Communication

Enantioselective Copper-Catalyzed Arylation-driven Semi-Pinacol Rearrangement of Allylic Alcohols with Diaryliodonium Salts

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Enantioselective Copper-Catalyzed Arylation-driven Semi-Pinacol Rearrangement of Tertiary Allylic Alcohols with Diaryliodonium Salts

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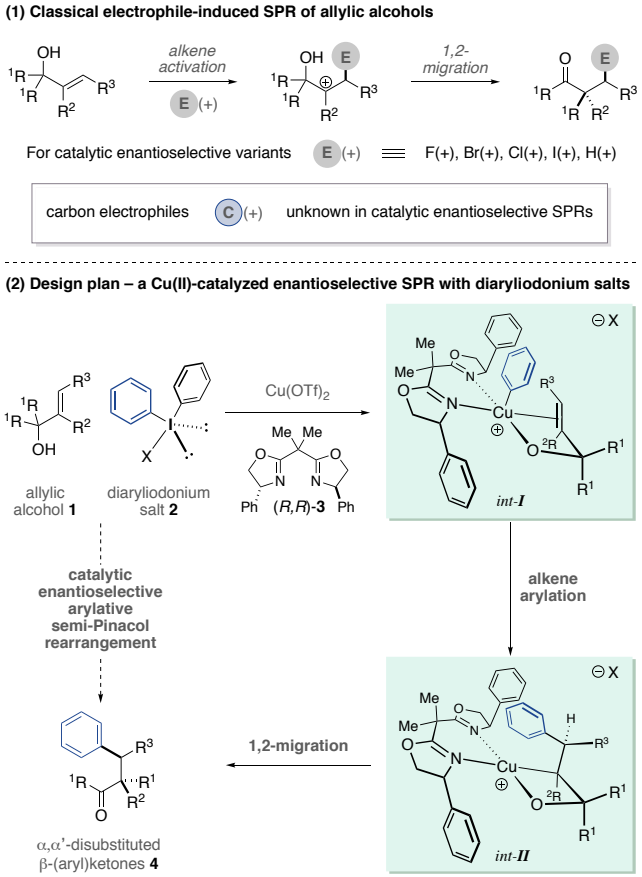
Supporting Information Placeholder

ABSTRACT: A copper-catalyzed enantioselective arylative semi-pinacol rearrangement of allylic alcohols using diaryliodonium salts is reported. Chiral Cu(II)-bisoxazoline catalysts initiate an electrophilic alkene arylation, triggering a 1,2-alkyl migration to afford a range of non-racemic spirocyclic ketones with high yields, diastereo- and enantioselectivities.

The class of reactions described as semi-pinacol rearrangements (SPRs) have become cornerstone transformations in complex molecule synthesis.[1] Described simply as a process in which a C–C or C–H bond attached to an oxygen-containing carbon atom undergoes a 1,2-migration to a vicinal electrophilic carbon center, SPRs are most easily defined by the nature of the electrophilic activation pathway. While the classical SPR involves activation of a leaving group, thereby generating the requisite electrophilic carbon, the use of allylic alcohols as substrates has dramatically expanded the efficacy of the generic transformation.[2] Based on the availability of allylic alcohols, there has been burgeoning interest in the development of catalytic enantioselective variants of this type of SPR;[3] notable seminal examples include alkene activation via halogenation[4a] and epoxidation,[4b-c] Brønsted acid-,[4d] palladium-,[4e-f] gold-,[4g-h] and Pd/Brønsted acid catalysis.[4i] Interestingly, catalytic enantioselective SPRs involving a C–C bond formation step as part of the alkene activation are rare (eqn. 1).[5] We reasoned that the asymmetric introduction of a carbon-based electrophile as part of a SPR would generate synthetically useful ketone scaffolds displaying vicinal quaternary and aryl-containing tertiary stereogenic centers, which would be non-trivial to form by alternate means.

Our laboratory,[6] and also that of MacMillan[7a,b], have introduced the use of asymmetric copper-bisoxazoline complexes in combination with diaryliodonium salts to provide convenient access to catalytically generated chiral aromatic electrophile equivalents.[7c] The chiral Cu(III)-aryl intermediates (formed as part of this activation mode) undergo union with nucleophiles such as enol silanes[6a,7a] and indoles,[7b] providing a means for enantioselective arylative cross coupling to versatile products with high enantioselectivities. Central to the success of these enantioselective arylations has been the apparent necessity for the substrate to engage in two-point binding with the Cu(III)-aryl intermediate.

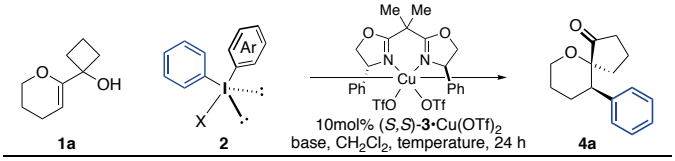


In an effort to demonstrate the wide-ranging applications of this enantioselective alkene arylation tactic, we speculated that allylic alcohols may participate in a bidentate coordination to the electrophilic Cu(III) species that could lead to an arylation-driven SPR. Our design plan for this process is shown in eqn. 2, and begins with binding of an allylic alcohol to the Cu(III)–Ar complex *int-**I***,[8] formed from the combination of allylic alcohol **1**, diaryliodonium salt **2** and the Cu-complex of bisoxazoline ligand (*R,R*)-**3**. Insertion of the Cu(III)–Ar bond to the ligated alkene generates a Cu(III)–alkyl intermediate *int-**II***. This species pos-

sesses the requisite partial positive charge adjacent to the carbinol to trigger the stereoselective 1,2-migration of one of the carbinol substituents and complete an arylation-driven SPR to non-racemic α,α'-disubstituted-β-arylketone **4**.[9]

To test this hypothesis, we selected allylic alcohol **1a**, in combination with conditions first identified from our work on the arylation of enolsilanes.[6a] We found that reaction of **1a** with diphenyliodonium triflate **2a**, 2,6-di-*tert*-butylpyridine (DTBP) as base and 10 mol% of $Cu(OTf)_2$•(*R,R*)-PhBox gave a low yield of racemic spirocyclic ketone **4a**, as a single diastereomer (Table 1, entry 1). Changing the counteranion of salt **2** from OTf to BF_4 gave 61% yield of **4a** with an enantiomeric ratio (e.r.) of 70:30 (entry 2). Inspired by this, we found that further adjustment of the salt **2** to include a PF_6 counteranion resulted in a reaction that gave 95% yield of **4a** in 92.5:7.5 e.r. (entry 3). Lowering the temperature of the reaction to 5 ˚C further increased the e.r. of **4a** without compromising the yield of the reaction (entry 4). Systematic investigation of other parameters revealed that changing the solvent away from dichloromethane (see supporting information), using inorganic bases in place of DTBP and changing the Cu-catalyst all had a deleterious effect on both yield and e.r. of the product (entries 4-7). Optimal conditions for the reaction were found to involve treatment of **1a** with 2 equivalents of (Mes)PhI–PF_6 **2c**, 2 equivalents of DTBP and 5mol% of catalyst (*R,R*)-**3**•$Cu(OTf)_2$ in a 0.3 M solution of dichoromethane at 5 ˚C for 48h, which gave a single diastereomer of spirocyclic ketone **4a** in 96% yield and an e.r. of 97:3.

Table 1. Selected optimization for enantioselective SPR



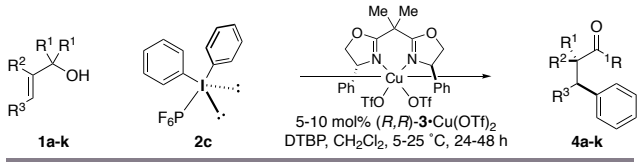
1a 2 4a

	X	Ar	Cu, mol%	base	T, ˚C	yield %	e.r.[a]
1[b]	OTf	Ph	$Cu(OTf)_2$, 10	DTBP	25	10	50:50
2[b]	BF_4	Ph	$Cu(OTf)_2$, 10	DTBP	25	61	70:30
3[b]	PF_6	Ph	$Cu(OTf)_2$, 10	DTBP	25	95	92.5:7.5
4	PF_6	Ph	$Cu(OTf)_2$, 10	DTBP	5	95	95.5:4.5
5	PF_6	Ph	$Cu(OTf)_2$, 10	Na_2CO_3	5	85	88:12
6	PF_6	Ph	CuCl, 10	DTBP	5	82	81:19
7	PF_6	Ph	$CuPF_6$, 10	DTBP	5	67	76:24
8	PF_6	Mes	$Cu(OTf)_2$, 10	DTBP	5	95	97:3
9	PF_6	Mes	$Cu(OTf)_2$, 5	DTBP	5	96	97:3

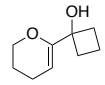
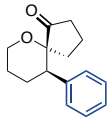
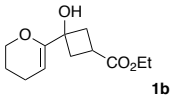
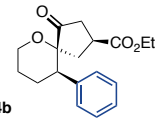
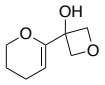
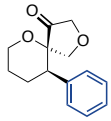
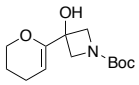
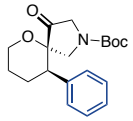
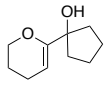
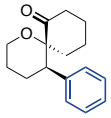
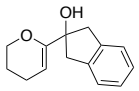
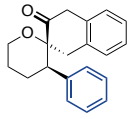
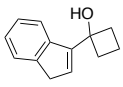
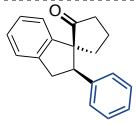
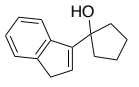
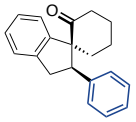
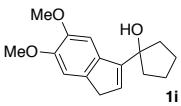
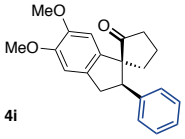
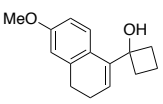
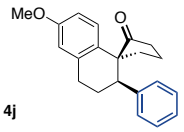
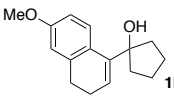
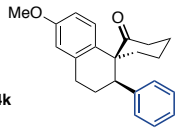
[a]d.r. for all reactions is >20:1, as determined by ^{1}H NMR. [b]Reactions required only 24h to reach completion.

With an optimal set of reaction conditions in hand, we next explored the scope of the enantioselective arylative SPR. First, the substituents directly appended to the allylic carbinol were varied. We found that a variety of cyclobutyl-derived allylic alcohols could be successfully employed as substrates (Table 2, **1a-d**). Particularly interesting was arylative SPR of oxetane and azetidine-containing substrates, which formed the single diasteroisomers of the corresponding spirocyclic tetrahydrofuranone and pyrrolidinone in good yield and high e.r. (**4c-d**). Cyclopentyl- and indane-derived system also underwent smooth arylative SPR to form the 6-6 spiroketones in excellent yields and diastereoselectivities and with 96:4 and 99.5:0.5 e.r. respectively (**4e-f**).

Table 2. Scope of allylic alcohol component.



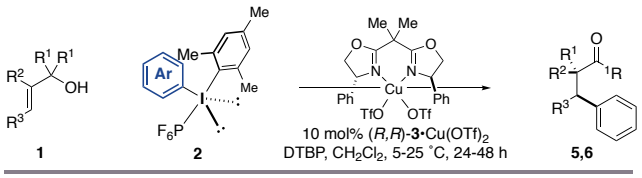
1a-k 2c 4a-k

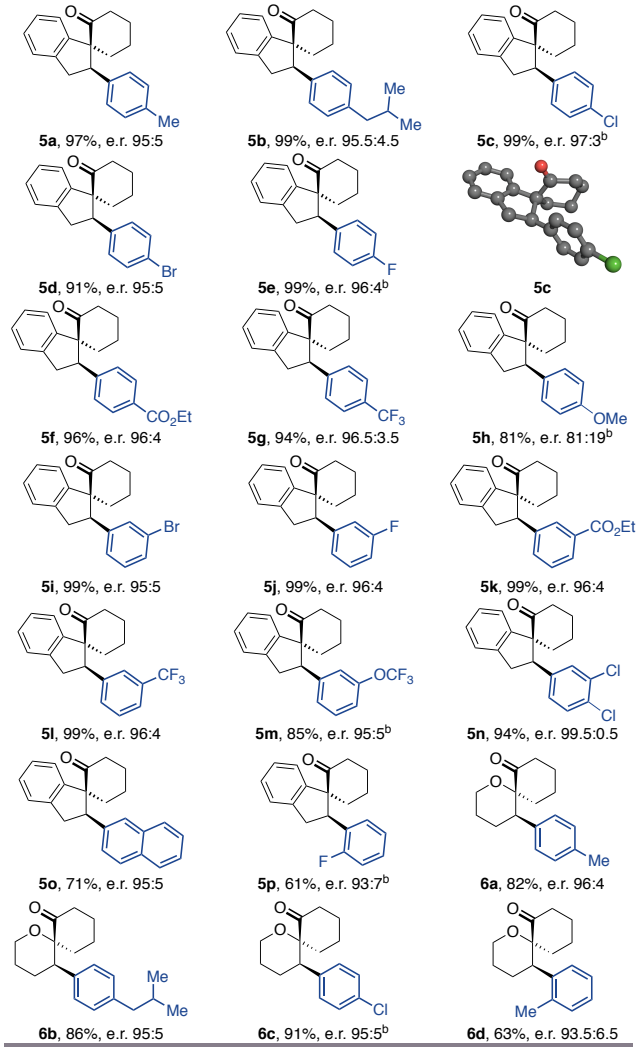
allylic alcohol		spiroketone product
 1a	**4a**, 96% yield d.r. >20:1 e.r. 97:3	 4a
 1b	**4b**, 92% yield d.r. >20:1 e.r. 90:10	 4b
 1c	**4c**, 77% yield d.r. >20:1 e.r. 91.5:8.5	 4c
 1d	**4d**, 86% yield d.r. >20:1 e.r. 92.5:7.5	 4d
 1e	**4e**, 96% yield d.r. >20:1 e.r. 96:4	 4e
 1f	**4f**, 85% yield d.r. >20:1 e.r. 99.5:0.5	 4f
 1g	**4g**, 97% yield d.r. 3:1 e.r. 95:5	 4g
 1h	**4h**, 98% yield d.r. >20:1 e.r. 95.5:4.5	 4h
 1i	**4i**, 96% yield d.r. >20:1 e.r. 97.5:2.5	 4i
 1j	**4j**, 63% yield d.r. 5:1 e.r. 95:5	 4j
 1k	**4k**, 63% yield d.r. >20:1 e.r. 92:8	 4k

In changing the tetrahyropyran ring, we found that the indene- and tetrahydronapthalene framework worked well

with both cyclobutyl and cyclopentyl carbinol substituents (**1g-k**) to form the corresponding products (**4g-4k**) in excellent yields and enantioselectivites. It was noticeable that for successful enantioselective arylative-SPR, the allylic alcohol substrate required inherent strain within the carbinol substituents; dimethyl or cyclohexyl derivatives did not undergo SPR. Importantly, spiroketone **5c** was crystalline, enabling assignment of the absolute configuration using X-ray diffraction of a single crystal. Moreover, recrystallization upgraded the e.r. to >99.5:0.5.

Table 3. Scope of diaryliodonium salt[a]



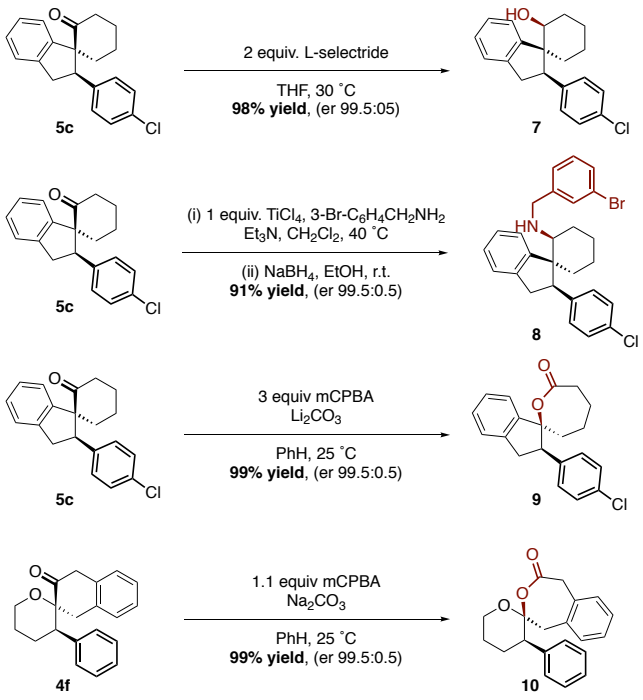


[a]d.r. for all reactions is >20:1, determined by ^{1}H NMR. [b]Reaction with symmetrical diaryliodonium salt.

Next, we explored the scope of the diaryliodonium salts that could be used in the catalytic enantioselective arylative SPR. First, using indene-derived allylic alcohol **1h**, we found that a broad range of substituted aryl groups could be transferred as part of the reaction (Table 3, **5a-p**). For example, arenes displaying electron donating and withdrawing substituents, useful functional handles for downstream transformations, extended arene systems and even the ortho-substituted arenes were all successfully applied in the catalytic SPR process to form the indane-derived spiroketones in excellent yields, diastereoselectivities and enantiomeric ratios. We also found that arylation of the tetrahydropyran-derived allylic alcohol **1e** was compatible with a number of diaryliodonium salts, delivering the desired products (**6a-d**) in high yields and e.r.

The β-aryl-α,α'-spirocyclic ketone moiety presents an interesting rigid scaffold with spatially defined functionality that may be useful as a starting point in the design of small molecules to probe biological processes. Towards this, we performed a series of simple transformations to elaborate the novel scaffolds by increasing stereochemical complexity or functional diversity (Scheme 1). Firstly, we found that the ketone **5c** could be reduced with L-selectride to give a single carbinol product **7**. A two-step reductive amination protocol from **5c** delivered secondary amine **8** in excellent yield and selectivity. Alternatively, Baeyer-Villiger oxidation with mCPBA transformed the cyclohexanone motif to a seven-membered ring spiro-lactone **9** in excellent yield. Finally, we found that a related oxidative ring expanding transformation on the tetrahydropyranyl-derived ketone **4f** produced the spiroketal **10** in almost quantitative yield.

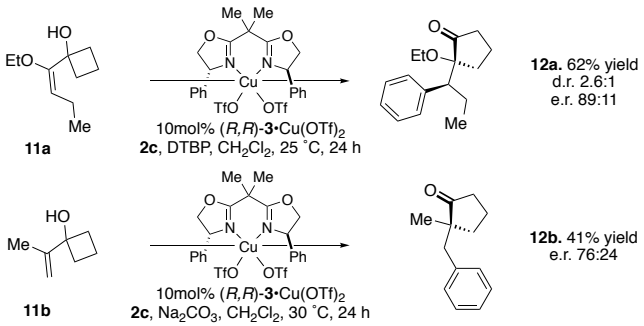
Scheme 1. Transformations of spirocyclic ketones



Finally, we conducted preliminary experiments to assess whether the enantioselective arylative SPR was compatible with acyclic allylic alcohol substrates. We were pleased to observe promising levels of enantioselectivity for simple cyclobutane-derived allylic alcohols **11a-b** to form monocyclic ketones **12a-b**. Although the selectivity is lower than for the cyclic substrates shown in Tables 1 and 2, the results in Scheme 2 suggest that a more general array

of allylic alcohols may be compatible with this enantioselective process; studies towards this ideal are ongoing.

Scheme 2. Preliminary SPRs on acyclic alkenes



In summary, we have developed an enantioselective Cu-catalyzed arylative SPR using diaryliodonium salts, which transforms allylic alcohols into spirocyclic ketones in high yield and enantiomeric ratios. The enantioenriched spirocyclic ketones display vincinal α,α'-quaternary and β-aryl tertiary centers,[10] often as single diastereomers, and can undergo complexity-generating reactions to a variety of novel molecular scaffolds. This operationally simple process uses readily available starting materials and a commercial catalyst and bisoxazoline ligand, which we believe will be useful to practitioners of chemical synthesis.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI: ##########################

Experimental procedures and characterization data for all compounds (PDF)

Crystallographic data for **5c** (CIF)

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Notes:

The authors declare no competing financial interests.

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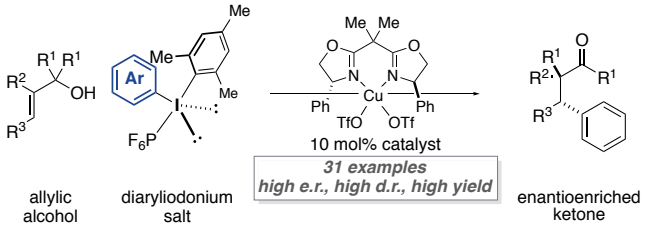
allylic alcohol
diaryliodonium salt
10 mol% catalyst
31 examples
high e.r., high d.r., high yield
enantioenriched ketone