C–H Activation

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Direct Regio- and Diastereoselective Synthesis of δ-Lactams from Acrylamides and Unactivated Alkenes Initiated by Rh^{III}-Catalyzed C–H Activation

*Sumin Lee, Natthawat Semakul, and Tomislav Rovis**

Abstract: *We report a Rh^{III}-catalyzed regio- and diastereoselective synthesis of δ-lactams from readily available acrylamide derivatives and unactivated alkenes. The reaction provides a rapid route to a diverse set of δ-lactams in good yield and stereoselectivity, which serve as useful building blocks for substituted piperidines. The regioselectivity of the reaction with unactivated terminal alkene is significantly improved by using Cp^t ligand on the Rh^{III} catalyst. The synthetic utility of the reaction is demonstrated by the preparation of a potential drug candidate containing a trisubstituted piperidine moiety. Mechanistic studies show that the reversibility of the C–H activation depends on the choice of Cp ligand on the Rh^{III} catalyst. The irreversible C–H activation is observed and becomes turnover-limiting with $[Cp^tRhCl_2]_2$ as catalyst.*

Nitrogen heterocycles are an essential structural unit found in a variety of biologically active molecules. Among them, the piperidine ring is the most prevalent N-heterocycle found in FDA approved drugs.[1] Consequently, numerous synthetic methods have been developed that often involve the cyclization of an acyclic precursor which need to be preassembled.[2] Convergent synthetic strategies involving two unique components have also received great attention.[3–6] Although these strategies are useful, they are limited to specific classes of coupling partners and deliver products with a narrow range of substitution patterns.

Alternatively, direct access to α,β-unsaturated-δ-lactams from simple precursors would prove useful since it can be easily converted into piperidine through well-established reduction reactions (Figure 1). In this context, Rh^{III}-catalyzed C–H activation/annulation strategy has been utilized to synthesize related N-heterocycles. Pioneering work by the groups of Fagnou et al.,[7] Miura/Satoh et al.,[8] Li et al.,[9] and our group,[10] has demonstrated the directed C–H activation of benzamides with alkynes to yield isoquinolones. The groups of Glorius[11] and Fagnou[12] introduced the *N*-acyloxy hydroxamate directing group, which allows alkene insertion to deliver dihydroisoquinolone. The asymmetric variant of this latter process has been developed by Rovis/Ward et al.,[13] Cramer et al.,[14] and others.[15] However, related vinyl C–H activation is much less explored. Only two examples of

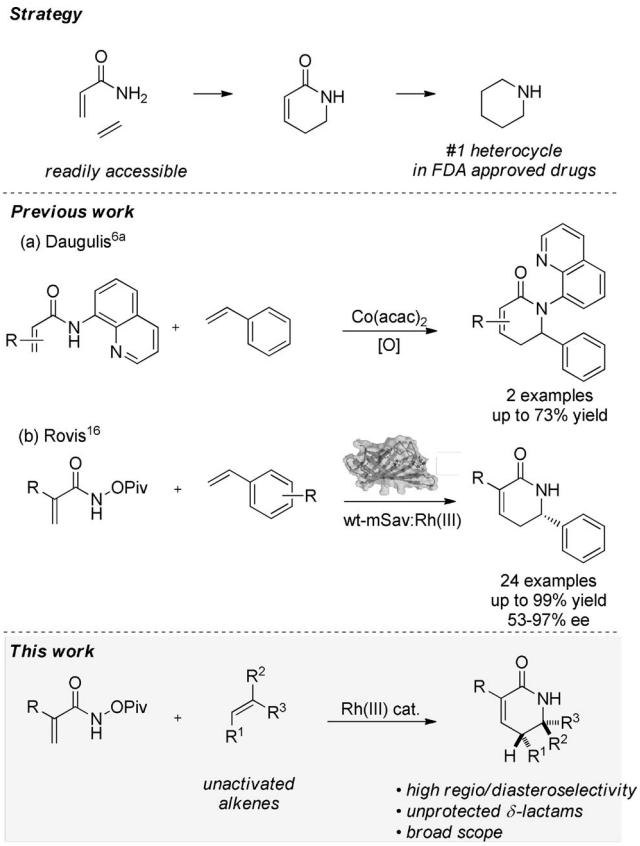

Figure 1. Synthesis of δ-lactams.

transition-metal-catalyzed vinyl C–H activation of acrylamides and the coupling with alkenes are documented. Specifically, the Daugulis groups has utilized the aminoquinoline directing group in the presence of a Co catalyst and a stoichiometric amount of oxidant (two examples).[6a] Recently, we reported asymmetric δ-lactam synthesis from N-(pivaloyloxy)acrylamides using a monomeric streptavidin artificial metalloenzyme.[16] In both cases, only reactions with styrene-type alkenes are reported.[17] Motivated by the relevance of the target δ-lactams, rapid access to the structure from readily available starting materials, and potential to achieve diverse substitution patterns, we set out to develop a Rh^{III}-catalyzed C–H activation/annulation method using N-pivaloyloxy acrylamides with unactivated alkenes.

We commenced the reaction development by examining the coupling of 2-benzyl-*N*-(pivaloyloxy)acrylamide (**1a**) and vinyl cyclopentane (**2a**) as model substrates. When $[Cp^*RhCl_2]_2$ is used as a catalyst, a nearly 1:1 mixture of regioisomers is formed in polar protic solvents (Table 1,

[*] S. Lee, Dr. N. Semakul, Prof. Dr. T. Rovis
Department of Chemistry, Columbia University
New York, NY 10027 (USA)
E-mail: tr2504@columbia.edu

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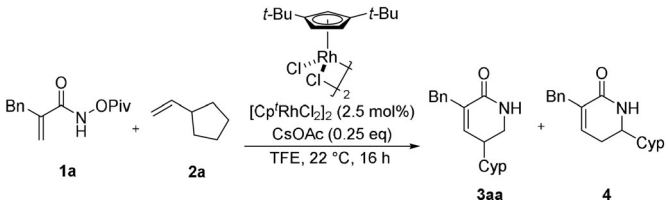
Table 1: Reaction optimization.



1a 2a 3aa 4

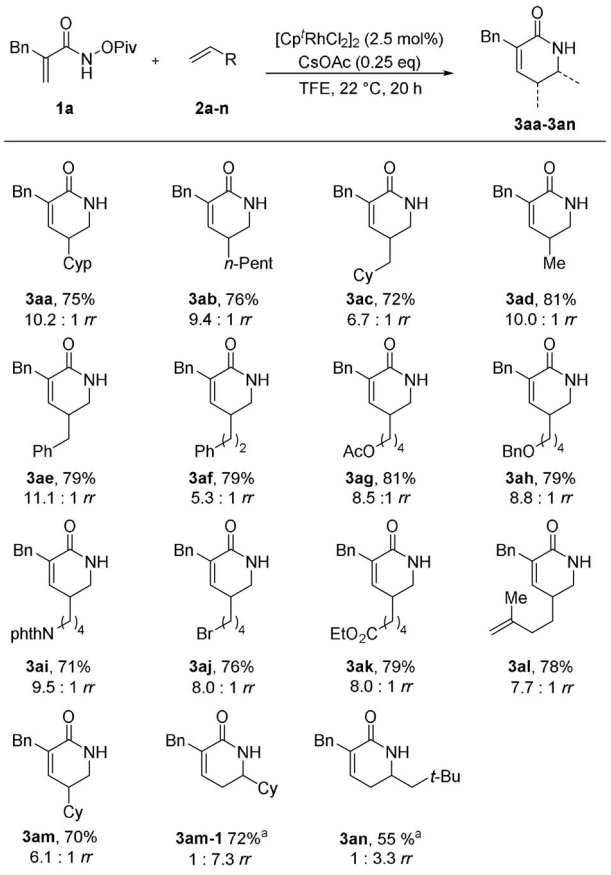
Entry	Catalyst	Solvent	Yield of **3aa**[a]	rr[a] (**3aa**/**4**)
1	$[Cp^*RhCl_2]_2$	MeOH	32	1:1.6
2	$[Cp^*RhCl_2]_2$	HFIP	34	1:1.1
3	$[Cp^*RhCl_2]_2$	TFE	38	1:1.1
4	$[Cp^tRhCl_2]_2$	MeOH	50	13.6:1
5	$[Cp^tRhCl_2]_2$	HFIP	54	8.7:1
6	**$[Cp^tRhCl_2]_2$**	**TFE**	**82**	**10.2:1**
7	$[Cp^*CoCl_2]_2$ or $[Cp^*IrCl_2]_2$	TFE	0	–

[a] Determined by ^{1}H NMR of unpurified reaction mixture. TFE = 2,2,2-trifluoroethanol.

entry 1–3). Inspired by previous work on the modification of Cp ligands on Rh^{III} catalyst to improve regioselectivity,[18] we conducted a Cp ligand screen and found that the regioselectivity could be significantly improved with commercially available Cp^t ligand (Cp^t = di-*tert*-butylcyclopentadienyl, entry 4–6). The regioisomers **3aa** and **4** are easily separable by column chromatography and the improved regioselectivity can be rationalized as a consequence of the steric repulsion between bulky Cp^t ligand and the substituent on the alkene coupling partner based on previous work with benzamides.[18c–f] Trifluoroethanol (TFE) was selected as a solvent for the optimized condition since it gives both good regioselectivity and good reaction yield compared to MeOH and HFIP. Other catalysts such as $[Cp^*CoCl_2]_2$ and $[Cp^*IrCl_2]_2$ failed to yield the desired product (entry 7).[19]

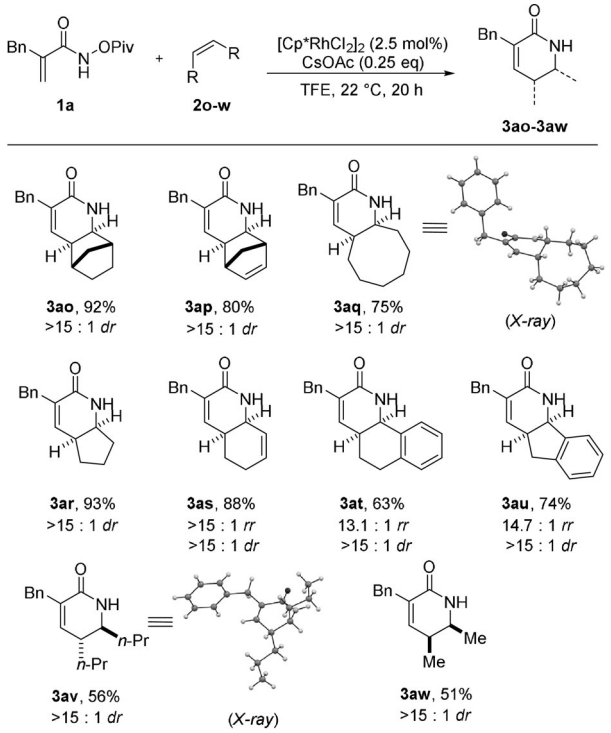
Having optimized the reaction conditions, we next explored the terminal alkene substrate scope using (**1a**) as an acrylamide coupling partner (Scheme 1). The reaction proceeded smoothly with terminal aliphatic alkenes such as 1-heptene (**2b**), allyl cyclohexane (**2c**), and gaseous propene (**2d**), giving the desired δ-lactam products in good yield and regioselectivity (**3aa**–**3ad**). A variety of functional groups such as phenyl, benzyl, protected alcohol or amine, bromide, and ester groups were all well tolerated (**3ae**–**3ak**). In the case of of 2-methyl-1,5-hexadiene (**2l**), insertion happened exclusively to give the mono-substituted terminal alkene over the gem-disubstituted alkene. Interestingly, vinyl cyclohexane (**2m**) and 4,4-dimethyl-1-pentene (**2n**) gave opposite regioisomers as the major product when $[Cp^*RhCl_2]_2$ was used as a catalyst.

Next, the substrate scope with respect to internal alkenes (Scheme 2). For internal alkenes, $[Cp^*RhCl_2]_2$ was used as a catalyst instead of $[Cp^tRhCl_2]_2$ due to the lower yield observed with the latter catalyst. Complex tricyclic structures were successfully constructed in a single step with excellent yields when norbornene (**2o**) and norbornadiene (**2p**) were used as coupling partners. [6,3,0] and [4,3,0] fused bicyclic δ-lactams were also formed with good yields when *cis*-cyclo-



3aa, 75%, 10.2 : 1 *rr*; **3ab**, 76%, 9.4 : 1 *rr*; **3ac**, 72%, 6.7 : 1 *rr*; **3ad**, 81%, 10.0 : 1 *rr*; **3ae**, 79%, 11.1 : 1 *rr*; **3af**, 79%, 5.3 : 1 *rr*; **3ag**, 81%, 8.5 :1 *rr*; **3ah**, 79%, 8.8 : 1 *rr*; **3ai**, 71%, 9.5 : 1 *rr*; **3aj**, 76%, 8.0 : 1 *rr*; **3ak**, 79%, 8.0 : 1 *rr*; **3al**, 78%, 7.7 : 1 *rr*; **3am**, 70%, 6.1 : 1 *rr*; **3am-1** 72%[a], 1 : 7.3 *rr*; **3an**, 55 %[a], 1 : 3.3 *rr*

Scheme 1. Scope with respect to terminal alkenes. Regioselectivity was determined by ^{1}H NMR of unpurified reaction mixture. Yield of isolated product given. [a] $[Cp^*RhCl_2]_2$ instead of $[Cp^tRhCl_2]_2$.

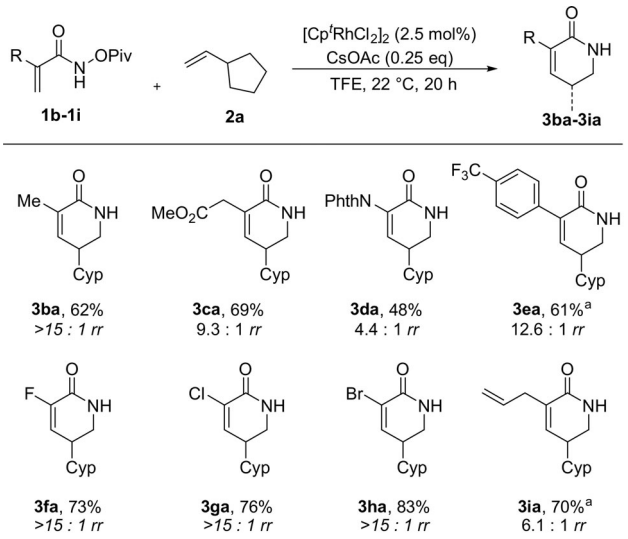


3ao, 92%, >15 : 1 *dr*; **3ap**, 80%, >15 : 1 *dr*; **3aq**, 75%, >15 : 1 *dr*; **3ar**, 93%, >15 : 1 *dr*; **3as**, 88%, >15 : 1 *rr*, >15 : 1 *dr*; **3at**, 63%, 13.1 : 1 *rr*, >15 : 1 *dr*; **3au**, 74%, 14.7 : 1 *rr*, >15 : 1 *dr*; **3av**, 56%, >15 : 1 *dr*; **3aw**, 51%, >15 : 1 *dr*

Scheme 2. Scope with respect to internal alkenes. Regioselectivity and diasteroselectivity were determined by ^{1}H NMR of unpurified reaction mixture. Yield of isolated product given.

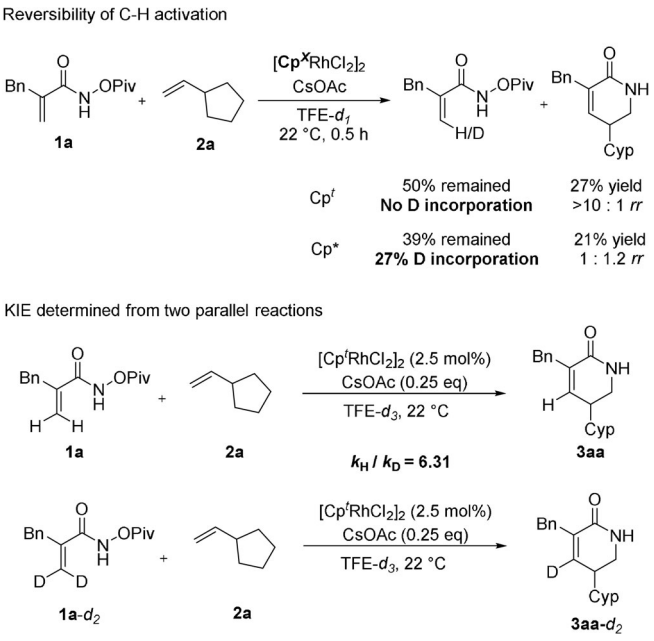
octene (**2q**) or cyclopentene (**2r**) were used. Surprisingly, cyclohexene did not lead to the desired product. Excellent regioselectivity was observed for the reactions with cyclohexa-1,3-diene (**2s**), 1,2- dihydronaphthalene (**2t**), and 1*H*-indene (**2u**). Acyclic internal olefins containing *cis* or *trans* configurations, such as (*E*)-oct-4-ene (**2v**) and (*Z*)-but-2-ene (**2w**), also provided the desired product (**3av**, **3aw**) in good yield. All reactions with internal alkenes were highly diastereoselective and relative stereochemistry of **3aq** and **3av** were unambiguously determined by X-ray crystallography, which confirms retention of stereochemistry during the migratory-insertion step.[20]

Finally, the scope with respect to acrylamides investigated using vinyl cyclopentane (**2a**) as a coupling partner (Scheme 3). N-(pivaloyloxy)acrylamides containing ester (**1c**), protected amine (**1d**), aryl (**1e**), and halide (**1f**–**1h**) groups delivered corresponding *δ*-lactam products with good yields and regioselectivities. 2-Methylene-*N*-(pivaloyloxy)-pent-4-enamide (**1i**), which contains two different terminal alkenes, gave *δ*-lactam exclusively, presumably due to the favored 5-membered rhodacycle formation after the C–H activation step.



Scheme 3. Scope with respect to acrylamides. Regioselectivity and diasteroselectivity were determined by ^{1}H NMR of unpurified reaction mixture. Yield of isolated product given. [a] 5 mol% of [Cp^{t}RhCl$_2$]$_2$.

To obtain mechanistic insight, we first investigated the C–H activation step of the reaction (Scheme 4). The reaction was conducted in TFE-d_1 and quenched when around 50% of the acrylamide substrate was consumed. Interestingly, the reversibility of the C–H activation depends on the Cp ligand on the Rh^{III} catalyst. When [Cp^{t}RhCl$_2$]$_2$ was used as catalyst, deuterium incorporation was not observed in the unreacted acrylamide, which suggests C–H activation is irreversible. In the case of [Cp*RhCl$_2$]$_2$, the C–H activation was reversible, showing 27% deuterium incorporation on the recovered acrylamide. Next, the kinetic isotope effect (KIE) was measured from two separated reactions, one with a normal



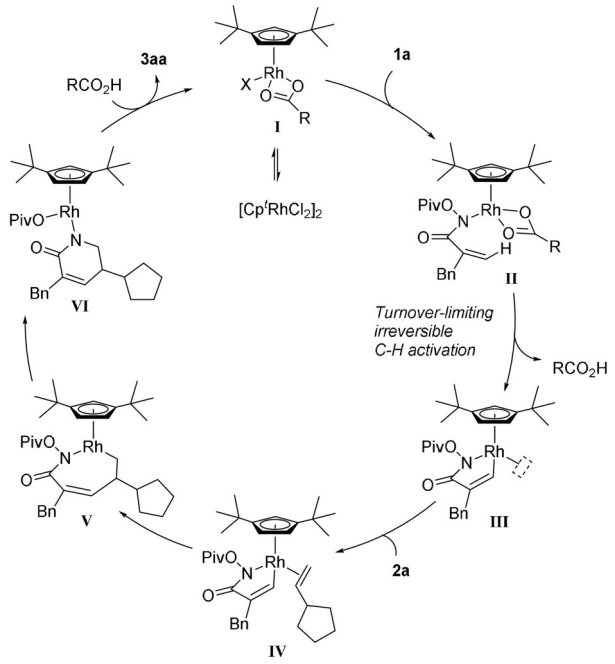
Scheme 4. Mechanistic investigation.

substrate containing a C–H bond and one with an analogous C–D bond.[21] The reaction was conducted in an NMR tube and the reaction progress was monitored in situ by ^{1}H NMR. The KIE value was calculated by comparing the initial reaction rate (slope) of each reaction (see the Supporting Information for details). The observed primary KIE (K_H/K_D) value of 6.31 suggests that C–H bond cleavage occurs during the turnover limiting step. Overall, both experiments indicate that C–H activation is irreversible and the turnover-limiting step when Cp^{t}Rh^{III} is used as a catalyst.

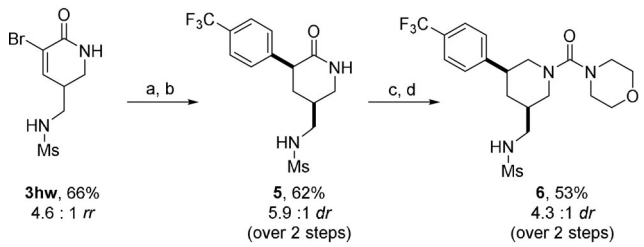
Based on previous work and our mechanistic investigation, we propose the following mechanism for the reaction (Scheme 5). First, coordination of the acrylamide substrate to active Rh^{III} catalyst **I** generates intermediate **II**. At this stage, turnover-limiting irreversible C–H activation occurs to form 5-membered rhodacycle **III**. Subsequently, an alkene coupling partner coordinates and forms 7-membered rhodacycle **V** through regioselective migratory insertion. After C–N bond formation/N–O bond cleavage steps, intermediate **VI** releases the *δ*-lactam product with regeneration of the active Rh^{III} catalyst **I**.

The utility of the developed method was demonstrated by the rapid synthesis of trisubstituted piperidine **6**, a potential drug candidate for cardiovascular disorders and tumors (Scheme 6).[22] The coupling reaction between 2-bromo-*N*-(pivaloyloxy)acrylamide (**1h**) and *N*-allylmethanesulfonamide (**2w**) gives the corresponding *δ*-lactam product (**3hw**) in a single step. The aryl moiety was installed through a Suzuki–Miyaura coupling reaction with 4-(trifluoromethyl)-phenylboronic acid, and subsequent alkene hydrogenation resulted in compound **5**. After amide reduction and N-acylation, trisubstituted piperidine **6** was successfully prepared.

In summary, we have developed a Rh^{III}-catalyzed synthesis of α,β-unsaturated-δ-lactams from N-(pivaloyloxy)-



Scheme 5. Proposed mechanism.



Scheme 6. Product derivatization. a) $PdCl_2(PPh_3)_2$ (10 mol%), 4-(trifluoromethyl)phenylboronic acid (3 equiv), dioxane/2 M Na_2CO_3 (0.06 M, 1:1), 60 °C, 1 h, 78%. b) Rh/C (10 wt%), H_2 (1 atm), MeOH (0.3 M), 22 °C, 4 h, 80%, 5.9:1 *dr*. c) BH_3·THF (5 equiv), THF, 60 °C, 3 h; 6 M HCl/MeOH, 60 °C, 3 h. d) Et_3N (1.5 equiv), morpholine-4-carbonyl chloride (1.2 equiv), 22 °C, 16 h. 53%, 4.3:1 *dr* (over 2 steps).

acrylamides and unactivated alkenes. With this method, various δ-lactams containing a wide array of functional groups and complex bi/tricyclic structures were synthesized with good yield and regio/diastereoselectivity. Mechanistic investigation suggests turnover-limiting irreversible C–H activation, subsequent regioselective migratory insertion, and C–N bond formation/N–O bond cleavage for the mechanism of the reaction.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkene functionalization · C–H activation · piperidines · Rhodium · δ-lactams

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[19] The reaction with styrene gives the opposite regioisomer (substituent close to new C–N bond) with both $[Cp^*RhCl_2]_2$ (64 %, >15:1 *dr*) and $[Cp^tRhCl_2]_2$ (63 %, >15:1 *dr*) catalysts. The reactions were conducted on a 0.1 mmol scale using **1a** (1.0 equiv), styrene (2.0 equiv), $[Cp^XRhCl_2]_2$ (2.5 mol %), and CsOAc (0.25 equiv) in TFE (0.3 M) at 22 °C.

[20] CCDC 1976881 and 1976882 (**3aq**, **3av**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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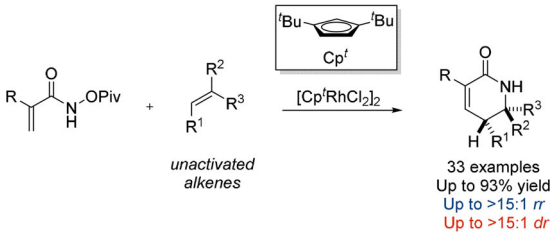
Communications

C–H Activation

S. Lee, N. Semakul,
T. Rovis* ——— ■■■–■■■

Direct Regio- and Diastereoselective Synthesis of δ-Lactams from Acrylamides and Unactivated Alkenes Initiated by Rh^{III}-Catalyzed C–H Activation



Regio- and diastereoselective synthesis of unprotected δ-lactams has been realized starting from readily accessible acrylamides and unactivated alkenes. The reaction provides an efficient means of synthesizing a diverse set of δ-lactams in good yield and stereoselectivity, which serve as useful building blocks for substituted piperidines.

