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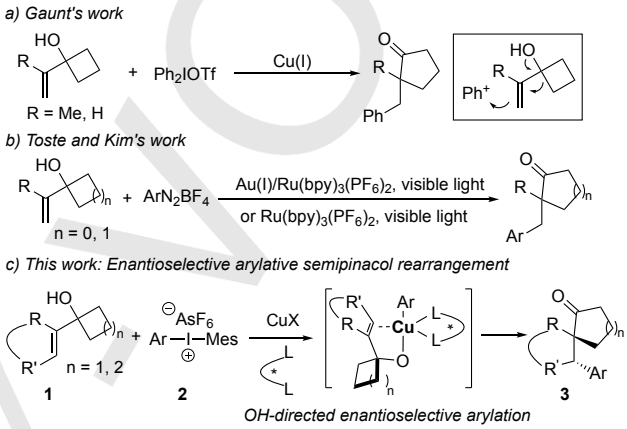
Copper-Catalyzed Enantioselective Domino Arylation/Semipinacol Rearrangement of Allylic Alcohols with Diaryliodonium Salts

Hua Wu, Qian Wang, Jieping Zhu*

Abstract: *A copper-catalyzed enantioselective arylative semipinacol rearrangement of allylic alcohols was developed. In the presence of a catalytic amount of an in situ generated chiral copper-bisoxazoline complex, reaction of allylic alcohols with diaryliodonium salts afforded spirocycloalkanones in high yields with high diastereo- and enantioselectivities. A two-point binding model engaging the carbon-carbon double bond and the proximal hydroxyl group was proposed to be responsible for the highly efficient chirality transfer.*

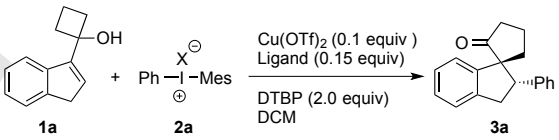
Semipinacol rearrangement of allylic alcohols triggered by electrophilic activation is an important transformation in organic synthesis.[1] The development of enantioselective version has been achieved only recently thanks to the advance of the organocatalysis.[2,3] Most of these asymmetric processes were initiated by protonation, halogenation and epoxidation leading to the concurrent formation of C-H or C-X bonds (X = halogen, O). Examples of arylative or alkylative semipinacol rearrangements were scarce.[4,5] In their 2012 paper dealing with the copper-catalyzed alkene arylation with diaryliodonium salts, Gaunt provided two examples of Cu-catalyzed synthesis of 2-benzylated cyclopentanones from vinylcyclobutan-1-ols and proposed that the reaction might be initiated by Friedel-Crafts type reaction of an alkene with a phenyl cation equivalent (Scheme 1a).[6] Two years later, Toste reported a detailed study on the arylative semipinacol rearrangement using aryldiazonium salt as arylating regent under dual gold/photoredox catalytic conditions (Scheme 1b).[7] Subsequently, Kim reported that the same transformation can be realized in the absence of gold catalysis.[8]

Being aware of the challenges associated with the development of asymmetric arylative semipinacol rearrangement and in connection with our ongoing research program dealing with enantioselective dicarbofunctionalization of alkenes.[9] We set out to examine the copper-catalyzed enantioselective arylative semipinacol rearrangement of allylic alcohols **1** using diaryliodonium salts **2** as electrophilic arylating reagents (Scheme 1c). On the basis of literature precedents,[10] we reasoned that the hydroxyl group could potentially serve as an anchoring point to engage the allylic alcohol **1** in a two-point binding model with the Ar-Cu(III) species. In the presence of an appropriate chiral ligand, one should be able to differentiate the two faces of the double bond, achieving therefore the enantioselective aryl transfer. A recent paper from Gaunt's group on the same subject prompted us to communicate herein our own results.[11] Spirocycloalkanones obtained in this process[12] are privileged scaffold in the development of chiral ligands/organocatalysis[13] and are known precursors for the synthesis of acetylcholinesterase and monoamine oxidase.[14]



Scheme 1. Domino arylation/semipinacol rearrangement of allylic alcohols.

Table 1. Optimization of the reaction conditions.[a]



Entry	Ligand	X	T (°C)	Y (%)[b]	d.r.[c]	*ee* (%)[d]
1	**L1**	OTf	50	trace	-	-
2	**L2**	OTf	50	67	5.8:1	9(53)
3	**L3**	OTf	50	trace	-	-
4	**L4**	OTf	50	trace	-	-
5	**L5**	OTf	50	65	2.1:1	52(70)
7	**L6**	OTf	50	70	4.3:1	5(38)
8	**L7**	OTf	50	54	5.5:1	25(57)
9	**L8**	OTf	50	75	2.1:1	75(74)
10	**L8**	BF_4	50	80	2.8:1	76(78)
11	**L8**	PF_6	50	85	3.1:1	86(85)
12	**L8**	AsF_6	50	87	3.0:1	86(87)
13	**L8**	SbF_6	50	82	2.7:1	86(84)
14[e]	**L8**	AsF_6	RT	88	3.0:1	92(88)
15[e,f]	**L8**	AsF_6	RT	trace	-	-
16[e,g]	**L8**	**AsF_6**	**RT**	**89**	**3.3:1**	**93(93)**

[a] **1a** (0.1 mmol), **2a** (0.13 mmol), $Cu(OTf)_2$ (0.01 mmol), Ligand (0.015 mmol), DTBP (0.2 mmol), DCM (1.0 mL), T (°C), 12 h. [b] Total isolated yields. [c] Determined by ^1H NMR spectroscopy. [d] Determined by SFC analysis on a chiral stationary phase. Values in the parenthesis is the *ee* of the minor isomer. [e] The reaction was conducted at 0.3 mmol scale of **1a** for 24 h. [f] $Cu(MeCN)_4PF_6$ (0.1 equiv) was used. [g] CuCl (0.1 equiv) was used. DTBP = 2,6-di-*tert*-butylpyridine.

Arylative semipinacol rearrangement of 1-(1*H*-inden-3-yl)cyclobutan-1-ol (**1a**) with mesityl(phenyl)iodonium trifluoromethanesulfonate (**2a**) was chosen as a benchmark reaction. Heating a CH_2Cl_2 solution of **1a** and **2a** in the presence of copper(II) triflate, PyBox **L1** (Figure 1) and 2,6-di-*tert*-butylpyridine (DTBP) afforded only a trace amount of the

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rearranged product **3a** (Table 1, entry 1). Using bidentate (*S,S*)-diphenylbisoxazoline **L2** as ligand under otherwise identical conditions provided the desired product **3a** in 67% yield, albeit with only 9% *ee* (entry 2). With **L5**, ligand of choice in Gaunt's work,[11] **3a** was isolated in 65% yield with 52% *ee* under these non-optimized conditions. Further experiments revealed that bisoxazoline **L8** derived from (1*R*,2*S*)-2-amino-1,2-diphenylethan-1-ol was the most effective (entry 9) leading to **3a** in 75% yield with *ee* of 75% and 74%, respectively, for the two diastereoisomers. The influence of different counteranions of the diaryliodonium salts on the reaction outcome was next examined (entries 9-13) and AsF_6 salt was found to be optimal (entry 12). Subsequent survey of reaction conditions varying the temperature and the copper sources allowed us to further improve the reaction efficiency (entries 14-16). Overall, the optimum conditions found consisted of performing the arylative semipinacol rearrangement of **1a** in CH_2Cl_2 (*c* 0.1 M) at room temperature in the presence of CuCl (0.1 equiv), chiral bisoxazoline **L8** (0.15 equiv) and DTBP (2.0 equiv). Under these conditions, spirocycloalkanone **3a** was obtained in 89% overall yield as a mixture of two separable diastereomers (d.r. 3.3:1) with 93% *ee* for both isomers (entry 16). That the reaction proceeded at room temperature might indicate the important role played by the proximal hydroxyl group since higher temperature (70 °C) was generally required for the arylation of simple 1*H*-indene.[6]

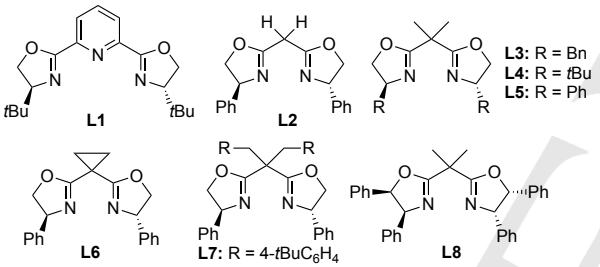
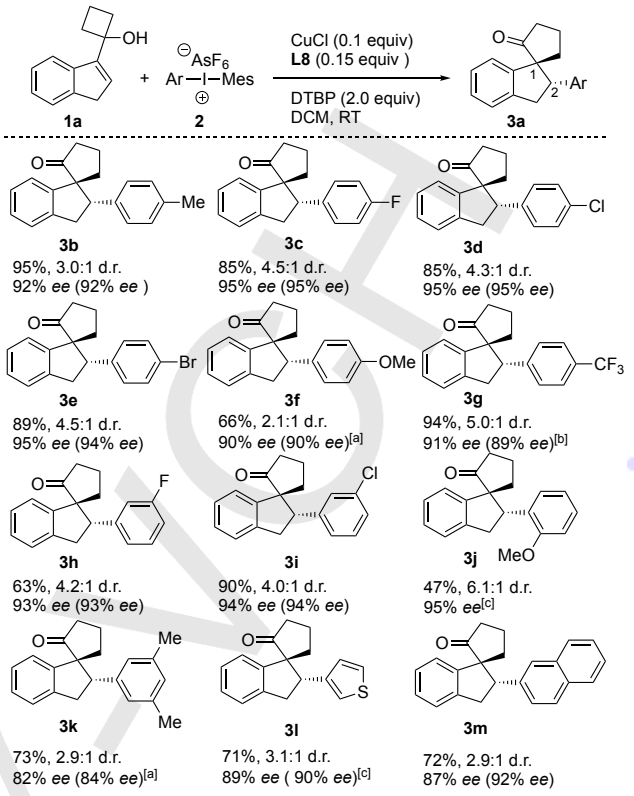
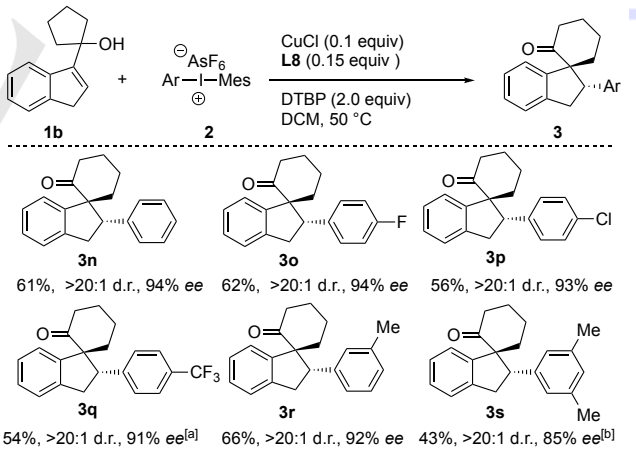


Figure 1. Structures of representative chiral ligands.

With the optimized conditions in hand, the scope of this enantioselective arylation/rearrangement cascade was next explored. Diaryliodonium salts bearing electron-neutral, eletron-withdrawing and electron-donating substituents underwent the desired arylative semipinacol rearrangement to generate spiro[4,4]nonan-1-ones **3** in good to high yields, with moderate diastereoselectivities and excellent enantioselectivities (Scheme 2). Substituents at *para*, *meta* and *ortho* positions were well tolerated (**3b-3j**). Strong electron-rich aromatics underwent this transformation equally well by performing the reaction at 50 or 60 °C in the presence of copper triflate as catalyst (**3f,3j**). 3,5-Dimethylphenyl, 2-naphthyl and heterocycle (2-thiophene) were transferred without event (**3k-3m**). Both diastereomers of **3** were obtained in excellent enantiomeric excesses and were fully characterized. The absolute configuration of the minor isomer **3a** was determined by single crystal X-ray diffraction analysis to be (1*S*,2*S*).[15] Consequently, the (1*R*,2*S*) configuration was assigned for the major stereoisomer. The sense of stereoselectivity is in accord with Guant's observation.



Scheme 2. Scope of the diaryliodonium salts with vinylcyclobutanol **1a**. [a] $Cu(OTf)_2$ (0.1 equiv) as the catalyst at 50 °C. [b] Bis(4-(trifluoromethyl)phenyl)iodonium hexafluoroarsenate was used. [c] $Cu(OTf)_2$ (0.1 equiv) as the catalyst at 60 °C.

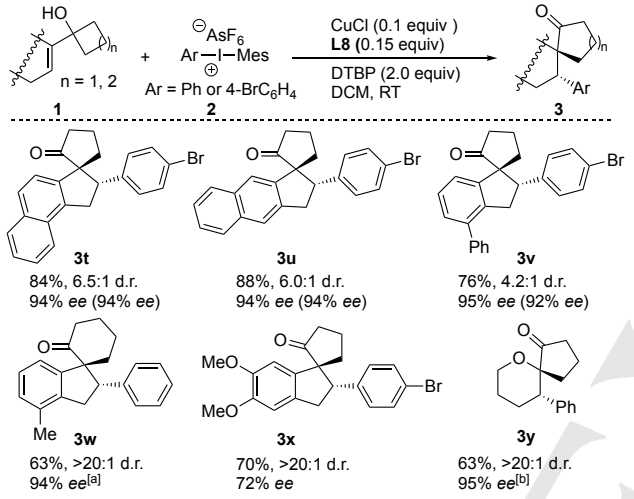


Scheme 3. Scope of the diaryliodonium salts with vinylcyclopentanol **1b**. [a] Bis(4-(trifluoromethyl)phenyl)iodonium hexafluoroarsenate was used. [b] $Cu(OTf)_2$ (0.1 equiv) as the catalyst at 50 °C.

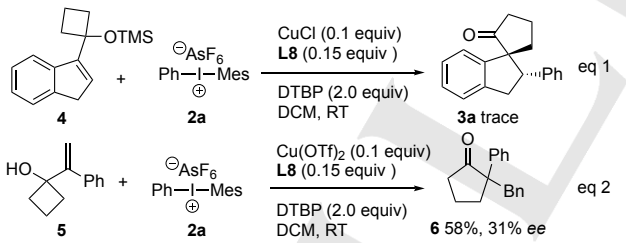
Encouraged by the aforementioned results, we decided to extend the reaction to vinylcyclopentanol **1b**, a more challenging substrate (ring strains: cyclobutane 26.7 kcal/mol, cylopentane 7.4 kcal/mol). Gratefully, a series of diaryliodonium salts with different electronic properties reacted with **1b** smoothly to provide the corresponding spiro[4,5]decan-1-ones **3n-3s** in good yields with excellent diastereo- and enantioselectivities (Scheme 3). The high diastereoselectivity observed in this series compared to that of vinylcyclobutanol

1a is noteworthy. The diminished ring strain release going from 5- to 6-membered ring might render the 1,2-migration process more selective.

A series of structurally diverse allylic alcohols was evaluated to further probe the reaction scope (Scheme 4). Vinylcyclobutanols with various substituents at different positions on the benzene ring underwent the arylative semipinacol rearrangement to furnish the desired products in high yields with good diastereoselectivities and excellent enantiomeric excesses (**3t-3w**). However, the dimethoxy-substituted vinylcyclobutanol was converted to spirocyclopentanone **3x** with diminished enantiomeric excess. Pleasantly, 1-(3,4-dihydro-2*H*-pyran-6-yl)cyclobutan-1-ol participated in this asymmetric arylative rearrangement process to provide **3y** in 63% yield with 95% *ee* (d.r. >20:1) by employing **L7** as the ligand for this reaction.



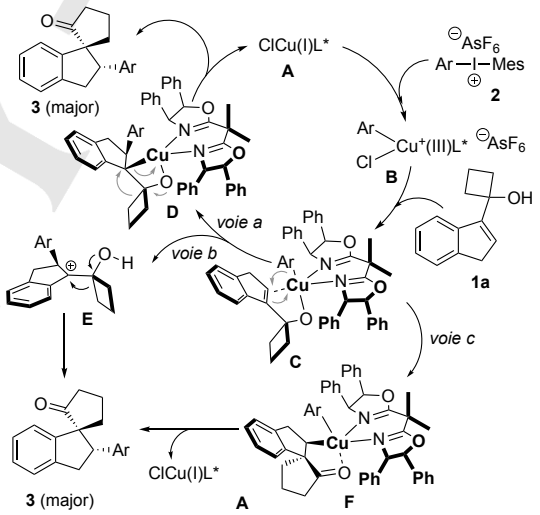
Scheme 4. Scope of the allylic alcohols. [a] At 50 °C. [b] $Cu(OTf)_2$ (0.1 equiv) as the catalyst and **L7** (0.15 equiv) as the ligand at 60 °C.



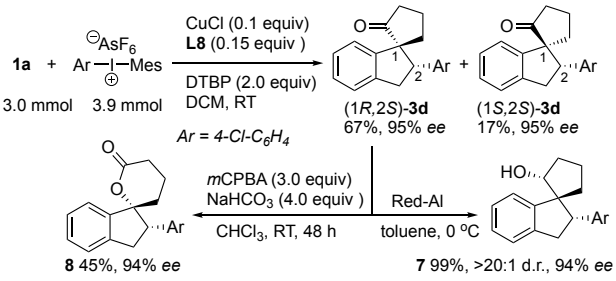
Scheme 5. Control experiments.

A series of control experiments were carried out in order to investigate the mechanism of this enantioselective arylative semipinacol rearrangement (Scheme 5). Only a trace amount of **3a** was observed when TMS-protected vinylcyclobutanol **4** was employed as a substrate indicating the importance of the free hydroxyl group in this transformation (eq 1).[10a,b] Importantly, vinylcyclobutanol without indene moiety **5** underwent this domino transformation to afford the desired product **6** in 58% yield with a noticeable *ee* of 31%. Since the phenylation of terminal double bond of **5** did not generate a stereocenter, the observed enantioselectivity can only be induced by the catalyst during the 1,2-alkyl migration step. This result implied that the semipinacol rearrangement involving the discrete cabocation intermediate as proposed previously might not be the only pathway and that the copper catalyst could well be involved in the rearrangement process.

Based on the results of these control experiments, a possible reaction pathway is depicted in Scheme 6. Oxidative addition of diaryliodonium salts **2** to the chiral Cu(I) complex **A** would generate Ar-Cu(III) species **B** which, upon coordination to both the hydroxyl group and the double bond would generate chelate **C**. Enantioselective *syn*-carbocupration[16] would afford intermediate **D** which, upon 1,2-alkyl migration with concurrent cleavage of the C-Cu bond in an S_N2 fashion would afford the major diastereomer of spirocycloalkanone **3** (*voie a*, Scheme 6). Formation of carbenium intermediate **E** from **C**, as previously proposed for the arylation of electron-rich alkenes, followed by semipinacol rearrangement could also be operating (*voie b*).[6] Alternatively, the domino process could also be initiated by semipinacol rearrangement from intermediate **C** to **F**.[7,17] that would be converted to **3** by reductive elimination with concurrent generation of the active Cu(I) catalyst.[18] Further experiments and theoretical studies would be needed to decipher the exact reaction mechanism.



Scheme 6. Possible reaction pathway.



Scheme 7. Scale-up reaction and synthetic transformations of (1*R*,2*S*)-**3d**.

Reaction of allylic alcohol **1a** with 4-Cl-substituted diaryliodonium salt on a 3.0 mmol scale proceeded smoothly to afford (1*R*,2*S*)-**3d** (95% *ee*) and (1*S*,2*S*)-**3d** (95% *ee*) in yields of 67% and 17%, respectively (Scheme 7). Reduction of (1*R*,2*S*)-**3d** with Red-Al afforded alcohol **7** in >99% yield (>

20:1 d.r., 94% *ee*), while the Baeyer-Villiger oxidation of (1*R*,2*S*)-**3d** (*m*CPBA, $NaHCO_3$, $CHCl_3$, RT) afforded the desired lactone **8** in 45% yield with 94% *ee*.

In summary, we developed an efficeint copper-catalyzed enantioselective arylative semipinacol rearrangement of allylic alcohols with diaryliodonium salts. While excellent enantioselectivity was observed for most of the substrate, the diastereoselectivity of the reaction was found to be substrate depending. In general, spiro[4,4]nonanes were formed with moderate d.r., whereas excellent diastereoselectivities (>20:1 d.r.) were observed with the formation of spiro[4,5]decanes.

Acknowledgements

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Keywords: semipinacol rearrangement • Ring expansion • diaryliodonium salt • homogeneous catalyst • Asymmetric catalysis

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Asymmetric Synthesis

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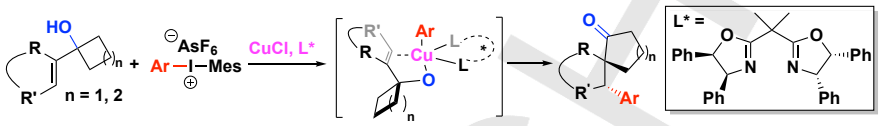
Copper-Catalyzed Enantioselective Domino Arylation/Semipinacol Rearrangement of Allylic Alcohols with Diaryliodonium Salts



Selective arylation and shift: *Copper-catalyzed enantioselective arylative semipinacol rearrangeme of allylic alcohols with diaryliodonium salts afforded spirocycloalkanones in good to high yields wi high diastereo- and enantioselectivities.*