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Cu-Catalyzed Cascades to Carbocycles: Union of Diaryliodonium Salts with Alkenes or Alkynes Exploiting Remote Carbocations

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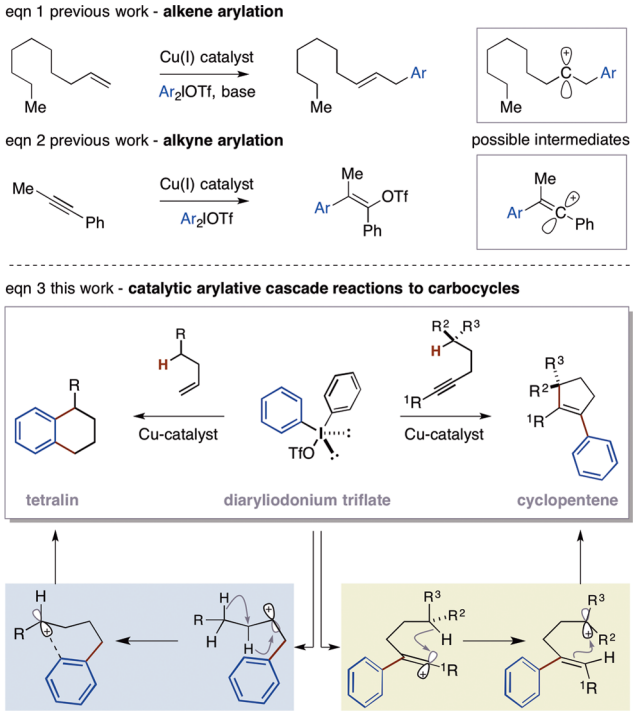
Supporting Information

ABSTRACT: Copper-catalyzed cascade reactions between alkenes or alkynes and diaryliodonium salts form carbocyclic products in a single step. Arylation of the unsaturated functional group is proposed to form a carbocation intermediate that facilitates hydride shift pathways to translocate the positive charge to a remote position and enables ring formation via a Friedel–Crafts-type reaction.

The reaction of alkenes and alkynes with carbon electrophiles provides an efficient method to form complex, functionalized carbocations that underpin a wide range of useful chemical transformations.[1] Recently, our group introduced the concept of aromatic electrophile equivalents generated from the combination of diaryliodonium salts and copper catalysts via the intermediacy of Cu(III)–aryl species.[2] We showed that this method can be used to engage alkenes and alkynes to form the basis for a number of new carbofunctionalization processes that proceed through putative trivalent and divalent carbocations.[2c,e,f] The interception of these reactive species via elimination or through attack with nucleophiles leads to useful alkene products (eqs 1 and 2). Here we report that by suppression of these pathway-terminating steps, the Cu-catalyzed arylation of alkenes and alkynes can be coupled with carbocation-induced hydride shift processes to formulate cascade reactions that generate complex carbocycles; alkenes undergo the arylative cascade reaction to give functionalized tetralins, whereas alkynes give complex cyclopentenes (eq 3). The efficacy of these transformations is evident from the manner in which the complexity of the products can be generated from simple starting materials in a single catalytic process.

Control of the fate of carbocations has been well-documented and underpins a number of well-established transformations. A particularly important pathway for these reactive species is hydride transfer, a process by which the σ electrons in a C–H bond move to intercept a nearby carbocation. Although the 1,2-hydride shift is most common, other pathways such as 1,5-hydride shifts are also known.[3] On the basis of our previous Cu-catalyzed arylation studies, we speculated that the presence of an unfunctionalized aliphatic substituent on the alkene or alkyne would coerce the putative carbocation-like intermediate into participation in hydride shift events. This would lead to a translocation of the carbocation to a position in the molecule that is remote from the original unsaturated functionality and would set up a reactive center that could be intercepted through a



Friedel–Crafts-type reaction, thereby leading to new carbocyclic frameworks (eq 3).[4,5]

Our initial studies focused on the cascade reaction with alkenes. The reaction of diphenyliodonium triflate (**1a**) with alkene **2a** under conditions similar to those used in our original alkene arylation (Table 1, entry 1),[2c] as expected, gave no tetralin product (**3a**), and a 70% yield of a 7.7:1 mixture of alkene regioisomers (not shown) was formed. However, when we reduced the amount of the base, 2,6-di-*tert*-butylpyridine (DTBP), to increase the concentration of triflic acid (TfOH) in the reaction mixture and favor the key carbocation intermediate (entries 2 and 3), we were delighted to find that tetralin **3a** was formed in moderate yield, and only trace quantities of alkenes were observed. Furthermore, the cyclization produced the tetralin framework exclusively, and the indane ring was not detected. Changing from a Cu(II) salt to a Cu(I) salt (entry 4), the use of 4 Å molecular sieves in place of DTBP (entries 5–8),[6] and the addition of TfOH ultimately led to an

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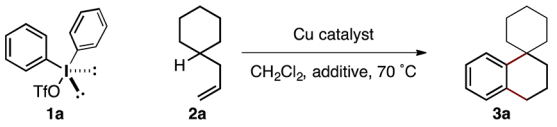
Table 1. Optimization of the Alkene Arylation Cascade



entry	Cu catalyst	additive (amount)	yield of **3a** (%)[a]
1	5 mol % $Cu(OTf)_2$	DTBP (200 mol %)	0
2	5 mol % $Cu(OTf)_2$	DTBP (70 mol %)	38
3	5 mol % $Cu(OTf)_2$	DTBP (50 mol %)	55
4	5 mol % $Cu(OTf)_2$·PhMe	DTBP (50 mol %)	62
5	5 mol % $Cu(OTf)_2$·PhMe	4 Å MS (0.17 g/mmol)	76 (65)
6	5 mol % $Cu(OTf)_2$·PhMe	4 Å MS (0.15 g/mmol)	58
7	5 mol % $Cu(OTf)_2$·PhMe	4 Å MS (0.22 g/mmol)	20
8	5 mol % CuTC	4 Å MS (0.17 g/mmol)	78 (67)
9	5 mol % CuTC, 5 mol % TfOH	4 Å MS (0.17 g/mmol)	84 (76)
10	no catalyst	4 Å MS (0.17 g/mmol)	0
11	no catalyst, 5 mol % TfOH	4 Å MS (0.17 g/mmol)	0

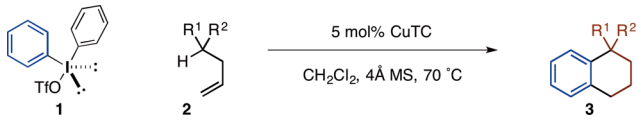
[a]Yields based on ^{1}H NMR analysis (yields of isolated products are shown in parentheses).

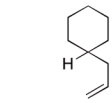
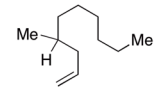
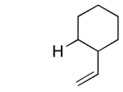
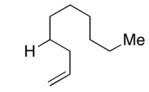
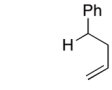
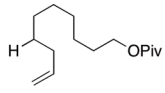
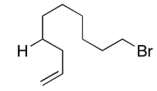
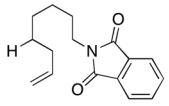
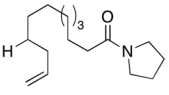
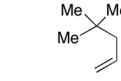
optimized process using the air-stable catalyst copper(I) thiophene-2-carboxylate (CuTC) that produced **3a** in 76% yield (entry 9). No reaction was observed in the absence of catalyst (entries 10 and 11).

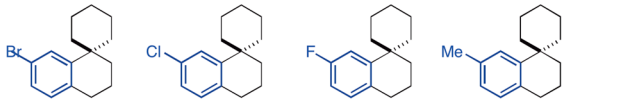
We next investigated the scope of this transformation by examining the alkene component. Simple aliphatic alkenes perform well under these conditions with cyclization onto methine carbons, providing good yields of the tetralins displaying all-carbon quaternary centers (Table 2: **3a**, **3b**). The cascade process can also generate polycyclic tetralins when the alkene is directly attached to a cycloalkane (**3c**). The reaction also works with systems involving cyclization onto an acyclic methylene carbon (**3d**), and we have shown that functionality can be incorporated into such substrates accommodating aromatic, halogen, carbonyl, and protected nitrogen groups (**3e**–**i**). Finally, alkenes lacking the capacity for the final hydride shift instead utilize a 1,2-alkyl shift to generate the key carbocation that leads to a tetralin displaying a substituent within the aliphatic ring (**3j**). Investigations into the aryl component revealed that both meta- and para-substituted arenes are effective in this transformation, while ortho-substituted arenes are, thus far, not tolerated.[7] The reaction works comparably with both electron-rich and electron-deficient aryl groups. Halide motifs are accommodated by the reaction conditions and provide further opportunities for postcascade modification of the tetralin scaffold.[8]

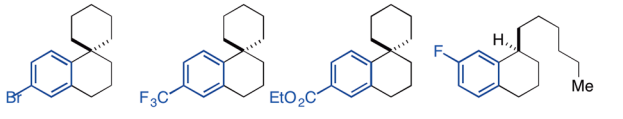
We also demonstrated how the Cu-catalyzed cascade process can streamline the synthesis of BMS-189453, a retinoid receptor agonist that has indications as a male contraceptive (Scheme 1).[8c] Alkene **2k** can be treated with **1f** under the standard conditions to give tetralin **3s** in 82% yield. Benzylic oxidation of **3s** produces tetralone **4** in (unoptimized) 55% yield. Heck reaction with styrene **5** produces the key intermediate **6** in 78% yield. Our strategy intercepts a late-stage intermediate (**6**) in the original synthesis in only three steps and overall would reduce by half the 11 steps previously required to obtain BMS-189453.

Table 2. Scope of the Alkene Arylation Cascade



Entry	Alkene	conditions	Yield, %	Product
1		10 mol% CuTC 5 mol% TfOH	76	**3a**
2		5 mol% CuTC 5 mol% TfOH	70	**3b**
3		5 mol% CuTC	52	**3c**
4		5 mol% $(CuOTf)_2$·PhMe	52	**3d**
5		10 mol% CuTC	62	**3e**
6		10 mol% CuTC 5 mol% TfOH	52	**3f**
7		5 mol% CuTC	54	**3g**
8		5 mol% CuTC 75 mol% TfOH	52	**3h**
9		5 mol% CuTC 75 mol% TfOH	52	**3i**
10		5 mol% CuTC 22 mol% TfOH	52	**3j**





A number of experiments were performed to probe the carbocation migration hypothesis of this reaction (Scheme 2). The parent alkene arylation process generates a mixture of allylbenzene **7** and styrene **8** (also see Table 1, entry 1).[2c] When we treated each of these alkenes with TfOH, we observed that **7** was converted to tetralin **3a** in high yield, whereas complete decomposition was observed when styrene **8** was subjected to the

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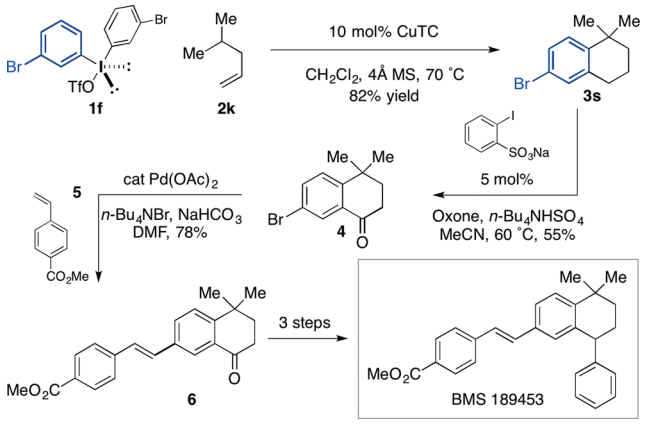
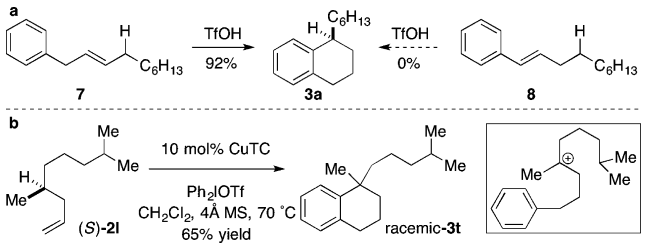
Scheme 1. Synthesis of BMS-189453



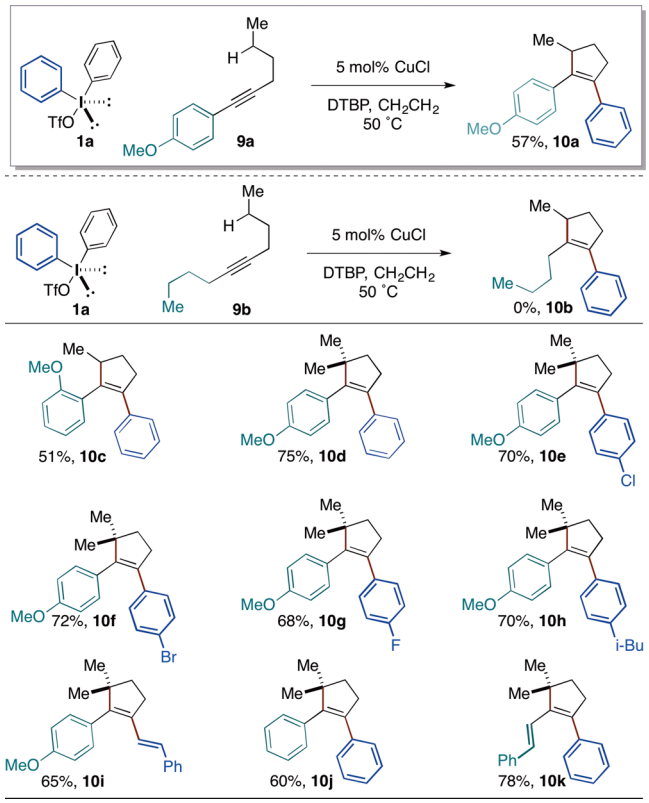
Scheme 2. Mechanistic Experiments



same treatment.[9] This suggests that the tetralin arises from a series of alkene isomerizations or 1,2-hydride shifts originating from the homobenzylic carbocation (eq 3) that is formed from the initial alkene arylation step[10,11] and that the yield of the reaction is likely linked to the regioselectivity (**7** vs **8**) in the initial Cu-catalyzed step. When the enantioenriched alkene **2l** was reacted under the standard conditions, only racemic **3t** was returned, further supporting the carbocation hypothesis.

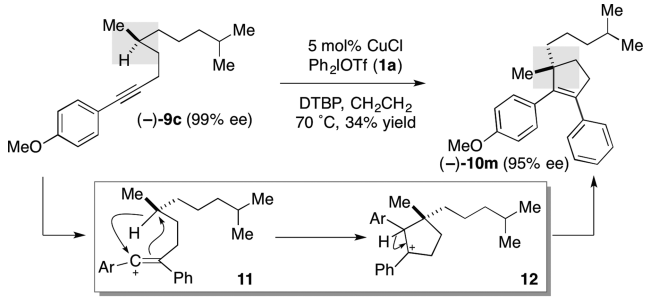
Next, we turned our attention to investigating a corresponding arylative cascade reaction starting from substituted alkynes (eq 3). Guided by the stabilization requirements of the putative divalent carbocation and previous observations relating to the intermediacy of these species in our Cu-catalyzed carbofunctionalization processes,[2d,e] we selected alkyne **9a** with an electron-rich aryl substituent at one end of the carbon−carbon triple bond and an *n*-butyl chain at the other. In this substrate, a number of C−H bonds are presented for potential engagement with the vinyl carbocation intermediate. Accordingly, when we treated **9a** under similar Cu-catalyzed conditions as in the alkene cascade we observed cyclopentene **10a**, originating from a 1,5-hydride shift with the pendant methylene group (Scheme 3). The vinyl carbocation-stabilizing group is best suited to an sp^2-hybridized substituent attached the alkyne, as alkyl analogues did not give the cyclic product **10b** and instead formed an acyclic tetrasubstituted alkenyl triflate (not shown). We obtained good yields of cyclopentenes when the hydride shift involved a methine center, in line with a more stable trivalent carbocation (to **10d**). A range of diaryliodonium salts can be successfully accommodated by the reaction (**10e**−**h**), and even a vinyl(aryl)-iodonium salt worked well to form diene **10i**. We also found that we could diverge from the requirement of strongly electron-donating aryl groups on the alkyne and showed that phenyl and styryl groups sufficiently stabilized the proposed vinyl carbocation to initiate the cascade carbocyclization to give the cyclopentene products (**10j**, **10k**).

Scheme 3. Alkyne Cyclization To Give Cyclopentenes



Intrigued by the mechanism of this process, we conducted an experiment with an enantioenriched alkyne. Remarkably, when we subjected (−)-**9h** to the standard conditions we formed the enantioenriched cyclopentene (−)-**10m** with minimal erosion of ee (Scheme 4).[12a] According to our alkene cascade hypothesis, a

Scheme 4. Retention of Stereochemical Integrity



1,5-hydride shift is concerted with the cyclization onto the vinyl cation

1,5-hydride shift should have taken place to translocate the carbocation to the tertiary carbon, destroying the resident stereogenicity, prior to Friedel−Crafts-type cyclization with the newly formed trisubstituted alkene (eq 3). However, the retention of stereogeneity suggests that there is a divergent pathway for the hydride shift onto the vinyl carbocation. On this basis, we revised the pathway for cyclopentene formation such that initial Cu-catalyzed alkyne arylation forms vinyl carbocation intermediate **11** (via the vinyl triflate).[12b] A concerted 1,5-hydride shift−carbocation interception would form **12** prior to the elimination that forms the product **10m**. We note that Metzger,[5a] Yamamoto,[5b] and Muniz[5c] reported studies on related electrophile-induced reactions of alkynes, the first of

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which also suggests a concerted 1,5-shift pathway. Our observation reinforces this model, and the enantioretention during this carbocation-mediated process represents an exciting and rare finding.

In summary, we have developed a distinct Cu-catalyzed cascade transformation to form tetralins and cyclopentenes from readily available starting materials. The related two processes are made mechanistically distinct by the way in which the initial carbocation intermediate is translocated to a remote carbon atom prior to its interception via a Friedel−Crafts-type reaction. A series of 1,2-hydride shifts define the arylative alkene cascade to tetralins through a classical cabocation-type pathway. In contrast, the cyclopentene formation is notable for a concerted 1,5-hydride shift process that retains stereochemical information at the site of the carbocation-type intermediate. Overall, we believe that the efficacy and mechanistic divergency of these strategies will be broadly useful for the design of novel carbocation reactions.[13]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(2) For selected examples, see: (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (b) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (c) Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773. (d) Bigot, A.; Williamson, A. E.; Gaunt, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 13778. (e) Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 5332. (f) Walkinshaw, A. J.; Xu, W.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 12532. (g) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260.

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(6) We believe that DTBP and molecular sieves serve as a buffer for the TfOH generated in the reaction or simply as a desiccant.

(7) For a review see: Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052.

(8) For examples, see: (a) Boehm, M. F.; Zhang, L.; Zhi, L.; McClurg, M. R.; Berger, E.; Wagoner, M.; Mais, D. E.; Suto, C. M.; Davies, P. J. A. *J. Med. Chem.* **1995**, *38*, 3146. (b) Endo, Y.; Takehana, S.; Ohno, M.; Driedger, P. E.; Stabel, S.; Mizutani, M. Y.; Tomioka, N.; Itai, A.; Shudo, K. *J. Med. Chem.* **1998**, *41*, 1476. (c) Chung, S. S. W.; Wang, X.; Roberts, S. S.; Griffey, S. M.; Reczek, P. R.; Wolgemuth, D. J. *Endocrinology* **2011**, *152*, 2492. (d) Wood, T. F.; Easter, W. M.; Carpenter, M. S.; Angiolini, J. *J. Org. Chem.* **1963**, *28*, 2248.

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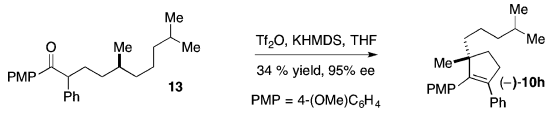
(10) (a) Bright, S. T.; Coxon, J. M.; Steel, P. J. *J. Org. Chem.* **1990**, *55*, 1338. Also see: (b) Schmerling, L.; Vesely, J. A. *J. Org. Chem.* **1973**, *38*, 312. (c) Olah, G. A.; Schilling, P.; Staral, J. S.; Halpern, Y.; Olah, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 6807. (d) Yonehara, F.; Kido, Y.; Morita, S.; Yamaguchi, M. *J. Am. Chem. Soc.* **2001**, *123*, 11310.

(11) When the reaction to form **3j** was performed with TfOD (Table 2, entry 10) we observed 15% deuterium incorporation at the two methylene positions in the aliphatic ring, which is suggestive of a hydride shift mechanism. This reaction was chosen for simplicity, and we note that it may not be representative of other substrates.

(12) (a) The configuration is assumed on the basis of retention of configuration. (b) Possible intermediacy of a vinyl triflate:



(13) For a related reaction using C−H activation on an alkene, see: Stang, E. M.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 14892.