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Polycyclic Aromatic Hydrocarbons

Regioselective Synthesis of Polyheterohalogenated Naphthalenes via the Benzannulation of Haloalkynes

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Abstract: Independent control of halide substitution at six of the seven naphthalene positions of 2-arylnaphthalenes is achieved through the regioselective benzannulation of chloro-, bromo-, and iodoalkynes. The modularity of this approach is demonstrated through the preparation of 44 polyheterohalogenated naphthalene products, most of which are difficult to access through known naphthalene syntheses. The outstanding regioselectivity of the reaction is both predictable and proven unambiguously by single-crystal X-ray diffraction for many examples. This synthetic method enables the rapid preparation of complex aromatic systems poised for further derivatization using established cross-coupling methods. The power and versatility of this approach makes substituted naphthalenes highly attractive building blocks for new organic materials and diversity-oriented synthesis.

Introduction

Polycyclic aromatic compounds substituted with multiple halides, or polyhalogenated aromatics (PHAs), are desirable targets for both synthetic elaboration and end-use application. They serve as divergent substrates for cross-coupling reactions, representing platforms for diversity-oriented synthesis[1] by means of converting each halide to new C–C, C–N, C–O, or C–S bonds. Haloarenes are also important precursors of larger aromatic architectures and conjugated polymers, and halide incorporation provides a means to tune many properties, including redox potentials, HOMO–LUMO energies, conformational structure, and crystal packing.[2] Finally, PHAs comprise flame-retardants, agrochemicals, and molecular recognition systems[3,4] with functions ranging from sensing[5] to halogen-bonding catalysis.[6]

Despite their importance, efficient, predictable, and modular methods to access PHAs remains challenging, particularly for aromatic systems larger than benzene. Introducing more than one halide type, such as through heterohalogenation processes,[7] increases the number of potential regioisomers. For the common halides {F, Cl, Br, I}, there are 30 dihalo- and >400 trihalobenzene regioisomers. The possibilities increase dramatically in larger systems. For example, the polyhalogenated naphthalene in Figure 1 (bottom) represents more than 3000 compounds if X^1–X^5 are every combination of five substituents {F, Cl, Br, I, H} and R and X^6 are held constant. If R is allowed to be any halogenated phenyl group, more than 5.8 million structures are possible.[8] In light of these possibilities, direct halogenation potentially affords complex mixtures and is limited to substitution patterns provided by the innate reactivity of the arene.[9] This problem has restricted the use of naphthalene moieties throughout organic synthesis and motivates the development of predictable, reliable methods to prepare polyheterohalogenated naphthalenes (PHHNs).

Cycloaddition strategies are useful for building carbocycles in a convergent manner.[10,11] The Cu-catalyzed benzannulation of acetylenes, including diarylacetylenes to provide 2,3-diarylnaphthalenes, was first reported by Yamamoto and co-workers,[12] although the regioselectivity of this transformation was not investigated. We recently employed a fluorobenzaldehyde cycloaddition partner (Figure 1, middle),[13] which provided single regioisomers for diarylacetylenes with significant electronic differences between their aryl substituents. However, the imperfect regioselectivity for diarylacetylenes lacking this electronic difference, combined with the poor reactivity of diarylacetylenes bearing even weak electron-withdrawing groups, limits the utility of this transformation. The possibility of overcoming both of these limitations motivated the present investigation of the benzannulation of haloalkynes.

Here we access specific PHHN regioisomers via the benzannulation of haloalkynes using arylbenzaldehydes (Figure 1, bottom). Our approach provides PHHNs in a programmable manner, enabling the controlled incorporation of halides at six of the eight positions of the naphthalene, along with diverse aryl substituents at the 2 position. As such, most of the PHHNs are unattainable by other methods, yet both the haloalkyne[14] and 2-(phenylethynyl)benzaldehyde substrates are prepared in one step from commercial building blocks: haloalkynes via halogenation of the corresponding terminal acetylene[14,15] or

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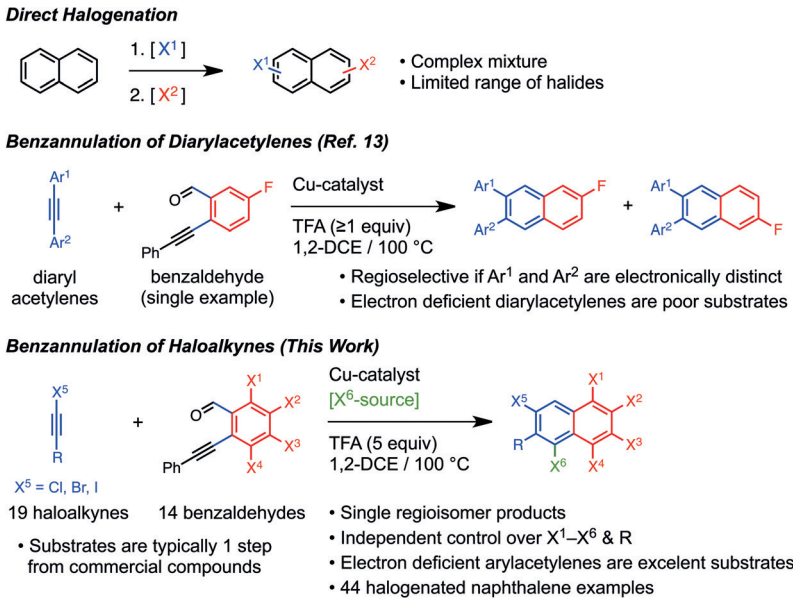


Figure 1. Illustration of synthetic challenge for naphthalene halogenation (top), previous work on the regioselective benzannulation of diarylacetylenes (middle), current work on the regioselective benzannulation of haloalkynes to access polyheterohalogenated naphthalenes (bottom).

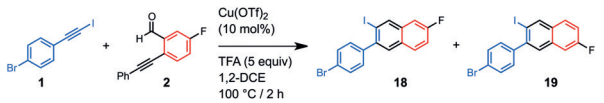
TMS-protected acetylene,[16] and substituted benzaldehydes from the corresponding 2-iodo or 2-bromobenzaldehyde.

Results and Discussion

We first optimized the benzannulation of iodoalkyne **1** with fluorobenzaldehyde **2** (Table 1). Under the optimized conditions (entry 1), the reaction of **1** (1 equiv, 0.05 M in 1,2-DCE) and excess **2** (1.7 equiv) in the presence of 10 mol% of $Cu(OTf)_2$ and CF_3CO_2H (5 equiv) affords naphthalene **18** in 94% yield with excellent regioselectivity (**18**:**19** > 98:2). Entry 2 illustrates that $Cu(OTf)_2$ is necessary for the formation of **18**, while the omission of CF_3CO_2H (entry 3) results in decreased yield and erosion of the regioselectivity. The use of AcOH instead of CF_3CO_2H (entry 4) provides **18** in only slightly diminished yield (86%), such that this modification might prove useful for acid-sensitive substrates. Substitution of the $Cu(OTf)_2$ catalyst for other transition metal Lewis acids, such as $Zn(OTf)_2$ (entry 5) or AgOTf (entry 6), highlight their viability as alternate catalytic systems for the regioselective benzannulation of haloalkynes, although slightly lower yields are obtained.

Having established optimal conditions, we explored the scope and limitations of aldehydes capable of benzannulating haloalkyne **1** (Table 2). A wide variety of aldehydes (**2**–**15**) provide polyfunctionalized naphthalenes (**18**–**31**) with yields ranging from 84–97%. Functionalization is formally transferred from the benzaldehyde to the naphthalene with complete regiochemical control to install a single halide (**18**–**24**) at any of the four possible positions on the naphthalene derived from the benzaldehyde moiety. Trifluoromethylated naphthalenes are also accessible (**25**). Naphthalenes decorated with two fluorine (**26**), two chlorine (**27**), three fluorine (**28**), two methyl (**30**), two methoxy (**31**) groups or no additional substituents (**29**) derived from the benzaldehyde reagent are viable targets. The limitations on the aldehyde component are illustrated by the

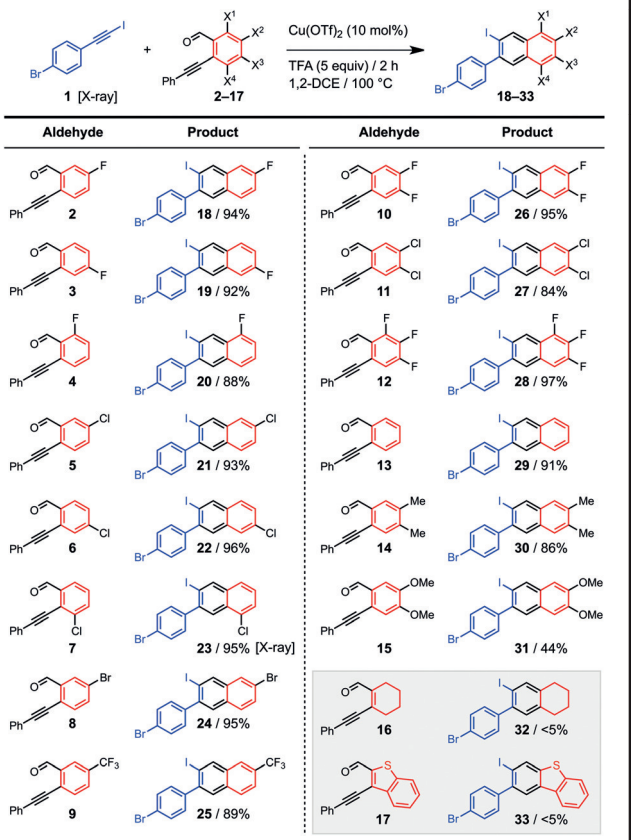
Table 1. Reaction outcomes upon deviating from the optimal conditions.[a]



Entry	Change to optimal conditions	Yield of **18** [%]	Ratio **18**:**19**
1	none	94	>98:2
2	no $Cu(OTf)_2$	<5	NA
3	no CF_3CO_2H	19	83:17
4	AcOH instead of CF_3CO_2H	86	>98:2
5	$Zn(OTf)_2$ instead of $Cu(OTf)_2$	81	>98:2
6	AgOTf instead of $Cu(OTf)_2$	76	>98:2

[a] Data measured by ^{19}F NMR spectroscopy with hexafluorobenzene as an internal standard. NA = not available.

Table 2. Benzaldehyde scope in the benzannulation of iodoalkyne **1**.



Reaction conditions: 0.05 M of **1** in 1,2-DCE with $Cu(OTf)_2$ (10 mol%) and CF_3CO_2H (5 equiv), 100 °C, 2 h. All yields are isolated yields. Reaction scale = 0.7 mmol haloalkyne, except for substrate **14** (0.6 mmol) and **15** (0.9 mmol).

unsuccessful attempt to form tetrahydronaphthalene derivative **32** by using cyclohexene-al **16**, which decomposes under the reaction conditions. Attempts at using 2-formylbenzothiophene **17** resulted in significant recovery of unreacted aldehyde and no appreciable formation of **33**.

The scope of haloalkynes compatible with the benzannulation using aldehydes **2**–**15** is demonstrated in Table 3. Nineteen iodo-, bromo-, and chloroalkynes (**34**–**51**) derived from substituted phenylacetylenes were successfully utilized, and each reliably provided only one observable naphthalene regioisomer with no deviation from our predictive model (vide infra). Single-crystal X-ray crystallography of eight naphthalene products (**23**, **56**, **60**, **64**, **68**, **71**, **78**, and **97**, Figure 2) proves the regiochemical outcome unambiguously, which is fully consistent with structural characterization using 2D NMR analysis.[17,18]

The reaction tolerates a wide range of substituents on the haloalkyne. In stark contrast to the benzannulation of diarylalkynes, which only tolerates electron-rich arenes,[13] haloalkynes attached to electron-deficient arenes are excellent substrates. Haloalkynes based on arenes substituted with a halide, an ester, an alkyne, or a nitrile form naphthalene products in excellent yields. Electron-rich arenes, such as the 4-methoxyphenyl-substituted bromoalkyne (**40**), afford the naphthalene product in a diminished yield, perhaps due to their decreased thermal stability. Haloalkynes lacking an arene (**52**–**54**) were poor substrates. The two-fold benzannulation of bis(haloalkynes) substrates (**49**–**51**) demonstrates the ability to prepare bis(naphthalenes) with useful halogenation patterns of interest for polymerization or the on-surface synthesis of carbon nanostructures.[19] Furthermore, bis(hetero-haloalkyne) **50** provides

Table 3. Substrate scope for haloalkyne benzannulation.

Reaction conditions: 0.05 M in haloalkyne substrate (0.5–1.2 mmol scale) in 1,2-DCE with $Cu(OTf)_2$ (10 mol%) and CF_3CO_2H (5 equiv), 100 °C, 2 h. All yields are isolated yields.

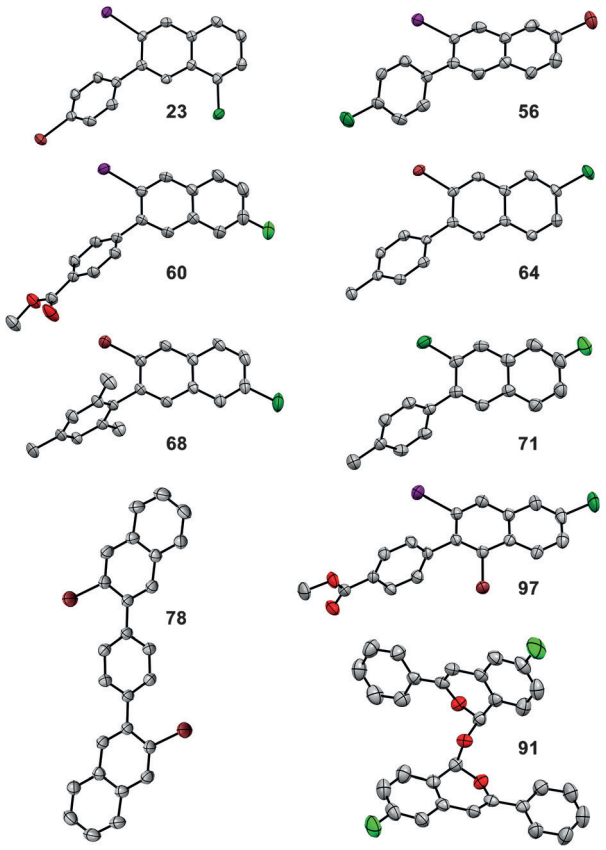
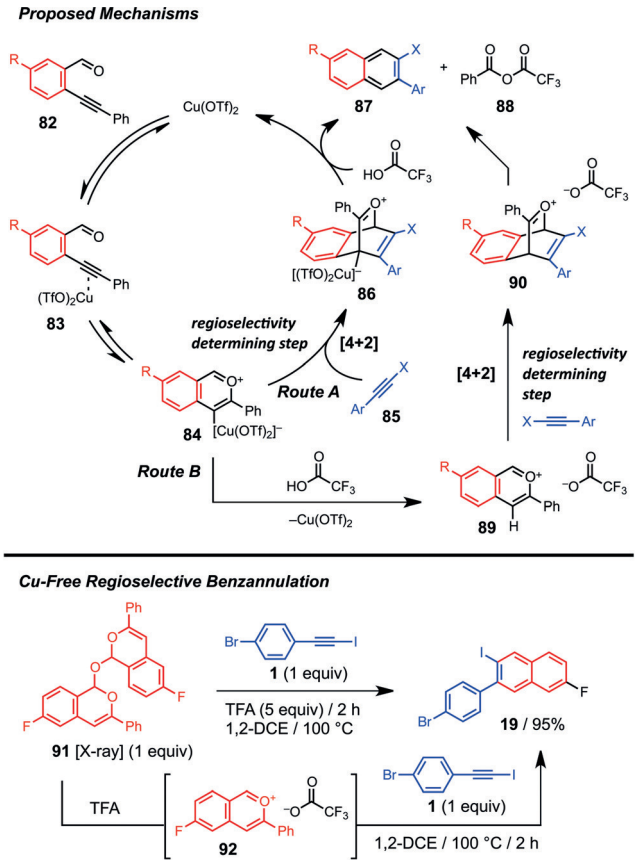


Figure 2. Single-crystal X-ray structures of naphthalene products **23**, **56**, **60**, **64**, **68**, **71**, **78**, **97**, and ketal **91** (thermal ellipsoids shown at the 50% probability level). Element coloring scheme: C = silver, O = light red, F = light green, Cl = dark green, Br = dark red, I = purple.



Scheme 1. Top: Proposed mechanistic scenarios: Route A: Benzopyrylium formation, formal [4+2] followed by protonation/retro [4+2]. Route B: Benzopyrylium formation, protonation of Cu-intermediate followed by formal [4+2], then retro [4+2]. Bottom: Cu-free regioselective benzannulation of haloalkynes **1** using ketal **91**, demonstrating the viability for Route B.

a desymmetrized building block for the synthesis of unsymmetrical structures or oligomeric materials.

Two mechanistic pathways are consistent with the observed reaction outcomes (Scheme 1), one of which (Route A) was proposed by Yamamoto and co-workers[12] for the benzannulation of diarylacetylenes and the other (Route B) is proposed here for the first time. In each route, $Cu(OTf)_2$ is proposed to complex to the alkyne of the benzaldehyde (**82**), providing **83** which cyclizes to a copper-bound benzopyrylium (**84**) that is the divergent point for two mechanistic pathways. In route A, C–C bond formation between the benzopyrylium and the haloalkyne precedes protonation of the Cu–C bond, whereas protonation occurs prior to C–C bond formation in route B. In route A, the formal [4+2] occurs while the copper is still bound to the benzopyrylium, followed by protonation of intermediate **86** and finally retro-[4+2] along with formation of mixed anhydride **88** provides naphthalene **87**. In route B, protonation of Cu-intermediate **84** occurs first, followed by the formal [4+2] cycloaddition of benzopyrylium **89** with the haloalkyne, and finally a retro[4+2] from adduct **90** to the naphthalene product (**87**) and anhydride **88**. To gain insight into the viability of route B, we reacted 1 equiv of ketal dimer **91** with 1 equiv of iodoalkyne **1** (0.05 M in 1,2-DCE) in the presence of 5 equiv of CF_3CO_2H at 100 °C for 2 h, which afforded halogenated naphthalene **19** in 95% yield as a single regioisomer (Scheme 1, bottom), the same isomer obtained via the $Cu(OTf)_2$ catalysis conditions with **3** instead of **91**. This result is consistent with the regioselectivity of the benzannulation being governed by the electronic nature of the substituents on the acetylene, for which we developed a DFT model to predict the regioselectivity outcome by calculating relative stabilities of a carbocation derived from the acetylene used in the reaction (see Supporting Information Figure S223).[17]

DFT calculations identified regioisomeric transition states associated with the first C–C bond forming step between the haloalkyne and benzopyrylium intermediates associated with both route A and route B (Figure 2).[17] The electronic energy difference between the proposed regioselectivity-determining transition states correctly predicts the experimentally observed regiochemical outcome. In route A, DFT predicts the major transition state is 5.6 kcal mol^{-1} lower in energy than the minor transition state (Figure 3), consistent with the exclusive formation of the observed regioisomer. As for route B (via the Cu-free benzopyrylium), DFT calculations of the regioisomeric transition states associated with the first C–C bond forming step predicts the major transition state being favored by 10.4 kcal mol^{-1} relative to the transition state corresponding to the unobserved regioisomer.[20] While we cannot conclusively rule out either route A or B, there is strong evidence for the viability of

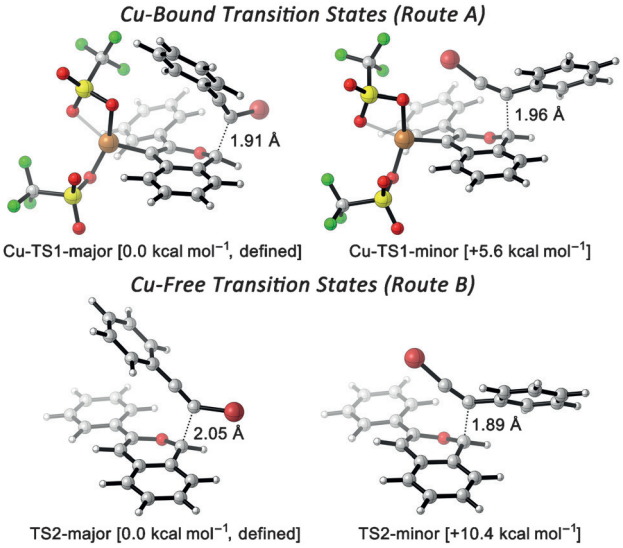


Figure 3. DFT calculated transition-states using B3LYP/6-31G(d) potentially responsible for the regioselectivity outcome in the benzannulation of haloalkynes: top: Route A, bottom: Route B (see Scheme 1). Element coloring scheme: C = silver, H = white, O = light red, F = light green, S = yellow, Br = dark red, Cu = bronze.

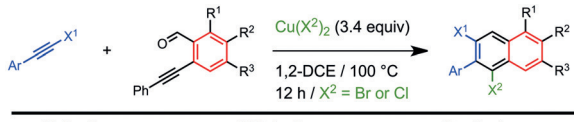
route B based on three observations: 1) the regioselective formation of **19** via a Cu-free route based on ketal dimer **91**; 2) the regiochemical outcome under $Cu(OTf)_2$ catalysis is dependent on the amount of CF_3CO_2H used (entry 3, Table 1); 3) DFT calculations of regioisomeric transition-states derived from a Cu-free benzopyrylium predict the correct regioisomer observed experimentally.

Based on the premise that the reaction proceeds via a Cu-bound benzopyrylium (**84**), regardless of whether protonation precedes the C–C bond formation with the haloalkyne, Cu-intermediate **84** provides a means to install an additional halide via functionalization of the Cu–C bond. In Table 4, we demonstrate this strategy based on using stoichiometric amounts of CuX_2, which both promotes the formation of the putative benzopyrylium and serves as the halide source. Although the reaction is regioselective, it is slower relative to the $Cu(OTf)_2$/CF_3CO_2H conditions, requiring approximately 12 h for complete haloalkyne consumption. Nevertheless, chloro-, bromo-, and iodoalkynes are all benzannulated to provide specific naphthalene products **93**–**99**, which contain up to four types of halogens. These reactions are sometimes accompanied by a naphthalene product formally derived from protolysis of the Cu–C bond in intermediate **84**, which may arise from adventitious water and was separable from the desired halogenated product in all cases except for the ester-containing 2-aryl naphthalene **97**. These results demonstrate predictable access to polyheterohalogenated naphthalenes with independent control of seven of the eight naphthalene positions.

Conclusion

We demonstrated a strategy to form complex PHHNs via a benzannulation reaction between haloalkynes and halogenated benzaldehydes. The high efficiency, complete regioselectivity, and demonstrated modularity of this approach will enable substituted naphthalenes to be used as synthetic intermediates in many new contexts. Insight into the reaction mechanism and the origin of the regioselectivity in these benzannulations was obtained from experimental and computational studies using DFT calculations, including those of transition states. As a result, a sound understanding of the reaction has emerged, including a model to predict the regiochemical outcome of this haloalkyne benzannulation. This method ultimately provides access to polyheterohalogenated naphthalenes with independent control of seven of the eight naphthalene positions. We are now using this transformation to prepare larger polycyclic aromatic hydrocarbon architectures with complex substitution patterns and employing these products as building blocks for the in-solution and on-surface synthesis of carbon nanostructures.

Table 4. Concomitant regioselective benzannulation of haloalkynes (0.7–0.9 mmol scale) and halogenation using CuX_2. All yields are isolated yields.



Haloalkyne	Aldehyde	Product
47	**2**	**93** X^2 = Cl / 55% **94** X^2 = Br / 43%
42	**2**	**95** / 59%
1	**2**	**96** / 77%
38	**5**	**97** X^2 = Br [X-ray] **98** X^2 = H 67% of **97**:**98** = 73:27
1	**12**	**99** / 78%

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Keywords: benzannulation · cycloaddition · halogenation · polycyclic aromatic hydrocarbons · reaction mechanisms

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[8] Over 29 million regioisomer are possible if X^6 is also allowed to vary as either F, Cl, Br, I, or H.

[9] The electrophilic mono- and dihalogenation of naphthalene provides mixtures of regioisomers. The synthetic challenges of rapidly accessing tri- or poly-heterohalogenated naphthalenes with regiochemical control dramatically increases the level of difficulty beyond current available methods, particularly if the desired isomer clashes with the innate reactivity of the arene. For further reading, see: a) J. F. Suyver, J. P. Wibaut, *Recl. Trav. Chim. Pays-Bas.* **2010**, *64*, 65 – 79; b) F. L. J. Sixma, J. P. Wibaut, *Recl. Trav. Chim. Pays-Bas.* **2010**, *69*, 577 – 584; c) J. P. Wibaut, F. L. J. Sixma, J. F. Suyver, *Recl. Trav. Chim. Pays-Bas.* **2010**, *68*, 525 – 546.

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