ChemComm

Intermolecular Cyclotrimerization of Haloketoalkynes and Internal Alkynes: Facile Access to Arenes and Phthalides

Journal:	*ChemComm*
Manuscript ID	CC-COM-08-2020-005706.R2
Article Type:	Communication

Authors

A. P. Silvestri,*[a,b] J. S. Oakdale*[a,c]

Affiliations

a Department of Chemistry, Scripps Research, 10550 North Torrey Pines Road, La Jolla, California 92037 USA

Current Address

b Unnatural Products, Inc., 2161 Delaware Ave., Santa Cruz, CA 95060 USA

c Materials Science Division, Lawrence Livermore National Laboratory, 7000 East Ave., Livermore, CA 94550 USA

Acknowledgements

This work was financed by Scripps Research. We acknowledge Scripps Research and Valery V. Fokin for generous use of hood space and chemicals. J.S.O. acknowledges the National Science Foundation for a graduate fellowship. We thank Curtis Moore and Arnold Rheingold of the UCSD Crystallography Facility, University of California, San Diego, for obtaining the atomic coordinates of compounds **2C** and **27**.

ChemComm

COMMUNICATION

Intermolecular Cyclotrimerization of Haloketoalkynes and Internal Alkynes: Facile Access to Arenes and Phthalides†

xx*[a,b] and xx*[a,c]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

A highly chemo- and regioselective cyclo(co)trimerization between 3-halopropiolamides and symmetrical internal alkynes is reported. The reaction is catalyzed by CpRuCl(COD) and proceeds under air at ambient temperature in ethanol with no additional precautions. Iodo-, bromo-, and chloropropiolamides, esters, and ketones are viable coupling partners and, in a 2:1 stoichiometry relative to internal alkyne, yield fully-substituted arenes in a single step. The highest regioselectivities (96% single isomer) were observed when employing 2° and 3°-halopropiolamides. A mechanistic hypothesis accounting for this selectivity is proposed. Notably, by using 1,4-butynediol as the internal alkyne, in-situ lactonization following [2+2+2]-cycloaddition generates therapeutically-relevant phthalide pharmacophores directly.

Alkyne cyclotrimerization offers a straightforward and atom economical route towards the synthesis of polyfunctionalized benzenes and other valuable cycloadducts.[1] Widespread application of this chemistry however, has been generally limited by poor regio- and chemoselectivity, particularly in cross-intermolecular [2+2+2] cycloadditions involving two or three alkynes. As a result, a number of methods have been developed to overcome these problems, the most notable being fixing the positions of the desired substituents and rendering the cycloaddition intramolecular.[2] However, a consequence of this approach is that the tether moiety linking the alkyne substituents remains in the penultimate product. This drawback spurred the development of degradable tethers featuring labile boron[3] and silicon[4] linkages. Despite these advances, reliable cyclization of alkynyl fragments remains challenging and examples of tether-free cross-cyclotrimerizations involving two or three alkynes are rare.[5] Herein, we describe a highly regio- and chemoselective formation of dihalogenated isophthalamides via a Ru(II)-catalyzed, intermolecular [2+2+2] cycloaddition of 3-halopropiolamides with internal alkynes.

Recently, CpRuCl(cod) complexes (Cp = cyclopentadienyl or Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl, cod = cyclooctadiene) were found to influence the regioselectivity of certain 1,3-diploar cycloadditions.[6] While investigating the reactivity of organic azides with haloalkynes, the authors of that study observed that electron-deficient haloalkynes underwent efficient trimerizations in the presence of CpRuCl(cod). 3-bromo-dimethylpropiolamide (**1**) reacts efficiently at room temperature to yield the 3,5,6-tribromo product **1A** as the dominant isomer (Scheme 1, A:B = 91:09).[6a,7] In comparison, the Cp*RuCl(cod) complex was ineffective, generating only trace product despite being widely-utilized as a general catalyst for cyclotrimerizations,[8] including several examples involving haloalkynes.[9] The decreased reactivity of [Cp*RuCl] relative to [CpRuCl] can be ascribed to the increased steric demands of the bulkier Cp* ligand.[6a,9c]

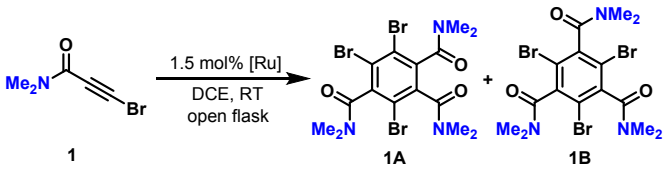
We next probed the reactivity of **1** and CpRuCl(cod) in the presence of 2-butyne (Scheme 2). Pleasingly, only two (**1C**, **1D**) out of the seven possible products (**1A, 1B, 1E – G**) were formed in any appreciable amount with **1C** being the dominate species. Increased yields of **1C** relative to **1D** could be achieved with ethanol (96:04) as the solvent in place of 1,2-dichloroethane (DCE; 82:18). In general, protic solvents gave the highest C:D ratios (see Table S1 in the supporting information). Regioisomers **1C** and **1D** were easily separated via column chromatography and recrystallization from ethyl acetate followed by x-ray crystallography confirmed their identities (Scheme 2B). Increasing the concentration of 2-butyne from 1 to 1.5 molar equiv. relative to **1**, was found to suppress the formation of **1A/B**. Finally, we wish to emphasize that this reaction does not require controlled addition techniques nor excessive amounts of either reactant in order to produce high chemoselectivities.

Tolane reacted in a similar manner to 2-butyne, and served as a less volatile alternative for further reaction optimization studies (see **2C/D**, Table 1). Only electron deficient alkynes bearing a terminal

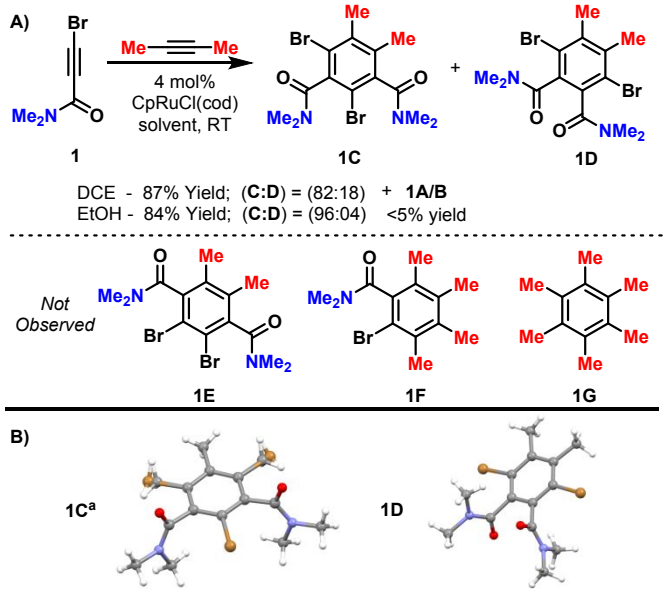
[a] *Department of Chemistry, xx*
[b] *Current Address: xx*
[c] *Current Address: xx*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Scheme 1. Ru(II)-catalyzed trimerization of 3-bromo-dimethylpropiolamide.



Scheme 2. A) Product distribution of cyclo(co)trimerization of 1 with 2-butyne. **B)** Crystal structures of **1C** and **1D**.



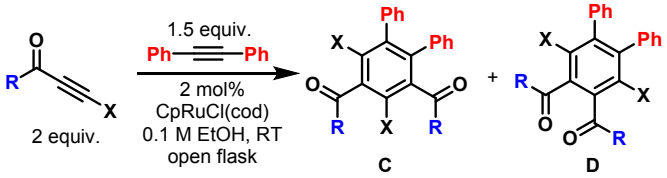
[a]50/50 Me/Br mirror-plane disorder.

halide substituent reacted with measurable chemo- and regioselectivity; haloalkynes without an electron withdrawing group delivered complex reaction mixtures. Cyclotrimerizations of methyl 3-bromopropiolate (**3**) and 3-bromo tolylynone (**4**) were briefly explored. Both **3** and **4** gave high yields with good chemoselectivities (entries 2 and 3), however the regioisomeric ratio of their products, **3C/D** and **4C/D** respectively, were considerably lower compared to **2C/D**. Complex reaction mixtures also arose when terminal alkynes, such as phenylacetylene, were used in place of tolane, thus narrowing the scope to halogenated propiolamides and internal alkynes.

Within this reactivity window, the identity of the halide substituent, chloro- (**5**), bromo- (**1**) and iodo- (**6**), had little effect on the **C:D** regioisomeric ratio (>94:<06) (entries 1, 4 & 5). In contrast, terminal alkyne **7** displayed poor chemoselectivity and only moderate regioselectivity (75:25 **C:D**), and required high catalyst loadings (20%) to achieve complete consumption of **7** (entry 6). The products, **7C/D**, were isolated in only 9% yield, with the majority of the starting material (**7**) being trimerized to give **7A/B**-derivatives. Secondary 3-halopropiolamide **8** also required high catalyst loadings and delivered product in a paltry 49% isolated yield (entry 7). The lack of reactivity is surprising considering halogenated azoles were obtained in good yield in our previous work for similar secondary propiolamide substrates,[1] although a more complex substrate bearing an amide located further away from the 3-halo-alkyne center fared well under these conditions (**23C**, Scheme 3). When terminal alkynes, instead of internal alkynes, are employed in this cycloaddition, an intractable mixture of complex products seemingly arising from oligomerization of the terminal alkyne (likely via formation of a Ru-vinylidene), in addition to cyclotrimerized 3-halopropiolamide, are produced. Finally, silyl-protected alkyne **9**, and alkyl substituted alkyne **10** failed to react altogether. Taken as a whole, it is clear that the observed chemoselectivity of this process is tied to the halide substituent and we tentatively assign this effect to the electron-withdrawing, albeit weak, nature of the halide substituent, which further increases the reactivity of the appended alkyne.[10] A mechanistic hypothesis detailing the origins of the observed chemo- and regioselectivites of this process can be found in the Supporting Information.

As before, bulkier Cp*RuCl(cod) did not perform as well as CpRuCl(cod). While similar C:D ratios were obtained, lower yields were observed (47%, see Table S1) and significantly higher catalyst loadings (>20x) were required to push the reaction to completion.

Table 1. Cyclotrimerization of 3-haloalkynes with tolane.[a]



Entry[a]	R	X	Yield	Ratio **C:D**
1[b]	(**1**) NMe_2	Br	82%	96:04 (**2C:D**)
2	(**3**) OMe	Br	88%	50:50 (**3C:D**)
3	(**4**) *p*MePhe	Br	96%	70:30 (**4C:D**)
4	(**5**) NMe_2	Cl	77%	97:03 (**5C:D**)
5	(**6**) NMe_2	I	84%	94:06 (**6C:D**)
6[c,d]	(**7**) NMe_2	H	9%	75:25 (**7C:D**)
7[c,e]	(**8**) NHBu	Br	49%	96:04 (**8C:D**)
8[c]	(**9**) NMe_2	TMS	N.R.	-
9[c]	(**10**) NMe_2	n-C_5H_{11}	N.R.	-

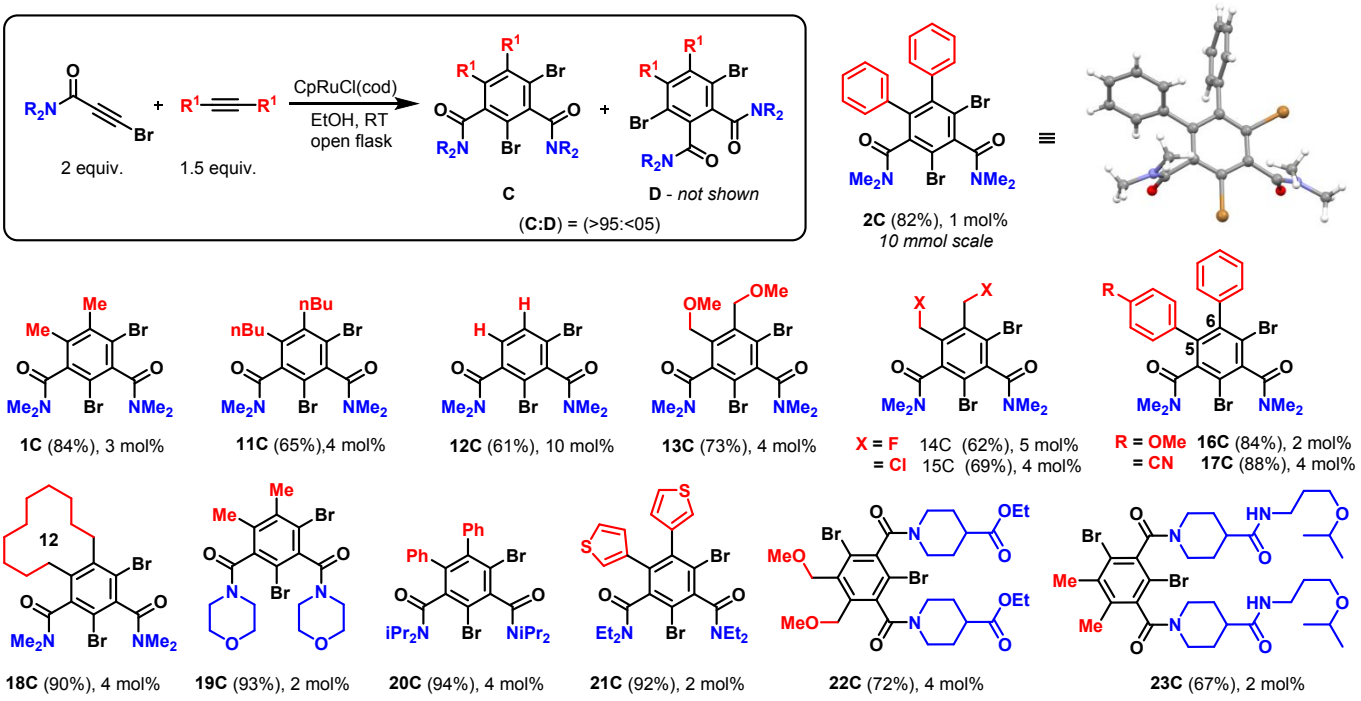
[a]Conditions: 0.1 M EtOH, 22 °C (RT), 1-4 hr, 2 mol% CpRuCl(cod) unless other noted. Isolated yield after silica gel chromatography. Ratio of C:D determined by ^{1}H NMR, GC/MS and LC/MS analysis. N.R. = no reaction. [b]1 mol% CpRuCl(cod). [c]20 mol% CpRuCl(cod). [d]**7A/B**, arising from the trimerization of **7**, was the predominate reaction product. [e]2 mol% CpRuCl(cod) yielded trace product.

The utility of this reaction can be further increased by employing a commercially available catalyst, $CpRuCl(PPh_3)_2$, in place of synthesized CpRu(cod)Cl. Reactions with $CpRuCl(PPh_3)_2$ required increased catalyst loadings (~2-3x that of CpRu(cod)Cl), warming of the reaction mixture to 60 °C to facilitate phosphine ligand dissociation and the addition of 5% (v/v) DCM in ethanol. Lastly, catalyst mortality was not significantly altered upon exposure to air, circumventing all inert atmosphere precautions that often accompany catalytic Ru(II) transformations.

The reaction scope examples presented in Scheme 3 were prepared in ethanolic solvent through portion-wise addition of CpRuCl(cod). In all cases, the 2,4-dibromo isomer **C** was favored in >95:<05 ratio over the 3,6-dibromo isomer **D** (not shown) and several compounds, especially those containing cyclic or bulky amide groups, were obtained as mixtures of atropisomers. With respect to the internal alkyne component, aliphatic derivatives (see for instance **11**, **18**, etc.) and substituted aliphatic derivatives (**13-15**, **22**) performed well and required slightly higher catalyst loadings compared to their bis-aryl alkyne counterparts. Unsymmetrical alkynes (**16**, **17**) gave

approximately 1:1 mixtures of inseparable isomers at the 5,6 position while still retaining a 96:04 ratio favoring the 2,4-dibromo substitution. Acetylene gas at atmospheric pressure also successfully participated in this reaction, although higher catalyst loading (10-mol%) was necessary to push the reaction to completion (**12**, 61%). Both heterocyclic propiolamide **19** and sterically encumbered amide **20** were trimerized efficiently, as were ester (**22**), and amide (**23**) containing derivatives.

We next focused our efforts on modifying the phthalamide products. Activation of the aryl halides through palladium-catalyzed cross-coupling reactions, (i.e. Sonogashira, Suzuki, Heck, etc.) returned either unreacted starting material or complex reaction mixtures. Attempts to hydrolyze the benzamide functionalities using either basic (for instance, KOH, ethylene glycol, 200 °C) or very acidic systems (i.e. conc. HCl or H_2SO_4, reflux) failed. Attempts to reduce



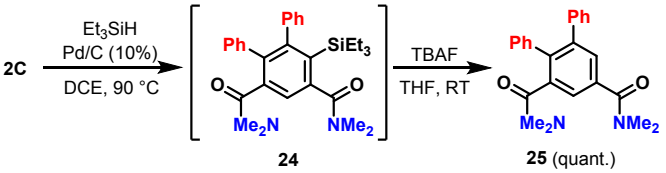
Reaction conditions: 0.1M EtOH, RT. *X mol%* refers to the minimum amount of CpRuCl(cod) required to fully consume the 3-halopropiolamide starting material: CpRuCl(cod) was added in 1 mol% portions. Isolated yields (%) are reported following silica gel chromatography. C:D ratio verified by ^{1}H NMR, GC/MS and LC/MS analysis. X-ray crystal structures of **2C** is shown.

the amide groups in **2C** were entirely unsuccessful (for instance, LAH/$AlCl_3$ in refluxing THF). In most cases **2C** was recovered unscathed although it was observed that Pd-catalyzed silane reduction yielded proto-debrominated products. Optimization of a triethylsilane reduction in the presence of palladium on carbon furnished silyl-derivative **24**, from which treatment with tetrabutylammonium fluoride cleanly generated dehalogenated **25** in quantitative yield (Scheme 4).

Our difficulties in achieving further transformations of these halogenated-isophthalamide products likely stems from severe steric hindrance experienced by both halide and amide substituents due to their tightly confined spatial arrangement. T*ertiary* benzamides have traditionally been used as reliable *ortho*-metalation directors.[11] However, one issue is the formation of 2,6-disubstituted benzamide products, which become resilient towards hydrolysis.[12] Hydrolysis of 2,6-disubstituted *secondary* benzamides is more facile,[13] yet we are unfortunately limited in scope to tertiary amides Table 1). Nonetheless, several synthetic strategies were developed to overcome the stubborn hydrolysis of 2,6-disubstituted benzamides, including phthalide formation through intramolecular lactonization.[14]

Treating a mixture of propiolamide **1** and 1,4-butyne-diol with Ru catalyst gave **26C** in 20% yield (Scheme 5A). Surprisingly, we found that the majority of starting material had been converted to **27** (50% yield) via lactonization of **26C**. Isolated **26C** was found to spontaneous eliminate gaseous dimethylamine in the solid state upon standing at room temperature and could be pushed to completion via treatment with 20% conc. HCl/H_2O solution. These sequential procedures were used to cleanly produce **27** in 70% isolated yield, and represent a valuable method to efficiently generate the core structure of biologically-active phthalides (Scheme 5B).[15]

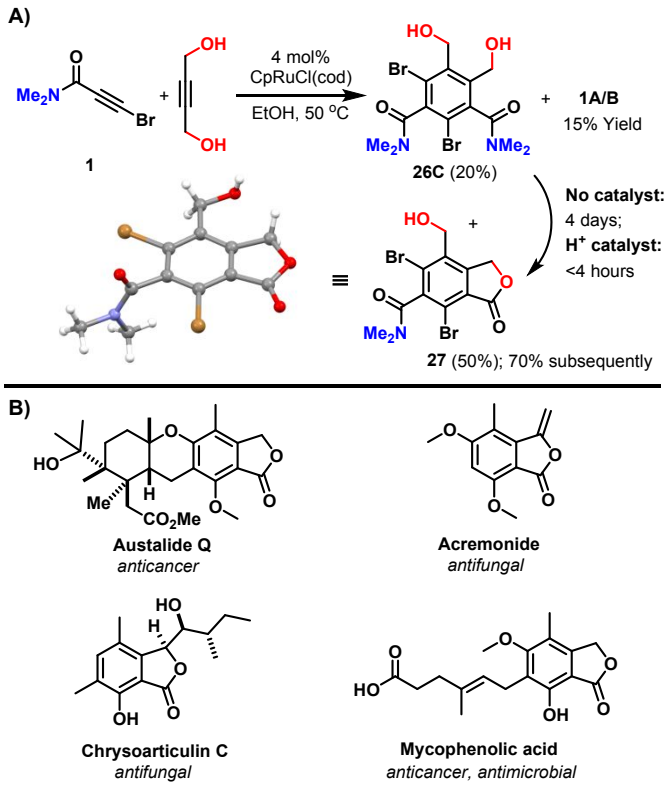
Scheme 4. Dehalogenation of compound **2C**.



The alkyne cyclo(co)trimerization protocol described here is an experimentally simple method for the tether-free construction of fully substituted dihalogenated isophthalamides from 3-halopropiolamides and internal alkynes. The halide substituent was found to be crucial for obtaining high chemoselectivities, while the tertiary-amide imparted the high regioselectivities observed in this process. Despite the limitations on the type of alkyne substrate that

can be employed, the reaction was found to be tolerant towards propiolamides adorned with a variety of functional groups. Intramolecular lactone formation following co-trimerization of 1,4-butyn-diol, proceeds readily, generating functionally-dense phthalides. We expect this method to aid in the synthesis and evaluation of therapeutically-relevant phthalides and their derivatives.

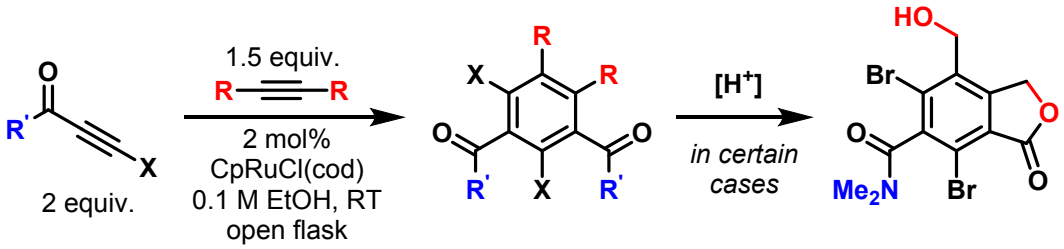
Scheme 5. A. Synthesis of phthalide **27**. Compound **26C** was converted to **27** spontaneously over 4 days or via acid catalysis within 4 h. X-ray crystal structures of **27** is shown. **B.** Representative biologically-active phthalides with structural similarity to **27**.



Acknowledgment

Notes and references

1 (a) M. Amatore and C. Aubert, *Eur. J. Org. Chem.* 2015, 265; (b) G. Dominguez and J. Perez-Castells, *Chem. Soc. Rev.* 2011, **40**, 3430.
2 For a seminal example, see: R. L. Funk and K. P. C. Volhardt, *J. Am. Chem. Soc.*, 1980, **102**, 5253.
3 (a) C. Heinz and N. Cramer, *J. Am. Chem. Soc.*, 2015, **137**, 11278; (b) Y. Yamamoto, J.-i. Ishii, H. Nishiyama and K. Itoh, *J. Am. Chem. Soc.*, 2005, **127**, 9625; (c) Y. Yamamoto, J.-i. Ishii, H. Nishiyama and K. Itoh, *J. Am. Chem. Soc.*, 2004, **126**, 3712.
4 Y. Zou, Q. Liu and A. Deiters, *Org. Lett.*, 2011, **13**, 4352; (b) S. Levin, R. R. Nani and S. E. Reisman, *Org. Lett.*, 2010, **12**, 780; (c) G. Chouraqui, M. Petit, P. Phansavath, C. Aubert and M. Malacria, *Eur. J. Org. Chem.*, 2006, 1413; (d) G. Chouraqui, M. Petit, C. Aubert and M. Malacria, *Org. Lett.,* 2004, **6**, 1519.
5 Highly selective, intermolecular cyclo(co)trimerizations of two or three different alkynes are scarce, for examples see: (a) A. Heya, T. Namba, J. Hara, Y. Shibata and K. Tanaka, *Tetrahedron Lett.*, 2015, **56**, 4938; (b) C.-Y. Wu, Y.-C. Lin, P.-T. Chou, Y. Wang and Y.-H. Liu, *Dalton Trans.*, 2011, **40**, 3748; (c) S. Kotha, V. Seema and S. M. Mobin, *Synthesis*, 2011, 1581; (d) G. Onodera, M. Matsuzawa, T. Aizawa, T. Kitahara, Y. Shimizu, S. Kezuka and R. Takeuchi, *Synlett*, 2008, 755; (e) K. Tanaka, G. Nishida, M. Ogino, M. Hirano and K. Noguchi, *Org. Lett.*, 2005, **7**, 3119; (f) H.-T. Chang, M. Jeganmohan and C.-H. Cheng, *Chem. Commun.*, 2005, 4955; (g) K. Tanaka and K. Shirasaka, *Org. Lett.*, 2003, **5**, 4697; (h) R. Takeuchi and Y. Nakaya, *Org. Lett.*, 2003, **5**, 3659; (i) V. Gevorgyan, U. Radhakrishnan, A. Takeda, M. Rubina, M. Rubin and Y. Yamamoto, *J. Org. Chem.*, 2001, **66**, 2835.
6 (a) J. S. Oakdale, R. K. Sit and V. V. Fokin, *Chem. Eur. J.*, 2014, **20**, 11101; B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia and V. V. Fokin, *J. Am. Chem. Soc.*, 2008, **130**, 8923; (c) S. Grecian and V. V. Fokin, *Angew. Chem. Int. Ed.*, 2008, **47**, 8285.
7 A similar transformation was reported, see: A. Allen, K. Villeneuve, N. Cockburn, E. Fatila, N. Riddell and W. Tam, *Eur. J. Org. Chem.*, 2008, 4178.
8 (a) Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama and K. Itoh, *J. Am. Chem. Soc.*, 2005, **127**, 605; (b) Y. Yamamoto, T. Arakawa, R. Ogawa and K. Itoh, *J. Am. Chem. Soc.*, 2003, **125**, 12143; (c) K. Kirchner, M. J. Calhorda, R. Schmid and L. F. Veiros, *J. Am. Chem. Soc.*, 2003, **125**, 11721.
9 (a) S. Melnes, A. Bayer and O. R. Gautun, *Tetrahedron*, 2012, **68**, 8463; (b) K. C. Nicolaou, J. Wang, Y. Tang, L. Botta, *J. Am. Chem. Soc.*, 2010, **132**, 11350; (c) Y. Yamamoto, K. Yamashita and Y. Harada, *Chem. Asian J.*, 2015, **5**, 946; (d) Y. Yamamoto, R. Takuma, T. Hotta and K. Yamashita, *J. Org. Chem.*, 2009, **74**, 4324; (e) Y. Yamamoto and K. Hattori, *Tetrahedron*, 2007, **64**, 847; (f) Y. Yamamoto, K. Hattori and H. Nishiyama, *J. Am. Chem. Soc.*, 2006, **128**, 8336.
10 (a) M. Yamagishi, J. Okazaki, K. Nishigai, T. Hata and H. Urabe, *Org. Lett.*, 2012, **14**, 34; and references therein. For a review of the reactivity of haloalkynes, see: (b) W. Wu and H. Jiang, *Acc. Chem. Res.*, 2014, **47**, 2483.
11 P. Beak and V. Sniekus, *Acc. Chem. Res.*, 1982, **15**, 306.
12 D. B. Reitz and S. M. Massey, *J. Org. Chem.*, 1990, **55**, 1375.
13 D. L. Comins and J. D. Brown, *J. Org. Chem.*, 1986, **51**, 3566.
14 (a) F. Faigl, A. Thurner, B. Z. Molnár, G. Simig, and B. Z. Volk, *Org. Process Res. Dev.*, 2010, **14**, 617; (b) Z. Li, Y. Gao, Y. Tang, M. Dai, G. Wang, Z. Wang and Z. Yang, *Org. Lett.*, 2008, **10**, 2017.
15 R. Karmakar, P. Pahari, D. Mal, *Chem. Rev.,* 2014, **114**, 6213.



R' = -NR_2, -NHR, OMe
X = halogen
R = alkyl, aryl

49-96% yield
Up to 96% single isomer

70% yield

A fully intermolecular Ru(II)-catalyzed cyclotrimerization of internal alkynes chemo- and regioselectively generates substituted arenes and phthalides in a single step.