Copper-Catalyzed Alkene Arylation with Diaryliodonium Salts

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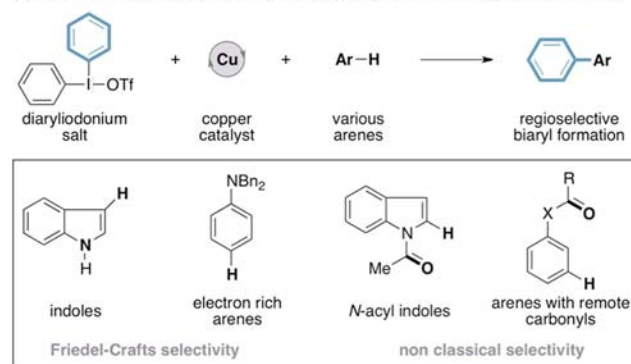
S *Supporting Information*

ABSTRACT: Alkenes and arenes represent two classes of feedstock compounds whose union has fundamental importance to synthetic organic chemistry. We report a new approach to alkene arylation using diaryliodonium salts and Cu catalysis. Using a range of simple alkenes, we have shown that the product outcomes differ significantly from those commonly obtained by the Heck reaction. We have used these insights to develop a number of new tandem and cascade reactions that transform readily available alkenes into complex arylated products that may have broad applications in chemical synthesis.

(1) Previous work – Copper-catalyzed direct arylation with diaryliodonium salts[4]

(2) This work – A new reactivity platform using copper-catalyzed alkene arylation

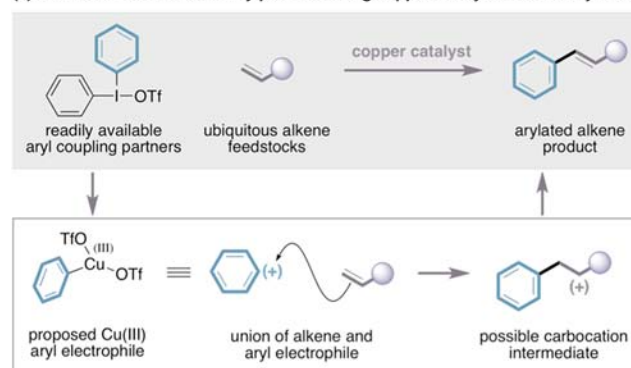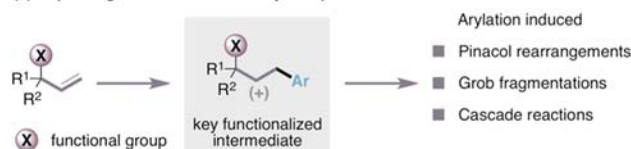(3) Exploiting the diverse reactivity of a possible carbocation intermediate

Chemical reactions that link alkenes and arenes are central to both industrial and academic research, as the products of their union provide a foundation upon which natural products, medicines, polymers, and fine chemicals can be synthesized. The development of novel reactions that exploit the vast array of alkene feedstocks therefore represents a continuing challenge to chemical synthesis.[1] While alkenes activated with functional groups tend to be predisposed toward bond-forming reactions, simple unfunctionalized alkenes are often less reactive as either nucleophiles or electrophiles. Many of these reactivity limitations have been overcome by using transition-metal (TM) catalysts, as evidenced by the Heck reaction, which takes advantage of the affinity of Pd(II)—aryl intermediates for the π system of alkenes.[2] While Cu-catalyzed processes have frequently paralleled Pd-catalyzed cross-couplings,[3a−d] Cu-catalyzed Heck-type coupling reactions are less common.[3e−i]

We have recently developed a new Cu-catalyzed arylation strategy that is often complementary to Pd-catalyzed methods.[4] On the basis of an original working hypothesis that Cu(III)—aryl intermediates[5] would be isoelectronic with the corresponding Pd(II) species, a series of Cu-catalyzed site-selective direct arylations can be used to form biaryl compounds from a range of simple arenes and diaryliodonium salts (eq 1).[6,7] While the precise mechanism remains unclear, this combination of a Cu catalyst and a diaryliodonium salt appears to behave as an activated aromatic electrophile, paralleling the Friedel—Crafts-type reactivity operational in more established electrophilic aromatic substitutions. We therefore investigated the arylation of alkenes based on this mechanistic postulate on the premise that such a catalytic process (eq 2) would potentially open up a wide and mechanistically distinct range of new C—C bond-forming reactions (eqs 2 and 3).[8,9] Furthermore, such a transformation would complement the recent reports of Cu-catalyzed alkene trifluoromethylation using hypervalent iodine reagents,[10] reinforcing the potential efficacy of the reaction

platform. Herein we describe the realization of this ideal through an operationally simple Cu-catalyzed process for the union of alkenes and arenes. This new Cu-catalyzed arylation may proceed by a reaction pathway displaying carbocation-like character, allowing the development of a number of novel tandem and cascade reactions that could expedite the synthesis of complex molecules.

To test our Cu-catalyzed alkene arylation, we treated 1-decene (**1a**) with diphenyliodonium triflate, 2,6-di-*tert*-butylpyridine (DTBP) as the base, and 10 mol % Cu(OTf)$_2$ in dichloroethane (DCE) at 70 °C, the standard conditions adopted in our previous studies.[4] We were pleased to find that

alkene arylation proceeded to give a mixture of **3a** and **4a** in reasonable yield (Table 1). Intriguingly, the nonconjugated

Table 1. Optimization of Cu-Catalyzed Alkene Arylation

entry	catalyst 10 mol%	X	solvent	yield 3a+4a %	ratio 3a:4a[a]
1	Cu(OTf)$_2$	OTf	DCE	61	3.5:1
2	Cu(OTFA)$_2$	OTf	DCE	38	2.7:1
3	Cu(OAc)$_2$	OTf	DCE	53	3.0:1
4	CuCl$_2$	OTf	DCE	49	2.7:1
5	CuCl	OTf	DCE	45	5.0:1
6	CuI	OTf	DCE	32	2.3:1
7	CuBr(PPh$_3$)$_3$	OTf	DCE	67	2.8:1
8	Cu(OTf)$_2$	BF$_4$	DCE	–	–
9	Cu(OTf)$_2$	OTf	CH$_2$Cl$_2$	95 (72)[b]	3.5:1[c]
10	no catalyst	OTf	DCE at 110 °C	39	1.8:1

[a]Yields and ratios were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b]Yield of isolated product after chromatography. [c]**3a** (E:Z = 5.5:1), **4a** (E:Z = 3.0:1).

major product **3a** contrasts with the outcome of a typical Heck reaction, which would produce a styrene. Encouraged by this initial result, we assessed the effect of varying the Cu catalyst, diaryliodonium salt, and solvent as well as the standard reaction parameters. The most pertinent observations during the optimization study were that (a) Cu(I) and Cu(II) salts catalyzed the reaction, (b) diphenyliodonium triflate was the superior coupling partner,[7] and (c) reaction was observed in the absence of the Cu catalyst only at 110 °C (entry 10). The optimal conditions gave alkene arylation in 72% yield as a 3.5:1 mixture of nonconjugated:styrene products (entry 9).[10]

On the basis of our catalyst screening (Table 1), we routinely assessed a number of Cu salts in our alkene scope study. While we did not identify any consistent trends between the Cu salt and the yield, some catalysts clearly worked better for some substrates than others. Along with arylation of linear terminal olefins (Table 2, entry 1), the arylation of cyclohexene proceeded smoothly, delivering a 4:1 ratio of styrene **4b** to allylic product **3b** (entry 2). This contrasts sharply with the typical outcome of Heck reactions on this substrate. Since Heck reactions on indenes[11a] and dihydronaphthalenes[11b] commonly afford mixtures of arylalkenes, we were pleased to find that our arylation process gave single isomers for these substrates (entries 3−5). Styrenes were arylated smoothly to give (E)-stilbene products (entries 6 and 7), and an allyl pivalate gave a single arylated regioisomer, **4h**, with no evidence of allylic substitution (entry 8). Enol ethers underwent exclusive arylation at the β-position (entry 9),[11c] whereas the corresponding Heck reaction frequently delivers the α-aryl product.[11d] Pleasingly, 1,1-disubstituted alkenes and a hetero-cyclic variant delivered products with a high selectivity for the isomer with the endocyclic double bond (entries 10 and 11).[11e] Vinylcyclohexene produced a mixture of three double-bond regioisomers, with the major isomer being the homoallylic arene product **5l** (entry 12). Heck reactions on substrates similar to those in entries 10−12 produce the styrenyl isomers exclusively.[11f,g] A trisubstituted alkene underwent arylation to give **3m**, although the yield was low, presumably because steric effects hindered the reaction. While less reactive alkenes such as *trans*-2-octene gave a complex mixture of arylation and isomerization products, placement of a trimethylsilyl group at

Table 2. Scope of the Alkene Arylation

entry	alkene	conditions	product	yield % (3:4)
1		10 mol% Cu(OTf)$_2$ CH$_2$Cl$_2$, 70 °C		**3a** 72 (3.5:1)
2		10 mol% CuTC CH$_2$Cl$_2$, 50 °C		**4b** 73 (1:4.0)[a]
3		10 mol% CuCl DCE, 70 °C		**4c** 64
4, 5		10 mol% Cu(OTf)$_2$ CH$_2$Cl$_2$, 70 °C		X = H, **4d** 82; X = OMe, **4e** 75
6, 7		10 mol% Cu(OTf)$_2$ CH$_2$Cl$_2$, 70 °C		X = H, **4f** 72; X = Me, **4g** 92
8		10 mol% CuCl DCE, 50 °C		**4h** 64[b]
9		10 mol% CuCl DCE, 50 °C		**4i** 61
10		10 mol% Cu(OTf)$_2$ CH$_2$Cl$_2$, 70 °C		**3j** 79 (11:1)
11		10 mol% CuCl DCE, 70 °C		**3k** 54
12		10 mol% CuCl DCE, 70 °C		**5l** 59 (4:1.3:1)[c]
13		10 mol% Cu(OTf)$_2$ CH$_2$Cl$_2$, 70 °C		**3m** 19
14		10 mol% Cu(OTf)$_2$ CH$_2$Cl$_2$, 70 °C		**3n** 52

[a]A 9% yield of a diarylated isomer was obtained. [b]An 8% yield of a diarylated isomer was obtained. [c]**5l**:**3l**:**4l** ratio.
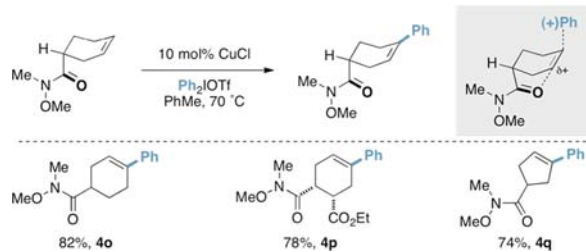
the terminal C atom gave only a single isomer, **3n**, with an alkenyl- and aryl-substituted stereogenic center (entry 14).

We selected a number of alkenes (from entries 1, 7, and 9) to test the catalyst-free reaction. With the exception of the highly reactive 4-methylstyrene (**1g**), none of these alkenes underwent any reaction in the absence of catalyst at 70 °C. In contrast to **1a**, which underwent catalyst-free arylation only at 110 °C, **1g** produced a 73% NMR yield of **4g** and dihydropyran **1i** a 10% NMR yield of **4i** at 90 °C in the absence of a Cu catalyst. While we rigorously excluded Cu from all of our control reactions, we cannot rule out the possibility that trace Cu (<10 ppm) that may have been present in the reagents or solvent could catalyze the reaction at higher temperatures.[12]

Our previous studies of meta arylation of pivanilides and α-aryl carbonyl compounds revealed a crucial reliance on the presence of a specifically located, remote carbonyl group to direct the selectivity.[4b,d] We observed a similar effect in our alkene arylation, whereby substituted, nonsymmetrical cyclo-hexenes undergo arylation exclusively at the remote alkene

carbon atom (Scheme 1). We propose that the carbonyl motif controls the selectivity by a neighboring-group effect that could

Scheme 1. Carbonyl-Directed Alkene Arylation

stabilize a developing positive charge or direct a reactive Cu species to the specific position.[13a]

Having demonstrated the new phenylation process on a range of alkenes, we were delighted to find that diaryliodonium salts with aryl groups displaying electron-rich, electron-deficient, halogen, and heterocyclic functionality also worked well (Table 3).[6]
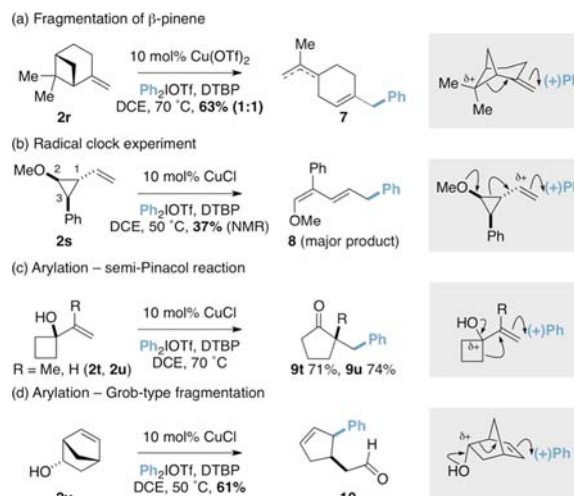
Table 3. Scope of Aryl Transfer in the Alkene Arylation

alkene	conditions	product		yield %
	10 mol% CuCl PhMe, 70 °C[a]		6a 4-F-C$_6$H$_4$	71
			6b 4-Cl-C$_6$H$_4$	80
			6c 4-(CO$_2$Et)-C$_6$H$_4$	85
			6d 4-(NO$_2$)-C$_6$H$_4$	71
			6e 3-Br-C$_6$H$_4$	83
			6f 3-(CF$_3$)-C$_6$H$_4$	84
			6g 2-F-C$_6$H$_4$	53
			6h 4-F-(3-C$_5$H$_3$N)	20
	10 mol% CuCl DCE, 50 °C		6i 4-Br-C$_6$H$_4$	77
			6j 4-Cl-C$_6$H$_4$	94
	10 mol% CuCl DCE, 50 °C		6k 4-Cl-C$_6$H$_4$	77
	10 mol% Cu(OTf)$_2$ CH$_2$Cl$_2$, 70 °C		6l 4-Me-C$_6$H$_4$	76
			6m 4-Cl-C$_6$H$_4$	73
			6n 4-F-C$_6$H$_4$	77
	10 mol% CuI, AgOTf CH$_2$Cl$_2$, 50 °C		6o 4-Br-C$_6$H$_4$	90
			6p 4-NO$_2$-C$_6$H$_4$	73[b]

[a]1.1 equiv of mesitylaryliodonium triflate and DTBP were used. [b]Yield determined by ^{1}H NMR spectroscopy.

Interestingly, many of the arylation reactions give products that could be formed through a mechanism involving the Friedel–Crafts-type reaction of an alkene with an aromatic electrophile, whereby the selectivity in the arylation step would be determined by the location of the resulting partial positive charge in the most stabilized position.[8] This hypothesis was further supported when we tested our Cu-catalyzed arylation on β-pinene (**2r**); here, we isolated **7**, a phenylated derivative of limonene, as a 1:1 mixture of elimination products (Scheme 2a). This product can be rationalized by arylation followed by either a carbocation- or a radical-mediated structural rearrangement of the bicyclo[3.1.1]heptane framework,[14] but a further experiment using terminal alkene **2s** substituted with New-
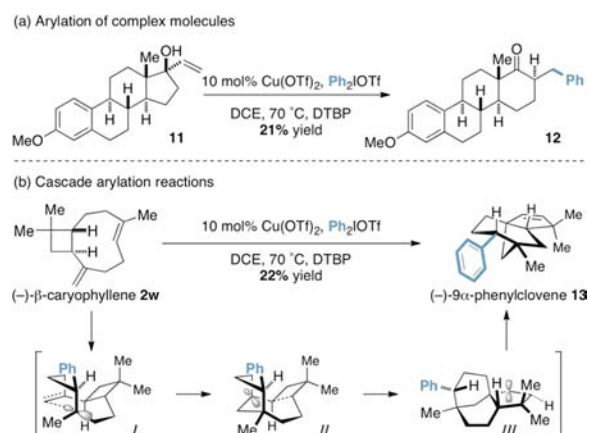
Scheme 2. Mechanistic Probes and New Tandem Reactions

comb's "radical clock" cyclopropane motif provided further mechanistic insight.[15] We established that arylation was accompanied by cyclopropyl ring fragmentation of the bond between C1 and C2 to afford enol ether **8** (Scheme 2b). This outcome suggests the intermediacy of a methoxy-stabilized carbocation, in line with Newcomb's model, and is based on the assumption that fragmentation of a cyclopropyl radical would be faster than oxidation of the radical to a carbocation.[13b]

While the precise reaction mechanism is not yet known, these studies provide a compelling model upon which to design new reactions founded on a putative carbocation intermediate. In particular, we reasoned that the strain-release-driven reactivity inherent within **2r** and **2s** could be applied to other readily available alkenes. We were pleased to find that cyclobutyl-derived tertiary allylic alcohols **2t** and **2u** afforded the corresponding benzylated cyclopentanones **9t** and **9u**, presumably via a mechanism involving tandem arylation and semipinacol ring-expanding rearrangement (Scheme 2c).[13c] Similarly, norbornenol (**2v**) was transformed into disubstituted cyclopentenal **10**, where the structural change upon arylation followed a Grob-type fragmentation pathway (Scheme 2d).[13d] We were able to effect our arylation—semipinacol rearrangement on estrol derivative **11**; the expansion of the D-ring to give **12** (Scheme 3a) represents an interesting change in the structural complexity of this steroid derivative.

Scheme 3. Arylation of Complex Molecular Scaffolds

Finally, by exploiting the presence of two reactive alkenes and a strained cyclobutane ring in the terpene β-caryophyllene (**2w**), we were able to engineer a cascade reaction that formed **13**, a phenylated analogue of the complex molecule clovene (Scheme 3b). We believe that this cascade reaction begins with arylation of the strained trisubstituted (*E*)-alkene to give **I**. This carbocation-like intermediate is intercepted through attack of the exomethylene group, generating a new carbocation adjacent to a cyclobutane (**II**) that subsequently fragments to form the clovene derivative after elimination from **III**. This remarkable process represents a novel transformation that mimics Barton's acid-mediated structural reorganization while introducing a new functional group embedded within the framework of the complex architecture.[16]

In summary, we have developed a new approach to alkene arylation using diaryliodonium salts and Cu catalysis. We have surveyed a range of simple alkenes and shown that the product outcomes differ significantly from those commonly obtained by the Heck reaction. Preliminary studies have shown that a carbocation-type mechanism may be involved in these reactions. We have used this hypothesis to design a number of new tandem and cascade reactions that transform readily available alkenes into complex molecules that may have broad synthetic appeal.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization 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.

■ ACKNOWLEDGMENTS

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