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Ruthenium-Catalyzed Cycloaddition of 1-Haloalkynes with Nitrile Oxides and Organic Azides; Synthesis of 4-Halo Isoxazoles and 5-Halo Triazoles

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Abstract

(Cyclopentadienyl)(cyclooctadiene) ruthenium(II) chloride [CpRuCl(cod)] catalyzes the reaction between nitrile oxides and electronically deficient 1-chloro-, 1-bromo- and 1-iodoalkynes leading to 4-haloisoxazoles. Organic azides are also suitable 1,3-dipoles, resulting in 5-halo-1,2,3-triazoles. These air tolerant reactions can be performed at room temperature with 1.25 equiv of the respective 1,3-dipole relative to the alkyne component. Reactive 1-haloalkynes include propiolic amides, esters, ketones and phosphonates. Post-functionalization of the halogenated azole products can be accomplished using palladium-catalyzed cross-coupling reactions as well as via manipulation of reactive amide groups. The lack of catalysis observed with Cp^{*}RuCl(cod) is attributed to steric demands of the Cp^{*} (η^5 -C₅Me₅) ligand in comparison to the parent Cp (η^5 -C₅H₅). This hypothesis is supported by the poor reactivity of (η^5 -C₅Me₄CF₃)RuCl(cod), which serves as an isosteric mimic of Cp^{*} and as an isoelectronic analog of Cp.

Keywords

Cycloaddition; Halides; Ruthenium; Alkynes; Regioselectivity

Introduction

Pentamethylcyclopentadienyl ruthenium(II) chloride, [Cp^{*}RuCl], based catalysts were introduced in 2005 as an effective and easy means for regioselective preparation of 1,5-disubstituted 1,2,3-triazoles^[1] as well as 3,4-disubstituted isoxazoles^[2] from terminal alkynes and organic azides (RuAAC; ruthenium catalyzed azide alkyne cycloaddition) or nitrile oxides, respectively. RuAAC had an immediate impact on organic chemistry and related fields,^[3] in that the substitution pattern of the resulting product was, and is a perfect complement to triazoles obtained by way of the well-known copper catalyzed (CuAAC), ‘click’ reaction,^[4] i.e. a 1,4-disubstituted 1,2,3-triazole. Although RuAAC has not yet become as robust as CuAAC, its ability to engage internal alkynes in cycloadditions is a

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distinct advantage,^[5] thus providing direct access to fully substituted triazoles and isoxazoles, often with high regioselectivity. The work herein details the development of a related ruthenium(II) methodology involving the activation of halogenated alkynes towards both nitrile oxides and organic azides using cyclopentadiene ruthenium(II) chloride [CpRuCl] based catalysts.

1,2,3-Triazoles and isoxazoles are important and synthetically useful aromatic heterocycles. Triazoles are thermodynamically and chemically stable molecules that are inert towards a wide range of conditions.^[6] The success of click cycloadditions is, in result of these properties, as the triazole ring is most often utilized as a reliable covalent connector.^[7] The compatibility of the azide and alkyne reactants with a wide range of conditions, the availability of methods for the ready introduction of these handles into a variety of structures, and their low reactivity with each other in the absence of a catalyst, make catalytic cycloadditions practical and easily adaptable to a variety of demands. As an exception to their well-known durability, we and others have reported that certain electron-deficient triazoles can serve as stable progenitors of reactive azavinyl carbenes (via the formal scission of the N1-N2 bond and the elimination of a molecule of dinitrogen).^[8] Thus, some triazoles themselves can serve as synthetic precursors for a variety of organic and heterocyclic molecules. In contrast to 1,2,3-triazoles, which are not found in natural products, isoxazoles of biogenic origin are known (for example, ibotenic acid and muscimol), and some have been used in pharmaceuticals, such as a COX-2 inhibitor Valdecoxib and an antibacterial penicillin analog Cloxacillin.^[9] The nitrogen-oxygen bond in the isoxazole ring is relatively weak and, similarly to electron deficient triazoles, its scission via hydrogenation^[10] or other metal-mediated reactions,^[11] reveals the isoxazole ring as a latent 1,3-dicarbonyl compound.^[12] Therefore, unsurprisingly, isoxazoles and their subsequent transformations, have served as important steps in the synthesis of complex molecules.^[13] Although several methods for the synthesis of isoxazoles are available, the 1,3-dipolar cycloaddition of corresponding nitrile oxides and alkynes is particularly attractive due to the direct formation of the C3-C4 carbon-carbon bond.^[14]

Having developed a direct copper-catalyzed route for the synthesis of 5-iodo-1,2,3-triazoles from 1-iodoalkynes,^[15] we were naturally curious about a similar ruthenium-mediated process, which could perhaps also engage 1-chloro and 1-bromoalkynes in cycloaddition reactions. The direct regiospecific generation of halo-azoles would be an important advantage of this method, as these compounds are known pharmacophores,^[16] as well as useful synthetic intermediates from which a variety of derivatives can be obtained by manipulation of the carbon-halogen bond.^[17] In addition to the above-mentioned copper-

catalyzed methods, which encompass 1-bromo and 1-iodoalkynes,^[15,18] halotriazoles can be accessed by trapping reactive triazolyl intermediates, including 5-triazolyl-copper,^[19] 5-aluminum,^[20] 5-bismuth,^[21] etc. or 4-triazolyl magnesium bromide^[22] analogs with electrophilic halide reagents. Alternatively, nucleophilic displacement of diazo,^[23] silyl,^[24] or stannyl^[25] groups directly attached to the triazole ring by a halide anion can be used in the synthesis of halotriazoles.

Although the direct halogenation of the isoxazole ring was reported by Claisen over a century ago,^[26] the reaction conditions are harsh and require the use of strong acids at elevated temperature. Some of these limitation have been addressed using electrophilic cyclization of 2-alkyn-1-one *O*-methyl oximes, which provides 4-substituted isoxazoles containing halides and selenium functional groups.^[27] The 1,3-dipolar cycloaddition between terminal alkynes and bromonitrile oxides is a means to provide 3-haloisoxazoles in good yield with high regioselectivity.^[28] However, examples of high yielding reactions involving 1-haloalkynes and nitrile oxides remain remarkably scarce.^[29] For example, thermal cycloadditions of nitrile oxides and 1-haloalkynes often either require alkynes substituted with highly activated hypervalent iodine species^[30] or a large excess of one of the reactants^[29c] and/or controlled addition of the nitrile oxide component.^[29b] Despite these precautions, these reactions still often result in mixtures of regioisomers with low to moderate yields.^[16a, 31]

To begin, we examined the room temperature reaction of (1-chloroethynyl)benzene and nitrile oxide precursor, 4-chloro-*N*-hydroxybenzimidoyl chloride (**2**). This reaction was predictably poor in the absence of a catalyst, resulting in low yields (<15%) of the desired chloroisoxazole. Disappointingly, Cp^{*}RuCl(cod), an efficient RuAAC catalyst, proved completely ineffective. However, replacement of the pentamethylcyclopentadienyl ligand (Cp^{*}) with the cyclopentadienyl ligand (Cp) resulted in a moderate improvement of both yield and regioselectivity. However, formation of furoxan, a consequence of nitrile oxide dimerization, remained an undesired side reaction.^[32] In stark contrast, electron-deficient halogenated alkynes as illustrated by 1-bromo-dimethylpropiolamide (**1**), readily participated in CpRuCl(cod) mediated catalysis. Details of their reactivity with organic nitrile oxides and azides are described below.

Results and Discussion

The reaction of bromoalkyne **1** and nitrile oxide (1.25 equiv) obtained from hydroximoyl chloride **2** in the presence of Hünig's base at ambient temperature produced a regioisomeric mixture of bromoisoxazoles favoring the 5-halogenated isomer by ca. 4:1 (**3b**:**3a**) with a combined isolated yield of ca. 35% (Scheme 1A). The addition of a catalytic amount of CpRuCl(cod) transformed this reaction into a completely regiospecific process that furnished the 4-bromoisoxazole product **3a** in good yield.^[33] A slight excess of hydroximoyl chloride was optimal, and CpRuCl(cod) catalyst loading could be reduced to as little as 3 mol%. Further optimization revealed that this reaction was air tolerant, and 1,4-dioxane, dichloroethane, dichloromethane and tetrahydrofuran (at 0.1–0.4 M concentration of the reactants) were identified as preferred reaction solvents. Ambient reaction temperature was optimal as dimerization of nitrile oxide noticeably increased at elevated temperature.

Hünig's base (diisopropylethylamine) was more effective than triethylamine, primarily due to the tendency of triethylamine to cross-react with the alkyne component via Michael addition.^[34] Experimentally, a typical reaction protocol dictates the addition of CpRuCl(cod) followed within seconds by the addition of Hünig's base.

The scope of this catalytic process with respect to both reactants is demonstrated in Figure 1. Propiolic amides and esters were prepared from propiolic acid through standard carbodiimide coupling protocols. Ynones were obtained through oxidation of propargyl alcohols with either 2-iodoxybenzoic acid (IBX) or manganese dioxide. Conversion to 1-iodo- and 1-bromoalkynes was facile and effected by a combination of catalytic silver nitrate and iodo- or bromosuccinimide, respectively.^[35] Finally, carbon tetrachloride in the presence of catalytic tetrabutylammonium fluoride yielded the corresponding 1-chloroalkynes.^[36] Overall, 1-haloalkynes employed in this study were easily prepared, bench stable, and easy to handle.

Aliphatic, aromatic and heteroaromatic nitrile oxides reacted readily with chloro-, bromo-, and iodoalkynes. Suitable alkynyl electron withdrawing groups included amides (cf. **9–11**, **16**, **19**), esters (cf. **6**, **20**), ketones (cf. **8**, **14–15**) and phosphonate (**12**). While alcohol **7** and tertiary amine **30** were tolerated, secondary and primary amines require the use of protecting groups, such as *t*-butyl carbamates (Boc; **26**, **27**). The lack of cross-reactivity of nitrile oxides with olefins was noteworthy: no isoxazoline byproducts were observed in the reactions of nitrile oxides (**13**, **17**).

The yield of 4-haloisoxazoles in the absence of the ruthenium catalyst remained consistently low when aryl nitrile oxides bearing electronically neutral or withdrawing *para*- and *ortho*-substituents were used. However, aryl nitrile oxides bearing electron donating groups were substantially more reactive and furnished 5-haloisoxazoles ("b" isomer ca. 4:1 ratio **b:a**) in good yields (a substrate scope was performed, see supporting information Table SI-2 for further details). In the case of these electron-rich nitrile oxides, increased catalyst loading, up to 10 mol%, was often necessary to ensure high regioselectivity in favor of 4-haloisoxazoles. For example, in the presence of 3 mol% catalyst, 4-bromoisoxazole **25** was isolated in a combined yield of 63% with a disappointing **a:b** ratio of 85:15. In contrast, increasing the catalyst loading (6 mol%) restored the **a:b** ratio to greater than 20:1.

In the presence of the same catalyst, organic azides reacted with 1-haloalkynes to provide 1,4-disubstituted 5-halogenated 1,2,3-triazoles (**5c**, Scheme 1B).^[37] Again, Cp*RuCl(cod) proved ineffective for this transformation. Acetonitrile, dimethylformamide and ethanol performed well as reaction solvents at 0.1–0.3 M concentration of the reactants. The reaction between **1** and phenethyl azide (**4**) was air tolerant, required as little as 3 mol% catalyst loading and proceeded to full conversion at room temperature in ~15 min. In contrast to the reaction of nitrile oxides, the rate of the thermal, uncatalyzed cycloaddition was negligible at ambient temperature, requiring prolonged heating at 95 °C for a period of 6 days to achieve full conversion. The regioselectivity of the thermal reaction eroded dramatically, to ca. 3:2 (**5c:5d**), compared to the catalytic process.

Acetonitrile outperformed other solvents in reactions with substrates other than **1**. Although dimethylformamide and ethanol were effective in the reactions of tertiary amides, halogenated primary (**34**, Figure 2) and secondary (**35**, **36**) propargylic amides, propargylic ester (**33**) as well as ynones (**32**, **43**) gave products in low yields. Furthermore, even with acetonitrile as a solvent, reactions of primary and secondary 1-halopropiolamides were particularly sluggish and required twice the catalyst loading as was needed for tertiary propargylic amide substrates. Gentle heating (to ca. 50 °C) proved beneficial for reducing the reaction time to several hours for these substrates. As for the azide component, primary alkyl azides reacted well at room temperature, while secondary azides benefited from gentle heating. Aryl azides, on the other hand, gave little to no product, mirroring previously reported reactivity of aryl azides under ruthenium catalysis.^[1c] Moving down the group, (Cl, Br, I), the overall isolated yield tended to decrease, a trend compounded and most noticeable with the use of secondary azides (cf. **45–47**). Overall the azide cycloaddition with 1-haloalkynes displayed similar functional group tolerance to its nitrile oxide counterpart.

Finally, the reaction of 1-haloalkynes with azides was also performed on a functionalized polystyrene substrate bearing CpRuCl(cod) at 55 °C for 12 h. An excess of haloalkyne **1** (4 equiv) was used in order to ensure complete conversion; the remaining starting material was subsequently removed during polymer precipitation from methanol. Conversion was confirmed by the disappearance of the azide IR stretch and the emergence of the amide carbonyl IR signal. Further, the dimethyl group provided distinguishable ¹H NMR signals and served as an additional identifying feature of the product.

To expand the synthetic utility of the halogenated azoles obtained under ruthenium catalysis, we examined selective transformations of the amide and halide functionalities. Palladium-catalyzed cross coupling reactions were briefly evaluated on both the iodo- and bromotriazoles (**38** and **5c**, Scheme 2) and bromoisoxazoles (**21** and **25**). Several examples involving halogenated triazoles are known,^[38] and following brief reaction pendant azide handles (**49**). The reaction was run with 10 mol% condition screening, we were likewise successful in replacing the halogen with ethynyl **51**, allyl **52**, acrylate **53** and aryl **54** groups. The 5-iodotriazole was more reactive compared to its brominated analog, which required increased reaction temperature and extended reaction time. Similarly, bromoisoxazole **21** was converted to the butyl acrylate **55** and allyl **56** derivatives, albeit in modest yield, using slightly modified published protocols.^[27a, 29b, 29c, 39]

Additionally, Weinreb amide^[40] derivatives **24–25** and **40–41**, were readily amenable for additional transformations (Scheme 3). Hydrolysis with lithium hydroxide was facile for chloro and bromo isoxazole (**61**, **62**) and triazole (**57**, **58**) derivatives. Nucleophilic acyl substitution with ethyl magnesium bromide furnished the corresponding ketone in good yield for the chlorinated derivatives (**24** → **63** and **40** → **59**). The brominated analogs underwent magnesium halogen exchange and thus tended to give the dehalogenated azoles upon workup. Similarly, reduction with lithium aluminium hydride yielded the aldehyde only with chlorotriazole **40**. The bromotriazole, as well as the chloro- and bromoisoxazoles gave complex reaction mixtures regardless of the hydride source (lithium aluminium hydride, diisobutylaluminum hydride, and Schwartz's reagent). In contrast, the 4,5-

disubstituted isoxazole **64**, obtained from brominated isoxazole **25**, readily underwent LAH reduction to yield aldehyde **65**.

For the cycloaddition of azides, the negligible rate of the background reaction, together with the stability of the substrates under the reaction conditions, allowed for a portion-wise introduction of catalyst (usually in 1 mol% increments) as required to push the reaction to completion. Thus the lowest amount of CpRuCl(cod) could be employed for the synthesis of 5-halotriazoles. In contrast, the much higher overall reactivity of nitrile oxides, their propensity for dimerization, and appreciable background reactivity with 1-haloalkynes makes this approach impractical for the preparation of 4-haloisoxazoles. As Table 1 illustrates, 1 mol% CpRuCl(cod) resulted in only 45% yield of bromoisoxazoles **3a+3b** (cf. entries 2 vs. 3). The eroded regioselectivity was ca. 80:20, in which the presence of **3b** is a direct result of the competing thermal cycloaddition. On the other hand, even though only 33% conversion was obtained with 1 mol% catalyst loading, the ratio of brominated triazole isomers remained high, >20:1 (**5c:5d**), and any unconverted starting material remained intact and available for further transformation.

Another aspect of the reactivity of 1-haloalkynes described in this study is their ability to readily undergo cyclotrimerization. Thus, in the absence of a reactive 1,3-dipolar partner, 1-bromoalkyne **1** underwent facile trimerization catalyzed by CpRuCl(cod) to provide fully substituted tribromobenzene derivatives **66e** and **66f** (Table 2, entry 1). Methyl 3-bromopropiolate (entry 2) and 3-bromo-*p*-tolylpropynone (entry 3) readily participated in similar annulations, giving **67e/f** and **68e/f**, respectively. The unsymmetrical 3,5,6-tribromo isomer was the major product in each case. Indeed, [Cp*RuCl]-based catalysts are well known and widely utilized for [2+2+2] cycloadditions involving 1,5- or 1-6-diyne and triyne based substrates.^[41] Several examples involving halogenated diyne systems have been reported^[42] and, furthermore, cyclotrimerization of ethyl 3-bromopropiolate was observed as an unintended side reaction in at least one other [Cp*RuCl] catalyzed methodology.^[43] The trimerization side reaction observed in this work can precipitously lower the yield of the desired halogenated azole by consuming three alkyne molecules. However, a slight excess of a 1,3-dipole partner was found to decrease the amount of this undesired byproduct. In essence, the 1,3-dipole disrupts this otherwise facile cyclotrimerization process and in doing so offers an important mechanistic insight into the reaction: both alkyne and nitrile oxide (or azide) must simultaneously coordinate to the ruthenium center as a crucial step during the reaction.

The coordination of a haloalkyne and a 1,3-dipole to the catalyst are likely dissociative ligand substitution events, wherein the dissociation of the bystander ligand(s), i.e. cycloocta-1,5-diene (cod) gives formally a 14-electron complex [CpRuCl]. [Cp*RuCl] is currently accepted as the active catalytic fragment involved in RuAAC as well as in the aforementioned cyclotrimerization reactions. By analogy, we propose that [CpRuCl] is the active catalytic species in the reactions described here. The triphenylphosphine complex of [CpRuCl], CpRuCl(PPh₃)₂, is readily commercially available. However, its catalytic activity and regioselectivity were disappointingly low, even at 10 mol% loading (Table 1, entry 5). We attribute this lack of reactivity to the higher affinity of phosphine ligands towards the ruthenium center, as compared to olefinic ligands.^[44] Triphenylphosphine would thus be

more reluctant than cod to undergo dissociation and ligand substitution more reluctantly than cyclooctadiene, hindering entry into the productive catalytic cycle. We observed similar trends in the RuAAC system, in which $\text{Cp}^*\text{RuCl}(\text{PPh}_3)_2$ -catalyzed cycloadditions required heating to at least 50 °C whereas the corresponding $\text{Cp}^*\text{RuCl}(\text{cod})$ -catalyzed process proceeds very efficiently at ambient temperature. For the reactions at hand, increasing the reaction temperature significantly improved regioselectivity (entry 6), however product yields remained low.

Examination of different halides as spectator ligands (bromide, entry 8 and iodide entry 9) revealed that the effect on regioselectivity was insignificant; the yield of isoxazole decreased in the order of $\text{Cl} > \text{Br} > \text{I}$. A cationic $[\text{CpRu}]^+$ catalyst, devoid of a halide ligand altogether, was introduced in the form of the acetonitrile complex, $\text{CpRu}(\text{MeCN})_3\text{PF}_6$. Surprisingly, the net outcome was nearly identical to the $\text{CpRuCl}(\text{cod})$ -catalyzed reaction (cf. entry 7 vs. 4). To better understand this observation, we sought to probe the reaction in more detail by monitoring its progress over time using reaction heat flow calorimetry. This technique registers heat flow produced by the system under investigation, in Watts per unit of time. This parameter is directly proportional to the rate of the reaction (unless several processes producing heat operate concurrently). Moreover, the area under the resulting heat flow vs. time trace can be correlated to conversion at any given time point, which can be confirmed using independent analytical techniques (i.e. NMR, chromatography).

The drastic differences in the performance of four catalysts are easy to appreciate even from a cursory examination of the traces of the reaction of chloroalkyne **69** and phenethyl azide **4** shown in Figure 3. For example, the $\text{CpRuCl}(\text{cod})$ (blue trace) is clearly more reactive than its cationic counterpart $\text{CpRu}(\text{MeCN})_3\text{PF}_6$ (red trace): whereas the reaction reached completion in a little over ten minutes using 2 mol% $\text{CpRuCl}(\text{cod})$, the cationic catalyst $\text{CpRu}(\text{MeCN})_3\text{PF}_6$ used at the same concentration resulted in only ca. 60% conversion and took nearly three hours to reach that point. The addition of 1 equiv (with respect to the catalyst) of tetrabutylammonium chloride (TBACl) to the reaction mixture prior to the addition of $\text{CpRu}(\text{MeCN})_3\text{PF}_6$ restored activity of the catalyst (green trace), thus further supporting the notion that the $[\text{CpRuCl}]$ fragment is the active catalytic species. Incidentally, in RuAAC, $[\text{Cp}^*\text{Ru}]^+$ is completely inactive.^[1d] Indeed, these 12-electron cationic $[\text{Cp}'\text{Ru}]^+$ (where $\text{Cp}' = \text{Cp}$ or Cp^*) species are particularly potent electrophiles, capable of interacting with a variety of six electron ligands including arenes, thereby facilitating the formation of mixed sandwich complexes.^[45] The dissociation of the chloride ligand often results in unproductive off-cycle pathways and as evidence, [2+2+2] cycloaddition methodologies employing $\text{Cp}^*\text{Ru}(\text{MeCN})_3\text{PF}_6$ require the addition of exogenous chloride.^[46] However, there is at least one example of a successful cyclotrimerization mediated by $\text{CpRu}(\text{MeCN})_3\text{PF}_6$ without the addition of a chloride salt,^[47] in which the substrate of choice, ethyl propiolate, bears striking similarity to the alkynes used in our studies. As an alternative explanation, 1-haloalkyne reactants can serve as a source of the anionic halide, and would account for the observed reactivity of the $[\text{CpRu}]^+$ fragment. While this proposal cannot be ruled out, we have no evidence to support it at this time.

The essential requirement for the cyclopentadienyl (Cp , $\eta^5\text{-C}_5\text{H}_5$) ligand was clear from the outset of this study, and both pentamethylcyclopentadiene (Cp^* , $\eta^5\text{-C}_5\text{Me}_5$) and indenyl ($\eta^5\text{-$

C₉H₇) complexes were completely ineffective (Table 1, cf. entries 10 and 12). The Cp*RuCl(cod) catalyst is a particularly intriguing case, as meager conversions (Figure 3, black trace) and poor regioselectivity (entry 10) were consistently observed with this complex under a variety of conditions. In comparison to the Cp ligand, the Cp* ligand is notable for increasing the solubility of resulting complexes, enhanced steric demands, and superior electron donating ability.^[48] Ultimately, the properties of the Cp* ligand can have a drastic effect on the chemical reactivity of the resulting transition metal complex. With respect to ruthenium complexes, the effects of Cp vs. Cp* on electronic properties are well documented. Electrochemical studies comparing ruthenocenes Cp'₂Ru (where Cp' = Cp or Cp*), show the Cp analog to be more difficult to oxidize and thus less electronically rich in comparison to the Cp* congener by ca. 0.5V (E^{o'} for Cp₂Ru is 1.03 V vs. 0.48 V for Cp₂*Ru).^[49] Additionally, electron spectroscopy for chemical analysis (ESCA, otherwise known as X-ray photoelectron spectroscopy, XPS) studies on Cp'₂Ru revealed a difference in the binding energies of the ruthenium (Ru(3d_{5/2})) inner shell electron of approximately 0.8 eV (280.7 eV for Cp and 279.9 for Cp*), thus further supporting the enhanced donation of the Cp* ligand.^[49a] Indeed, the value of 0.8 eV is substantial and Gassman et al. have suggested that “the substitution of two Cp* ligands for Cp ligands has an electronic effect approaching that of a one-electron reduction of the metal.”^[48b]

The steric demands of the bulkier Cp* vs. Cp ligand are also a significant factor. The calculated corresponding cone angles of the two ligands were determined to be 146° vs. 100°, respectively.^[50] Increased kinetic stabilization due to steric shielding is directly observed in the stability of isolable monomeric forms of coordinatively unsaturated complexes,^[51] and likely plays a critical role in facilitating steps within catalytic cycles.

In order to correlate the contribution of steric and electronic properties of the Cp' ligands with the observed catalytic activity differences of CpRuCl(cod) and Cp*RuCl(cod) complexes, we synthesized 1,2,3,4-tetramethyl-5-(trifluoromethyl)cyclopentadienide (η^5 -C₅Me₄CF₃)^[52] to serve as an isosteric mimic of Cp* and as an isoelectronic replacement of Cp.^[53] XPS studies of cyclopentadienide derivatives indicated that the addition of each methyl group to the Cp' ligand lowers the binding energy of the inner shell electrons of a complexed metal by ~0.08 eV, while one trifluoromethyl group raises the binding energy by ~0.35 eV.^[49b, 52, 54] Preparation of (η^5 -C₅Me₄CF₃)RuCl(cod) thus gave a complex with electronic properties nearly identical to CpRuCl(cod), while retaining the steric bulk otherwise provided by the Cp* ligand. The reactivity of this complex (Table 1, entry 11) was both underwhelming and strikingly similar to that of Cp*RuCl(cod) (compare entries 10 vs. 11). Based on this observation, we conclude that the substantial increase in catalytic activity of CpRuCl(cod) vs. the Cp* congener is directly related to the diminished steric hindrance of the Cp ligand compared to the bulkier Cp* ligand.

Further, halogenated alkynes can be viewed as a special class of internal alkynes and thus should fall within the reactivity profile of [Cp*RuCl]-based catalysis with azides and nitrile oxides. At this point we took a step back and explored terminal alkyne **70** (with an H atom in place of Br). As expected, Cp*RuCl(cod) was a very effective catalyst (Table 3), and the observed regioselectivity was as anticipated (entry 3). In contrast, CpRuCl(cod) gave low conversions, although it still favored the 1,5-disubstituted triazole isomer **71d**, even if with

moderate selectivity. A qualitative assessment (using substrates shown in Figures 1 and 2) indicated that 1-iodoalkynes were less reactive than 1-bromoalkynes which in turn were less reactive than 1-chloroalkynes. While several factors are likely at play here, it is difficult to avoid using a sterics argument to explain, at least in part, the poor performance of $\text{Cp}^*\text{RuCl}(\text{cod})$ in the cycloadditions of 1-haloalkynes.

Drawing on the conclusions of the present work, as well as from five independent DFT studies of the RuAAC mechanism,^[1d, 55] catalysis likely begins with shedding of the cycloocta-1,5-diene ligand and coordination of the 1-haloalkyne and azide or nitrile oxide to give **Ru_A-A** and **Ru_A-NO** intermediates, respectively. The organic azide ligand has been computationally shown to act as a σ -donor via its proximal (N1) nitrogen. We have also proposed that nitrile oxides coordinate in similar fashion via their carbon atom.^[2] To explain the regioselectivity trends observed in the current study, we propose a similar sequence of key interactions and events: organic azide acts as a terminal electrophile, wherein its N3 nitrogen is attacked by the nucleophilic C2 of the alkyne component in the first covalent bond-forming step, producing **Ru_intT**. Similarly, we propose that C2–O bond formation occurs between the π -coordinated haloalkyne and the σ -coordinated (through carbon) nitrile oxide, likewise producing **Ru_intI**, which showcases the “umpolung” reactivity of nitrile oxide upon its coordination to the ruthenium catalyst. These proposals are consistent with the observed regioselectivity of the reaction.

Conclusion

The catalytic method for engaging 1-haloalkynes in ruthenium catalyzed reactions with nitrile oxides and organic azides described here provides convenient access to 4-haloisoxazoles and 5-halotriazoles. Reactive alkynes include 1-chloro, bromo and iodo derivatives and must contain an electron withdrawing group, such as an amide, ester, ketone or phosphonate. $\text{CpRuCl}(\text{cod})$ was identified as the most active catalyst and $[\text{CpRuCl}]$ was confirmed as the active catalytic fragment upon shedding of the cycloocta-1,5-diene ligand. The product azoles can be further derivatized via catalytic cross-coupling reactions, thus exploiting the potential of the halogen substituent. Although these catalytic cycloadditions appear to be similar to the RuAAC reaction, which is catalyzed by $[\text{Cp}^*\text{RuCl}]$ complexes, only Cp-based analogs are active catalyst when 1-haloalkynes are used. To explain this dramatic difference, $(\eta^5\text{-C}_5\text{Me}_4\text{CF}_3)\text{RuCl}(\text{cod})$ was designed and synthesized to at as an

isosteric mimic of Cp* (η^5 -C₅Me₅) and as an isoelectronic mimic of Cp (η^5 -C₅H₅). Its lack of catalytic activity was similar to that of Cp*RuCl(cod), thus suggesting that the steric encumbrance imparted by the Cp* ligand is detrimental to the reaction.

Experimental Section

General Procedure for the preparation of 4-haloisoxazoles

A 50 mL round bottom flask was charged with 3-bromo-dimethylpropiolamide (**1**; 528 mg, 3.0 mmol), 4-chloro-*N*-hydroxybenzimidoyl chloride (**2**; 709 mg, 3.75 mmol) and a stirring bar. Tetrahydrofuran (10 mL) was then added, followed by 3 mol% CpRuCl(cod) (28 mg, 0.09 mmol), immediately followed by the addition of 0.746 mL diisopropylethylamine (DIPEA; 542 mg, 4.2 mmol). The reaction mixture was stirred at room temperature and deemed complete by TLC analysis after 1.5 h, during which time the color of the solution turned from orange to dark brown. The crude reaction mixture was then concentrated onto silica gel via rotary evaporation and subjected to column chromatography (SiO₂, 25→35 EtOAc-hexanes; R_f = 0.27 at 30% EtOAc-hexanes) to provide **3a** as a tan crystalline solid (775 mg, 2.35; 78%).

General Procedure for the preparation of 5-halotriazoles

A 50 mL round-bottomed flask was charged with 3-bromo dimethylpropiolamide (**1**; 570 mg, 3.24 mmol), phenethyl azide (**4**; 595 mg, 4.05 mmol) and a stirring bar. Acetonitrile (9 mL) was added, followed by CpRuCl(cod) (28 mg, 0.09 mmol, 3 mol%). The resulting orange reaction mixture turned dark brown over the course of several minutes and was subsequently stirred at room temperature overnight. TLC analysis the following morning confirmed the completion of the reaction. The crude mixture was then concentrated onto silica gel via rotary evaporation and subjected to column chromatography (SiO₂, 30→50 EtOAc-hexanes; R_f = 0.15 in 30% EtOAc-hexanes) to provide **5c** as a tan powder (891 mg, 2.76 mmol; 85%).

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33. The regiochemistry of the 4-haloisoxazole product was confirmed in two ways; A) Compound **3a** was subjected to magnesium-halogen exchange with ethyl magnesium bromide followed by a subsequent proton quench with methanol to yield the parent 4-proto-isoxazole. Concurrently the same compound was prepared for comparison purposes through the copper catalyzed cycloaddition of alkyne **70** + hydroximoyl chloride **2**. B) An x-ray crystal structure of compound **8** was obtained. See supporting information for experimental details.
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Figure 1.

Ruthenium catalyzed cycloaddition of 1-haloalkynes and nitrile oxides. Synthesis of 4-haloisoxazoles. General reaction conditions and notes: CpRuCl(cod) 3–10 mol% catalyst loading, 1,4-dioxane or tetrahydrofuran (0.1–0.4 M), 1.2–1.5 equiv hydroximoyl chloride and DIPEA, rt. See supporting information for further details. Isolated yields after column chromatography. Regioselectivity, i.e. **a:b** ratio, was determined using a combination of ¹H NMR and LC/MS analysis to be >20:1 unless otherwise noted, “**b**” isomer is not shown. [a] Regioselectivity eroded slightly to 19:1 **a:b**. [b] The **a:b** ratio was 85:15 with 3 mol% catalyst loading. **25a** was isolated pure in 46% yield, overall combined isolated yield (**25a** + **25b**) was 63%.

Figure 2.

Ruthenium catalyzed cycloaddition of 1-haloalkynes and azides. Synthesis of 5-halo-1,2,3-triazoles. General reaction conditions and notes: CpRuCl(cod) 3–10 mol% catalyst loading, acetonitrile or dimethylformamide (0.1–0.3 M), 1.25 equiv azide. See supporting information for further details. Isolated yields after column chromatography.

Regioselectivity, i.e. **c:d** ratio, was determined using a combination of ^1H NMR and LC/MS analysis to be >20:1 unless otherwise noted, “**d**” isomer is not shown. [a] Regioselectivity eroded slightly to 19:1 **a:b**. [b] 12% recovered 1-iodo dimethylpropiolamide (starting material) with 10 mol% catalyst loading.

Figure 3. Reaction progress measured by heat flow calorimetry. All reactions were run under a nitrogen atmosphere. TBACl = *tert*-butylammonium chloride

Scheme 1.

CpRuCl(cod) catalyzed cycloaddition of 1-bromo dimethylpropiolamide (**1**) with 4-chloro-N-hydroxybenzimidoyl chloride (**2**, see A) and phenethyl azide (**4**, see B). Reaction conditions and notes: Isolated yields after column chromatography. Regioselectivity was determined using a combination of ¹H NMR and GC/MS or LC/MS analysis. [a] 0.35 mmol **1**, 1.25 equiv **2**, 1.4 equiv DIPEA, 1,4-dioxane, rt, 3 h. [b] 3 mmol **1**, 1.25 equiv **2**, 1.4 equiv DIPEA, THF, rt, 1 h. [c] 0.17 mmol **1**, 1.1 equiv **4**, toluene-d₈, 90 °C, 6 d. [d] 3.2 mmol **1**, 1.25 equiv **4**, MeCN, rt, 1 h. [e] 100% conversion monitored by ¹H NMR.

Scheme 2.

Palladium catalyzed cross-coupling reactions. Reaction conditions: a. (*tert*-butyl)-4-ethynylbenzene (3 equiv), 10 mol% PdCl₂(PPh₃)₂, CuI, DIPEA, toluene, 120 °C. b. allyltributylstannane (1.5 equiv), 10 mol% Pd(OAc)₂, PPh₃, DMF, 95 °C. c. butyl acrylate (3 equiv), 10 mol% Pd(OAc)₂, (*n*-Bu)₄NCl, NaHCO₃, DMF, 95 °C (X = I) or 120 °C (X = Br). d. *p*-tolylboronic acid (1.5 equiv), 10 mol% Pd(OAc)₂, K₂CO₃, DMF, 95 °C. e. allyltributylstannane (1.5 equiv), 10 mol% PdCl₂(PPh₃)₂, KF, DMF, 120 °C.

Scheme 3.

Weinreb amide transformations. Reaction conditions: a. LiOH, THF/H₂O, rt. b. EtMgBr, THF, 0 °C. c. LAH, THF, 0 °C. d. *p*-tolylboronic acid (2 equiv), 10 mol% PdCl₂(PPh₃)₂, NaHCO₃, DMF/H₂O, 120 °C. [a] Halogen-magnesium exchange occurred to provide the dehalogenated proto-azole product. [b] Reduction resulted in a complex reaction mixture.

Table 1 Catalyst screen for the reactions of bromoalkyne **1** with nitrile oxide **2** and azide **4**.

entry	catalyst	mol%	isoxazoles 3a+3b %, ^[a] [3a:3b]	triazoles 5c+5d %, ^[b] [5c:5d]
1	None	-	35, [20:80]	100, [65:35]
2	CpRuCl(cod)	1	45, [80:20]	33, [>20:1]
3	CpRuCl(cod)	3	79, [>20:1]	100, [>20:1]
4	CpRuCl(cod)	10	73, [>20:1]	100, [>20:1]
5	CpRuCl(PPh ₃) ₂	10	36, [40:60]	<5, [n/a]
6 ^[c]	CpRuCl(PPh ₃) ₂	10	31, [>20:1]	35, [>20:1]
7	CpRu(MeCN) ₃ PF ₆	10	77, [>20:1]	100, [>20:1]
8	CpRuBr(cod)	10	68, [>20:1]	n/a
9	CpRuI(cod)	10	49, [>20:1]	n/a
10	Cp*RuCl(cod)	10	9, [65:35]	30, [70:30]
11	(η^5 -C ₅ Me ₄ CF ₃)RuCl(cod)	10	13, [65:35]	28, [80:20]
12	(η^5 -C ₉ H ₇)RuCl(PPh ₃) ₂	10	13, [90:10]	n/a

Reaction conditions are identical to those in Scheme 1:

^[a] Isolated yields after column chromatography.^[b] Conversions based on ¹H NMR integration relative to diphenylmethane as an internal standard.^[c] Reaction temperature = 60 °C. All ratios were determined by ¹H NMR.

Table 2

CpRuCl(cod) catalyzed cyclotrimerization of 1-bromoalkynes.

entry	R =	product	yield	ratio [e:f]
1	NMe ₂ (1)	66e + 66f	80%	[90:10] ^[a]
2	OMe	67e + 67f	80%	[80:20] ^[a]
3	p-PhMe	68e + 68f	94%	[>20:1] ^[b]

1 mol% catalyst loading based on total mmol of 1-bromoalkyne. Isolated yields after column chromatography.

^[a] **e:f** ratio determined by GC/MS analysis.^[b] **e:f** ratio determined by ¹H NMR.

Table 3 Reactions of terminal alkyne **70** with azide **4**.

entry	conditions	Conversion [c:d]	Ratio [c:d]
1	toluene-d ₈ , 95 °C	100%	[53:47]
2	5 mol% CpRuCl(cod), CD ₃ CN, rt	20%	[10:90]
3	5 mol% Cp [*] RuCl(cod), CD ₃ CN, rt	100%	[0:100]
4	5 mol% CuI, TTTA, THF, rt	n/a	[100:0]

Entries 1–3 were monitored by ¹H NMR, conversions are based on integration relative to diphenylmethane as an internal standard. **c:d** ratios were determined by GC/MS analysis. TTTA = tris-(tert-butyl-triazolylmethyl)amine.