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Copper-Catalyzed Enantioselective Arylative Desymmetrization of Prochiral Cyclopentenes with Diaryliodonium Salts

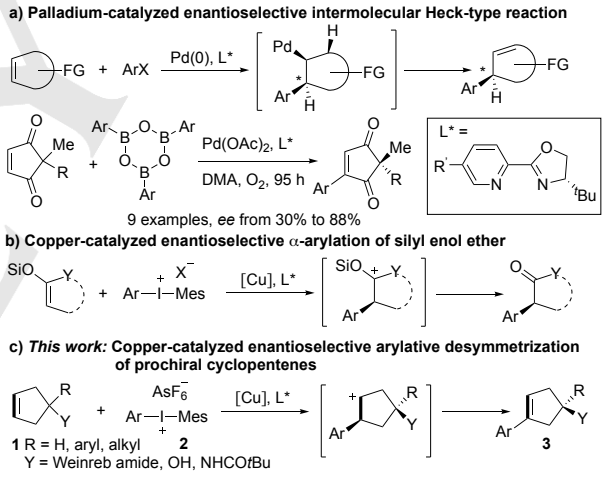
Hua Wu, Qian Wang, Jieping Zhu*

Abstract: *A copper-catalyzed enantioselective arylative desymmetrization of prochiral cyclopentenes with diaryliodonium salts was developed. In the presence of a catalytic amount of the in situ generated chiral copper-bisoxazoline complex, reaction of 4-substituted or 4,4-disubstituted cyclopent-1-enes with the diaryliodonium hexafluoroarsenate afforded the chiral arylated products in good yields with excellent enantioselectivities. Use of the cyclohexyl-containing Box ligand was essential for the high enantioselectivity. Transformation of the enantioenriched adducts to other chiral building blocks was also documented.*

Since the seminal work of Shibasaki[1] and Overman[2] on the enantioselective intramolecular Heck reaction for the creation of chiral quaternary carbon centers,[3] significant efforts have been dedicated to the enantioselective arylation of alkenes by intermolecular Heck-type reactions.[4] The first report came from Hayashi and co-workers who disclosed in 1991 a Pd-catalyzed enantioselective arylation of 2,3-dihydrofuran with aryl triflates.[5] Conditions allowing the use of aryl diazonium salts[6] and arylhalides[7] have been subsequently developed for the enantioselective arylation of cycloalkenes and asymmetric arylation of acyclic alkenyl alcohols using a redox-relay strategy has been documented.[8] Intrinsic to the mechanism of the Heck reaction, arylation of small ring cycloalkenes afforded generally products with a double bond shifted away from the newly formed C(sp^2)-C(sp^3) bond, creating therefore the chiral stereocenter (Scheme 1a). To the best of our knowledge, Lee's work on Pd(II)-catalyzed oxidative desymmetrization of 2,2-disubstituted cyclopentene-1,3-diones with arylboroxine is an only example in which carbon-carbon double bond was not shifted.[9-10] In this case, the Pd-bearing stereocenter formed after *cis*-carbopalladation can be epimerized via the Pd-enolate intermediate, rendering therefore the subsequent *cis* β-H elimination possible.

Parallel to palladium-catalyzed transformations, copper-catalyzed arylation of alkenes[11] and arenes[12] with diaryliodonium salts[13] has attracted much recent attention. However, its enantioselective variants remain rare in spite of the great synthetic significance of such processes. In 2011, Gaunt[14] and MacMillan[15] reported independently the first examples of Cu-catalyzed enantioselective α-arylation of silyl enol ethers with diaryliodonium salts (Scheme 1b). This was followed by enantioselective arylative cyclization of tryptamines[16] and allylic amides,[17] and arylative semipinacol rearrangement.[18] All these examples involved the use of highly electron-rich alkenes or strained ring systems bearing a neighboring heteroatom or an internal nucleophiles to stabilize/trap the incipient carbenium intermediates.

In connection with our ongoing research interests dealing with the transition metal catalyzed enantioselective carbofunctionalization of alkenes,[19] we became interested in the enantioselective copper-catalyzed arylation of alkenes and documented recently an enantioselective arylative semipinacol rearrangement.[18b] We report herein the first examples of copper catalyzed enantioselective arylative desymmetrization of prochiral 4-substituted and 4,4-disubstituted cyclopentenes with diaryliodonium salts for the synthesis of enantioenriched cyclopentenyl carboxamides, cyclopentenyl alcohols and *N*-cyclopentenyl pivalamides in high to excellent enantiomeric excesses (Scheme 1c).[20] To the best of our knowledge, this work represents the first examples of Cu-catalyzed enantioselective arylation of simple isolated double bonds.



Scheme 1. Enantioselective arylation of alkenes.

To realize the planned asymmetric transformation, we need to identify a chiral catalyst that can differentiate not only the two faces of the double bond, but also the sterically unbiased two C(sp^2) carbons. We started our investigation using **1a** and **2a** as the model substrates (Table 1). The arylative desymmetrization was carried out in DCM (80 °C, sealed tube) in the presence of 2,6-di-*tert*-butylpyridine (DTBP, 1.2 equiv), $Cu(OTf)_2$ (0.1 equiv) and a chiral ligand (0.2 equiv). Only a trace amount of product **3a** was formed using **L1** or **L2** (Figure 1) as ligand (entries 1-2), whereas the desired cyclopentenyl carboxamide **3a** was isolated in a reasonable yield and *ee* in the presence of **L3** (entry 3) or **L4** (entry 4). Using **L5** as ligand afforded the desired product in 56% yield with poor enantioselectivity (entry 5), whereas Pybox **L6** was inefficient in catalyzing the transformation (entry 6). *Gem*-dibenzyl substituted (*S,S*)-diphenylbisoxazoline **L7** failed to catalyze the desired transformation indicating the importance

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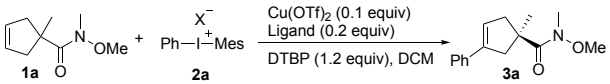
of the alkyl substituents on the catalytic activity of the Cu-bisoxazoline complex (entries 7 vs 3). Therefore, further ligand screening was focused on different bisoxazolines derived from (*S*)-phenylglycinol (**L8-L11**). While the reaction with ligand **L8** afforded **3a** with low *ee* (entry 8), the same reaction in the presence of ligands **L9** or **L10** having a cyclopentyl and a cyclohexyl group, respectively, gave **3a** with significantly higher *ee* (93 and 95%, entries 9 and 10) than *gem*-dimethylated ligand **L3**. Further increasing the ring size (**L11**) afforded the product with diminished *ee* (entry 11). Using **L10** as ligand, the effect of the counteranion of the diaryliodonium salts on the reaction outcome was examined (X = OTf, PF_6, SbF_6, entries 12-14). As it is seen, a significant counteranion effect was observed and AsF_6^- remained optimal among those examined in terms of both yield and *ee*. Subsequent survey of reaction conditions varying the solvents and the copper sources did not improve the reaction efficiency (entries 15-17). Overall, the optimum conditions found consisted of performing the arylative desymmetrization of **1a** in DCM (*c* 0.1 M) at 80 °C in the presence of $Cu(OTf)_2$ (0.1 equiv), chiral bisoxazoline **L10** (0.2 equiv) and DTBP (1.2 equiv). Under these conditions (entry 10), **3a** was obtained in 76% yield with 95% *ee*.[21]

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



entry	Ligand	X	Solvent	yield (%)[b]	*ee* (%)[c]
1	**L1**	AsF_6	DCM	trace	-
2	**L2**	AsF_6	DCM	trace	-
3	**L3**	AsF_6	DCM	65	63
4	**L4**	AsF_6	DCM	48	70
5	**L5**	AsF_6	DCM	56	-12
6	**L6**	AsF_6	DCM	trace	-
7	**L7**	AsF_6	DCM	trace	-
8	**L8**	AsF_6	DCM	61	10
9	**L9**	AsF_6	DCM	71	93
10	**L10**	**AsF_6**	**DCM**	**76**	**95**
11	**L11**	AsF_6	DCM	65	51
12	**L10**	OTf	DCM	77	30
13	**L10**	PF_6	DCM	51	81
14	**L10**	SbF_6	DCM	70	94
15	**L10**	AsF_6	DCE	52	93
16	**L10**	AsF_6	Toluene	53	12
17[d]	**L10**	AsF_6	DCM	trace	-

[a] **1a** (0.2 mmol), **2a** (0.24 mmol), $Cu(OTf)_2$ (0.02 mmol), Ligand (0.04 mmol), DTBP (0.24 mmol), DCM (2.0 mL), 80 °C, 12 h in a sealed tube. [b] Isolated yield. [c] Determined by SFC analysis on a chiral stationary phase. [d] CuCl (0.1 equiv) was used. DTBP = 2,6-di-*tert*-butylpyridine.

A number of diaryliodonium salts with various electronic properties were successfully converted into the corresponding arylated cyclopentenyl carboxamides in moderate to high yields with high to excellent *ees* (Scheme 2). Substituents at *para*, *meta* positions were well-tolerated (**3a-3m**). The 4-methoxyphenyl, an electron-rich aromatic group, was transferred selectively at the expense of the mesityl group to afford the corresponding product with excellent enantioselectivity (**3h**). 3,5-Dimethylphenyl and 2-naphthyl groups were transferred to cyclopentene without event (**3n-3o**). Thiophenylated cyclopentene **3p** can also be prepared, albeit with low yield. Unfortunately, the reaction involving vinyl, alkynyl and 3-indolyl aryliodonium hexafluoroarsenates afforded a complex mixture mainly due to the instability of the reagent at the reaction temperature. We noted that the aryliodonium hexafluoroarsenates were less stable than their corresponding triflate salts. The absolute configuration of **3d** was determined to be *R* by single crystal X-ray diffraction analysis.[22] Consequently, that of the other cyclopentenyl carboxamides was assigned accordingly.

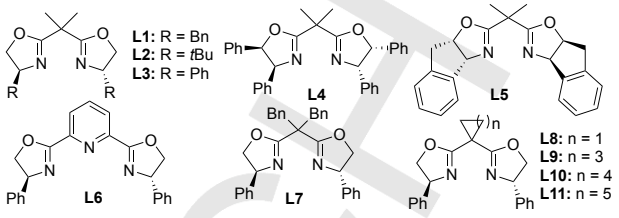
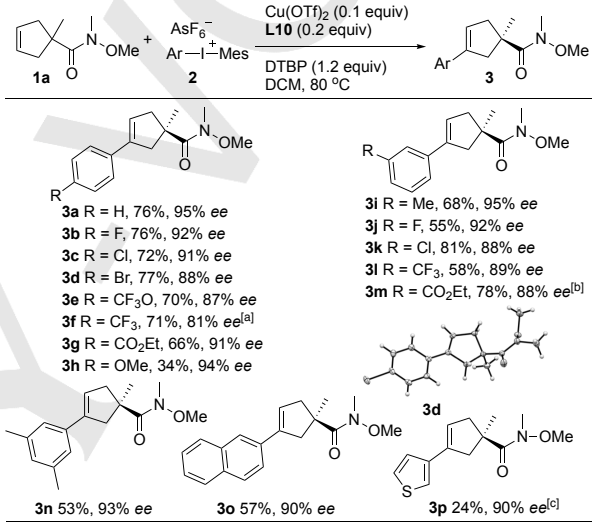
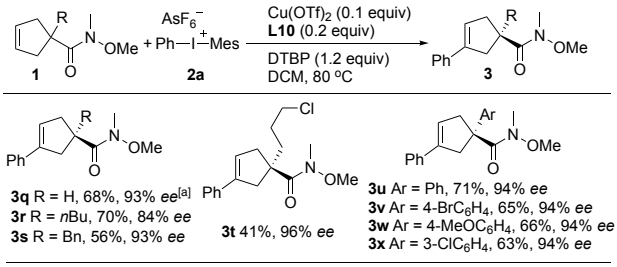


Figure 1. Structures of the representative chiral ligands.



Scheme 2. Scope of the diaryliodonium salts **2**. The reaction was performed on 0.2 mmol scale. Enantiomeric excess was determined by SFC analysis on a chiral stationary phase. [a] At 70 °C. [b] The reaction performed at 1.0 mmol scale afforded **3m** in 71% yield with 87% *ee*. [c] At 60 °C.



Scheme 3. Scope of the cyclopentenes **1**. The reaction was performed on 0.2 mmol scale (*c* 0.1 M). Enantiomeric excess was determined by SFC analysis on a chiral stationary phase. [a] *c* 0.2 M.

Various substituted cyclopentenes were next examined as reaction partners (Scheme 3). The α-unsubstituted amide was phenylated to afford the desired product (**3q**) in good yield with excellent enantiomeric excess. Different aliphatic (butyl, benzyl, 3-chloropropyl) and aromatic substituents with different electronic properties at the α-position of the Weinreb amide were compatible with this arylative desymmetrization process affording the desired products (**3r-3x**) in good yields with

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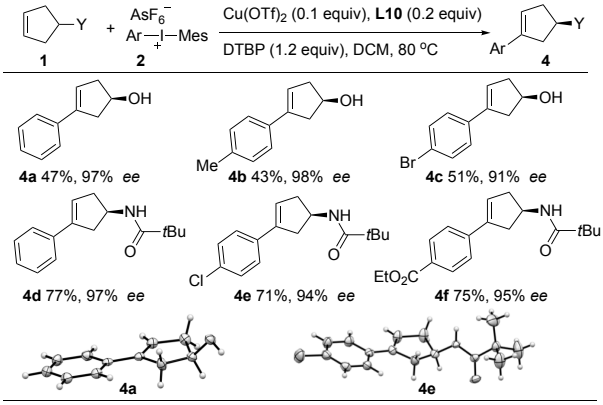
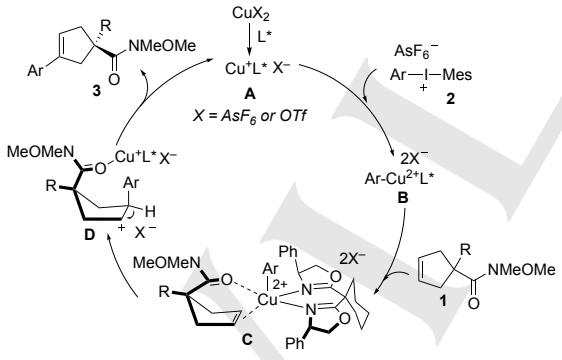
excellent *ees*. We note that arylation of cyclopent-3-ene-1-carboxylic acid, its secondary and tertiary amide derivatives under standard conditions afforded the arylated products in only low to moderate yields. On the other hand, the methyl ester was converted to the phenylated product in 66% yield with 70% *ee* (see SI for details).



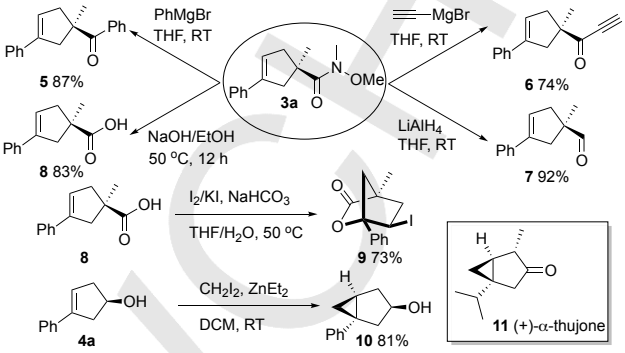
Scheme 4. Desymmetrization of cyclopent-3-en-1-ol and *N*-(cyclopent-3-en-1-yl)pivalamide. The reaction was performed on 0.2 mmol scale. Enantiomeric excess was determined by SFC analysis on a chiral stationary phase.

Phenols and alcohols are known to react with diaryliodonium salts to afford aryl ethers.[23] Therefore, we were delighted to find that submitting the cyclopent-3-en-1-ols to our standard reaction conditions led selectively to the corresponding arylated cyclopentenyl alcohols (**4a-4c**) with excellent *ees*, albeit in moderate yields (Scheme 4). Pleasantly, *N*-(cyclopent-3-en-1-yl)pivalamide underwent arylative desymmetrization smoothly to afford the corresponding products **4d**-**4f** in good yields with excellent *ees*. The absolute configuration of **4a** and **4e** was determined to be *R* by single crystal X-ray diffraction analysis and that of the others in these series was assigned accordingly.[22]



Scheme 5. Possible reaction pathway.

A possible reaction pathway is depicted in Scheme 5. Oxidative addition of diaryliodonium salt **2** to the in situ formed Cu(I) species **A**[24] would generate an Ar-Cu(III) intermediate **B**.[25] which, upon coordination to both the carbonyl group of the Weinreb amide and the double bond would generate complex **C**. The formation of this chelate and the nature of the C2-symmetric ligand allowed effective differentiation of the two faces of the double bond as well as the otherwise sterically unbiased C(sp^2) carbons. Electrophilic arylation of the double bond would generate the carbenium intermediate **D** with concurrent generation of the chiral center. Removal of the most acidic benzylic proton would then allow the regeneration of the double bond leading to the observed product **3**.



Scheme 6. Synthetic transformations of **3a** and **4a**.

Further transformations of these chiral cyclopentenes were performed to illustrate their synthetic potential (Scheme 6). Nucleophilic addition of Grignard reagents to **3a** at room temperature afforded the corresponding ketones **5** and **6** in high yields. Reduction of **3a** with $LiAlH_4$ delivered aldehyde **7** in 92% yield. Saponification of **3a** (NaOH in ethanol, 50 °C) furnished carboxylic acid **8** (83%), which was subsequently converted to the bridged bicycle **9** (73%) under standard iodolactonization conditions. Finally, the hydroxyl group-directed Simmons-Smith cyclopropanation of **4a** under Furukawa conditions.[26] afforded bicycle **10** in 81% yield as a single diastereomer. This represented an efficient access to the analogues of thujone (**11**), an inhibitor of the γ–aminobutyric acid A (GABAA) receptor.[27]

In summary, we have presented the first example of copper-catalyzed enantioselective arylative desymmetrization of prochiral 4-substituted or 4,4-disubstituted cyclopent-1-enes with diaryliodonium salts and documented that an achiral counteranion of iodonium salts had an important effect on the enantioselectivity of the reaction. Weinreb amide, hydroxyl group and pivalamide were all effective directing groups in this transformation. The reaction provided a practical, straightforward access to a wide range of structurally diverse enantioenriched arylated cyclopentenes, difficultly accessible otherwise. This Cu-catalyzed arylative desymmetrization process complemented well the classic Heck reaction.

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Keywords: desymmetrization • asymmetric synthesis • diaryliodonium salt • homogeneous catalyst • Heck reaction

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[20] One single example of racemic reaction was described in the Scheme 1 of ref 11a.

[21] The ratio of ligand/Cu salt influenced significantly the reaction outcome (See SI for details). While the copper salt chelated to one bidentate ligand might be the active catalyst, the presence of a second equivalent of ligand might accelerate the dissociation of the product from the metal salt, hence the turnover of the catalyst, and at the same time stabilize the copper salt in the form of $CuXL_2$.

[22] CCDC 1569766 (**3d**), CCDC 1568887 (**4a**) and CCDC 1572522 (**4e**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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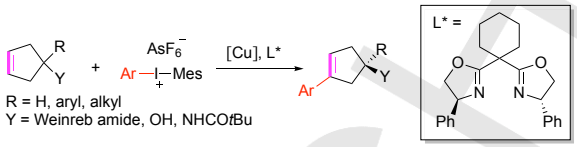
Layout 1:

Asymmetric Synthesis

*Hua Wu, Qian Wang, and Jieping Zhu**_____ ***Page – Page***

Copper-Catalyzed Enantioselective Arylative Desymmetrization of Prochiral Cyclopentenes with Diaryliodonium Salts



No shift: *In the presence of a catalytic amount of the in situ generated chiral copper-bisoxazoline complex, reaction of 4-substituted or 4,4-disubstituted cyclopent-1-enes with the diaryliodonium hexafluoroarsenate afforded the chiral arylated products in good yields with excellent enantioselectivities. Double bond was not migrated in this transformation.*