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Harnessing Stereospecific *Z*-Enamides through Silver-Free Cp*Rh(III) Catalysis by Using Isoxazoles as Masked Electrophiles

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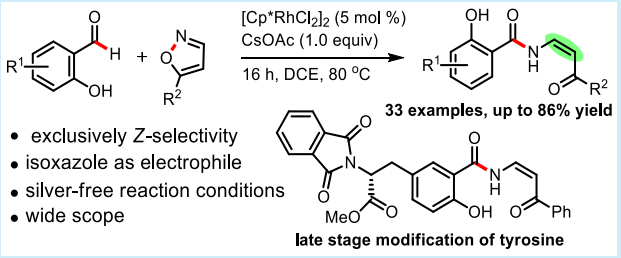
Supporting Information

ABSTRACT: The stereospecific synthesis of *Z*-enamides is described in this paper. For the first time, isoxazoles have been employed as electrophiles in C−H functionalization to afford thermodynamically less stable *Z*-enamides utilizing salicylaldehydes in an atom- and step-economic fashion. The stereochemistry of enamides might originate from the relative disposition of atoms present in isoxazole and the intramolecular hydrogen bonding. The reaction showed excellent scope as several structurally and electronically diverse salicylaldehydes and isoxazoles reacted efficiently.



The secondary enamides have received immense attention in synthetic organic chemistry due to their pervasiveness in various bioactive natural products[1] and a range of marine metabolites.[2] Moreover, assessing the stability and polarizability of the enamides, they have been used as versatile synthetic intermediates for the synthesis of heterocycles,[3] in cross-couplings/Heck reactions,[4] in asymmetric hydrogenation/halogenation,[5] and recently in C−H functionalization.[6] The inevitability of the enamide motif and its unambiguous geometry, for excellent potency, have been demonstrated by structure−activity relationship (SAR) studies. Earlier reports of enamide synthesis comprise condensation of carbonyl groups with amides,[7] acylations of imines,[8] Curtius rearrangement,[1b,9] and elimination of β-hydroxy-α-silylamides (Peterson reaction).[10] Subsequently, transition-metal (Pd, Cu)-catalyzed[11] cross-coupling of substituted vinyl derivatives with amides have been found to be a surrogate approach to access a wide range of enamides. Unfortunately, these methods often lead to poor yields and scarce of *E*/*Z* selectivity and often require anhydrous as well as harsh reaction conditions (eminent temperature, strong base).[12] Although the synthetic strategy involving the metalation/functionalization of ynamides[13] and the hydroamidation of alkynes[14] had attracted chemists, these methods lacked broad substrate scope. Gold-catalyzed isomerization of propargylic alcohol[15] (Meyer−Schuster rearrangement) and the isomerization of *N*-allyl amides under transition-metal[16] catalysis could implement a diverse alternative to the coupling reactions. Stoichiometric oxidation of *N*-alkyl amide using a metal-free approach[17] also offered a new synthetic route. However, this method failed to furnish stereospecific products, particularly the thermodynamically less feasible *Z*-enamides (Figure 1).[18]

To anticipate this intricacy in the synthesis of enamide functionality, we have found an advanced strategy, with potentially a broader synthetic application, using the activation of an aldehyde C−H bond through a metal-catalyzed selective

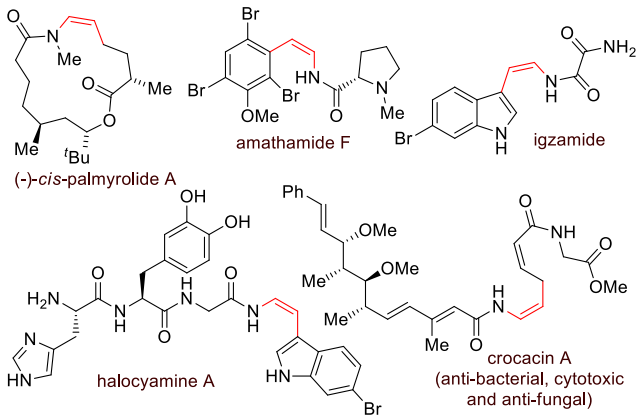


Figure 1. Bioactive natural products containing a *Z*-enamide.

electrophilic C−H functionalization (Scheme 1). To the best of our knowledge, to serve our purpose of obtaining *Z*-enamides, for the first time, we have employed isoxazole as an electrophile in C−H functionalization which can be easily accessed from the corresponding ketone derivatives.[18] We envisioned that (a) isoxazole can be used as a masked form of 1,3-imino carbonyl electrophile and can act as an enamine source and (b) the structural rigidity of isoxazole might be transferred to achieve our desired stereospecific formation of *Z*-enamides. Herein, we disclose a novel, silver-free Rh-catalyzed C−H functionalization approach for the synthesis of acyclic enamides with an exclusive *Z*-selectivity. Our synthetic strategy comprises a benign catalytic system, high functional group tolerance, and appreciable yields. The conserved geometry of enamides is confirmed by the ^{1}H NMR analysis and is likely to be aroused from the relative

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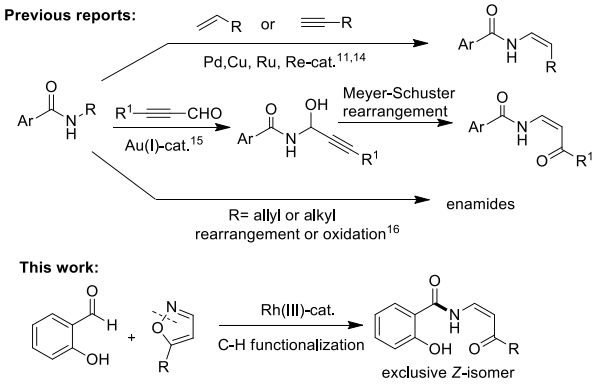
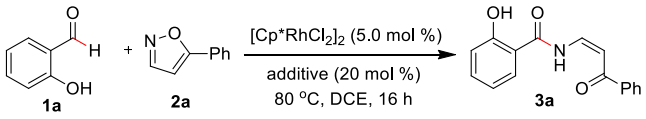
Scheme 1. C−H Activation Strategy for Enamide Synthesis



disposition of nitrogen and oxygen atoms present in **2**, and *Z*-enamide is further stabilized by the intramolecular hydrogen bonding.[11d,f]

To test the feasibility of our hypothesis, we initiated our study on the identification of appropriate reaction conditions by screening reaction parameters for the coupling of salicylaldehyde **1a** and isoxazole **2a** (Table 1). By using

Table 1. Optimizations of the Reaction Conditions[a]



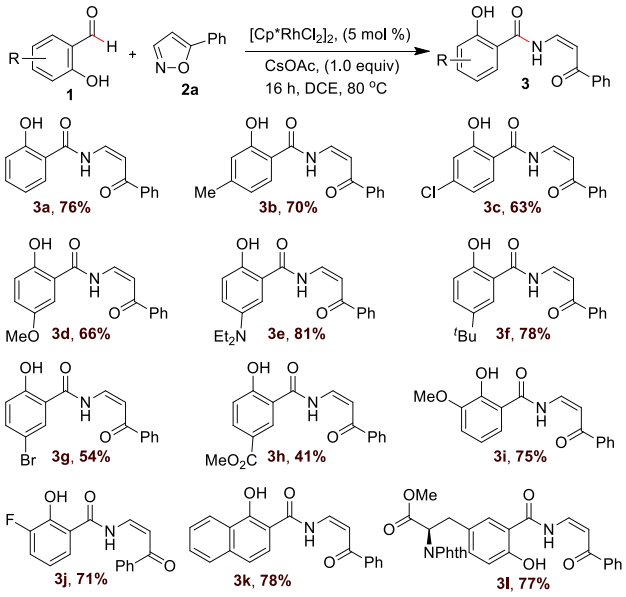
entry	solvent	catalyst	additive	temp (°C)	yield[b] (%)
1	DCE	$[Cp^*RhCl_2]_2$	$AgSbF_6$	80	45
2	TCE	$[Cp^*RhCl_2]_2$	$AgSbF_6$	80	30
3	DCM	$[Cp^*RhCl_2]_2$	$AgSbF_6$	80	38
4	$CHCl_3$	$[Cp^*RhCl_2]_2$	$AgSbF_6$	80	trace
5[c]	DCE	$[Cp^*RhCl_2]_2$	CsOAc	80	76
6[c]	DCE	$[Cp^*RhCl_2]_2$	NaOAc	80	25
7[c]	DCE	$[Cp^*RhCl_2]_2$	KOAc	80	30
8[c]	DCE	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	80	trace
9	DCE	$[Cp^*RhCl_2]_2$		80	nd
10[c]	DCE		CsOAc	80	nd
11[c]	DCE	$[Cp^*RhCl_2]_2$	CsOAc	rt	trace
12[c]	DCE	$[Cp^*RhCl_2]_2$	CsOAc	60	62
13[c]	DCE	$Cp^*Co(CO)I_2$	CsOAc	80	nd
14[c]	DCE	$[Cp^*IrCI_2]_2$	CsOAc	80	nd
15[c]	DCE	[Ru(*p*-cymene) $Cl_2]_2$	CsOAc	80	nd

[a]Reaction conditions: salicylaldehydes **1a** (0.2 mmol), isoxazole **2a** (0.3 mmol), catalyst (6.2 mg, 5 mol %), additive (0.04 mmol, 20 mol %), DCE (1.5 mL), 80 °C, 16 h. [b]Isolated yield. [c]1.0 equiv of additive was used.

$[Cp^*RhCl_2]_2$ (5.0 mol %) as a catalyst and $AgSbF_6$ (20 mol %) as an additive in DCE solvent, only 45% of our desired product **3a** was isolated (entry 1). Switching to other chlorinated solvents such as tetrachloroethane, dichloromethane, and chloroform under identical reaction conditions did not provide any better results (entries 2−4). Upon changing the additive from $AgSbF_6$ to different acetate sources, a dramatic change in the yield of **3a** was observed. Among different acetate salts studied, while 1.0 equiv of CsOAc provided **3a** in 76% yield (entry 5), other acetate sources under the identical reaction conditions were not very effective (entries 6−8). This result indicates a pivotal role of a CsOAc base in this amination reaction. The product **3a** was not detected upon performing this reaction either in the absence of any additive or catalyst (entries 9 and 10). On conducting the reaction at lower temperature yield of **3a** was deteriorated, and the reaction was almost stopped at room temperature (entries 11 and 12). Switching the catalyst from Rh(III) to its cobalt or iridium congeners failed to provide any product **3a** (entries 13 and 14).

Once suitable reaction conditions were obtained, the scope of the salicylaldehydes was studied by keeping isoxazole **2a** as a model electrophile (Scheme 2). Salicylaldehyde **1b** bearing an

Scheme 2. Scope of Salicylaldehydes[a,b]



[a]Reaction conditions: salicylaldehydes **1** (0.2 mmol), isoxazole **2a** (0.3 mmol), catalyst (6.2 mg, 5 mol %), CsOAc (0.2 mmol, 1.0 equiv), DCE (1.5 mL). [b]Isolated yields.

electron-donating methyl group at the *para* position to the aldehyde reacted smoothly with **2a** to form enamide **3b** in 70% yield. Similar reactivity was recognized in the case of electron-deficient aldehyde **1c** furnishing enamide **3c** in 63% yield. Notably, salicylaldehydes bearing electron-donating methoxy, diethylamine, and *tert*-butyl functional groups at the C5-position of **1** also responded well under the optimized conditions to provide **3d−f** in excellent yields (66−81%). 5-Bromosalicylaldehyde delivered enamide **3g** in 54% yield. On the contrary, salicylaldehyde **1h** bearing an electron-deficient ester group provided **3h** in lower yield. Salicylaldehydes **1i,j** bearing either electron-donating methoxy or -withdrawing fluoride functional groups at the C3-position provided **3i** and **3j** in 71−75% yields. Similarly, 1-hydroxy-2-naphthaldehyde also took part in the catalysis to furnish enamide **3k** in 78% yield. Considering that the enamide functional groups are widespread in medicines and natural products, late-stage modification of tyrosine **1l** was also tested, and the desired product **3l** was isolated in 77% yield, displaying a broader synthetic utility of this catalytic system.

After the scope of the salicylaldehydes was studied, we next investigated the reactivity of a range of isoxazole derivatives **2** with salicylaldehyde **1a** (Scheme 3). Isoxazoles bearing 4-fluoro-, 4-chloro-, and 4-bromo-substituted phenyl rings at the

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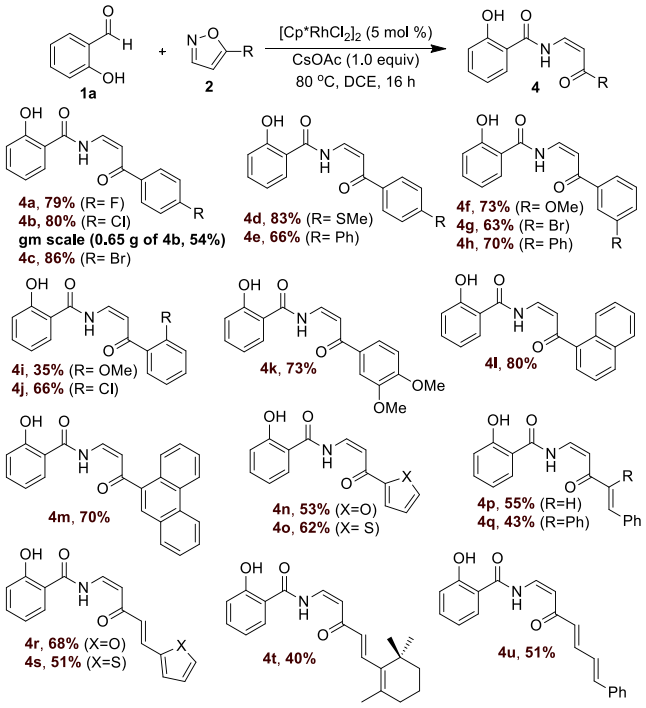
Scheme 3. Scope of Isoxazoles[a,b]

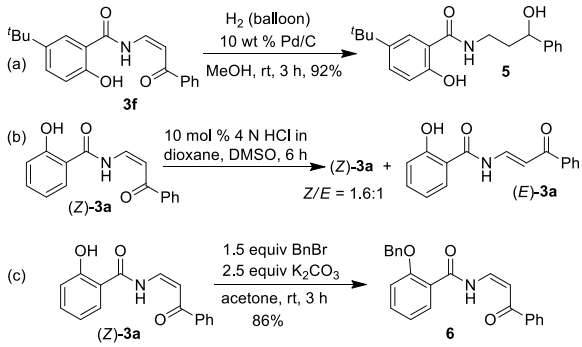


[a]Reaction conditions: salicylaldehydes **1a** (0.2 mmol), isoxazole **2** (0.3 mmol), catalyst (6.2 mg, 5 mol %), CsOAc (0.2 mmol, 1.0 equiv), DCE (1.5 mL). [b]Isolated yields.

C5-position reacted efficiently to provide enamides **4a**–**c** in 79–86% yields. To show the applicability of the method, a gram-scale synthesis of **4b** was also executed. A similar reactivity was recorded when the phenyl ring of isoxazoles was substituted with thiomethyl or phenyl groups (**4d**,**e**, 66–83% yields). Upon changing the substitution position from *para* to *ortho* or *meta*, the enamide formation still worked very efficiently. Several isoxazoles containing either electron-donating (methoxy and phenyl) or withdrawing (chloro and bromo) groups substituted on the phenyl ring underwent smooth reaction to provide enamides **4f**–**j** in good yields. However, in the case of *O*-methoxy substitution, **4i** was isolated in lower yield. Isoxazole **2k** bearing an electron-rich phenyl substitution also reacted smoothly to form enamide **4k** in 73% yield. On replacing the R group of isoxazoles **2** with aromatic hydrocarbons naphthalene **2l** and phenanthrene **2m**, the potency of isoxazoles toward catalysis remained consistent and delivered enamides **4l** and **4m** in 80 and 70% yields, respectively. The same propensity of the isoxazoles toward catalysis was obtained even in the case of heterocycle substituents and afforded enamides **4n**,**o** in 53–62% yields. After the aryl-substituted isoxazoles were screened, the reactivity of the corresponding alkenyl-substituted isoxazoles was investigated. Isoxazoles bearing styrene **2p** or stilbene **2q** substituents underwent smooth reaction to afford enamides **4p** and **4q** in 43–55% yields. These results clearly demonstrate the stability of alkenes under the reaction conditions. A similar result was obtained in the case of substrates **2r** and **2s**. Pleasingly, even 1,3-diene-substituted isoxazoles **2t**,**u** were also very effective, providing highly conjugated enamides **4t**,**u** in modest yields.

Considering various functional groups present in our synthesized enamides, different chemical transformations are executed. Along this line, the enamide **3f** was reduced to *N*-alkylamide **5** by using Pd/C catalyst and molecular hydrogen in excellent yield (Scheme 4a). Our attempt to convert (*Z*)-**3a**

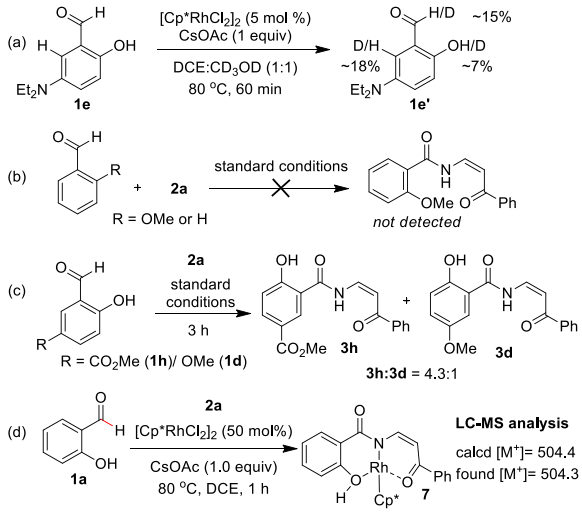
Scheme 4. Synthetic Utility of Enamide



to (*E*)-**3a** only provided 38% of the isomerized enamide (Scheme 4b).[15] The free phenol present in **3a** was also readily protected as benzyl ether **6** (86% yield) by using benzyl bromide (Scheme 4c).

To understand the mechanistic pathway of the enamide formation, the deuterium-labeling experiments were executed with substrate **1e** in the absence of isoxazole by using isotopically labeled solvents (Scheme 5a). We found for the

Scheme 5. Deuterium-Labeling Study and Competition Experiment



sufficient C–H/D exchange of the aldehyde C–H bond that the correct combination of additives and catalysts is essential. The reversibility of the C–H activation step is supported by this sufficient amount of H/D scrambling. Eventually, a sufficient amount of H/D scrambling has also been observed at the *ortho* position of the aromatic C–H bond; however, no amination product was detected. The methyl-protected salicylaldehyde did not provide any enamide, indicating the necessity of free hydroxyl group for the functionalization of aldehyde C–H bond (Scheme 5b). Interestingly, when a competition reaction between two electronically different salicylaldehydes **1d** and **1h** was carried out, the electron-deficient aldehyde coupled to form enamide **3h** at a higher rate

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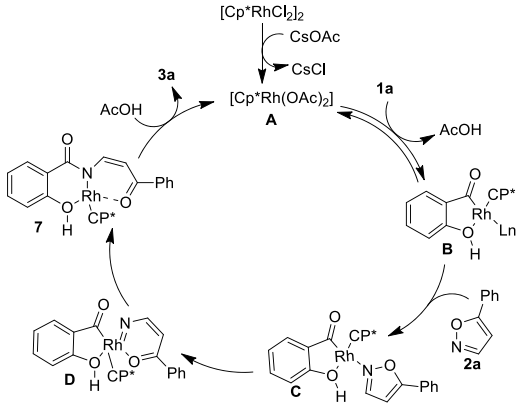
which may be attributed due to higher acidity of the phenolic group of **1h** (Scheme 5c).

On the basis of previous literature reports[19] and our mechanistic studies, a plausible catalyst cycle is proposed in Scheme 6. In the presence of CsOAc, an active catalyst **A** is

Scheme 6. Plausible Mechanism



generated which undergoes C−H metalation with salicylaldehyde **1a** to form a five-membered rhodacycle **B** through the directed C−H functionalization. The coordination of **2a** with the intermediate **B** generates intermediate **C**, which experiences a N−O bond cleavage with the concomitant formation of nitrido intermediate **D**. Subsequent migration/insertion of nitrene into the Rh−C bond generated a tripodal intermediate **7** where the structural rigidity of oxazole was retained. LC−MS analysis of the crude reaction mixture also supports the formation of intermediate **7** (Scheme 5d),[18] which upon protonolysis regenerates catalyst **A** and offers the desired *Z*-enamide product **3a**, stabilized by the intramolecular hydrogen bonding.

In conclusion, we have developed a phenol-directed umpolung reactivity of aldehydes using Cp*Rh(III)-catalyzed C−H functionalization to achieve stereospecific acyclic *Z*-enamides. The polarity of N−O bond of isoxazoles have been utilized as a masked electrophile under our reaction conditions to mark this a complete step- and atom-economic strategy. Silver-free reaction conditions leads our method toward a greener approach. A variety of salicylaldehydes and isoxazoles have successfully responded to make this method versatile. The existence of intermediate, detected by LC−MS analysis, justifies the final step of the catalytic cycle. We hope that our method of stereospecific *Z*-enamide synthesis will be instrumental for further applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04130.

Experimental procedures, spectroscopic data, and NMR spectra of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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