Ruthenium-Catalyzed Intramolecular Arene C(sp^2)-H Amidation for Synthesis of 3,4-Dihydroquinolin-2(1*H*)-ones

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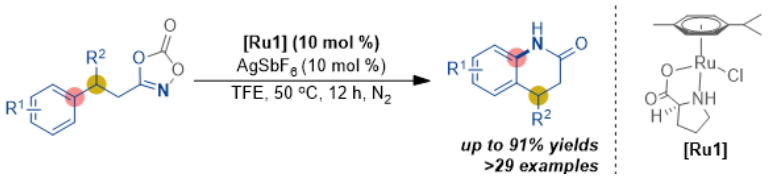
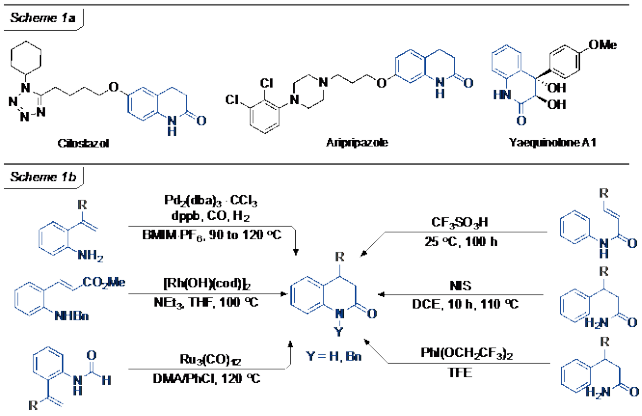
Supporting Information Placeholder

ABSTRACT: We report the [Ru(*p*-cymene)(L-proline)Cl] (**[Ru1]**) catalyzed cyclization of 1,4,2-dioxazol-5-ones to form dihydroquinoline-2-ones in excellent yields and regioselectivity via a formal intramolecular arene C(sp^2)-H amidation. The reactions of the 2- and 4-substituted aryl dioxazolones proceeds initially through spirolactamization via electrophilic amidation at the arene site, which is *para*- or *ortho*- to the substituent. Hammett correlation study showed that the spirolactamization is likely to occur by electrophilic nitrenoid attack at the arene, which is characterized by a negative ρ value = -0.73.



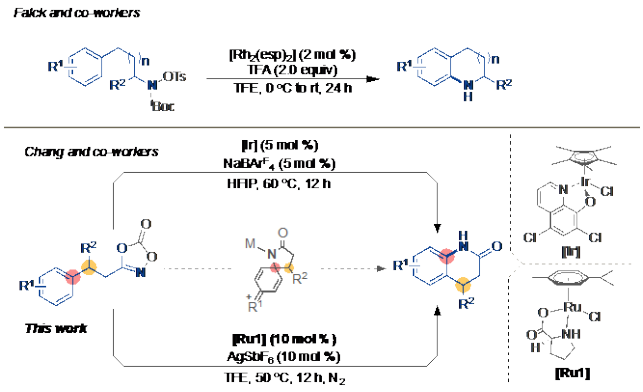
3,4-Dihydroquinolin-2(1*H*)-ones are privileged skeletons found in many bioactive compounds;[1a-b] some notable examples are cilostazol,[1c] aripripazole[1d] and Yaequinolone A1 (isolated from *Penicillium sp*. FKI-2140;[1e] Scheme 1a). Apart from Friedal-Crafts cyclization, classical routes to the dihydroquinolin-2-one skeletons include acid-mediated cyclization of *N*-phenylcinnamamides,[2] oxidative cyclization of aryl methoxyamides by hypervalent iodine reagents,[3] and NIS-initiated free radical cyclization of 3-phenylpropanamides.[4]

Scheme 1. Examples of Dihydroquinolin-2-one Formation



Transition metal-catalyzed cyclizations of 2-aminostyrenes are known to offer an alternative route to dihydroquinolin-2-ones (Scheme 1b). For instance, Alper and co-workers reported the Pd-catalyzed cyclocarbonylation of 2-aminostyrenes in ionic liquid medium.[5] In 2010, Youn and co-workers demonstrated the Rh(I)-catalyzed domino conjugate addition-cyclization of (*E*)-methyl 3-(2-(benzylamino)phenyl)acrylates with organoboroxines.[6] Recently, Chang and co-workers also reported Ru-catalyzed olefin hydrocarbamoylation of *N*-(2-vinylphenyl)-formamides to afford dihydroquinolin-2-ones.[7] Yet, these methodologies rely on the use of specially designed arylamine moieties, which often require tedious multi-step synthesis.

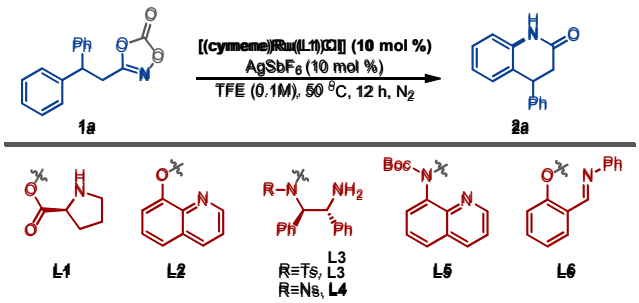
Scheme 2. Examples of Metal-Catalyzed Intramolecular Arene C(sp^2)-H Aminations and Amidations



Regiocontrolled direct arene aminations/amidations constitutes an atom- and step-economical approaches for arylamines/-amides synthesis (Scheme 2). In this regard, Falck and co-workers developed dirhodium-catalyzed electrophilic C(aryl)–H amination to give tetrahydroquinolines using NH_2/NH(alkyl)-*O*-(sulfonyl)-hydroxyamines as reagents,[8] and the reaction is believed to proceed by electrophilic amination by some reactive Rh-nitrenoid species. Of particular interest, Chang and co-workers reported the Cp*Ir(III)-catalyzed intramolecular nitrenoid C(aryl)–H insertion employing dioxa-

zolones,[9a-c] which are readily derived from carboxylic acids feedstock. Recently, we reported Ru(II)-catalyzed enantioselective intramolecular nitrenoid C(sp^3)–H bond insertion of dioxazolones to afford γ-lactams in up to 95 %*ee*.[10] Here, we describe the Ru-catalyzed intramolecular C(aryl)–H amidation using dioxazolones as the nitrenoid reagents to furnish dihydroquinolin-2-ones. Analogous to the Cp*Ir(III) system, the Ru-catalyzed dihydroquinolin-2-one formations proceeds by tandem electrophilic spirocyclization and C–C migration.

Table 1. Optimization of Reaction Conditions



entry	deviation from standard conditions	% yield (%*ee*)[a,b]
1	none	76 (30)
2	**L2** instead of **L1**	78
3	**L3** instead of **L1**	<2
4	**L4** instead of **L1**	<2
5	**L5** instead of **L1**	63
6	**L6** instead of **L1**	<2
7	DCE instead of TFE	9(53)
8	acetone instead of TFE	21(63)
9	MeOH instead of TFE	13(52)
10	EtOH instead of TFE	21(53)
11	HFIP instead of TFE	65(15)
12	rt instead of 50 °C	38(29)
13	40 °C instead of 50 °C	48(32)
14	60 °C instead of 50 °C	78(29)

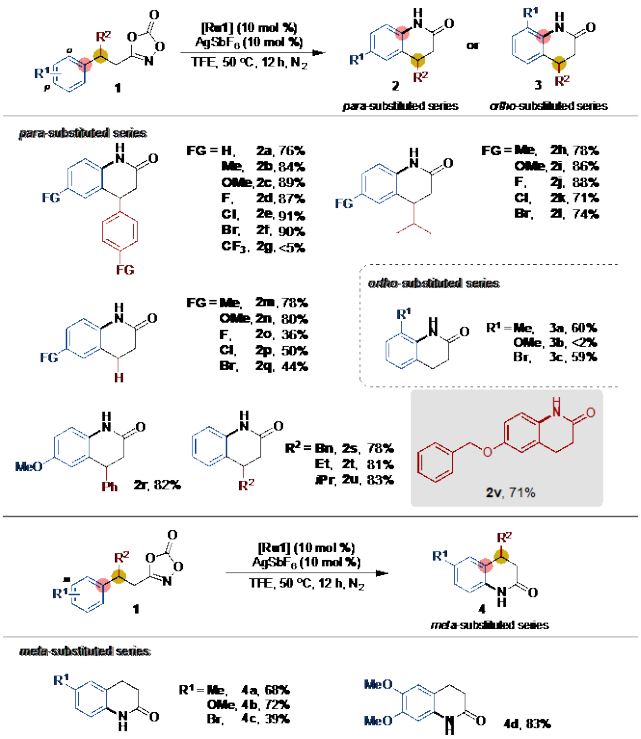
[a]Reaction conditions: **1a** (0.1 mmol), catalyst (10 mol %), $AgSbF_6$ (10 mol %), solvent (1 mL) at 50 °C for 12 h under N_2 unless other specified; Isolated yield. [b]*ee* is determined by HPLC with a chiral column; (*S*)-**2a** is the major isomer (see Supporting Information for details).

In Table 1, treatment of dioxazolone **1a** (0.1 mmol) with **[Ru1]** (10 mol %) containing (*L*)-proline as ligand and $AgSbF_6$ (10 mol %) in TFE (1 mL) at 50 ºC for 12 h, 4-phenyl-3,4-dihydroquinolin-2(1*H*)-one (**2a**) was obtained in 76% yield with 30 %*ee* (entry 1). Performance of Ru catalysts bearing several ligands has been compared. The Ru catalyst with 8-hydroxyquinoline (**L2**) as ligand was found to give comparable results as (*L*)-proline (**L1**). However, those complexes bearing ligands derived from *R,R*-DPEN (**L3–4**) are ineffective catalysts with full recovery of **1a**. Analogous to **L1**, *N*-Boc-8-aminoquinoline (**L5**) is effective ligand for productive result (**2a**: 63% yield). Yet, the catalyst bearing Schiff base ligand **L6** failed to effect significant transformation.

While the reaction conducted in DCE resulted in poor product yield (9%), **2a** was produced in 21% yield with 63 %*ee* when acetone was the solvent. While employing MeOH and EtOH as solvents produced similar results as for acetone (entries 9–10), the analogous reactions conducted in HFIP afforded **2a** in 65% yield. Performing the reaction at lower temperatures did not show significant improvement.

Table 2 depicts the intramolecular C(aryl)–H amidations for the *ortho*-, *meta*- and *para*-substituted 1,4,2-dioxazol-5-ones with **[Ru1]** as catalyst. For the *para-substituted* dioxazolones (**1b–1q**, **1r** and **1v**), their dihydroquinolin-2-one products were characterized by skeletal rearrangement involving migration of the pre-existing (aryl-alkyl) C–C bond from the position *para* to the substituent in the substrates to the position *meta* to the substituent in the products. In all cases, the anticipated products due to amidation at the *meta* position to the substituents were not obtained. Similar results were also reported for the analogous Cp*Ir(III)-catalyzed intramolecular C(aryl)–H amidation reactions.[9b-d]

Table 2. Substrate Scope Studies of *para*-, *ortho*- and *meta*-Substituted 1,4,2-Dioxazol-5-ones



For the *diaryl-substituted* dioxazolones, those bearing electron-donating Me and OMe and -withdrawing halogen (F, Cl and Br) groups were effectively transformed to their dihydroquinolin-2-one **2b** – **2f** in up to 90% yields. Yet, reaction of **1g** bearing 4-CF_3 substituent afforded **2g** in < 5% yield. The analogous reactions for the *monoaryl-substituted* series, dihydroquinolin-2-one **2h–2n** were formed in 71–88% yields. Yet, those halogenated analogues **2o–2q** were formed in moderate ~40% yields. Apparently, the amidation is preferentially directed to the more electron-rich arene moieties. For instance, the reaction of **1r** led to selective C–H amidation at methoxy-substituted arene (**2r**: 82%). In all cases, the dihydroquinolin-2-ones formation is characterized by skeletal C-C migration

with the C–N bond being formed at the *para* position to the *para*-substituent. Notably, the Ru-catalyzed cyclization of 3-(4-(benzyloxy)phenethyl)-1,4,2-dioxazol-5-one (**1v**) would afford 6-(benzyloxy)-3,4-dihydroquinolin-2(1*H*)-one (**2v**) in 71% yield. According to literature, **2v** exhibits anticonvulsant activities for treating bipolar disorder and neuropathic pain.[11]

For the *ortho*-substituted substrates (Table 2), facile reaction of 3-(2-methylphenethyl)-1,4,2-dioxazol-5-one afforded **3a** in 60% yields. Again, **3a** is characterized by skeletal C–C migration with the C–N bond being forged at the position *ortho* to the substituent. In this work, transformation of 3-(2-methoxyphenethyl)-1,4,2-dioxazol-5-one to **3b** was less successful. Yet, the analogous 2-bromo-substituted derivative reacted successfully to furnish **3c** in 59% yield. Compared to the current Ru-catalyzed system, the Cp*Ir catalyst would produce both the C–C migration product and the direct C–H amidation product in a ratio of 1:1.2.[9b-d]

For the *meta*-substituted dioxazolones, the Ru-catalyzed cyclization of 3-(3-Y-substituted phenethyl)-1,4,2-dioxazol-5-one (Y = Me, OMe and Br) furnished the corresponding dihydroquinoline-2-ones **4a–4c** in 39–72% yields. In all cases, the C–N bond formation occurred at the *para* position to the *meta*-substituents. Apparently, skeletal C–C arrangement is not involved in the dihydroquinolin-2-one formations. Reaction of the dioxazol-5-one bearing *meta*- and *para*-OMe substituents produced **4d** exclusively in 83% yield, presumably via direct C–H amidation without skeletal rearrangement. Yet, the formation of **4a–4d** may also occur via spirocyclization at the *meta*-position to the substituent, followed by skeletal C–N rearrangement. The two pathways appear to be difficult to be differentiated.

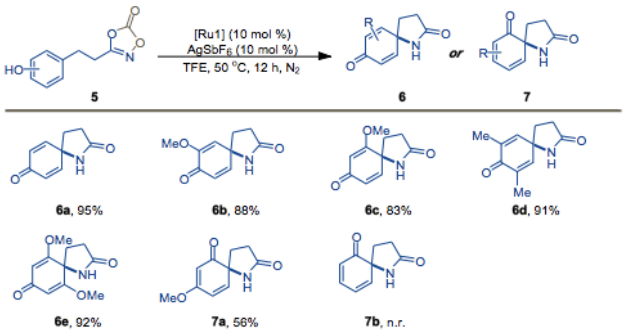
Assuming Ru-nitrenoid intermediates, amidation at the benzylic C(sp^3)–H, 2^0 C(sp^3)–H and 3^0 C(sp^3)–H sites are likely to be competitive.[10] Here the regioselectivity was assessed by reacting dioxazolones containing benzyl (**1s**), ethyl (**1t**) and isopropyl (**1u**) sidearms under the Ru-catalyzed conditions. To our delight, the amidation is directed exclusively to the aryl C(sp^2)-H bond, rather than the benzylic C(sp^3)-H (**2s**), 2^0 C(sp^3)-H (**2t**) and 3^0 C(sp^3)-H (**2u**) bonds, and the desired amidation products were obtained in 78–83% yields.

The reactions of the *para*- and *ortho*-substituted dioxazolones afforded the dihydroquinoline-2-ones involving skeletal C–C rearrangement. We postulated that the reactive Ru-nitrenoid intermediate should initiate the cyclization by electrophilic amidation at the *para*- / *ortho*-position to the substituent to form some spirolactam intermediates, and the subsequent skeletal C–C rearrangement should afford the observed products. A similar mechanism was reported for the analogous Cp*Ir(III)-catalyzed intramolecular aryl C–H amidation.[9b-d]

To probe the spirolactam formation, 3-(4-hydroxyphenethyl)-1,4,2-dioxazol-5-one (**5a**) was employed as model substrate for the Ru-catalyzed amidation, and the desired azaspiro[4.5]deca-6,9-diene-2,8-dione (**6a**) was isolated in 95% yield (Table 3). Notably, replacing the 4-OMe substituent in **1n** with hydroxyl group (**5a**) led to successful trapping of the spirolactam intermediate. Similarly, those phenol-based dioxazolones bearing OMe and Me groups at the *ortho*- and *meta*- positions underwent spirolactamization in excellent yield (**6b**; 88%; **6c**; 83%; **6d**: 91%; **6e**: 92%). Apparently, the nitrenoid attack at the *ortho*-position to the hydroxy group should be facile to furnish **7a** in 56% yield. Yet, presence of a OMe group appears to be critical for effective reaction since production of spirolactam **7b** was unsuccessful for lacking a *para*-methoxy substituent.

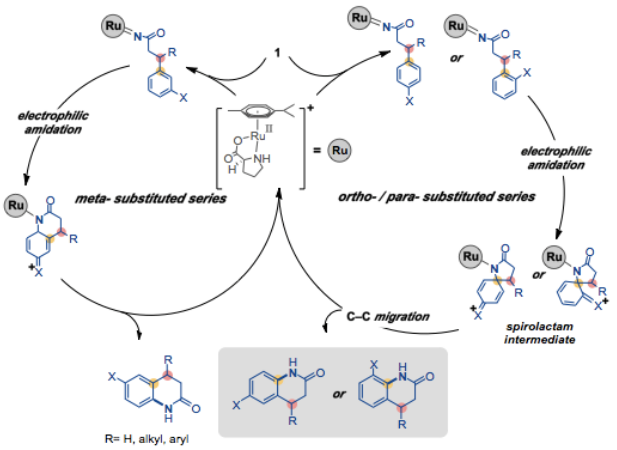
The nature of the spirolactamization transition state has been examined by Hammett correlation study using a series of 4-substituted dioxazolones **1-Y** (Y = OMe, Me, H, F and Cl) as substrates. On this work, dioxazolone **1-Y** was subjected to the standard conditions: **1-Y** (0.1 mmol), **[Ru1]** (10 mol %) and $AgSbF_6$ (10 mol %) in TFE (1 mL) for 30 min. With ~10–20% substrate conversion, the yields of the dihydroquinolin-2-ones were determined by ^{1}H NMR spectroscopy (see Supporting Information for details). By plotting the log k_Y/k_H (Y = OMe, Me, H, F and Cl) versus Hammett σ_{para} constant, a straight line (R^2 = 0.98) with slope (ρ) = -0.73 (see Supporting Information). The negative ρ value implies the Ru-nitrenoid attack on the aryl ring is likely to be electrophilic in nature.

Table 3. Scope of Dearomative Spirocyclization Reaction



Scheme 3 depicts the proposed mechanism of the aryl C–H amidation of the 2- and 4-substituted dioxazolones. Assuming some Ru-nitrenoid as active intermediates, electrophilic attack of the nitrenoid moiety at the *ortho*- and *para*-positions to the substituents should afford the spirolactams. The regioselectivity of the amidation was probably favored by π-conjugation of the substituents, resulting in enhanced electron density at the *ortho*- and *para*- positions of the substituent. The spirolactams should undergo skeletal C–C migration to form the dihydroquinolin-2-ones. For the 3-substituted dioxazolones, the product formation may proceed by direct electrophilic attack *para*- to the substituent. However, a mechanism involving tandem spirocyclization and C–N skeletal rearrangement cannot be negated.[12]

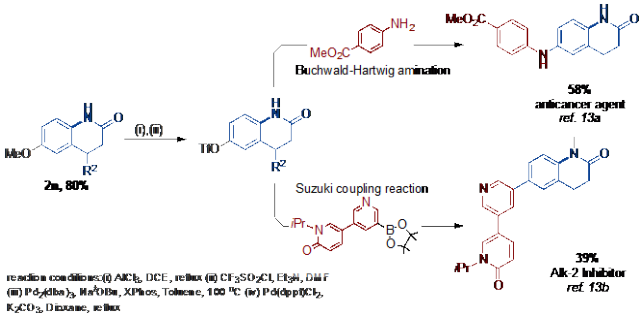
Scheme 3. Proposed Mechanism



To our delight, the Ru-catalyzed C(aryl)–H amidation can be performed in gram-scale. For instance, treating **1a** (2 mmol, 0.534 g) with 10 mol % **[Ru1]** and 10 mol % of $AgSbF_6$ in TFE at 50 ºC for 12 h gave **2a** in 61 % isolated yield (see Supporting Information).

Late-stage functionalization of the dihydroquinoline-2-ones can offer a convenient synthesis of methyl 4-((2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)amino)benzoate (anticancer agent)[13a] and 6-(1'-isopropyl-6'-oxo-1',6'-dihydro-[3,3'-bipyridin]-5-yl)-1-methyl-3,4-dihydroquinolin-2(1*H*)-one (Alk-2 inhibitor).[13b] For instance, dihydroquinolin-2-one (**2n:** 80% yield prepared in this work) was transformed to its *O*-triflate derivative using $AlCl_3$ followed by CF_3SO_2Cl treatment.[14] Subsequent coupling with methyl 4-aminobenzoate (Buchwald-Hartwig amination) and 1-isopropyl-5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[3,3'-bipyridin]-6(1*H*)-one (Suzuki coupling) are known to afford the target medicinal products (Scheme 4).

Scheme 4. Late-Stage Functionalization of Dihydroquinolin-2-one **2n**



In conclusion, we have developed Ru-catalyzed cyclization of 1,4,2-dioxazol-5-ones to afford dihydroquinolin-2-ones. For the *ortho*- and *para*-substituted dioxazolones, the Ru-nitrenoid insertion occurs preferentially at the *ortho*-/ *para* position to the substituents resulting in spirolactamization, followed by skeletal C–C/C–N rearrangement with remarkable regioselectivity. Since dihydroquinoline-2-ones are valuable pharmacophores, the successful development of this Ru-catalyzed reaction enables facile access to this important class of compounds from abundant hydrocarbon feedstocks. This method should be of utility to synthetic and medicinal chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General information, experimental details, screening studies and NMR spectral data (PDF).

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Notes

The authors declare no on competing financial interest.

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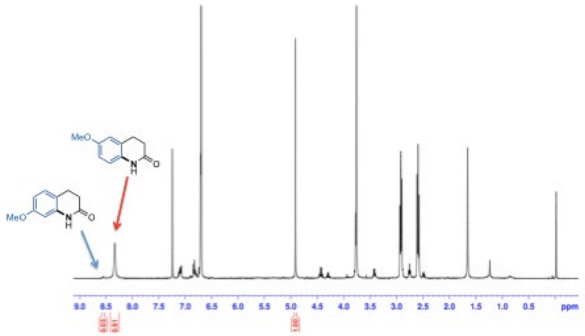
(12) With **1n** as substrate, careful analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed two distinct NH proton signals at δ_H 8.4 and 8.6 ppm corresponding respectively to 6-methoxy-3,4-dihydroquinolin-2(1*H*)-one (**2n**; C–C migration product) and 7-methoxy-3,4-dihydroquinolin-2(1*H*)-one (C–N migration product) in a ratio of >20:1.



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