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Regiodivergent Access to Five- and Six-Membered Benzo-Fused Lactams: Ru-Catalyzed Olefin Hydrocarbamoylation

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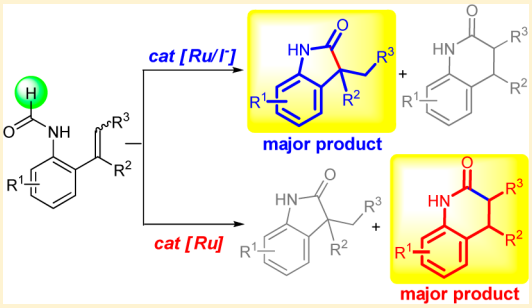
Supporting Information

ABSTRACT: We report herein a new strategy of the Ru-catalyzed intramolecular olefin hydrocarbamoylation for the regiodivergent synthesis of five- and six-membered benzo-fused lactams starting from *N*-(2-alkenylphenyl)formamides. Using a combined catalyst of $Ru_3(CO)_{12}$/Bu_4NI in DMSO/toluene cosolvent (catalytic system A), a 5-*exo*-type cyclization proceeds favorably to form indolin-2-ones as a major product in good to excellent yield. When the reaction was conducted in the absence of halide additives in DMA/PhCl (catalytic system B), 3,4-dihydroquinolin-2-ones were obtained in major in moderate to high yield via a 6-*endo* cyclization process. An excellent level of regioselectivity was observed with a variety of substrates to deliver 5-*exo*- or 6-*endo*-cyclized lactams. It was found that while the selective cyclization was controlled primarily by the choice of catalytic systems employed, it was also greatly influenced by the structural nature of substrates. A halide-bridged trinuclear complex $[Ru_3(CO)_{10}(\mu_2\text{-I})]^-$ is postulated to be an active species in the catalytic system A. Two reaction pathways are proposed, in which the Ru-catalyzed oxidative addition of formyl C−H or N−H bond initiates the subsequent cyclization processes.



INTRODUCTION

Transition metal-catalyzed hydroacylation reaction,[1] a process involving an insertion of unsaturated compounds (such as alkenes,[2] alkynes,[3] or ketones[4]) into activated C−H bond of aldehydes, constitutes one of the most economical and efficient methods for the C−C bond formation.[5] It is surprising to realize that whereas hydroacylation has been well studied, the related hydroesterification[6] and, more notably, hydrocarbamoylation have been less explored. In particular, the latter case is mainly due to the difficulty of insertion of suitable metals into the formamido C−H bonds when compared to the corresponding aldehyde bonds. As a result, only a few metal-mediated systems including ruthenium[7] and nickel[8] have been scrutinized for the hydrocarbamoylation. However, in the Ru-catalyst systems, the developed procedures often require CO atmosphere because of a competitive, irreversible decarbonylation of activated intermediates.[7a,b,e] In this regard, we reported that a chelation strategy could be utilized to effectively suppress the undesired decarbonylation of ruthenium acyl hydride intermediates eventually to achieve efficient intermolecular hydrocarbamoylation reaction.[7c]

On the other hand, an intramolecular hydrocarbamoylation process allows an atom-economical access to synthetically attractive amido-containing heterocycles. Up to now, only a few methods have been reported for this purpose. In 2009, Nakao and Hiyama described an elegant example of cyclization of homoallylic formamides to give γ-lactams catalyzed cooperatively by nickel and Lewis acid.[8c] Recently, Cramer revealed an asymmetric version of this reaction using a novel chrial diaminophosphine oxide.[8a] In addition, Carreira et al. developed a Ru-catalyzed 5-*endo*-cyclization of allylic formamides to yield substituted pyrrolidones under CO atmosphere.[7a] In this approach, only five-membered ring products were obtained even with substrates bearing homoallylic and bishomoallylic tethers.

Despite these impressive advances, we envisioned that a stereodivergent intramolecular hydroamidation would be highly interesting and attractive to obtain nitrogen-containing heterocycles when readily available *N*-(2-alkenylphenyl)formamides are used as a common starting material. Herein, we present our new development of the Ru-catalyzed selective cyclization procedures without requiring external CO atmosphere (Scheme 1).

In this approach, it is especially noteworthy that two feasible cyclization modes (5-*exo* vs 6-*endo*) can be controlled starting from the same starting materials simply by tuning the catalytic conditions, thus giving rise to both indolin-2-one (**2**) and 3,4-dihydroquinolin-2-one (**3**) derivatives. To the best of our knowledge, this is the first example of regiodivergent cyclization method in the intramolecular olefin hydrocarbamoylation reaction.[9] In needs to be emphasized that both of the resulting

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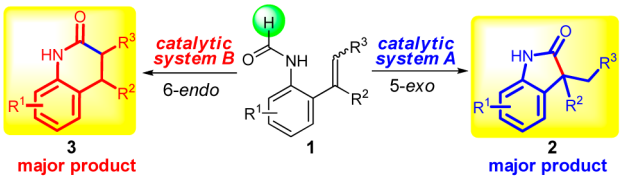
Scheme 1. Regiodivergent Intramolecular Hydrocarbamoylation of *N*-(2-Vinylphenyl)formamides To Form Indolin-2-ones or 3,4-Dihydroquinolin-2-ones



√ Regiodivergent protocol for indolin-2-one or dihydroquinolin-2-one
√ Complete atom-economy
√ High efficiency and selectivity
√ Broad substrate scope
√ No external CO atmosphere required

five- and six-membered benzo-fused lactam skeletons are core structures of numerous natural products, marketed drugs (or their candidates), and synthetic compounds as exemplified in Figure 1.[10,11] As a consequence, a new efficient and selective method for the construction of benzo-fused lactams is highly desirable.

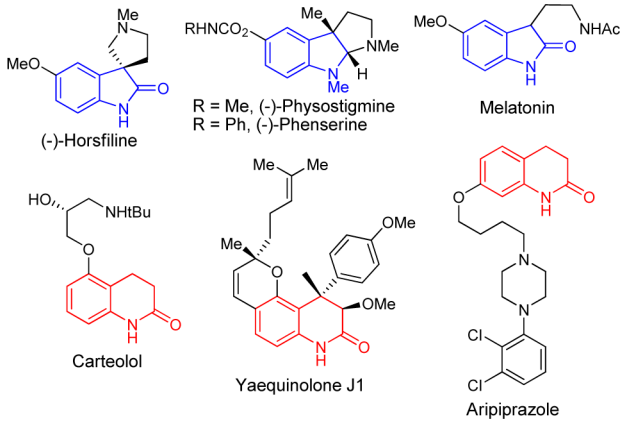
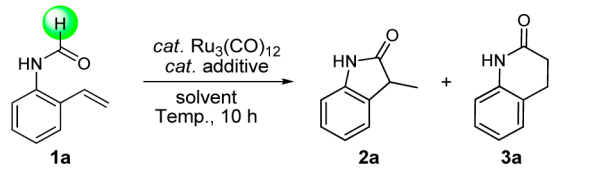


Figure 1. Pharmaceuticals and natural products containing indolinone (top) and dihydroquinolinone (bottom) structure.

RESULTS AND DISCUSSION

We initiated our optimization experiments of an intramolecular hydrocarbamoylation reaction using *N*-(2-vinylphenyl)-formamide **1a** (Table 1)[12] on the basis of our previous studies of the Ru-catalyzed intermolecular hydroesterification and hydroamidation of olefins and alkynes.[6e,g−i,7c] We were pleased to find that the reaction indeed did proceed leading to cyclized products. Using $Ru_3(CO)_{12}$ catalyst (5 mol %) and Bu_4NI additive (15 mol %), the conversion was smooth at 120 °C to furnish a mixture of five- and six-membered lactams (**2a** and **3a**, respectively) in a high combined yield (entry 1). Interestingly, the ratio of two isomeric products was found to be dependent on solvents employed. For instance, it was increased to 8.4:1 favoring indolin-2-one (**2a**) in DMSO (entry 2). The selectivity was further improved up to 12−13:1 in relatively nonpolar solvents (dioxane or toluene), but sacrificing their reactivity to some extents (entries 3,4). A cosolvent system turned out to be most satisfactory in terms of both product yield and regioselectivity, and an equal mixture of DMSO and toluene was found to be most optimal, thus allowing the use of slightly

Table 1. Optimization of Reaction Conditions[a]



entry	Ru (mol %)	additive (mol %)	T (°C)	solvent	yield (%) (**2a**:**3a**)[b]
1	5	Bu_4NI (15)	120	DMF	89 (5.8:1)
2	5	Bu_4NI (15)	120	DMSO	94 (8.4:1)
3	5	Bu_4NI (15)	120	dioxane	79 (12.2:1)
4	5	Bu_4NI (15)	120	toluene	78 (13.1:1)
5	5	Bu_4NI (15)	120	DMSO/toluene (3:1)	91 (9.1:1)
6	5	Bu_4NI (15)	120	DMSO/toluene (1:1)	95 (10.9:1)
7[c]	***4***	***Bu_4NI (12)***	***120***	***DMSO/toluene (1:1)***	***96 (11.1:1)***
8[c]	0	Bu_4NI (12)	120	DMSO/toluene (1:1)	NR
9[c]	4	Bu_4NI (12)	100	DMSO/toluene (1:1)	36 (8.0:1)
10[c]	4	Bu_4NI (12)	140	DMSO/toluene (1:1)	96 (11.0:1)
11[c]	4	Bu_4NCl (12)	120	DMSO/toluene (1:1)	93 (6.4:1)
12[c]	4	Bu_4NBr (12)	120	DMSO/toluene (1:1)	90 (9.3:1)
13[c]	4	NaI (12)	120	DMSO/toluene (1:1)	88 (10.8:1)
14	4	none	120	DMSO/toluene (1:1)	72 (1:2.0)
15	5	none	120	DMSO	84 (1:1.2)
16	5	none	120	DMA	96 (1:1.6)
17	5	none	120	xylene	85 (1:4.5)
18	5	none	120	PhCl	82 (1:5.1)
19	***5***	***none***	***120***	***DMA/PhCl (1:5)***	***89 (1:5.1)***

[a]Reactions in 0.2 mmol scale (0.5 M). [b]Combined yield and ratio (**2a**:**3a**) of crude reaction mixture determined by ^1H NMR (internal standard: 1,1,2,2-tetrachloroethane). [c]For 6 h. NR = No reaction.

lower amounts of catalyst (entries 6,7). On the other hand, no desired product was obtained in the absence of ruthenium catalyst (entry 8). The reaction efficiency was also sensitive to the reaction temperatures (entry 9), while the selectivity was not altered at higher temperature (entry 10). Whereas ammonium salts of chloride or bromide resulted in slightly decreased regioselectivity (entries 11,12), NaI displayed almost a similar level of additive effects when compared to Bu_4NI (entry 13).

During the course of our studies, we found that the regioselectivity was changed to an opposite direction, now favoring a six-membered lactam (**3a**) *in the absence of halide additives* (entry 14). We were pleased to see that the selectivity was further increased upon modulating the solvent systems: the 6-*endo* cyclization is more favored in less polar solvents (entries 15−18). In this line, chlorobenzene (PhCl) turned out to be one of the most effective solvents delivering 6-*endo* products predominantly. In addition, the use of a cosolvent system (DMA/PhCl, 1:5) brought about increased product yields while maintaining the regioselectivity still high when compared to that in PhCl only (entry 19). Although this selectivity for the 6-*endo*-type cyclization is not as high as for the 5-*exo*-route, this

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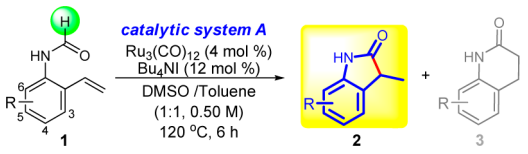
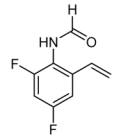
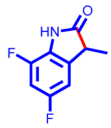
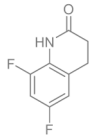
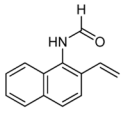
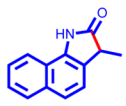
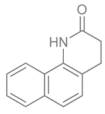
result is significant in that both benzo-fused lactam isomers are readily accessible at our will simply by tuning the catalytic systems starting from the same starting materials. It is also noteworthy that no external CO atmosphere was required in the current regiodivergent intramolecular olefin hydrocarbamoylation procedures.

With the promising optimal conditions, we first examined the scope of *N*-(2-vinylphenyl)formamides with diverse arene substituents for the synthesis of indolinones under the catalytic system A (Table 2). The cyclization proceeded smoothly

Table 2. Substrate Scope for Indolin-2-one Synthesis[a]



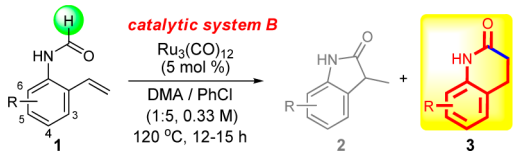
entry	substrate	product		Yield (%)[b] (2:3)
1	R = H, **1a**	**2a**	**3a**	89 (**11.1**:1)
2	R = 3-Me, **1b**	**2b**	**3b**	90 (**10.9**:1)
3	R = 4-Me, **1c**	**2c**	**3c**	84 (**10.7**:1)
4	R = 5-Me, **1d**	**2d**	**3d**	81 (**10.1**:1)
5	R = 6-Me, **1e**	**2e**	**3e**	93 (**11.4**:1)
6	R = 4-OMe, **1f**	**2f**	**3f**	79 (**8.4**:1)
7	R = 4-OCF_3, **1g**	**2g**	**3g**	92 (**9.5**:1)
8	R = 4-OPh, **1h**	**2h**	**3h**	91 (**9.8**:1)
9	R = 4-F, **1i**	**2i**	**3i**	87 (**11.6**:1)
10	R = 4-Cl, **1j**	**2j**	**3j**	96 (**11.4**:1)
11	R = 4-Br, **1k**	**2k**	**3k**	83 (**13.5**:1)
12	R = 4-CO_2Me, **1l**	**2l**	**3l**	85 (**11.6**:1)
13	R = 4-CN, **1m**	**2m**	**3m**	68 (**12.7**:1)
14	R = 5-CF_3, **1n**	**2n**	**3n**	85 (**9.2**:1)
15	R = 5-COMe, **1o**	**2o**	**3o**	80 (**10.2**:1)
16	 **1p**	 **2p**	 **3p**	83 (**11.7**:1)
17	 **1q**	 **2q**	 **3q**	93 (**11.8**:1)

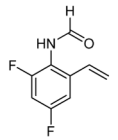
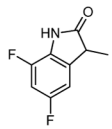
[a]Reactions in 0.3 mmol scale. [b]Combined yields of isolated products: ratio of crude reaction mixture determined by ^{1}H NMR (internal standard: 1,1,2,2-tetrachloroethane).

irrespective of the electronic nature of substituents to afford the desired products in good to excellent yields (68–96%) as well as a high level of regioselectivity (8.4–13.5:1). Importantly, from the synthetic point of view, the resulting two isomers could be easily separated by silica gel column chromatography. The position of arene substituents little affected the reaction efficiency and selectivity as demonstrated representatively by a methyl group (entries 2–5). On the other hand, the selectivity for the formation of five-membered lactams (**2**) was slightly higher with substrates having electron-deficient substituents when compared to the electron-donating groups at the same position. For instance, whereas substrates with 4-alkoxy and phenoxy substituents were cyclized to produce indolin-2-ones with the ratio of 8.4–9.8:1 (entries 6–8), it became more selective (11.4–13.5:1) from starting materials having halide groups at the same position (entries 9–11). Various functional groups commonly encountered in organic synthesis were well tolerated, such as alkoxy (entries 4–5), phenoxy (entry 6), halides (entries 7–9 and 16), ester (entry 12), cyano (entry 13), trifluoromethyl (entry 14), and ketone (entry15). A substrate bearing two substituents was readily cyclized with high efficiency (entry 16). In addition, a reaction of a naphthalene substrate (**1q**) was facile under the catalytic system A leading to the corresponding product (**2q**) in excellent yield and selectivity (entry 17).

As the next step, we also investigated the substrate scope for the synthesis of 3,4-dihydroquinolin-2-ones under the catalytic system B that do not employ halide additives (Table 3). In general, this 6-*endo*-type cyclization took place in good yields and modest to high selectivity. It was interesting to observe that the selectivity (5-*exo* vs 6-*endo*) was changed dramatically depending on the substitution position. For instance, while the reaction occurred highly selectively (1:6.2–13.1) with sub-

Table 3. Substrate Scope in the Synthesis of 3,4-Dihydroquinolin-2-ones[a]



entry	substrate	product		Yield (%)[b] (2:3)
1	R = H, **1a**	**2a**	**3a**	85 (1:**5.1**)
2	R = 3-Me, **1b**	**2b**	**3b**	95 (1:**13.1**)
3	R = 4-Me, **1c**	**2c**	**3c**	85 (1:**6.2**)
4	R = 5-Me, **1d**	**2d**	**3d**	86 (1:**8.3**)
5	R = 6-Me, **1e**	**2e**	**3e**	63 (1.1:1)
6	R = 4-OMe, **1f**	**2f**	**3f**	77 (1:**8.9**)
7	R = 4-OCF_3, **1g**	**2g**	**3g**	82 (1:**5.8**)
8	R = 4-OPh, **1h**	**2h**	**3h**	83 (1:**8.5**)
9	R = 4-F, **1i**	**2i**	**3i**	83 (1:**4.9**)
10	R = 4-Cl, **1j**	**2j**	**3j**	91 (1:**3.1**)
11	R = 4-Br, **1k**	**2k**	**3k**	78 (1:1.1)
12	R = 4-CO_2Me, **1l**	**2l**	**3l**	82 (1:**3.2**)
13	R = 4-CN, **1m**	**2m**	**3m**	58 (1:**3.6**)
14	R = 5-CF_3, **1n**	**2n**	**3n**	75 (1:**3.1**)
15	R = 5-COMe, **1o**	**2o**	**3o**	72 (1:1.3)
16	 **1p**	 **2p**	 **3p**	73 (1:**3.0**)

[a]Reactions in 0.3 mmol scale. [b]Combined yield of isolated products: ratio of crude reaction mixture determined by ^{1}H NMR (internal standard: 1,1,2,2-tetrachloroethane).

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strates bearing a methyl group at the 3-, 4-, and 5-positions (entries 2−4), the cyclization was not selective when it is located at the 6-position (entry 5). This result is in a stark contrast to the 5-*exo*-cyclization process wherein the selectivity was maintained high regardless of the substitution position (Table 2, entries 2−5).

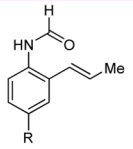
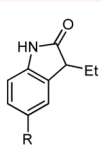
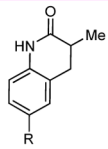
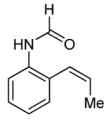
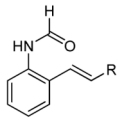
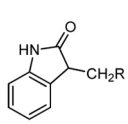
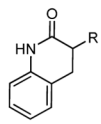
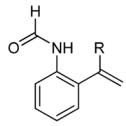
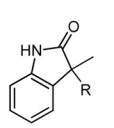
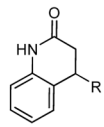
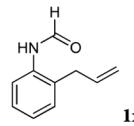
The notable difference of selectivity between two cyclization modes is noteworthy providing a hint for the mechanistic description (vide infra). In addition, the favorable formation of six-membered lactams under catalytic system B was more pronounced with substrates bearing electron-donating substituents. For example, a high level of selectivity for the 6-*endo*-cyclization process was observed when alkoxy or phenoxy groups were substituted (entries 6−8), whereas it was decreased with halide-containing substrates (entries 9−11). Functional group tolerance was found to be excellent under the present catalytic system B as in the case of the 5-*exo*-cyclization.

Next, we scrutinized the scope of substrate variants containing different olefins other than a vinyl group (Table 4). We were pleased to observe that the regiodivergent synthesis was also possible with these derivatives to furnish either 5-*exo*- or 6-*endo*-cyclized lactams with satisfactory selectivity. The intramolecular hydrocarbamoylation proceeded smoothly for the insertion into an *E*-propenyl group leading to 3-ethylindolidin-2-one (**2r**) and 3-methyl-3,4-dihydroquinolin-2-one (**3r**) as major products under catalytic systems A and B, respectively (entries 1−2). A similar trend with regard to reactivity and selectivity was observed with a substrate (**1s**) bearing 4-chloro substituent (entries 3,4). In addition, when *Z*-propenyl isomer (*cis*-**1r**) was allowed to react, the olefinic geometry was found to little affect the outcome of reactivity and selectivity (entries 5,6). It was interesting to compare the pattern of selectivity in the cyclization of substrates bearing vinyl and propenyl moieties, although the exact reason is not clear at the current stage. While higher selectivity was observed in the formation of indolin-2-ones (5-*exo*) from vinyl-containing substrates when compared to 6-*endo*-cyclization process (Table 2), cyclization of substrates bearing a propenyl group proceeded with lower selectivity for the 5-*exo*-process but with higher preference for the 6-*endo*-products (Table 3).

The introduction of a benzylic substituent at the vinyl terminus (**1t**) displayed no detrimental effect on the reactivity and selectivity in the 5-*exo*-process (entry 7). However, modest efficiency and selectivity were observed when **1t** was subjected to the 6-*endo*-procedure (catalytic system B, entry 8). It was found that a replacement of the vinyl terminus from benzyl (**1t**) to phenyl group (**1u**) resulted in more distinctive outcomes. Whereas the 5-*exo*-process took place exclusively under the employed system A albeit in lower yield (entry 9), **1u** was not reactive under the 6-*endo*-cyclization procedure (entry 10).

The above observed selectivity pattern led us to postulate that the hydrocarbamoylation process is sensitive more to the steric environment of substrates particularly around the olefinic moiety, thus giving rise to the regiodivergent routes. To test this hypothesis, two additional substrates (**1v** and **1w**) bearing *gem*-disubstituted olefinic groups were prepared and subjected to the cyclization conditions. As expected, whereas the 5-*exo*-process was not selective (entry 11), 6-*endo*-cyclization of **1v** was much more favored to afford 4-methyl-3,4-dihydroquinolin-2-one (**3v**) with excellent selectivity (1:14.5, entry 12). This behavior was shown more distinctly with a bulkier gem-alkenyl substituent (**1w**). When **1w** bearing α-phenylvinyl moiety was subjected to the catalytic system B, only a six-membered lactam

Table 4. Scope of Substrates Bearing Various Olefins[a]

entry	substrate	catalytic system	product		Yield (%)[b] (**2a**:**3a**)
			 + 		
1	R = H, *trans*-**1r**	A	**2r**	**3r**	90 (**4.3**:1)
2	*trans*-**1r**	B	**2r**	**3r**	83 (1:**10.0**)
3	R = Cl, **1s**	A	**2s**	**3s**	92 (**3.9**:1)
4	**1s**	B	**2s**	**3s**	80 (1:**13.6**)
5		A	**2r**	**3r**	88 (**4.2**:1)
6	*cis*-**1r**	B	**2r**	**3r**	79 (1:**11.0**)
			 + 		
7	R = Bn, **1t**	A	**2t**	**3t**	84 (**6.2**:1)
8	**1t**	B	**2t**	**3t**	40 (1:**3.6**)
9	R = Ph, **1u**	A	**2u**	**3u**	52[c] (**2u** only)
10	**1u**	B	**2u**	**3u**	(< 5)
			 + 		
11	R = Me, **1v**	A	**2v**	**3v**	70 (1.3:1)
12	**1v**	B	**2v**	**3v**	83 (1:**14.5**)
13	R = Ph, **1w**	A	**2w**	**3w**	58 (1.7:1)
14	**1w**	B	**2w**	**3w**	69 (**3w** only)
15		A	**2r**	**3r**	91 (**2.2**:1)
16	**1x**	B	**2r**	**3r**	(64)[d] (1:**9.7**)

[a]Catalytic system A: **1** (0.3 mmol), $Ru_3(CO)_{12}$ (5 mol %), Bu_4NI (15 mol %), DMSO/toluene (1:1, 0.5 M), 120 °C, 20 h. Catalytic system B: **1** (0.3 mmol), $Ru_3(CO)_{12}$ (5 mol %), DMA/PhCl (1:4, 0.33 M), 120 °C, 24−36 h. [b]Combined yield of isolated products: yield in parentheses and ratio of crude reaction mixture determined by ^{1}H NMR. [c]NMP was used as solvent, 36 h. [d]DMA/PhCl (1:5, 0.33 M, 16 h), and 21% of *trans*-**1r** was also detected.

3w was exclusively obtained (entry 14), while selectivity of its 5-*exo*-process under catalytic system A was modest (entry 13). To the best of our knowledge, this route accessible to **2v** and **2w** represents the first example of generating a quaternary carbon center through an olefin hydrocarbamoylation reaction, although the selectivity still remained moderate at the present stage.

It was notable to observe that a substrate **1x** having an allylic double bond underwent the cyclization to afford **2r** and **3r** as products (entries 15,16), which are the same products obtained from the reaction of propenyl-substituted substrates (*cis*- and *trans*-**1r**, entries 1,2 and 5,6). Interestingly, seven-membered compounds (4,5-dihydrobenzo-[*b*]-azepin-2-one) were not

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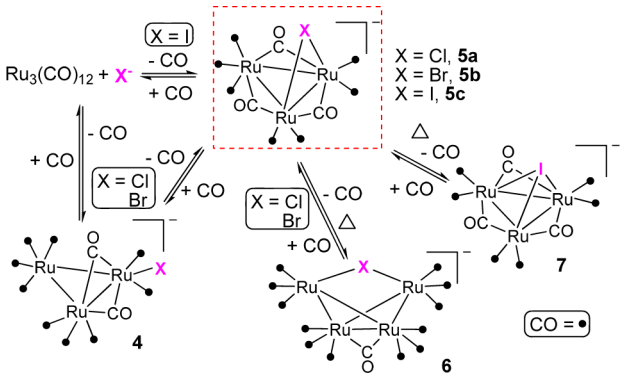
detected in this cyclization reaction. In addition, isomerization of an allylic double bond to *trans*-propenyl olefin (from **1x** to *trans*-**1r**) was observed to occur in a notable extent (21% after 16 h) during the course of the cyclization (entry 16), which provides a mechanistic implication that a metal hydride forms under the employed catalytic conditions (vide infra).

In our previous report,[6e] it was shown that the addition of certain halides resulted in a dramatic enhancement in reaction efficiency in the Ru-catalyzed intermolecular hydroesterification of alkenes and alkynes.[13] For example, ammonium iodide was found to display significant improvement, whereas the effects were less pronounced with the corresponding chloride or bromide salts. In the present intramolecular hydrocarbamoylation, however, the type of halides does not seem to display much distinctive influence on the reactivity, suggesting that the catalytically active species might have similar structures irrespective of halide additives.

It is known that a series of ruthenium complexes is generated when a solution of $Ru_3(CO)_{12}$ is treated with halide ions (Scheme 2).[14] Notably, it is shown that the halide-bridged

Scheme 2. Halide-Mediated Interconversion between $Ru_3(CO)_{12}$ and Its Halide Complexes[14a]

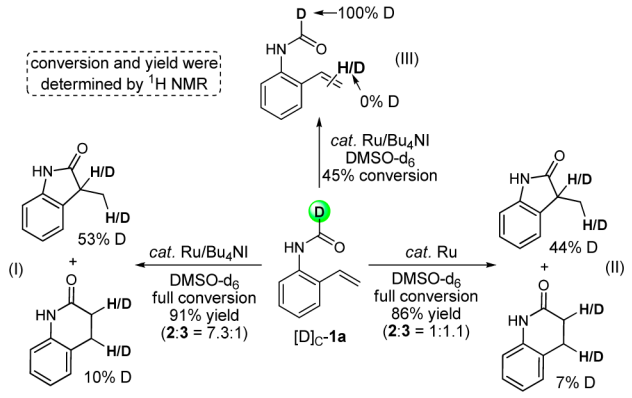


complexes are readily interconverted and that the exact position of equilibrium depends on both CO pressure and halide types employed. For instance, $Ru_3(CO)_{12}$ reacts with chloride or bromide ion to form initially $[Ru_3(CO)_{11}(X)]^-$ (**4**), which is converted to a bridging species $[Ru_3(CO)_{10}(\mu_2\text{-}X)]^-$ (**5a** or **5b**) and then to tetranuclear clusters $[Ru_4(CO)_{13}(\mu_2\text{-}X)]^-$ (**6**) having a bridged halide ligand. In the case of iodide, direct formation of a bridged complex **5c** was observed, which is then transformed to $[Ru_3(CO)_9(\mu_3\text{-}I)]^-$ (**7**) with a triply bridged iodide ligand. Because the equilibrium between $Ru_3(CO)_{12}$ and its monomeric $Ru(CO)_5$ species needs high CO pressure,[15] it is reasonable to rule out a possibility that the added halide ions dissociate the trinuclear precursor into a monomeric species under the present reaction conditions. On the basis of these results, we postulate that complexes **5** might be a common catalytically active species responsible for the 5-*exo*-cyclization process under catalytic system A.[16]

It needs to be empathized that the regioselectivity toward the 5-*exo* and 6-*endo*-cyclization is significantly altered by the presence of halides, suggesting that a different catalytic cycle might be operative by the additives in the present carbamoylation. This stands in contrast to our previous Ru-catalyzed hydroesterificaton,[6e] in which halide additives did not change the regioselectivity for the formation of linear versus branched isomeric esters.

To probe the working modes in the current cyclization reaction, we conducted a series of experiments with isotopically labeled substrates (Scheme 3).[17] Under both catalytic

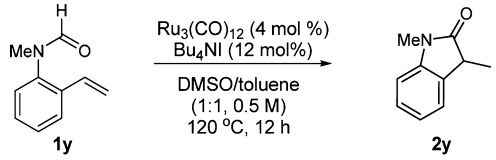
Scheme 3. Isotopic Studies with $[D]_C$-1a



conditions (A and B), the reaction of substrate $[D]_C$-**1a** bearing C−D at the formyl carbon afforded a five-membered lactam with a high level of deuterium incorporation at the C3 and methyl moiety, while a six-membered isomer was incorporated with a much lower deuterium extent (eqs I and II). These results suggest that: (i) an initial insertion of the reactive catalyst into a formyl C−H bond is involved under both catalytic systems; and (ii) the subsequent olefin hydrometalation process is reversible and nonselective. When the reaction mixture was analyzed at a partial conversion, no loss in the extent of deuterium contents at the formyl C−D bond was observed (eq III). In addition, the olefinic double bond of recovered $[D]_C$-**1a** was not scrambled with any deuterium. This result implies that the Ru-mediated cleavage of a formyl C−D bond is presumably irreversible, leading to the corresponding ruthenium acyl hydride species.

The direct activation of a formamido C−H bond in the present hydrocarbamoylation reaction was also supported by the cyclization of a tertiary amide substrate **1y**, which afforded the corresponding five-membered ring product **2y** albeit in low yield (Scheme 4). This stands in contrast with the observation

Scheme 4. Reaction of a Tertiary Amide Substrate 1y



^{1}H NMR: 40% coversion, 16% yield

made by Carreira et al. in their Ru-catalyzed cyclization of allylic formamides, in which the free amide N−H bond was essential for the reaction progress.[7a]

The isotopic study was repeated, this time with a substrate $[D]_N$-**1a** containing a N−D bond (Scheme 5).[17] Under both catalytic systems A and B, deuterium was incorporated to a significant extent in each five- and six-membered cyclic product when the reaction was completed (eqs IV and V). This observation suggests that Ru-mediated cleavage of the N−D bond is also involved in the catalytic cycle and that the subsequent olefin insertion step is reversible and nonselective. When the reaction was interrupted at 70% conversion, the

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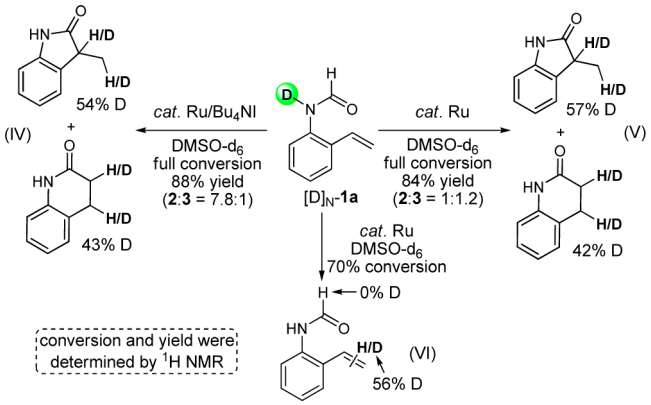
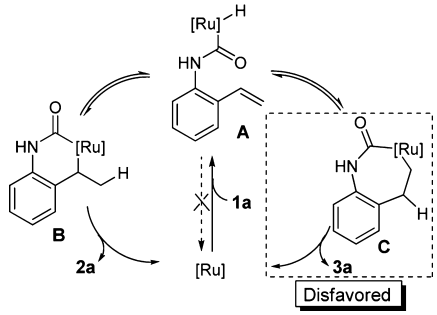
Scheme 5. Isotopic Studies with $[D]_N$-1a



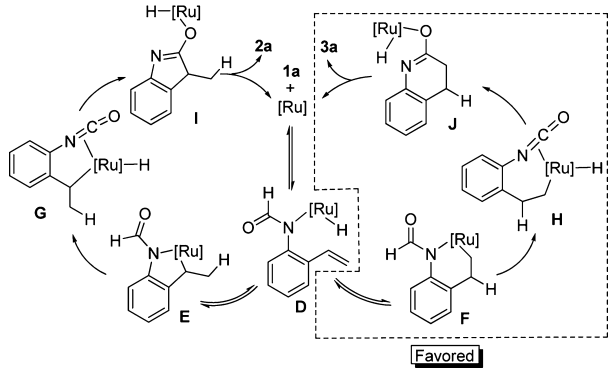
recovered starting material (**1a**) was analyzed to have a significant level of deuterium incorporation at the olefinic double bond (eq VI), implying that the Ru-mediated cleavage of a amido N−D bond is presumably reversible leading to the corresponding ruthenium deuteride species. A large difference in the deuterium incorporation in six-membered products from two isotopic starting materials $[D]_C$-**1a** and $[D]_N$-**1a** can be rationalized by taking an assumption that the 6-*endo*-cyclization process proceeds more effectively via a N−H bond cleavage pathway.

On the basis of the above observations and previous reports by us and others,[7] two reaction pathways are proposed for the Ru-catalyzed olefin hydrocarbamoylation (Schemes 6 and 7).

Scheme 6. Proposed Reaction Pathway of Direct Activation of the Formyl C−H Bond



Scheme 7. Proposed Reaction Pathway of Initial Activation of the N−H Bond



They differed in the way of ruthenium-mediated cleavage of formyl C−H or amido N−H bond, although it is too early to clearly favor one over the other at the present stage. As described above, cleavage of formyl C−H bond by the active ruthenium complex is believed to proceed irreversibly leading to an acylruthenium hydride species **A**. Subsequent reversible insertion of the olefin into the Ru−H bond can afford either six-membered (**B**) or seven-membered ruthenacycle (**C**), which undergoes a reductive elimination step to provide indolin-2-one (**2a**) or 3,4-dihydroquinolin-2-one (**3a**), respectively. In addition, a path leading to six-membered lactams is postulated to be less favored as evidenced by the low deuterium incorporation in the six-membered lactam from a reaction of $[D]_C$-**1a** (Scheme 3, eqs I and II).

On the other hand, an alternative pathway can also be envisioned to operate, in which ruthenium cleaves an amido N−H bond first leading to an amdioruthenium hydride species **D** (Scheme 7). Subsequent olefin insertion into **D** may occur in two directions leading to a five-membered ruthenacycle **E** or a six-membered analogue **F**. At this stage, these ruthenacycles are assumed to undergo β-hydride abstraction from a formyl C−H bond to yield the corresponding isocyanate intermediates **G** or **H**, respectively. In fact, Carreira et al. suggested that this route would be responsible for their hydrocarbamoylation reaction of allylic formamdies under similar ruthenium catalysis conditions.[7a] Subsequent insertion of alkylruthenium moiety into the in situ generated isocyanate group will deliver cyclic imidates **I** or **J**, and then finally reductive cleavage and tautomerization will release the desired products **2a** or **3a** with the concomitant regeneration of catalyst. Again, it is proposed that the 6-*endo*-cyclization process is favored under the catalytic system B, although detailed studies are required.

Although more comprehensive mechanistic investigations are required to present an unambiguous explanation for the dichotomy between 5-*exo* and 6-*endo* pathways, we assume at the present stage that halide additives play an important role by changing the composition of catalytically active metal species. In addition, we noticed that the choice of solvent also brought about the change in selectivity in this regiodivergent cyclization.

CONCLUSIONS

In summary, we have developed the Ru-catalyzed intramolecular olefin hydrocarbamoylation of *N*-(2-alkenylphenyl)-formamides for the regiodivergent synthesis of indolin-2-ones and 3,4-dihydroquinolin-2-ones. Two convenient catalytic conditions (A and B) were optimized for each type of isomeric products. The reaction is featured to be atom-economical with high efficiency and selectivity over a wide range of substrates. Isotopic studies led us to propose two mechanistic pathways, which differed in the way of ruthenium-mediated initial cleavage of formyl C−H or amido N−H bond. While the regioselectivity of the cyclization process is believed to be primarily controlled by the nature of catalytic species generated in situ, it is also dependent on the structural nature of the substrates. Further studies on the synthetic applications and mechanistic details are currently underway.

ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of new compounds (^{1}H and ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) See the Supporting Information for details of experiments with isotopically labeled substrates.