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Rhodium(III)-Catalysed C-H Activation/Annulation with Vinyl Esters as an Acetylene Equivalent

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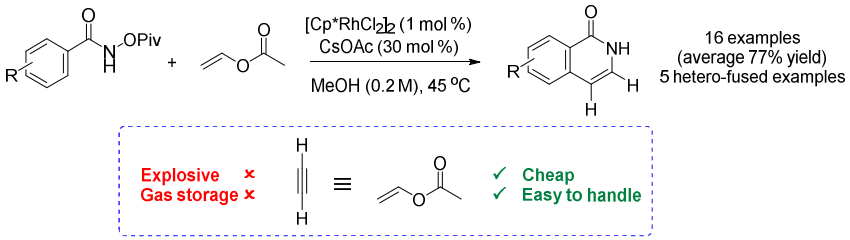
Supporting Information Placeholder



The behavior of electron-rich alkenes in rhodium-catalysed C-H activation/annulation reactions is investigated. Vinyl acetate emerges as a convenient acetylene equivalent, facilitating the synthesis of fifteen 3,4-unsubstituted isoquinolones, as well as select heteroaryl-fused pyridones. The complementary regiochemical preferences of enol ethers versus enol esters/enamides is discussed.

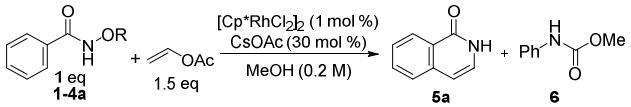
Isoquinolin-1(2*H*)ones are of significant interest, due to their prevalence in alkaloidal natural products and synthetic therapeutic agents.[1] Most routes for the assembly of the heterocyclic skeleton require *ortho*-difunctionalised benzene starting materials from which the heterocyclic ring is elaborated.[2] A more general and efficient approach would involve annulation of the heterocyclic ring to a *mono*functionalised arene starting material. Examples of such approaches include intramolecular Friedel-Crafts reactions of benzamidoalkyl acetals,[3] thermal rearrangement (>250 °C) of cinnamoyl azides,[4] or multi-step approaches involving reaction of *ortho*-lithiated benzamide derivatives with α-dicarbonyl compounds.[5]

Recent advances in C-H activation/annulation reactions[6] facilitate the construction of a variety of benzo-fused heterocycles by insertion of alkenes or alkynes into cyclometallated intermediates generated from educts such as benzamides,[7,8] aryl imines,[9] and anilides.[10] Specifically relevant to the current study, annulation of benzamides with alkynes under rhodium catalysis in the presence of an external oxidant (usually two equivalents of a copper(II) salt) generates isoquinolinones.[7] This approach is characterised by the relatively harsh conditions required for C-H activation and the generation of large quantities of metal waste, and has been superceded by the introduction of benzoyl hydroxamic acids and derivatives as substrates by Fagnou and Glorius.[8] Here, the hydroxamate function acts both as a superior directing group for C-H activation (facilitating milder reaction conditions and the use of less-reactive alkene substrates) and an 'internal' oxidant, whereby cleavage of the N-O bond replaces the use of external co-oxidants in maintaining the active rhodium(III) oxidation state.

To date, the alkynes and alkenes used to intercept the arylmetal species in the aforementioned reactions have been either electronically neutral or electron-deficient. The only exception to this is a single example of the annulation of an enol ether (dihydrofuran) to *N*-(pivaloyloxy)benzamide under rhodium(III) catalysis.[8b] We were inspired to investigate the behaviour of electron-rich vinyl esters, enol ethers and enamides more generally, since (depending on the regiochemical preferences of the annulation reactions) these simple starting materials could be employed as new enolate or acyl anion equivalents in C-H activation chemistry. We describe the outcomes of this work below, in which vinyl acetate, a cheap bulk chemical, behaves as an acetylene equivalent to facilitate the synthesis of a range of 3,4-unsubstituted isoquinolin-1(2*H*)ones and related heterocycle-fused pyridones.

We first examined the behavior of vinyl acetate with a range of benzoyl hydroxamate derivatives **1**-**4a**, based on the reaction conditions adopted by Fagnou and Glorius.[8b-c] As shown in Table 1, the reaction of benzohydroxamic acid **1** produced isoquinolone **5a** in 26% yield, but the reaction of *N*-methoxybenzamide **2** failed to produce any of the expected product. Both *N*-(acetoxy)- and *N*-(pivaloyloxy)benzamide (**3** and **4a**) reacted to give isoquinolone **5a** with encouraging yields of 79% and 69% respectively (entries 3 and 4, Table 1). We suspected therefore that in the reaction in entry 1, substrate **1** was being acylated by vinyl acetate, generating the more reactive substrate **3** *in situ*. A subsequent ^{1}H NMR study confirmed the formation of *N*-(acetoxy)benzamide **3** in the reaction mixture prior to the appearance of the isoquinolone **5**.

Table 1. Isoquinolone formation by annulation with vinyl acetate.[a]



entry	reactant	R	temp °C	isolated yield %	conversion ^{1}H NMR
				5a	**6 %**
1	**1**	H	60	26	17
2	**2**	Me	60	0	0
3	**3**	Ac	60	79	15
4	**4a**	Piv	60	69	11
5	**4a**	Piv	25	87[b]	0
6	**4a**	Piv	45	87	0
7[c]	**4a**	Piv	45	86[c]	0

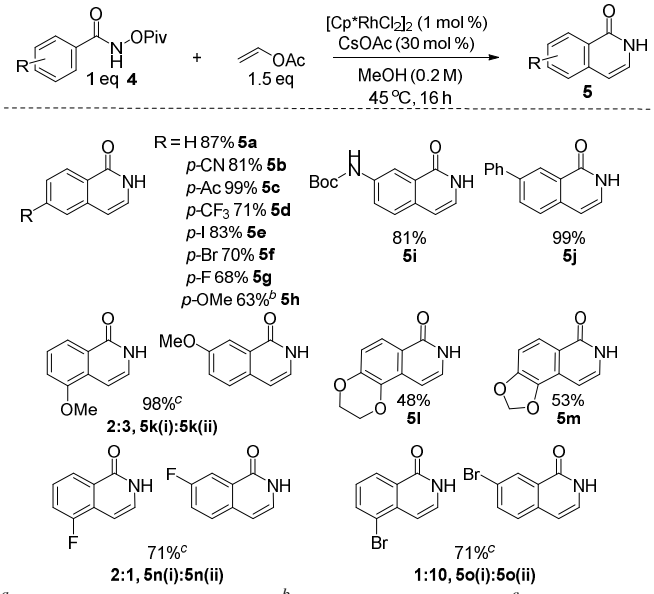
[a]See Supporting Information. [b]72 h. [c]Using vinyl laurate in place of vinyl acetate.

We focused on pivaloyl hydroxamate **4a** for further optimization. A significant by-product observed in entries 1, 3 and 4 was methyl phenyl carbamate **6**, arising from Lossen rearrangement of the *N*-benzoyl hydroxamates and trapping of the resulting isocyanate by methanol. Control experiments showed this reaction only occurred in the presence of $[Cp^*RhCl_2]_2$, suggesting the rearrangement of an *N*-metallated hydroxamic acid intermediate.[11] The Lossen rearrangement was substantially retarded at lower temperatures, and carrying out the annulation at r.t. over 72 hours or, more usefully, at 45 °C for 16 hours, gave in each case an 87% yield of isoquinolone **5** with no traces of **6** visible in the crude NMR (entries 5, 6). Less volatile esters such as vinyl laurate may be substituted for vinyl acetate (entry 7), but substitution on the vinyl group was less well tolerated (see Supporting Information).

The product isoquinolone **5a** presumably arises by elimination of acetic acid from a dihydroisoquinolone intermediate, and is the synthetic equivalent of a direct hydroxamate/alkyne annulation reaction using acetylene as the alkyne. To our knowledge, the use of gaseous alkynes in C-H activation/annulation reactions has not been investigated. Given the hazards and operational difficulties associated with such a process, the availability of a cheap and convenient synthetic equivalent such as vinyl acetate would be of significant utility.[12] Importantly, the potential value of our process is underscored by the wide occurrence of 3,4-unsubstituted isoquinolones in biologically active materials.[1] We therefore sought to establish the scope of the reaction utilising a broad range of substrates, the results of which are summarised in Scheme 1.

Under the optimized conditions, hydroxamic esters **4b-d**, bearing electron-withdrawing groups reacted to give the corresponding isoquinolones in excellent yields ranging from 71-99% (**5b-d**). Halogens were well tolerated, with 6-iodo-, bromo- and fluoroisoquinolones **5e-5g** being formed in reasonable to good yields (68-83%). Interestingly, introduction of an electron-rich *para*-methoxy group resulted in a low yield of **5h** (31%) and significant quantities of the carbamate arising from Lossen rearrangement were seen. Carrying out the reaction at lower temperature/higher concentration returned a 63% yield.

Scheme 1. Substrate scope of the C-H activation/-annulation with vinyl acetate.[a, b]



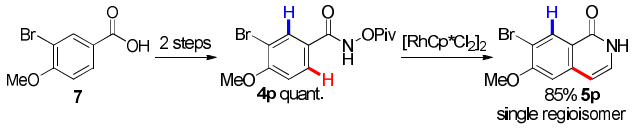
[a]See Supporting Information. [b] MeOH (0.4 M), 30 °C. [c]The regioisomeric ratio was determined by ^{1}H NMR analysis.

In order to investigate regiochemical effects in non-symmetrically-substituted substrates, compounds **4i-4o** were prepared. As expected, in the reactions of substrates **4i** and **4j**, C-H activation occurred at the less-hindered position *para*- rather than *meta*- to the phenyl/*N*-Boc substituent, giving **5i** and **5j** as single regioisomers. However, the *meta*-methoxy derivative **4k** gave a 98% yield of a 2:3 mixture of regioisomers **5k(i)**:**5k(ii)**, while the protocatechuic acid derivatives **4l** and **4m** furnished exclusively the contiguously-substituted regioisomers **5l** and **5m**; the higher selectivity presumably reflects the reduced steric demands of these cyclic ethers/acetals. The reaction of *meta*-fluorinated substrate **4n** produced an inseparable mixture of regioisomers favouring the contiguously substituted product (71%, **5n(i):5n(ii)**, 2:1). The *ortho*-directing effect of strongly electronegative substituents on rhodium-mediated C-H activation has been noted previously[13] and in this case is almost certainly a kinetic preference given the likely irreversibility of the C-H insertion step under these conditions.[8b] Consistent with the requirement for a strongly electronegative substituent to exert this effect, substituting the fluorine for a bromine atom gave predominantly the 7-bromoisoquinolone by reaction at the less-hindered site.

The utility of the approach was further demonstrated in the synthesis of isoquinolone **5p**, an intermediate in the synthesis of the hepatitis C protease inhibitor MK-1220.[14] The four-step discovery chemistry route to **5p** involves a high temperature (250 °C) rearrangement of a cinnamoyl azide, and proceeds in

overall 35% yield. The optimized process route delivers the material in overall 55% yield but requires five steps. By application of our standard conditions, commercially-available acid **7** was converted to the desired isoquinolone in an optimised 85% yield as a single regioisomer in just three steps (Scheme 2). Overall, the annulation reaction was successful across 16 substrates with an average yield of 77%.

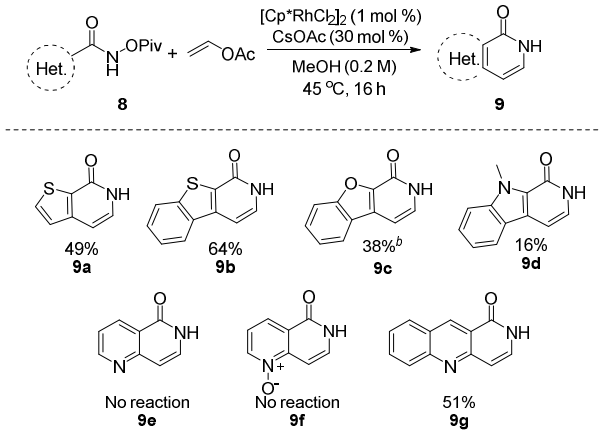
Scheme 2. Synthesis of intermediate for MK-1220.[14]



[a]See Supporting Information for conditions.

Having established a robust synthetic approach to isoquinolones, we attempted to apply the methodology to heterocyclic systems (Scheme 3). Reactions of (benzo)thiophene derivatives **8a** and **8b** proved successful, albeit in lower yields compared with the benzenoid systems (**9a** 49% and **9b** 64%). Benzofuranyl and *N*-methylindolyl substrates **8c** and **8d** displayed poorer reactivity, the former requiring 48h to reach completion in 38% yield, and the latter giving only 16% of **9d**. A recent study highlighted large rate differences in rhodium-mediated C-H activation reactions of various (hetero)aryl imines, and similar variance appears to apply to substrates **8**.[15]

Scheme 3. Heterocyclic substrate scope.[a]

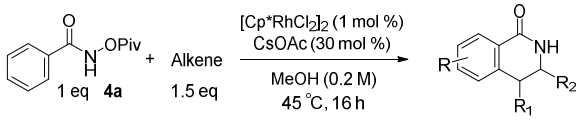


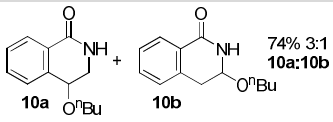
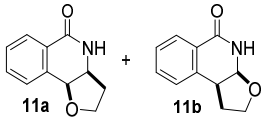
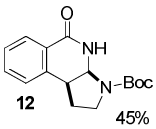
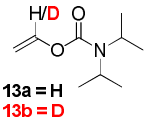
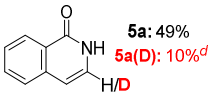
[a]See Supporting Information. [b]Reaction time 48 h.

Nicotinamide derivative **8e** returned only unreacted starting material, as did *N*-oxide **8f** (despite the known enhanced reactivity of such substrates in C-H activation[16]), potentially suggesting detrimental co-ordination of the rhodium. Consistent with this, the quinoline-3-carboxylic acid-derived **8g**, wherein dative coordination would be disfavoured by the C8 hydrogen, gave benzo[*b*][1,6]naphthyridin-1(2*H*)-one **9g** in 51% yield.

We were interested to probe the regiochemistry of the annulation reactions. Since we had been unable to observe any intermediates *en route* to the isoquinolones, we studied the reactions of vinyl ethers, in the hope that aromatizing elimination might be slowed. Indeed, reaction of butyl vinyl ether led to a 3:1 mixture of dihydroisoquinolones **10a** and **10b** (Table 2, entry 1; regiochemistry confirmed by NOESY studies).

Table 2. Alkene substrate scope.[a]



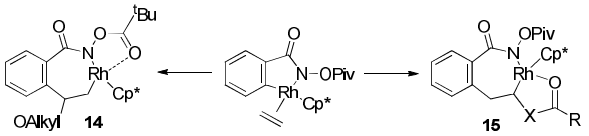
entry	alkene	products
1[b]		 74% 3:1 **10a:10b**
2		 **Isolated:** 79%[c] >20:1, **11a:11b** Reported: 77%[c] >20:1, **11b:11a**
3		 45%
4		 **5a:** 49% **5a(D):** 10%[d]

[a]See Supporting Information. [b] Reaction at 30 °C with 5 equivalents of alkene. [c] Conditions as described by Fagnou *et al.*[8b] [d] NMR yield using internal standard (mesitylene).

The predominant formation of benzylic ether **10a** rather than aminoacetal **10b** was surprising in view of Fagnou's report that dihydrofuran gave the aminoacetal **11b** as the sole product.[8b] We therefore repeated Fagnou's reaction, attaining a near identical yield of the reported single regioisomer, but whose identity was shown by NOESY and X-ray crystallographic studies (see Supporting Information) to be benzylic ether **11a**. Thus, after structural reassignment of Fagnou's result, the regiochemical behaviour of enol ethers is such as to consistently favour the benzylic ether products. However, the reaction of *N*-Boc-dihydropyrrole gave hemiaminal **12** as a single regioisomer, whose structure was also confirmed crystallographically (see Supporting Information). This suggests the regiochemistry is not solely governed by electronic factors. While reaction of selectively isotopically-labelled vinyl ace-

tate would allow unambiguous assignment of the regiochemical outcome, such compounds are not known in the literature and despite extensive efforts we were unable to identify a suitable synthetic route. However, we prepared *O*-vinyl-*N,N*'-diisopropyl carbamate **13a** which, although less reactive than vinyl acetate, did produce isoquinolone **5a** in 49% yield. The selectively monodeuterated variant **13b** (prepared by directed lithiation of **13a** and deuterium quenching; 87% D-incorporation), gave a reproducibly poor yield of **5a** but we were able to confirm spectroscopically incorporation of deuterium almost exclusively at the C3-position (85% D-incorporation; >97% regioselectivity). This suggests two competing factors govern the regiochemistry of reaction with electron-rich alkenes (Figure 1): electronic factors favour formation of intermediate **14** by migration of rhodium to the more electron-rich carbon of enol ethers. However, where coordinating groups are present on the heteroatom, the regiochemistry is reversed, possibly by formation of a competing co-ordinatively saturated complex **15**.[17]

Figure 1. Regiochemical preferences in alkene insertion.



In summary, a facile method for the preparation of 3,4-unsubstitued isoquinolones by rhodium-catalysed C-H activation/annulation has been established, using vinyl acetate as a cheap and safe alternative to acetylene. The reaction is highly efficient and tolerant of a broad range of aromatic substituents. The regiochemical preferences of arylrhodium complexes for insertion to electron-rich alkenes has been probed for the first time. The synthetic utility of vinylic esters as acetylene equivalents will have broader applicability in C-H activation chemistry and further studies will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data and crystallographic information for all compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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