactam **3oa** in moderate yield and 90.5:9.5 er. 2,3-Di-methyl-substituted acrylamide **1p** performed well with (*R*)-**Rh2** and (BzO)₂ as the catalytic system, giving **3pa** in 87 % yield and 91:9 er.

Next, the suitability of various allenes for the transformation was tested (Scheme 3). We first examined the relevance of arene for the transposition of the olefin as it stabilizes by conjugation and found a good tolerance for substituted benzyl allenes. A series of arene substituents with different electronic and steric parameters gave lactams **3ab-3af** in good yields (64–78 %) and excellent selectivity (96:4–97:3 er). Ethyl ester-substituted allene **2g** also participated in the transformation giving α,β -unsaturated ester **3ag** in 42 % yield and 95:5 er. Notably, allenes with no bias for a stabilization of the product double bond by conjugation perform equally well. Aliphatic allenes – considered challenging substrates in Cp^*M -catalyzed annulations^[14h,15d] – coupled smoothly. For instance, the reaction tolerates a wide range functional groups such as ester (**3aj**, **3an**), nitrile (**3ak**), hydroxyl (**3al**) and ether (**3am**) functionalities, providing lactams **3** with a similar range of yields and enantioselectivity. Moreover, allenes with 2-furanyl group (**2o**) and phthalimide (**2p**) were found suitable, generating corresponding lactams **3ao** (57 % yield, 93:7 er) and **3ap** (88 % yield, 94:6 er), respectively.

Scheme 3. Allene scope for asymmetric lactam formation. [a] Conditions: 0.1 mmol **1a**, 0.2 mmol **2**, 2.5 μmol **Rh4**, 10 μmol AgOAc, 0.21 mmol (BzO)₂Cu in 1.0 mL PhCN, 50 °C, 3 d; [b] 4 d.

To illustrate the potential synthetic utility of the transformation, several functionalizations of the product were performed

(Scheme 4). The *N*-tosyl group of **3aa** was smoothly cleaved with Sml₂ providing secondary amide **4** in 95 % yield. A 1,4-addition proceeded with Gilman cuprate (MeLi and CuI) gave rise to saturated lactam **5** having three contiguous stereogenic centers with a 4.2:1 dr.^[19] Moreover, **3aa** was smoothly reduced in a 1,4-fashion employing 1,3,2-diazaphospholene **6**^[20] as the catalyst and pinBH as terminal reductant. Lactam **7** was with excellent chemoselectivity, good yield and a dr of 2.4:1.

The following mechanism for the enantioselective alkenyl C–H functionalization/[4+1] annulation of acryl amides with allenes is suggested taking preceding reports into account (Scheme 5).^[15] The increased acidity of the N–H groups of **1a** enhances binding of the active chiral $\text{Cp}^*\text{Rh}^{\text{III}}$ complex. The catalytic cycle begins by a carboxylate-mediated and amide-directed CMD-type C–H activation leading to five-membered rhodacycle **I**. Migratory insertion of allene **2a** provides interconverting allyl-rhodium species **IIa**, **IIb** and **IIc**. Instead of reductive elimination that would lead to [4+2]-products, β -H elimination is preferred generating diene **III**. The rhodium hydride adds in the enantio-determining step across the double bond to give rhodacycle **IV**. In turn, reductive elimination delivers lactam **3** and generates a $\text{Cp}^*\text{Rh}^{\text{I}}$ species. This is subsequently regenerated to the active $\text{Cp}^*\text{Rh}^{\text{III}}$ complex by oxidation with the Cu^{II} salt, thus closing the catalytic cycle.

Scheme 5. Proposed mechanism for the [4+1]-annulation.

In summary, we report an enantioselective alkenyl C–H activation of acrylamides by chiral $\text{Cp}^*\text{Rh}^{\text{III}}$ -complexes and their subsequent C–C and C–N bond formation with allenes. This results in a net [4+1]-annulation which gives a straightforward access to chiral functionalized α,β -unsaturated γ -lactams with a quaternary stereocenter in enantioselectivities of up to 97:3 er. Noteworthy, the allene serves as a one-carbon unit in the [4+1]-annulation. The protocol operates under mild reaction conditions, is tolerant to a wide variety of functional groups and hence practical for synthetic applications. The exploitation of further enantioselective alkenyl C–H functionalization for atom-economic complexity-generating transformation is in process.

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S.-G. Wang, Y. Liu, and N. Cramer*

Page No. – Page No.
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An efficient $\text{Cp}^*\text{Rh}^{\text{III}}$ -catalyzed enantioselective alkenyl C-H functionalization/[4+1] annulation of acryl amides and Allenes gives access to synthetically relevant 2*H*-pyrrol-2-ones with a quaternary stereocenter in excellent selectivity of up to 97:3 er. The reaction operates under mild conditions and displays a broad functional group tolerance. The allene serves as a one-carbon unit in the [4+1]-annulation.