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Rh(III)-Catalyzed Coupling of Benzamides with Propargyl Alcohols via Hydroarylation—Lactonization

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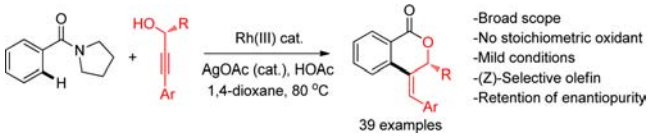
ABSTRACT



Rh(III)-catalyzed C−H activation and annulation of 1-benzoylpyrrolidine with propargyl alcohols has been achieved for an efficient synthesis of (4-benzylidene)isochroman-1-one. Highly enantioenriched products were obtained starting from optically pure propargyl alcohols.

C−H activation mediated by transition metals has been extensively studied as a strategy for the construction of complex structures in synthetic organic chemistry.[1] This strategy takes advantage of the ubiquity of the C−H bond, which amounts to step- and atom-economy. In addition to the widely explored C−H activation/functionalization reactions catalyzed by transition metals such as Pd, Ru, and Cu,[1] Rh(III) complexes have been well-recognized as catalysts for C−H activation.[2] Thus Rh(III)-catalyzed C−H activation stands out with high activity, broad substrate scope, and high functional group tolerance. With the assistance of chelating groups, C−H bonds can insert under redox-neutral conditions into a variety of unsaturated molecules, such as aldehydes,[3] imines,[4] azides,[5] isocyanates,[6] aziridines,[7] diazo compounds,[8] and methylenecyclopropanes.[9]

Despite the significance of a directing group, the role of the directing group is often limited to the coordination effect, and subsequent *in situ* intramolecular functionalization of the directing group is limited.[10] In 2012, Shi reported Rh(III)-catalyzed annulative coupling between benzimides

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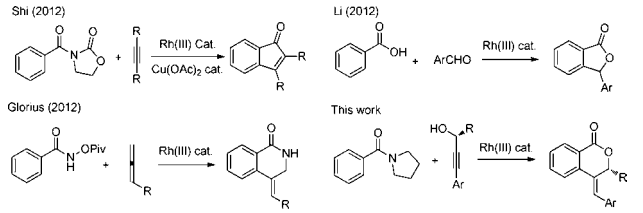
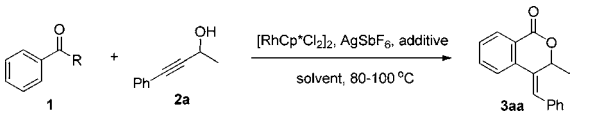
Scheme 1. Rh-Catalyzed C−H Activation/Cyclization



and alkynes for the synthesis of indenones (Scheme 1).[11] Li reported Rh(III)-catalyzed annulation of benzoic acids with benzaldehydes.[12] In all cases, the directing group also acts as an electrophile. To further broaden the scope and applications of Rh(III)-catalyzed C−H activation reactions, it is necessary to design other catalytic systems with an *in situ* functionalizable bifunctional directing group. Tertiary amide groups are directing groups in a number of C−H activation systems,[13] including the hydroarylation of alkynes catalyzed by Ru(II)[14] and occasionally by Rh(III) complexes.[15] We reasoned that the dual role of the amide group may allow the coupling of benzamides with propargyl alcohols to give hydroarylation/lactonazation products (Scheme 1). Although the *aza*-analogue of such a lactone has been elegantly synthesized by Glorius (Scheme 1),[16] the oxo-analogue has not been achieved. We now report an efficient synthesis of (4-benzylidene)isochroman-1-ones via Rh(III)-catalyzed C−H activation.

We initiated our studies with the coupling of a benzamide with propargyl alcohol **2a** (Table 1). A cationic system ($[RhCp^*Cl_2]_2/AgSbF_6$) was employed as the catalyst in the presence of PivOH. While essentially no reaction occurred for PhC(O)NHMe, coupling did occur when a tertiary benzamide such as $PhC(O)NMe_2$ was applied

Table 1. Optimization Studies[a]



entry	R	additive (equiv)	solvent	temp (°C)	yield[b] (%)[b]
1	NHMe	PivOH (2.0)	DCE	100	trace
2	NMe_2	PivOH (2.0)	DCE	100	(25)
3	NEt_2	PivOH (2.0)	DCE	100	(59)
4	**P**[c]	PivOH (2.0)	DCE	100	80 (66)
5	**P**[c]	–	DCE	100	11
6	**P**[c]	AgOAc (0.2)	DCE	100	58
7	**P**[c]	AgOAc (0.2)/PivOH (2.0)	DCE	100	(64)
8	**P**[c]	AgOAc (0.2)/PivOH (2.0)	dioxane	100	(70)
9	**P**[c]	AgOAc (0.2)/AcOH (2.0)	dioxane	90	86 (73)
10	**P**[c]	AgOAc (0.2)/AcOH (2.0)	THF	90	79
11[d]	**P**[c]	AgOAc (0.2)/AcOH (2.0)	dioxane	80	91 (85)

[a] Reaction conditions: $[RhCp^*Cl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), additive, amide (0.3 mmol), and **2a** (0.45 mmol) in a solvent (3 mL) at 100 °C for 18 h. [b] HPLC yield using biphenyl as an internal standard; isolated yield in parentheses. [c] **P** = pyrrolidinyl. [d] Amide (0.45 mmol) and **2a** (0.3 mmol) were used.

(Table 1, entry 2). The efficiency of the coupling reaction was significantly improved when $PhC(O)NEt_2$ was used, from which the product (**3aa**) was isolated in 59% yield (entry 3) and was fully characterized. It has been reported that 1-benzoylpyrrolidine (**1a**) can display higher reactivity than other tertiary amides in C−H activation reactions.[14a,b] Indeed, the reaction efficiency slightly increased when **1a** was employed (entry 4). An acid additive such as PivOH proved necessary likely owing to its role in facilitating C−H activation[1b,c] and/or subsequent esterification (entries 4, 5). Addition of AgOAc (20 mol %) proved beneficial for this reaction, and 1,4-dioxane is the optimal solvent. Thus **3aa** was isolated in 73% yield when both AgOAc (20 mol %) and AcOH (2 equiv) were employed as additives (entry 9). Gratifyingly, an isolated yield of 85% was reached when the reaction temperature was lowered to 80 °C with the propargylic alcohol being a stoichiometric limiting reagent (entry 11). We noted that a previous synthesis of such lactones started from 2-iodobenzoic acid and allenes via Pd(0)-catalyzed C−I functionalization, with the possibility of a mixture of *Z*/*E* isomers.[17]

The scope and limitation of this coupling system were next explored (Scheme 2). In the coupling with **1a**, a broad spectrum of electron-donating (**3ab**, **3ad**, **3ak**, **3am**) and -withdrawing (**3ae**, **3ah**, **3ai**) as well as halogen (**3af**, **3ag**, **3an**) groups at the *ortho*, *meta*, and *para* positions of the benzene ring of the propargyl alcohol are compatible, and the corresponding products were isolated in good to high yield. These preinstalled ester, cyano, and halogen groups in the products should allow further chemical manipulations. The aryl group can also be extended to a 3-thiophenyl

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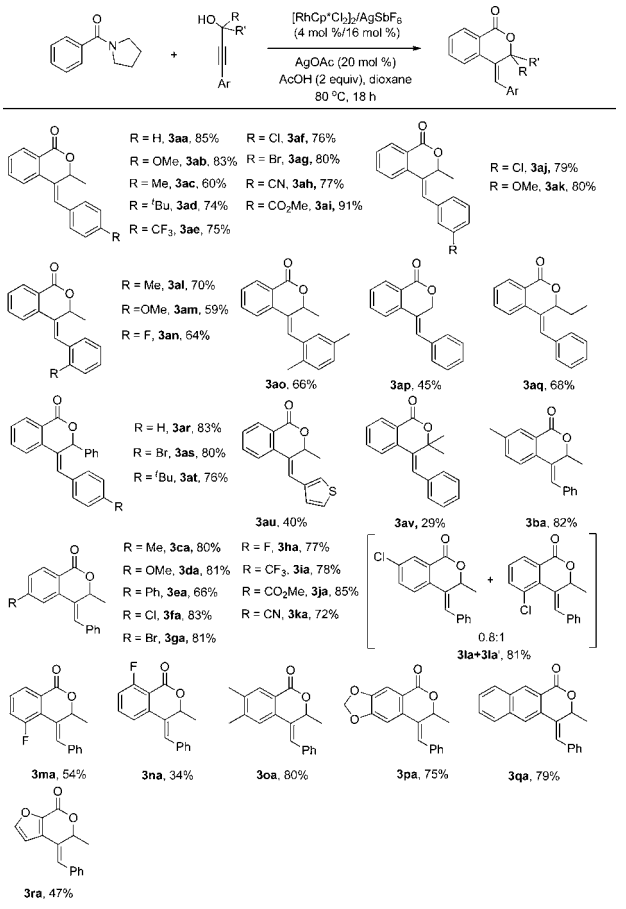
Scheme 2. Substrate Scope[a,b]

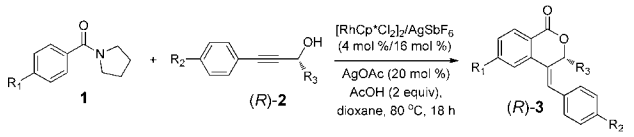


[a] Reactions conditions: **1a** (0.45 mmol), **2** (0.3 mmol), $[RhCp^*Cl_2]_2$ (0.012 mmol), $AgSbF_6$ (0.048 mmol), AgOAc (0.06 mmol), AcOH (0.6 mmol), 1,4-dioxane (3 mL), 80 °C, 18 h, under Ar. [b] Isolated yield after column chromatography.

ring, albeit with lower activity (**3au**). Furthermore, the secondary alcohol motif is compatible with ethyl (**3aq**) and phenyl (**3ar**, **3as**, **3at**) substituents with essentially no loss of reactivity. Primary (**3ap**) and tertiary (**3av**) alcohols also underwent coupling, albeit in a lower yield. In all cases, no isomerization to any isocoumarin has been observed. In contrast to the high reactivity of propargyl alcohols bearing an aryl terminus, methyl- and trimethylsilyl-terminated ones failed to give any desired product, consistent with previous reports on the poor reactivity of dialkyl-substituted alkynes in hydroarylation reactions via C−H activation.[14,15]

The scope of the 1-benzoylpyrrolidine substrate was next explored in the coupling with **2a**. Electron-withdrawing and -donating groups and halogen groups at the *para* position of the 1-benzoylpyrrolidine is fully tolerated (72−85% yield). Interestingly, the regioselectivity of *meta*-substituted 1-benzoylpyrrolidines varies with the *meta* substituent. For relatively bulky *meta* groups, the C−H functionalization occurs at the less hindered *ortho* position (**3ba**, **3oa**, **3pa**, and **3qa**). In stark contrast, the coupling of *meta*-F substituted 1-benzoylpyrrolidine occurs exclusively at the more hindered *ortho* position (**3ma**) because the coordination effect of the fluoro group dominates its steric hindrance.[18] The fluorine may also act as an effective electron-withdrawing group to increase the *ortho* selectivity. Interestingly, a mixture of two isomeric products was isolated for *meta*-Cl functionalized 1-benzoylpyrrolidine (**3la** and **3la′**). This coupling reaction seems sensitive to the steric hindrance of the *ortho* substituent. Thus poor conversion was achieved for *o*-Me substituted 1-benzoylpyrrolidine, while replacing the *o*-Me with an *o*-F afforded **3na** in 34% yield. In addition to benzamide substrates, the coupling of a furanamide afforded **3ra** in moderate yield.

Table 2. Synthesis of Enantioenriched Products[a]



entry	R_1	R_2	R_3	product	yield[b] (%)	ee (%)
1	H	H	Me	(*R*)-**3aa**	86	97.3
2	Me	H	Me	(*R*)-**3ca**	83	94.1
3	Br	H	Me	(*R*)-**3ga**	78	96.0
4	H	OMe	Me	(*R*)-**3ab**	85	95.7
5	H	CO_2Me	Me	(*R*)-**3al**	92	94.2
6	H	H	Ph	(*R*)-**3ar**	80	95.9
7	H	Br	Ph	(*R*)-**3as**	77	97.7
8	H	^{t}Bu	Ph	(*R*)-**3at**	75	95.7

[a] Reactions conditions: **1a** (0.45 mmol), (*R*)-**2** (0.3 mmol), $[RhCp^*Cl_2]_2$ (0.012 mmol), $AgSbF_6$ (0.048 mmol), AgOAc (0.06 mmol), AcOH (0.6 mmol), 1,4-dioxane (3 mL), 80 °C, 18 h, under Ar. [b] Isolated yield after column chromatography.

Synthesis of enantioenriched lactones was performed next (Table 2). Coupling (*R*)-**2a** (99% *ee*) with **1a** afforded (*R*)-**3aa** with high enantiopurity. This indicates that the C−O bond remains intact. Consistently high enantiopurities were obtained when other optically pure propargyl alcohols or 1-benzoylpyrrolidines were coupled.

The synthetic applications of the lactone have been demonstrated in several derivatization reactions. $LiAlH_4$ reduction of (±)-**3aa** afforded diol **4** in high yield (Scheme 3). To take advantage of the ester directing group, Rh-catalyzed oxidative olefination at the *ortho* position has been carried out to give **5** in 69% yield.

Several experiments have been performed to probe the reaction mechanism (Scheme 4). H/D exchange studies have been performed for **1a** in the presence of acetic acid-d_4 (8 equiv) but in the absence of any propargyl alcohol. ^{1}H NMR revealed significant H/D exchange (75% D) at the *ortho* positions of **1a**, indicative of the reversibility of the

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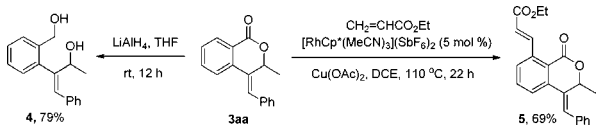
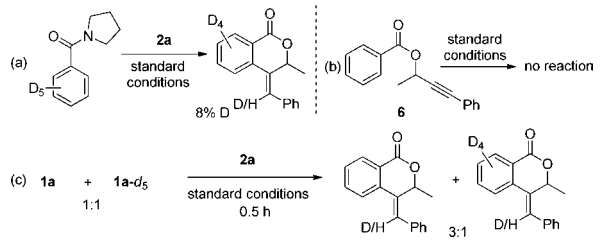
Scheme 3. Derivatization of a Lactone Product



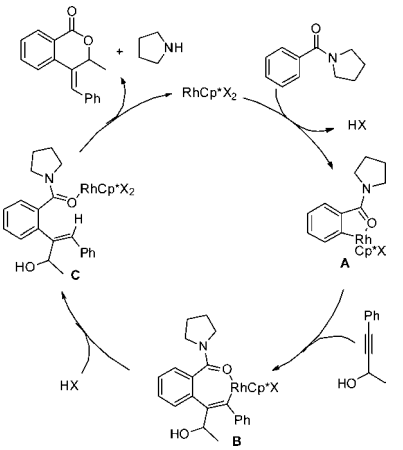
Scheme 4. Mechanistic Studies



C−H activation in the absence of a propargyl alcohol. When **1a**-d_5 was coupled with **2a** under the standard conditions, **3aa**-*d* was isolated without any H/D scrambling in the arene backbone but with deuterium incorporation at the vinylic position (8% D). These results indicate the irreversibility of C−H activation when the alkyne is present. Competitive coupling between **1a** and **1a**-d_5 gave an intermolecular value of $k_H/k_D = 3.0$, suggesting that C−H cleavage is involved in the rate-limiting step. To probe the sequence of C−H insertion vs esterification, ester **6** has been prepared, and no reaction occurred when it was subjected to the standard conditions, indicating that it is not a real intermediate. Therefore the hydroarylation should occur prior to the esterification. We noted that allene could be a possible intermediate as was generated in Meyer−Schuster rearrangement.[19] However, our stereochemical data (essentially the same enantiopurity was transferred from (*R*)-**2a** to (*R*)-**3aa**) seem to suggest that no allene species was involved. To gain further mechanistic insight, a competitive reaction has been performed using an equimolar amount of **1g** and **1d**, where the corresponding products **3ga** and **3da** were obtained in a 1:3 ratio (^{1}H NMR) (see SI). This result suggests that coordination of the amide oxygen plays an important role since an electron-donating *para* group tends to facilitate this coupling.

A plausible mechanism is given in Scheme 5 on the basis of our experimental data and literature precedents.

Scheme 5. Proposed Reaction Mechanism



Cyclorhodation of 1-benzoylpyrrolidine (**1a**) affords intermediate **A**. Subsequent regioselective insertion of the propargyl alcohol gives a seven-membered rhodacycle **B**. Protonolysis gives an alkenylation intermediate **C**, and this proposed protonolysis agrees with the observed H/D exchange at the vinylic position of when **1a**-d_5 was used. Metal (Rh or Ag) catalyzed lactonization furnished the final product with the release of a pyrrolidine (detected by GC).

In summary, we have developed Rh(II)-catalyzed C−H functionalization of 1-benzoylpyrrolidine with propargyl alcohols. The electrophilic amide functionality acts as an *in situ* functionalizable directing group. A broad scope of substrates have been defined. The stereochemisty of the propargyl alcohol is retained; highly enantio-enriched lactones can be obtained. This coupling system extended the scope and applicability of Rh-catalyzed C−H activation/coupling reactions of arenes and may find applications in the synthesis of complex structures.

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Supporting Information Available. Standard experimental procedure and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.