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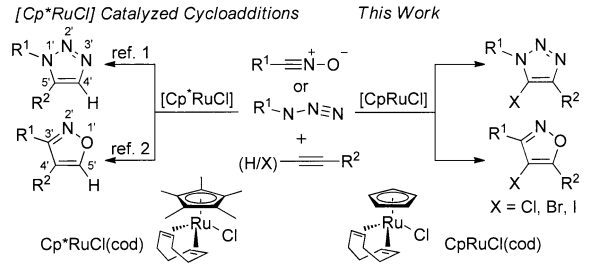
Ruthenium-Catalyzed Cycloadditions of 1-Haloalkynes with Nitrile Oxides and Organic Azides: Synthesis of 4-Haloisoxazoles and 5-Halotriazoles

James S. Oakdale, Rakesh K. Sit, and Valery V. Fokin*[a]

Abstract: (Cyclopentadienyl)(cyclooctadiene) ruthenium(II) chloride [CpRuCl(cod)] catalyzes the reaction between nitrile oxides and electronically deficient 1-choro-, 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 equivalents 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 by using palladium-catalyzed cross-coupling reactions and by manipulation of reactive amide groups. The lack of catalysis observed with [Cp*RuCl(cod)] (Cp* = pentamethylcyclopentadienyl) is attributed to steric demands of the Cp* (η^5-C_5Me_5) ligand in comparison to the parent Cp (η^5-C_5H_5). This hypothesis is supported by the poor reactivity of [(η^5-$C_5Me_4CF_3$)RuCl(cod)], which serves as a an isosteric mimic of Cp* and as an isoelectronic analogue of Cp.

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 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 1,4-triazoles obtained by way of the well-known copper-catalyzed (CuAAC) click reaction.[4] Although RuAAC has not yet become as robust as CuAAC, its ability to engage internal alkynes in cycloadditions is a 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 by using cyclopentadiene ruthenium(II) chloride [CpRuCl]-based catalysts (Scheme 1).



Scheme 1. Ruthenium-catalyzed cycloadditions.

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 part, a direct 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, makes 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 (through 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

[a] J. S. Oakdale, Dr. R. K. Sit, Prof. Dr. V. V. Fokin
Department of Chemistry, The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-7562
E-mail: fokin@scripps.edu

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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 been used 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]

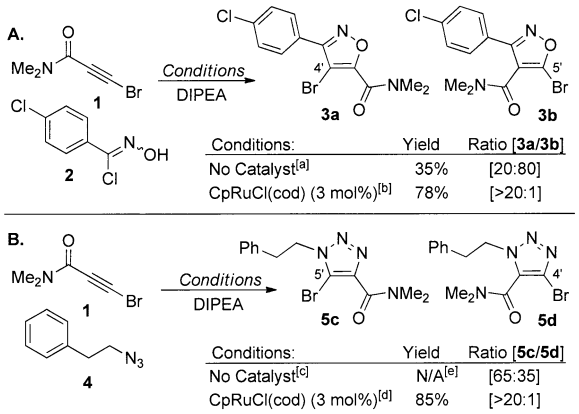
After having developed a direct copper-catalyzed route for the synthesis of 5-iodo-1,2,3-triazoles from 1-iodoalkynes,[15] we were naturally curious about a similar ruthenium-mediated process, which could perhaps also engage 1-chloro and 1-bromoalkynes in cycloaddition reactions. The direct regiospecific generation of haloazoles 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,[15,18a–c] an iridium-catalyzed process to access 4-bromo-triazoles was recently developed.[18d] Halotriazoles can also be accessed by trapping reactive triazolyl intermediates, including 5-triazolyl-copper,[19] 5-aluminum,[20] 5-bismuth,[21] or 4-triazolyl magnesium bromide[22] analogues 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*-hydroxybenzimdoyl 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 with the cyclopentadienyl ligand 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-dimethyl-propiolamide (**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 approximately 4:1 (**3b**/**3a**) with a combined isolated yield of approximately 35% (Scheme 2A). 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 THF (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 by Michael addition.[34] Experimentally, a typical reaction protocol dictates the addition of [CpRuCl(cod)] followed within seconds by the addition of Hünig's base.



Scheme 2. [CpRuCl(cod)]-catalyzed cycloaddition of 1-bromodimethylpropiolamide (**1**) with 4-chloro-*N*-hydroxybenzimdoyl chloride (**2**) (A) and phenethyl azide (**4**) (B). Isolated yields after column chromatography are shown. Regioselectivity was determined using a combination of ^{1}H NMR spectroscopy and GCMS or LCMS analysis. [a] **1** (0.35 mmol), **2** (1.25 equiv), DIPEA (1.4 equiv), 1,4-dioxane, RT, 3 h. [b] **1** (3 mmol), **2** (1.25 equiv), DIPEA (1.4 equiv), THF, RT, 1 h. [c] **1** (0.17 mmol), **4** (1.1 equiv), [D_8]toluene, 90 °C, 6 d. [d] **1** (3.2 mmol), **4** (1.25 equiv), MeCN, RT, 1 h. [e] 100% conversion monitored by ^{1}H NMR spectroscopy.

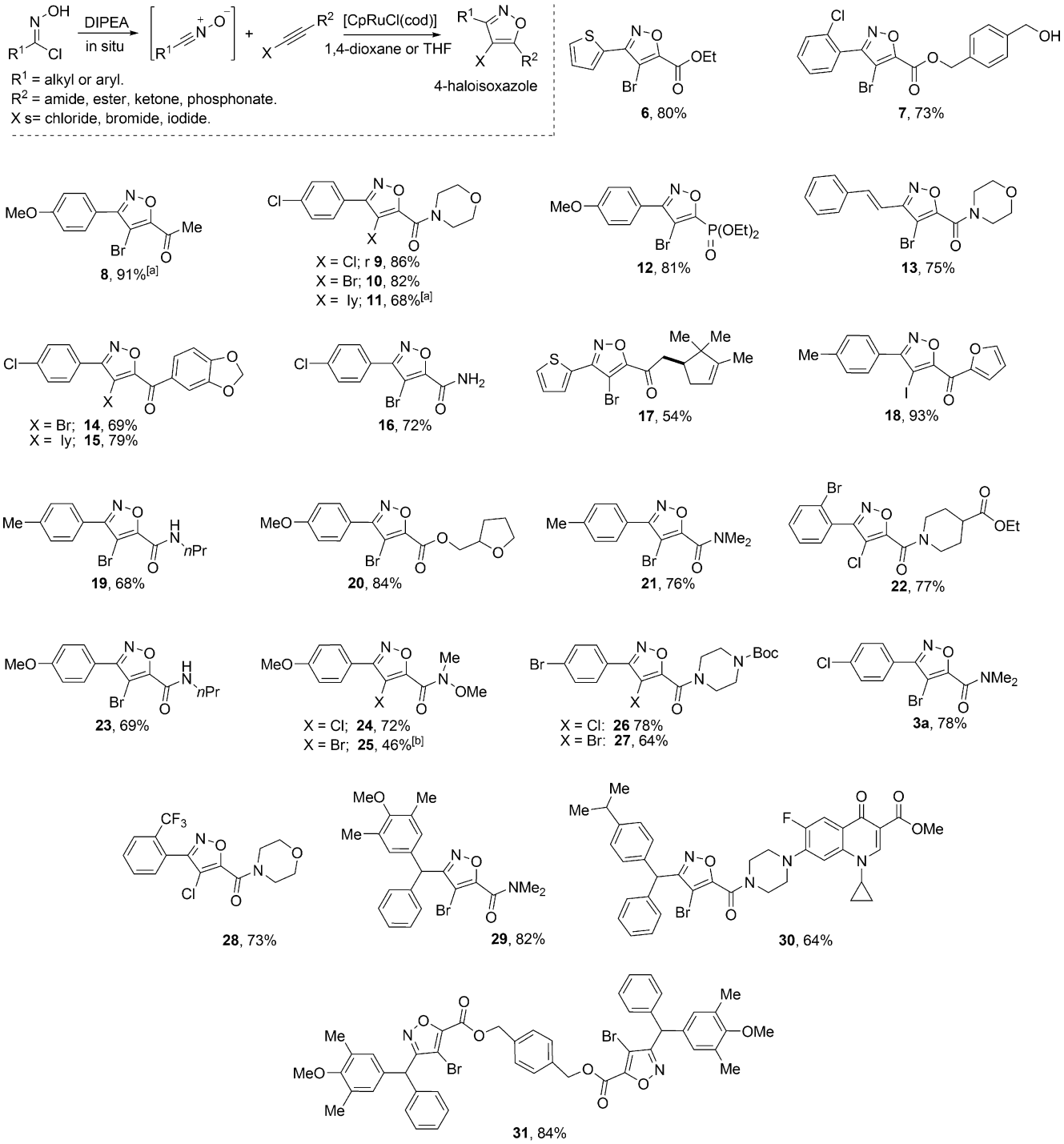


Figure 1. Ruthenium-catalyzed cycloaddition of 1-haloalkynes and nitrile oxides. Synthesis of 4-haloisoxazoles: [CpRuCl(cod)] 3–10 mol% catalyst loading, 1,4-dioxane or THF (0.1–0.4 M), 1.2–1.5 equiv hydroximoyl chloride and DIPEA, RT; see the Supporting Information for further details. Isolated yields after column chromatography are given. Regioselectivity, that is, **a**/**b** ratio, was determined by using a combination of ^{1}H NMR spectroscopy and LCMS analysis to be >20:1 unless otherwise noted; the"**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. **25 a** was isolated pure in 46% yield, overall combined isolated yield (**25 a** + **25 b**) was 63%.

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-chloroal-

kynes.[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 *tert*-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-haloisxoazoles ("**b**" isomer approximately 4:1 ratio **b**/**a**) in good yields (a substrate scope was preformed, see the Supporting Information, Tables 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 2B).[37] Again, [Cp*RuCl(cod)] proved ineffective for this transformation. Acetonitrile, DMF, and ethanol performed well as reaction solvents at a 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 six days to achieve full conversion. The regioselectivity of the thermal reaction eroded dramatically, to approximately 3:2 (**5c**/**5d**), compared to the catalytic process.

Acetonitrile outperformed other solvents in reactions with substrates other than **1**. Although DMF 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

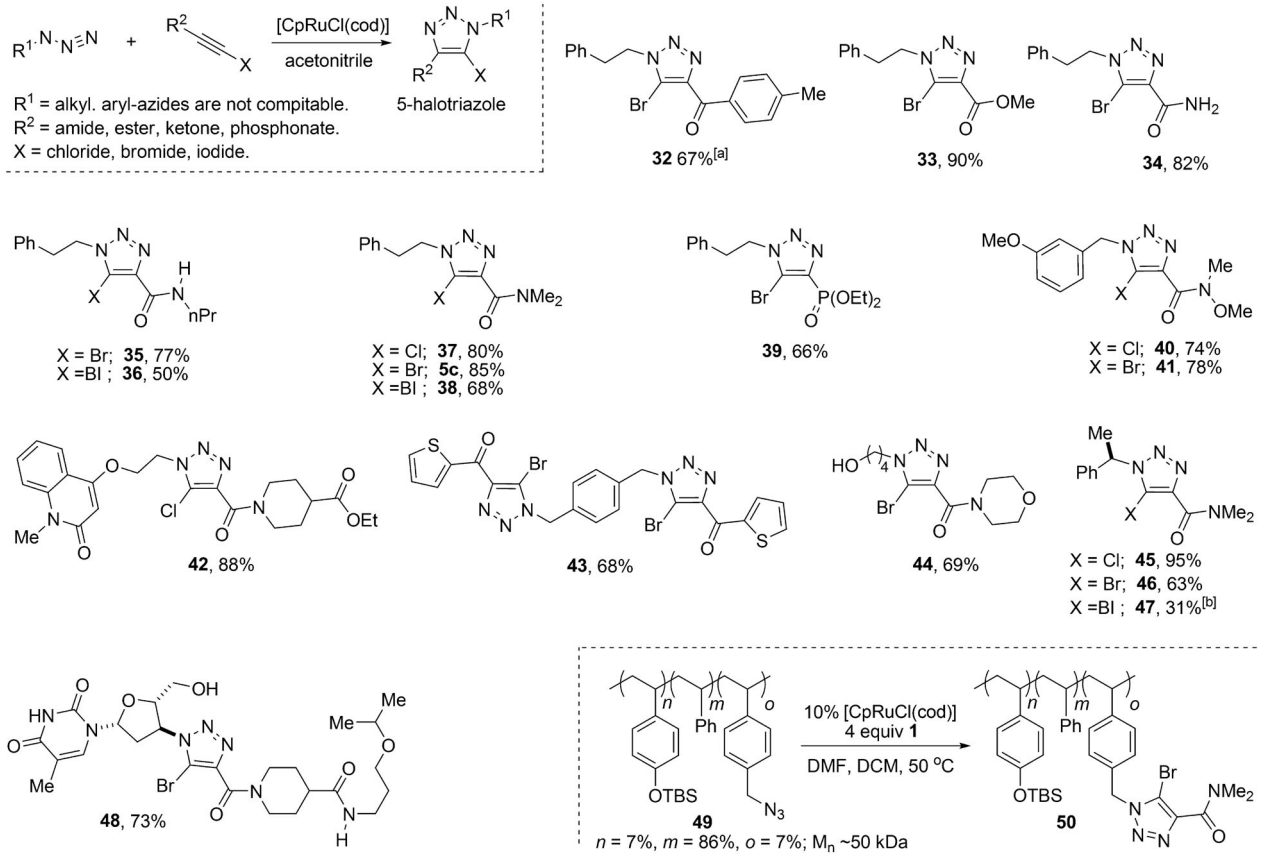


Figure 2. Ruthenium-catalyzed cycloaddition of 1-haloalkynes and azides. Synthesis of 5-halo-1,2,3-triazoles: [CpRuCl(cod)] 3–10 mol% catalyst loading, acetonitrile or dimethylformamide (0.1–0.3 M), 1.25 equiv azide; see the Supporting Information for further details. Isolated yields after column chromatography. Regioselectivity, that is, **c**/**d** ratio, was determined using a combination of ^{1}H NMR spectroscopy and LCMS analysis to be >20:1 unless otherwise noted, The "**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.

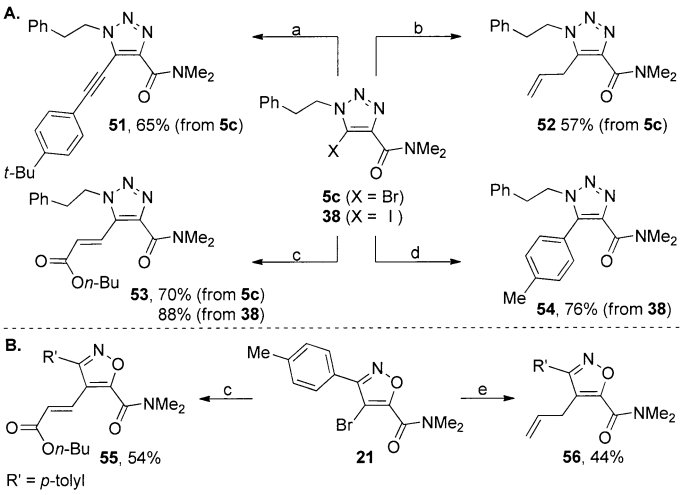
low yields. Furthermore, even with acetonitrile as a solvent, reactions of primary and secondary 1-halopropiolamides were particularly sluggish and required twice the catalyst loading as was needed for tertiary propargylic amide substrates. Gentle heating (to ca. 50 °C) proved beneficial for reducing 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 pendant azide handles (**49**). The reaction was run with 10 mol% [CpRuCl(cod)] at 55 °C for 12 h. An excess of haloalkyne **1** (4 equiv) was used 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 ^{1}H NMR spectroscopic signals and served as an additional identifying feature of the product.

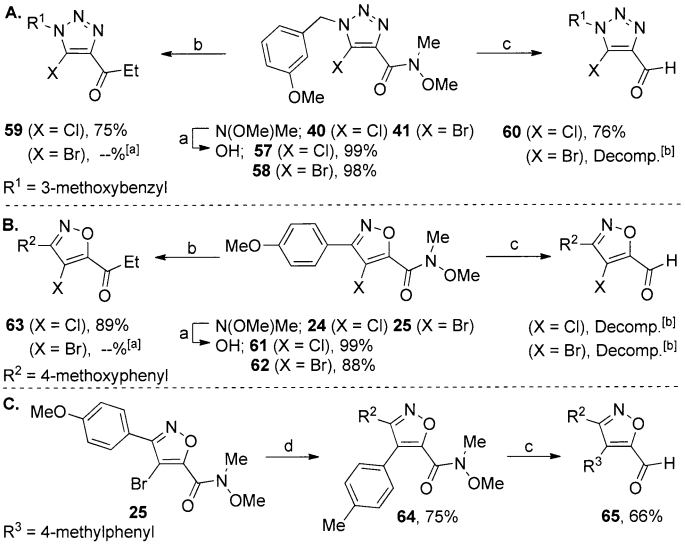
To expand the synthetic utility of the halogenated azoles obtained under ruthenium catalysis, we examined selective transformations of the amide and halide functionalities. Palladium-catalyzed cross-coupling reactions were briefly evaluated on both the iodo- and bromotriazoles (**38** and **5c**, Scheme 3) and bromoisoxazoles (**21** and **25**). Several examples involving halogenated triazoles are known,[38] and following brief reaction-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 analogue, 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, by using slightly modified published protocols.[27a,29b,c,39]

Additionally, Weinreb amide[40] derivatives **24**–**25** and **40**–**41**, were readily amenable for additional transformations (Scheme 4). Hydrolysis with lithium hydroxide was facile for chloro- and bromoisoxazole (**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 analogues underwent magnesium–halogen exchange and thus tended to give the dehalogenated azoles upon workup. Similarly, reduction with lithium aluminum 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 aluminum 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 portionwise introduction of catalyst (usually in 1 mol% increments) as re-



Scheme 3. Palladium-catalyzed cross-coupling reactions: a) (*tert*-butyl)-4-ethynylbenzene (3 equiv), $[PdCl_2(PPh_3)_2]$ (10 mol%) CuI, DIPEA, toluene, 120 °C; b) allyltributylstannane (1.5 equiv), 10 mol% $Pd(OAc)_2$, PPh_3, DMF, 95 °C; c) butyl acrylate (3 equiv), 10 mol% $Pd(OAc)_2$, $(nBu)_4NCl$, $NaHCO_3$, DMF, 95 °C (X = I) or 120 °C (X = Br); d) *p*-tolylboronic acid (1.5 equiv), 10 mol% $Pd(OAc)_2$, K_2CO_3, DMF, 95 °C; e) allyltributylstannane (1.5 equiv), 10 mol% $[PdCl_2(PPh_3)_2]$, KF, DMF, 120 °C.



Scheme 4. Weinreb amide transformations: a) LiOH, THF/H_2O, RT; b) EtMgBr, THF, 0 °C; c) LAH, THF, 0 °C; d) *p*-tolylboronic acid (2 equiv), $[PdCl_2(PPh_3)_2]$ (10 mol%) $NaHCO_3$, DMF/H_2O, 120 °C. [a] Halogen–magnesium exchange occurred to provide the dehalogenated proto-azole product. [b] Reduction resulted in a complex reaction mixture.

quired 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 an only 45% yield of bromoisoxazoles **3a**+**3b** (cf. Table 1, entries 2 vs. 3). The eroded regioselectivity was approximately 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: 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), that is, 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. Although triphenylphosphine complex of [CpRuCl], $[CpRuCl(PPh_3)_2]$ is commercially available, 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 is more reluctant to undergo dissociation and ligand substitution than cyclooctadiene, thus hindering entry into the productive catalytic cycle. We observed similar trends in the RuAAC system, in which $[Cp^*RuCl(PPh_3)_2]$-catalyzed cycloadditions required heating to at least 50 °C, whereas the corresponding [Cp*RuCl(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.

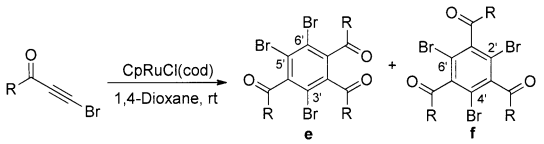
Examination of different halides as spectator ligands (bromide, Table 1, entry 8 and iodide entry 9) revealed that the effect on regioselectivity was insignificant; the yield of isoxazole decreased in the order of Cl > Br > I. A cationic $[CpRu]^+$ catalyst, devoid of a halide ligand altogether, was introduced in the form of the acetonitrile complex, $[CpRu(MeCN)_3]PF_6$. Surprisingly, the net outcome was nearly identical to the [CpRuCl-

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

Entry	Catalyst	mol%	Isoxazoles **3a**+**3b**%[b] (**3a**/**3b**)	Triazoles **5c**+**5d**%,[c] [**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	$[CpRuC(PPh_3)_2]$	10	36 (40:60)	<5 (n/a)
6[d]	$[CpRuCl(PPh_3)_2]$	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	$[(\eta^5\text{-}C_5Me_4CF_3)RuCl(cod)]$	10	13 (65:35)	28 (80:20)
12	$[(\eta^5\text{-}C_9H_7)RuCl(PPh_3)_2]$	10	13 (90:10)	n/a

[a] Reaction conditions are identical to those in Scheme 1. [b] Isolated yields after column chromatography. [c] Conversions based on ^{1}H NMR integration relative to diphenylmethane as an internal standard. [d] Reaction temperature = 60 °C. All ratios were determined by ^{1}H NMR spectroscopy.

Table 2. [CpRuCl(cod)]-catalyzed cyclotrimerization of 1-bromoalkynes.[a]



Entry	R=	Product	Yield [%]	Ratio **e**/**f**
1	NMe_2 (**1**)	**66e**+**66f**	80	90:10[b]
2	OMe	**67e**+**67f**	80	80:20[b]
3	*p*PhMe	**68e**+**68f**	94	>20:1[c]

[a] 1 mol% catalyst loading based on total mmol of 1-bromoalkyne. Isolated yields after column chromatography. [b] **e**/**f** ratio determined by GCMS analysis. [c] **e**/**f** ratio determined by ^{1}H NMR spectroscopy.

(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 by using independent analytical techniques (i.e., NMR spectroscopy, 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, [CpRuCl(cod)] is clearly more

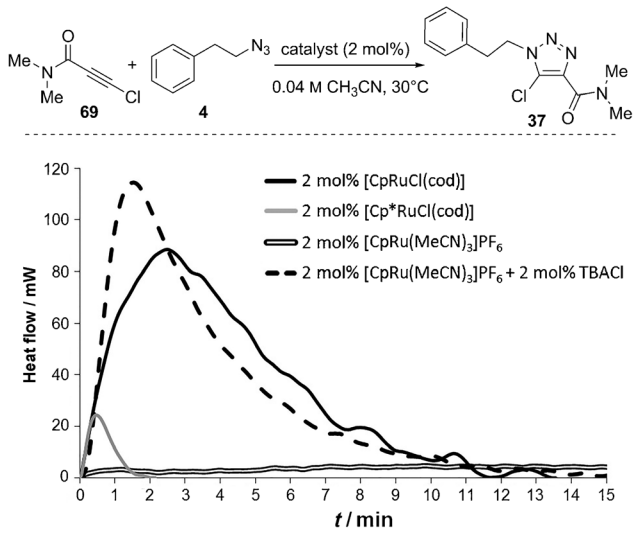


Figure 3. Reaction progress was measured by heat flow calorimetry. All reactions were run under a nitrogen atmosphere. TBACl = *tert*-butylammonium chloride.

reactive than its cationic counterpart $[CpRu(MeCN)_3]PF_6$, whereas the reaction reached completion in a little over ten minutes when using 2 mol% [CpRuCl(cod)], the cationic catalyst $[CpRu(MeCN)_3]PF_6$ used at the same concentration resulted in only approximately 60% conversion and took nearly three hours to reach that point. The addition of one equivalent (with respect to the catalyst) of tetrabutylammonium chloride (TBACl) to the reaction mixture prior to the addition of $[CpRu(MeCN)_3]PF_6$ restored activity of the catalyst, thus further supporting the notion that the [CpRuCl] fragment is the active catalytic species. Incidentally, in RuAAC, $[Cp^*Ru]^+$ is completely inactive.[1d] Indeed, these 12-electron cationic $[Cp'Ru]^+$ (in which Cp′ = 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 $[Cp^*Ru(MeCN)_3]PF_6$ require the addition of exogenous chloride.[46] However, there is at least one example of a successful cyclotrimerization mediated by $[CpRu(MeCN)_3]PF_6$ 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 $[CpRu]^+$ fragment. While this proposal cannot be ruled out, we have no evidence to support it at this time.

The essential requirement for the Cp (η^5-C_5H_5) ligand was clear from the outset of this study, and both Cp* (η^5-C_5Me_5) and indenyl (η^5-C_9H_7) 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) 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 versus Cp* on electronic properties are well documented. Electrochemical studies comparing ruthenocenes $[Ru(Cp')_2]$ (in which Cp′ = Cp or Cp*), show the Cp analogue to be more difficult to oxidize and thus less electronically rich in comparison to the Cp* congener by approximately 0.5 V ($E^{\circ\prime}$ for $[Ru(Cp)_2]$ is 1.03 V vs. 0.48 V for $[Ru(Cp^*)_2]$).[49] Additionally, electron spectroscopy for chemical analysis (ESCA, otherwise known as X-ray photoelectron spectroscopy, XPS) studies on $[Ru(Cp')_2]$ revealed a difference in the binding energies of the ruthenium ($Ru(3d_{5/2})$) inner shell electron of approximately 0.8 eV (280.7 for Cp and 279.9 eV 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]

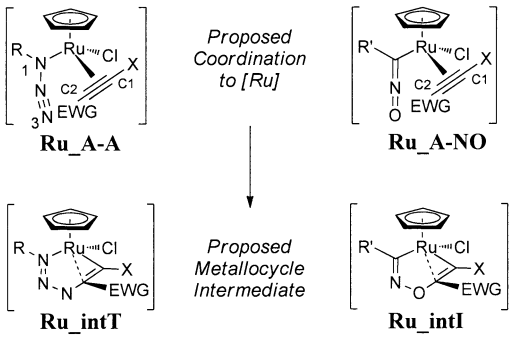
The steric demands of the bulkier Cp* versus Cp ligand are also a significant factor. The calculated corresponding cone angles of the two ligands were determined to be 146 versus 100°, respectively.[50] Increased kinetic stabilization due to steric shielding is directly observed in the stability of isolable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

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-$C_5Me_4CF_3$)[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, whereas one trifluoromethyl group raises the binding energy by ~0.35 eV.[49b,52,54] Preparation of [(η^5-$C_5Me_4CF_3$)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)] versus 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 **71 d**, 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 [Cp*RuCl(cod)] in the cycloadditions of 1-haloalkynes (Scheme 5).

Drawing on the results 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 by its proximal (N1) nitrogen atom. We have also proposed that nitrile oxides coordinate in a 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



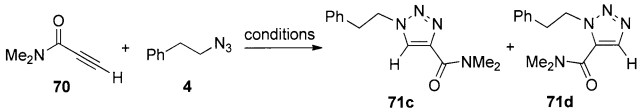
Scheme 5. Proposed key intermediates in the ruthenium-catalyzed reactions.

"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 a 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. [CpRuCl(cod)] was identified as the most active catalyst and [CpRuCl] was confirmed as the active catalytic fragment upon shedding of the cycloocta-1,5-diene ligand. The product azoles can be further derivatized by 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 [Cp*RuCl] complexes, only Cp-based analogues are active catalysts when 1-haloalkynes are used. To explain this dramatic difference, [(η^5-$C_5Me_4CF_3$)RuCl(cod)] was designed and synthesized to act as an isosteric mimic of Cp* (η^5-C_5Me_5) and as an isoelectronic mimic of Cp (η^5-C_5H_5). Its lack of catalytic activity was similar to that of [Cp*RuCl(cod)], which thus suggests that the steric encumbrance imparted by the Cp* ligand is detrimental to the reaction.

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



Entry	Conditions	Conversion [%] (**c** + **d**)	Ratio **c**/**d**
1	[D_8]toluene, 95 °C	100	53:47
2	5 mol% [CpRuCl(cod)], CD_3CN, RT	20	10:90
3	5 mol% [Cp*RuCl(cod)], CD_3CN, RT	100	0:100
4	5 mol% CuI, TTTA, THF, RT	n/a	100:0

[a] Entries 1–3 were monitored by ^{1}H NMR spectroscopy, conversions are based on integration relative to diphenylmethane as an internal standard. **c**/**d** ratios were determined by GCMS analysis. TTTA = tris-(tert-butyl-triazolylmethyl)amine.

Experimental Section

General procedure for the preparation of 4-haloisoxazoles

A 50 mL round-bottomed flask was charged with 3-bromodimethylpropiolamide (**1**; 528 mg, 3.0 mmol), 4-chloro-*N*-hydroxybenzimidoyl chloride (**2**; 709 mg, 3.75 mmol) and a stirring bar. THF (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 diiso-

propylethylamine (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 (SiO_2, 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 (SiO_2, 30→50 EtOAc-hexanes; $R_f = 0.15$ in 30% EtOAc/hexanes) to provide **5c** as a tan-colored powder (891 mg, 2.76 mmol; 85%).

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Keywords: alkynes · cycloadditions · halides · regioselectivity · ruthenium

[1] a) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999; b) M. M. Majireck, S. M. Weinreb, *J. Org. Chem.* **2006**, *71*, 8680–8683; c) L. K. Rasmussen, B. C. Boren, V. V. Fokin, *Org. Lett.* **2007**, *9*, 5337–5339; d) B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930.

[2] S. Grecian, V. V. Fokin, *Angew. Chem.* **2008**, *120*, 8409–8411; *Angew. Chem. Int. Ed.* **2008**, *47*, 8285–8287.

[3] a) A. Qin, J. W. Y. Lam, C. K. W. Jim, L. Zhang, J. Yan, M. Häussler, J. Liu, Y. Dong, D. Liang, E. Chen, G. Jia, B. Z. Tang, *Macromolecules* **2008**, *41*, 3808–3822; b) A. Tam, U. Arnold, M. B. Soellner, R. T. Raines, *J. Am. Chem. Soc.* **2007**, *129*, 12670–12671; c) H. Nulwala, K. Takizawa, A. Odukale, A. Khan, R. J. Thibault, B. R. Taft, B. H. Lipshutz, C. J. Hawker, *Macromolecules* **2009**, *42*, 6068–6074; d) M. Empting, O. Avrutina, R. Meusinger, S. Fabritz, M. Reinwarth, M. Biesalski, S. Voigt, G. Buntkowsky, H. Kolmar, *Angew. Chem.* **2011**, *123*, 5313–5317; *Angew. Chem. Int. Ed.* **2011**, *50*, 5207–5211; e) J.-M. Kee, B. Villani, L. R. Carpenter, T. W. Muir, *J. Am. Chem. Soc.* **2010**, *132*, 14327–14329; f) M. Tischler, D. Nasu, M. Empting, S. Schmelz, D. W. Heinz, P. Rottmann, H. Kolmar, G. Buntkowsky, D. Tietze, O. Avrutina, *Angew. Chem.* **2012**, *124*, 3768–3772; *Angew. Chem. Int. Ed.* **2012**, *51*, 3708–3712; g) W. S. Horne, C. A. Olsen, J. M. Beierle, A. Montero, M. R. Ghadiri, *Angew. Chem.* **2009**, *121*, 4812–4818; *Angew. Chem. Int. Ed.* **2009**, *48*, 4718–4724.

[4] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708–2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064.

[5] Internal alkynes here refer to alkynes featuring carbon substituents on each acetylenic carbon atom.

[6] M. Juricek, P. H. J. Kouwer, A. E. Rowan, *Chem. Commun.* **2011**, *47*, 8740–8749.

[7] a) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302–1315; b) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952–3015.

[8] a) S. Chuprakov, S. W. Kwok, V. V. Fokin, *J. Am. Chem. Soc.* **2013**, *135*, 4652–4655; b) N. Selander, B. T. Worrell, S. Chuprakov, S. Velaparthi, V. V. Fokin, *J. Am. Chem. Soc.* **2012**, *134*, 14670–14673; c) S. Chuprakov, J. A. Malik, M. Zibinsky, V. V. Fokin, *J. Am. Chem. Soc.* **2011**, *133*, 10352–10355; d) T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 14972–14974.

[9] a) e. M. T. M. V. D. Pinho, *Curr. Org. Chem.* **2005**, *9*, 925–958; b) J. B. Sperry, D. L. Wright, *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723–740.

[10] P. G. Baraldi, A. Barco, S. Benetti, F. Moroder, G. P. Pollini, D. Simoni, *J. Org. Chem.* **1983**, *48*, 1297–1302.

[11] M. Nitta, T. Kobayashi, *J. Chem. Soc. Perkin Trans. 1* **1985**, 1401–1406.

[12] a) A. I. Kotyatkina, V. N. Zhabinsky, V. A. Khripach, *Russ. Chem. Rev.* **2001**, *70*, 641–653; b) K. C. Coffman, T. A. Palazzo, T. P. Hartley, J. C. Fettinger, D. J. Tantillo, M. J. Kurth, *Org. Lett.* **2013**, *15*, 2062–2065.

[13] a) P. G. Baraldi, A. Barco, S. Benetti, G. P. Pollini, D. Simoni, *Synthesis* **1987**, 857–869; b) A. L. Smith, E. N. Pitsinos, C. K. Hwang, Y. Mizuno, H. Saimoto, G. R. Scarlato, T. Suzuki, K. C. Nicolaou, *J. Am. Chem. Soc.* **1993**, *115*, 7612–7624; c) B. Heasley, *Angew. Chem.* **2011**, *123*, 8624–8627; *Angew. Chem. Int. Ed.* **2011**, *50*, 8474–8477.

[14] T. V. Hansen, P. Wu, V. V. Fokin, *J. Org. Chem.* **2005**, *70*, 7761–7764.

[15] J. E. Hein, J. C. Tripp, L. B. Krasnova, K. B. Sharpless, V. V. Fokin, *Angew. Chem.* **2009**, *121*, 8162–8165; *Angew. Chem. Int. Ed.* **2009**, *48*, 8018–8021.

[16] a) P.-A. Fournier, M. Arbour, E. Cauchon, A. Chen, A. Chefson, Y. Ducharme, J.-P. Falgueyret, S. Gagné, E. Grimm, Y. Han, R. Houle, P. Lacombe, J.-F. Lévesque, D. MacDonald, B. Mackay, D. McKay, M. D. Percival, Y. Ramtohul, R. St-Jacques, S. Toulmond, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2670–2674; b) R. Palin, L. Abernethy, N. Ansari, K. Cameron, T. Clarkson, M. Dempster, D. Dunn, A.-M. Easson, D. Edwards, J. Maclean, K. Everett, H. Feilden, K.-K. Ho, S. Kultgen, P. Littlewood, D. McArthur, D. McGregor, H. McLuskey, I. Neagu, S. Neale, L.-A. Nisbet, M. Ohlmeyer, Q. Pham, P. Ratcliffe, Y. Rong, A. Roughton, M. Sammons, R. Swanson, H. Tracey, G. Walker, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 892–898; c) J. He, L. Feng, J. Li, R. Tao, F. Wang, X. Liao, Q. Sun, Q. Long, Y. Ren, J. Wan, H. He, *Bioorg. Med. Chem.* **2012**, *20*, 1665–1670.

[17] a) B. T. Worrell, J. E. Hein, V. V. Fokin, *Angew. Chem.* **2012**, *124*, 11961–11964; *Angew. Chem. Int. Ed.* **2012**, *51*, 11791–11794; b) H. A. Michaels, J. T. Simmons, R. J. Clark, L. Zhu, *J. Org. Chem.* **2013**, *78*, 5038–5044.

[18] a) B. H. M. Kuijpers, G. C. T. Dijkmans, S. Groothuys, P. J. L. M. Quaedflieg, R. H. Blaauw, F. L. van Delft, F. P. J. T. Rutjes, *Synlett* **2005**, 3059–3062; b) J. García-Álvarez, J. Diez, J. Gimeno, *Green Chem.* **2010**, *12*, 2127–2130; c) J. García-Álvarez, J. Diez, J. Gimeno, F. J. Suárez, C. Vincent, *Eur. J. Inorg. Chem.* **2012**, 5854–5863; d) E. Rasolofonjatovo, S. Theeramunkong, A. Bouriaud, S. Kolodych, M. Chaumontet, F. Taran, *Org. Lett.* **2013**, *15*, 4698–4701.

[19] a) W. S. Brotherton, R. J. Clark, L. Zhu, *J. Org. Chem.* **2012**, *77*, 6443–6455; b) V. Malnuit, M. Duca, A. Manout, K. Bougrin, R. Benhida, *Synlett* **2009**, 2123–2126; c) Y.-M. Wu, J. Deng, Y. Li, Q.-Y. Chen, *Synthesis* **2005**, 1314–1318; d) B. Wang, J. Zhang, X. Wang, N. Liu, W. Chen, Y. Hu, *J. Org. Chem.* **2013**, *78*, 10519–10523; e) R. Yan, K. Sander, E. Galante, V. Rajkumar, A. Badar, M. Robson, E. El-Emir, M. F. Lythgoe, R. B. Pedley, E. Årstad, *J. Am. Chem. Soc.* **2012**, *134*, 703–709.

[20] Y. Zhou, T. Lecourt, L. Micouin, *Angew. Chem.* **2010**, *122*, 2661–2664; *Angew. Chem. Int. Ed.* **2010**, *49*, 2607–2610.

[21] B. T. Worrell, S. P. Ellery, V. V. Fokin, *Angew. Chem.* **2013**, *125*, 13275–13279; *Angew. Chem. Int. Ed.* **2013**, *52*, 13037–13041.

[22] A. Krasiński, V. V. Fokin, K. B. Sharpless, *Org. Lett.* **2004**, *6*, 1237–1240.

[23] a) E. Lieber, T. S. Chao, C. N. R. Rao, *Can. J. Chem.* **1959**, *37*, 118–119; b) G. L'Abbé, L. Beenaerts, *Tetrahedron* **1989**, *45*, 749–756.

[24] J. Huang, S. J. F. Macdonald, J. P. A. Harrity, *Chem. Commun.* **2009**, 436–438.

[25] A. Darwish, M. Blacker, N. Janzen, S. M. Rathmann, S. Czorny, S. M. Hillier, J. L. Joyal, J. W. Babich, J. F. Valliant, *ACS Med. Chem. Lett.* **2012**, *3*, 313–316.

[26] L. Claisen, O. Lowman, *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 1149–1157.

[27] a) J. P. Waldo, R. C. Larock, *J. Org. Chem.* **2007**, *72*, 9643–9647; b) J. P. Waldo, R. C. Larock, *Org. Lett.* **2005**, *7*, 5203–5205; c) O. Debleds, E.

Gayon, E. Ostaszuk, E. Vrancken, J.-M. Campagne, *Chem. Eur. J.* **2010**, *16*, 12207 – 12213.
[28] D. Chiarino, M. Napoletano, A. Sala, *J. Heterocycl. Chem.* **1987**, *24*, 43 – 46.
[29] a) M. L. McIntosh, M. R. Naffziger, B. O. Ashburn, L. N. Zakharov, R. G. Carter, *Org. Biomol. Chem.* **2012**, *10*, 9204 – 9213; b) J. A. Crossley, D. L. Browne, *J. Org. Chem.* **2010**, *75*, 5414 – 5416; c) Y.-Y. Ku, T. Grieme, P. Sharma, Y.-M. Pu, P. Raje, H. Morton, S. King, *Org. Lett.* **2001**, *3*, 4185 – 4187.
[30] a) T. Kitamura, Y. Mansei, Y. Fujiwara, *J. Organomet. Chem.* **2002**, *646*, 196 – 199; b) P. J. Stang, P. Murch, *Tetrahedron Lett.* **1997**, *38*, 8793 – 8794; c) E. Kotali, A. Varvoglis, A. Bozopoulos, *J. Chem. Soc. Perkin Trans. 1* **1989**, 827 – 832.
[31] a) K. Takenaka, S. Nakatsuka, T. Tsujihara, P. S. Koranne, H. Sasai, *Tetrahedron: Asymmetry* **2008**, *19*, 2492 – 2496; b) J. J. Letourneau, C. Riviello, M. H. J. Ohlmeyer, *Tetrahedron Lett.* **2007**, *48*, 1739 – 1743; c) P. D. Stein, D. M. Floyd, S. Bisaha, J. Dickey, R. N. Girotra, J. Z. Gougoutas, M. Kozlowski, V. G. Lee, E. C. K. Liu, *J. Med. Chem.* **1995**, *38*, 1344 – 1354.
[32] a) Z.-X. Yu, P. Caramella, K. N. Houk, *J. Am. Chem. Soc.* **2003**, *125*, 15420 – 15425; b) F. De Sarlo, *J. Chem. Soc. Perkin Trans. 1* **1974**, 1951 – 1953.
[33] The regiochemistry of the 4-haloisoxazole product was confirmed in two ways: 1) 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**. 2) An X-ray crystal structure of compound **8** was obtained. See the Supporting Information for experimental details.
[34] C. J. Cavallito, *J. Am. Chem. Soc.* **1955**, *77*, 4159 – 4160.
[35] H. Hofmeister, K. Annen, H. Laurent, R. Wiechert, *Angew. Chem.* **1984**, *96*, 720 – 722; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 727 – 729.
[36] Y. Sasson, O. W. Webster, *J. Chem. Soc. Chem. Commun.* **1992**, 1200 – 1201.
[37] The regiochemistry of the 5-halotriazole product was confirmed for compounds **5c** and **46** by magnesium–halogen exchange with ethyl magnesium bromide followed by subsequent quenching with methanol. For comparison purposes, the corresponding 5-proto derivatives were also prepared through CuAAC from **70** and the requisite azides. See the Supporting Information for experimental details.
[38] a) Y. Carcenac, F. David-Quillot, M. Abarbri, A. Duchene, J. Thibonnet, *Synthesis* **2013**, *45*, 633 – 638; b) A. R. Bogdan, K. James, *Org. Lett.* **2011**, *13*, 4060 – 4063; c) J. Deng, Y.-M. Wu, Q.-Y. Chen, *Synthesis* **2005**, *8*, 2730 – 2738.
[39] T. Haddad, R. Gershman, R. Dilis, D. Labaree, R. B. Hochberg, R. N. Hanson, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5999 – 6003.
[40] a) S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815 – 3818; b) S. Balasubramaniam, I. S. Aidhen, *Synthesis* **2008**, *23*, 3707 – 3738.
[41] Y. Yamamoto, T. Arakawa, R. Ogawa, K. Itoh, *J. Am. Chem. Soc.* **2003**, *125*, 12143 – 12160.
[42] a) Y. Yamamoto, K. Hattori, H. Nishiyama, *J. Am. Chem. Soc.* **2006**, *128*, 8336 – 8340; b) Y. Yamamoto, K. Hattori, *Tetrahedron* **2008**, *64*, 847 – 855; c) K. C. Nicolaou, J. Wang, Y. Tang, L. Botta, *J. Am. Chem. Soc.* **2010**, *132*, 11350 – 11363.
[43] A. Allen, K. Villeneuve, N. Cockburn, E. Fatila, N. Riddell, W. Tam, *Eur. J. Org. Chem.* **2008**, 4178 – 4192.
[44] M. O. Albers, D. J. Robinson, A. Shaver, E. Singleton, *Organometallics* **1986**, *5*, 2199 – 2205.
[45] a) P. J. Fagan, M. D. Ward, J. C. Calabrese, *J. Am. Chem. Soc.* **1989**, *111*, 1698 – 1719; b) D. Rondon, B. Chaudret, X. D. He, D. Labroue, *J. Am. Chem. Soc.* **1991**, *113*, 5671 – 5676; c) M. Jiménez-Tenorio, M. C. Puerta, P. Valerga, *Eur. J. Inorg. Chem.* **2004**, 17 – 32.
[46] a) J. A. Varela, L. Castedo, C. Saá, *Org. Lett.* **2003**, *5*, 2841 – 2844; b) J. A. Varela, L. Castedo, C. Saá, *J. Org. Chem.* **2003**, *68*, 8595 – 8598.
[47] E. Rüba, R. Schmid, K. Kirchner, M. J. Calhorda, *J. Organomet. Chem.* **2003**, *682*, 204 – 211.
[48] a) J. R. Sowa, R. J. Angelici, *J. Am. Chem. Soc.* **1991**, *113*, 2537 – 2544; b) P. G. Gassman, D. W. Macomber, J. W. Hershberger, *Organometallics* **1983**, *2*, 1470 – 1472.
[49] a) P. G. Gassman, C. H. Winter, *J. Am. Chem. Soc.* **1988**, *110*, 6130 – 6135; b) P. G. Gassman, J. R. Sowa, M. G. Hill, K. R. Mann, *Organometallics* **1995**, *14*, 4879 – 4885.
[50] M. D. Curtis, K. B. Shiu, W. M. Butler, J. C. Huffman, *J. Am. Chem. Soc.* **1986**, *108*, 3335 – 3343.
[51] For examples of coordinatively unsaturated half-sandwich ruthenium(II) complexes, see: a) B. K. Campion, R. H. Heyn, T. D. Tilley, *J. Chem. Soc. Chem. Commun.* **1988**, 278 – 280; b) T. J. Johnson, K. Folting, W. E. Streib, J. D. Martin, J. C. Huffman, S. A. Jackson, O. Eisenstein, K. G. Caulton, *Inorg. Chem.* **1995**, *34*, 488 – 499; c) J. Huang, H.-J. Schanz, E. D. Stevens, S. P. Nolan, *Organometallics* **1999**, *18*, 2370 – 2375.
[52] P. G. Gassman, J. W. Mickelson, J. R. Sowa, *J. Am. Chem. Soc.* **1992**, *114*, 6942 – 6944.
[53] a) Y. Imazaki, E. Shirakawa, R. Ueno, T. Hayashi, *J. Am. Chem. Soc.* **2012**, *134*, 14760 – 14763; b) A. Mercier, W. C. Yeo, J. Chou, P. D. Chaudhuri, G. Bernardinelli, E. P. Kundig, *Chem. Commun.* **2009**, 5227 – 5229; c) H.-J. Zhang, B. Demerseman, Z. Xi, C. Bruneau, *Eur. J. Inorg. Chem.* **2008**, 3212 – 3217.
[54] L. P. Barthel-Rosa, J. R. Sowa, P. G. Gassman, J. Fischer, B. M. McCarty, S. L. Goldsmith, M. T. Gibson, J. H. Nelson, *Organometallics* **1997**, *16*, 1595 – 1603.
[55] a) E. Boz, N. Ş. Tüzün, *J. Organomet. Chem.* **2013**, *724*, 167 – 176; b) M. Lamberti, G. C. Fortman, A. Poater, J. Broggi, A. M. Z. Slawin, L. Cavallo, S. P. Nolan, *Organometallics* **2012**, *31*, 756 – 767; c) D.-R. Hou, T.-C. Kuan, Y.-K. Li, R. Lee, K.-W. Huang, *Tetrahedron* **2010**, *66*, 9415 – 9420; d) Y.-B. Zhou, Z.-F. Ke, C.-Y. Zhao, *Huaxue Xuebao* **2006**, *64*, 2071 – 2078.

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1-Haloalkyne cycloadditions: Ruthenium(II)-catalyzed ([CpRuCl(cod)], 1,5-cod = cyclooctadiene, Cp = cyclopentadienyl; see scheme) azide–alkyne and nitrile oxide–alkyne cycloadditions provide a convenient and regioselective means for the preparation of 5-halo-1,2,3-triazoles and 4-haloisoxazoles from electron-deficient 1-chloro-, 1-bromo-, and 1-iodoalkynes.

Transition-Metal Catalysis

*J. S. Oakdale, R. K. Sit, V. V. Fokin**

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Ruthenium-Catalyzed Cycloadditions of 1-Haloalkynes with Nitrile Oxides and Organic Azides: Synthesis of 4-Haloisoxazoles and 5-Halotriazoles