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Catalytic Enantioselective Diarylation of Alkenes

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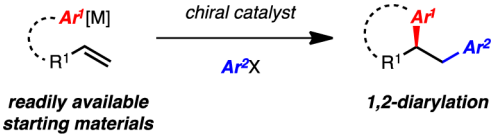
Supporting Information

ABSTRACT: A method for the catalytic enantioselective diarylation of alkenes is presented. The method allowed for the synthesis of highly enantioenriched 2,3-dihydrobenzofurans and indolines containing molecules from readily available substrates. Furthermore, this method allowed for the enantioselective synthesis of quaternary carbons. Based on mechanism studies, the process likely functions by enantioselective insertion of an alkene into an Ar−CuBenzP* complex to generate a Csp^3−Cu complex. Capture of this intermediate with an ArX led to formation of the desired product.

Diarylation of alkenes represents an important strategy for chemical synthesis because readily available starting materials are rapidly converted to significantly more complex and useful compounds (Scheme 1). Accordingly, several

Scheme 1. Inter- and Intramolecular Diarylation of Alkenes



catalytic alkene diarylation strategies are known.[1,2] These methods can allow for the introduction of either different aryl groups or two identical aryl groups across several classes of alkenes. Despite these advances, catalytic enantioselective variants of these processes are rare. The only known enantioselective alkene diarylation was recently reported by Sigman et al. (Scheme 2A). In this Pd-catalyzed example, acyclic dienes can undergo diarylation with good levels of enantioselectivity, albeit moderate yield.[1o] It should also be noted that Fu et al. have recently reported a related highly enantioselective aryl-alkylation of alkenes promoted by a chiral Ni-catalyst (Scheme 2B).[3]

Our lab has taken an interest in Cu-catalyzed alkene interrupted cross-coupling.[4] These efforts have recently led to the disclosure of a Cu-catalyzed alkene diarylation reaction.[2] Key to the success of this reaction was the identification of rigid dppBz ligands as ideal for providing good yields of the diarylated products. Herein, we disclose a significant advance of our method to include highly enantioselective examples (Scheme 2C).[5,6] Notably this method provides access to all-carbon quaternary centers, which, despite recent advances, is still a contemporary challenge in organic synthesis.[7]

Optimization of the enantioselective reaction was carried out through evaluation of chiral ligands. Based on the success of the

Scheme 2. Enantioselective Diarylation of Alkenes

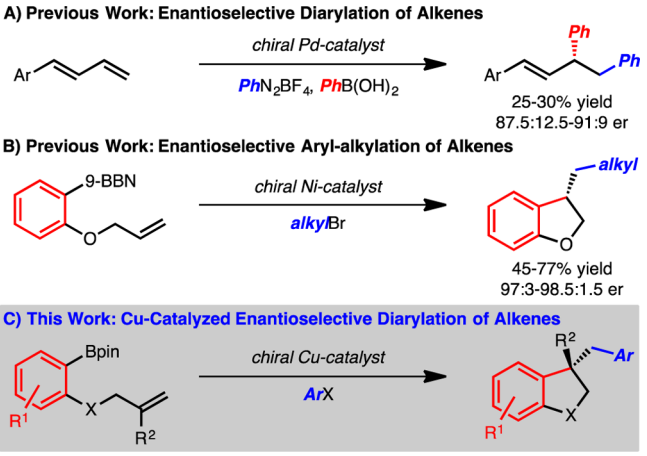
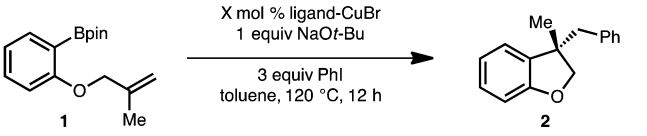
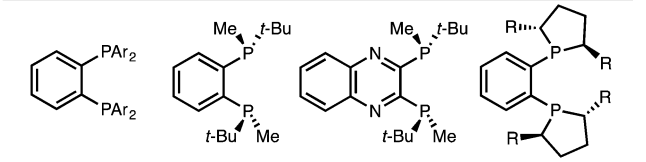


Table 1. Reaction Optimization[a]



entry	X mol %	ligand	temp (°C)	yield (%)[b]	e.r.[c]
1	5	dppBz-Me	120	78	--
2	5	Me-DuPhos	120	70	60:40
3	5	*i*-Pr-DuPhos	120	34	82:18
4	5	QuinoxP*	120	69	92:8
5	5	BenzP*	120	76	97:3
6	***3***	***BenzP****	***120***	***77***	***98:2***
7	1	BenzP*	120	36	97:3
8	3	BenzP*	100	<5	n.d.



[a]See the SI for experimental details. [b]Determined by ^{1}H NMR analysis (400 MHz) with an internal standard. [c]Determined by HPLC analysis with a chiral column.

dppBz scaffold (Table 1, entry 1), related Me-DuPhos was evaluated and led to the formation of **2** in 70% yield and 60:40

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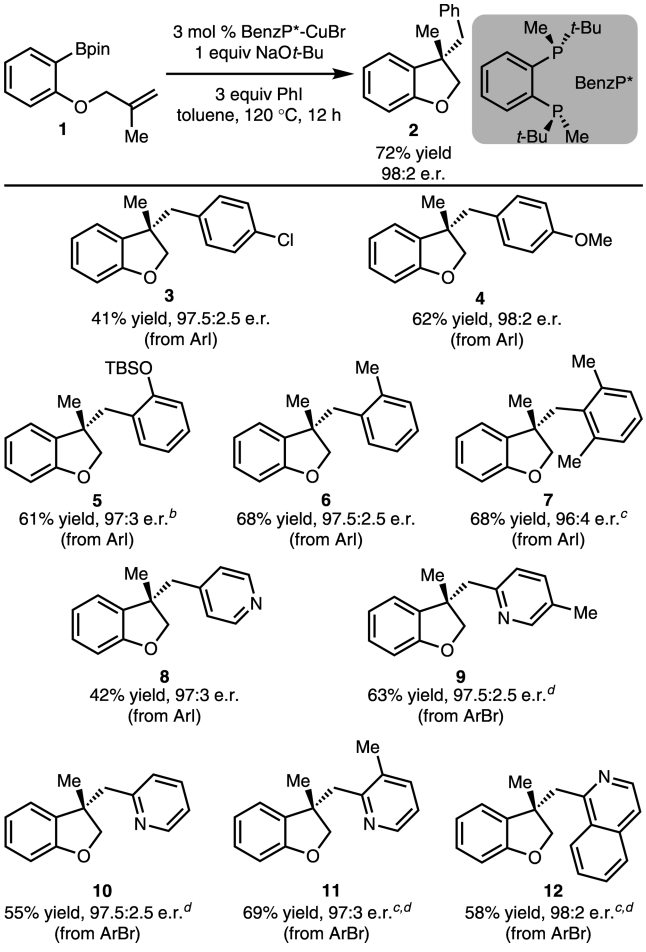
e.r. (Table 1, entry 2). To increase the stereodescriminating environment and hence the enantioselectivity, the sterically larger *i*-PrDuPhos was assessed (Table 1, entry 3). While use of this ligand led to an increase in the enantioselectivity (82:18 e.r.), the yield was considerably lower (34%). Only when QuinoxP* and BenzP* ligands were examined was the combination of good yield and excellent enantioselectivity observed, with the latter being superior (Table 1, entries 4–5).[8] Further optimization revealed that slightly lower catalyst loading (3 mol %) provided the product in similar yield and enantioselectivity. It should be noted that high levels of enantioselectivity were observed despite the high temperatures required for reactivity.

The scope of this process was evaluated with respect to both the substrate and aryl halide.[9,10] As illustrated in Scheme 3, a variety of aryl iodides underwent reaction to provide 2,3-dihydrobenzofurans **2**–**8** with uniformly good enantioselectivity. Notable examples include the use of a heterocycle (4-iodopyridine, product **8**) and sterically encumbered aryl iodides (products **5**–**7**). In addition to the use of aryl iodides, 2-bromo pyridine derivatives were also found to function well in this process (**9**–**12**). At this time, the use of aryl bromides is limited to 2-bromo pyridine derivatives.

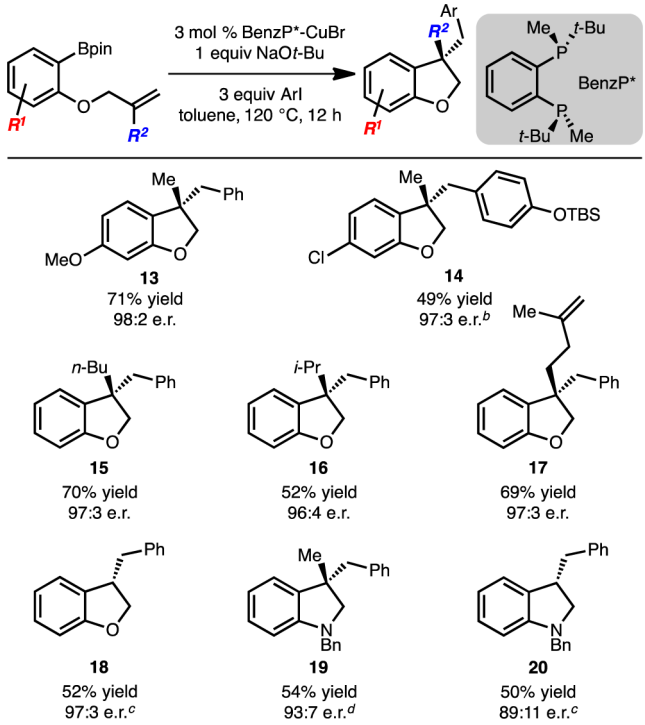
Scheme 3. Reaction with Various Aryl Halides[a]



[a]See the SI for experimental details. In all cases 4–10% of the direct cross-coupling is observed in the unpurified reaction mixture. Yield of isolated product shown (average of two experiments). Enantiomeric ratio (e.r.) determined by HPLC analysis with chiral column. [b]e.r. determined as the corresponding phenol. [c]1.5 equiv ArX used. [d]With 5 mol % BenzP*-CuBr

A variety of substituted arylboronic esters underwent reaction (Scheme 4). Both electron-rich (product **13**) and

Scheme 4. Reaction with Various Substrates[a]



[a]See the SI for experimental details. In all cases 4–10% of the direct cross-coupling is observed in the unpurified reaction mixture. Yield of isolated product shown (average of two experiments). Enantiomeric ratio (e.r.) determined by HPLC analysis with chiral column. [b]e.r. determined as the corresponding phenol. [c]10 equiv PhI used at 140 °C with 1 mol % BenzP*-CuBr [d]With 5 mol % BenzP*-CuBr

electron-poor substrates (product **14** and **22**) function with good yield and enantioselectivitiy. Substrates with substitution *ortho* to the boronic ester failed to undergo diarylation. With respect to the alkene component, the reaction was tolerant of various alkyl-substitution. For example, a sterically demanding *i*-Pr unit (product **16**) and additional alkene substitution were tolerated (product **17**). It is also important to emphasize that the method also allowed for the formation of tertiary centers in good enantioselectivity (product **18** and **20**). Finally, while formation of indoline-derived products were achieved (**19** and **20**), the related indane or six-membered ring products could not be formed. For the latter cases, the formation of products resulting from direct cross-coupling prior to cyclization was observed. At the present time, the method does not tolerate substitution of the alkene at the terminal position (e.g., 1,2-disubstituted alkenes).

The utility of the method was demonstrated in the straightforward synthesis of a CB2 receptor agonist (Scheme 5).[11] The synthesis commenced with catalytic enantioselective diarylation of substrate **21** (prepared in three steps) with PhI to provide benzofuran **22** in 51% yield and 96:4 e.r. Palladium-catalyzed carbonylation of the aryl chloride with $Mo(CO)_6$ under microwave conditions provided the target molecule (**23**) in 57% yield.[12,13] The current synthesis of **23** requires nine steps and a resolution to separate enantiomers.[11b]

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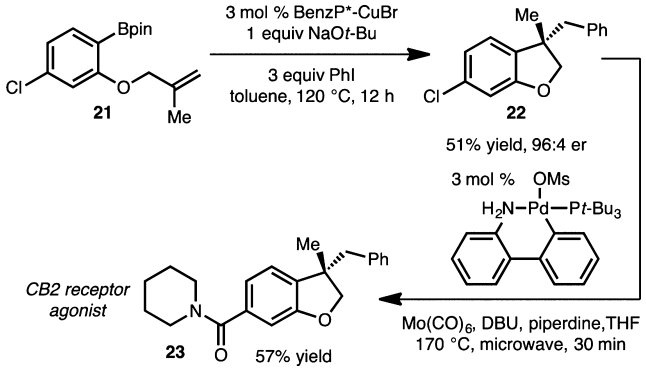
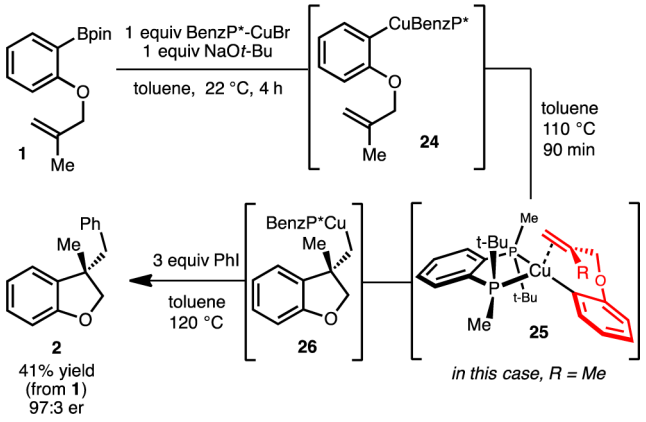
Scheme 5. Straightforward Synthesis of a CB2 Receptor Agonist



Studies have been carried out to elucidate the mechanism of this process (Scheme 6). Treatment of ArBpin **1** with BenzP*-

Scheme 6. Study of Reaction Mechanism



CuBr and NaO*t*-Bu led to formation of Ar–Cu complex **24** as determined by NMR analysis.[14] When this complex was heated to 110 °C for 90 min Csp^3–Cu complex **26** was observed by NMR. Finally, addition of PhI and further heating at 120 °C led to generation of **2** in 97:3 e.r. We suspect that the enantiodetermining step is the migratory insertion event. Based on the stereochemical outcome of the reaction, pretransition-state assembly **25** is proposed.[15] Key to the model is the orientation of the CH_2O-substituent toward the small Me-group of the catalyst. This positions the R-substituent away from the steric bulk of the catalyst. Furthermore, the model is in complete agreement with the observations presented in Scheme 4 that enantioselectivity is largely unaffected by the size of the R-substituent (compare R = H (**18**), 97:3 e.r. and R = *i*-Pr (**16**), 96:4 e.r.).

In conclusion, we have developed a catalytic enantioselective method for alkene diarylation. The method provides access to a variety of 2,3-dihydrobenzofuran and indoline scaffolds from simple starting materials in high enantioselectivity. Future directions will focus on development of other alkene functionalization reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10176.

Experimental procedures and analytical data (PDF)

Crystallographic data (CIF)

Spectroscopy data (PDF)

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Notes

The authors declare no competing financial interest.

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(9) Only (*R*,*R*)-BenzP* is commercially available. While (*S*,*S*)-BenzP* can be prepared, the synthesis is cumbersome (see ref 8). To address this issue, use of related commercially available chiral ligand (*S*,*S*)-QuinoxP* allowed for formation of (*R*)-**2** in 61% yield and 94:6 e.r. See the SI for details.
(10) The major byproducts from the reaction consist of a compound arising from Clasien rearrangement and a deallylation product. See the SI for details.
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(14) Intermediate **24** could be isolated in 75% yield (see the SI for details).
(15) The absolute stereochemistry of product **14** was unequivocally established through X-ray crystallographic analysis of a derivative (see the SI for details). The stereochemistry for all other products was assigned by analogy.

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