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Synthesis of Benzyl Amines via Copper-Catalyzed Enantioselective Aza-Friedel–Crafts Addition of Phenols to *N*-Sulfonyl Aldimines

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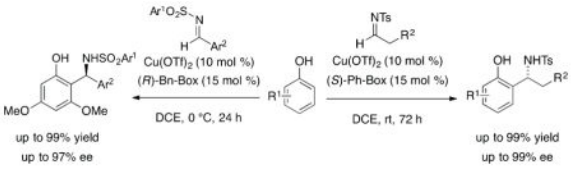
Abstract

A new copper-catalyzed enantioselective aza-Freidel-Crafts reaction between phenols and *N*-sulfonyl aldimines that provides chiral secondary benzylamines in good to excellent yields and excellent enantioselectivities (up to 99% ee) is disclosed. In particular, excellent scope with alkylimines was observed for the first time. The synthetic utility of the products was demonstrated in the first enantioselective synthesis of a dual orexin receptor antagonist, a compound that contains an amine-bearing stereocenter adjacent to a bis-*ortho*-functionalized arene.

Graphical abstract



Chiral benzyl amines are ubiquitous in many biologically active compounds, including the anticancer and antimalarial natural product strychnopentamine,[1,2] a class of synthetic dual orexin receptor antagonists,[3,4] and a designed inhibitor of the frataxin/ubiquitin interaction.[5] The field of asymmetric aza-Friedel–Crafts phenol addition to ketimines[6–8] and to aryl[9–15] and propargyl aldimines[16] to produce chiral benzylamines has been vigorously explored in recent years. Conversely, examples of highly enantioselective additions of phenols to alkyl

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Accession Codes

CCDC 1588079–1588080 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Notes

The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00282.

Experimental procedures and chiral HPLC traces of all new compounds (PDF)

NMR spectra of all new compounds (PDF)

aldimines are sparse. Most aza-Friedel–Crafts examples have focused on phenol or naphthol additions to aryl aldimines,[17–20] while the few alkyl aldimine examples have generated corresponding benzylamines in moderate yields and ee's.[18]

Analogous additions of indoles to imines have also been reported.[21] In particular, Zhou developed an enantioselective indole addition to aryl imines using a commercially available $Cu(OTf)_2$ and 4-benzyl bis(oxazoline) catalyst system.[22] Herein, we report our exploration of enantioselective phenol additions to alkyl aldimines, which has resulted in the identification of a catalytic enantioselective protocol employing chiral copper(II) catalysts. Synthetically, these new reactions are particularly effective at installing an enantioenriched chiral secondary amine-bearing carbon in between (ortho to) two functional groups of an arene, such as those found in the above-mentioned bioactive compounds (e.g., Scheme 1).[1–5] Such a transformation could be challenging due to the steric hindrance associated with the product and potential precursors.

To scope out the feasibility, several catalyst systems were tried to promote enantioselective addition of the mildly activated 3,5-dimethylphenol **1a** to *N*-tosyl-hydrocinnamaldehyde imine **2a**. Superior reactivity was observed with $Cu(OTf)_2$ and bis-(oxazoline) ligands, compared to reactions with alternate catalysts (see Supporting Information (SI) for details). Thus, $Cu(OTf)_2$ complexes with various chiral bis(oxazoline) ligands were screened for reactivity and enantioselectivity. The (*S*)-Ph-Box ligand afforded the best reactivity and enantiomeric excess of the ligands tested (Table 1, entry 4, 54% yield, 84% *ee*). In an attempt to increase the atom-economy of the reaction, the ratio of phenol to imine used was reduced from 5 to 1.5 equiv. This led to a reduction in isolated yield from 54% to 38% (compare Table 1 entries 4 to 9). Fortunately, when the solvent was changed from CH_2Cl_2 to 1,2-dichloroethane (DCE), a 53% yield of **3a** was obtained in 94% enantiomeric excess (Table 1, entry 13, 1.5 equiv of phenol used). Room temperature was found to be the best temperature for high enantioselectivity while maintaining synthetically useful yields. A reaction time of 72 h was chosen, as the reactions at 24 and 48 h provided lower isolated yields (compare Table 1, entries 13 to 18 and 19). No product was obtained when $Cu(OTf)_2$ was omitted (Table 1, entry 20).

With the optimal conditions for the aza-Friedel–Crafts reaction of alkyl aldimines in hand (Table 1, entry 13), the scope of phenols viable in the additions to the *N*-tosyl-hydrocinnamaldehyde imine **2a** and the *N*-tosyl-*n*-butyraldehyde imine **2b** was investigated (Scheme 2). 3,5-Dimethoxyphenol, an electron-rich nucleophile, required reduced temperature to provide benzylamine **3b** selectively and to avoid uncatalyzed background reactions (both ortho- and para-addition). Using 3-bromo-5-methoxyphenol and 5-bromobenzene-1,3-diol gave high overall yields; however, both reactions afforded two products each. In both cases, excellent ee's were found for the addition between the oxygens of the phenols (products $\mathbf{3c_1}$ and $\mathbf{3d_1}$), and more modest ee's were found for each regioisomer ($\mathbf{3c_2}$ and $\mathbf{3d_2}$). Mono-TBS-protected resorcinol also gave excellent overall yield and a ~5:1 ratio of regioisomers **3e**. Product **3f** derived from MOM-protected-4-bromoresorcinol was formed in excellent yield and ee. Additionally, 3-trimethylsilylresorcinols were effective nucleophiles for providing benzylamines $\mathbf{3g_1}$, $\mathbf{3g_2}$, and **3h** in excellent yields. Silylresorcinol adduct **3h** was formed as a single regioisomer. *N*-

Cbz-3-aminophenol also reacted with imine **2a** to form product **3i** in good yield and excellent enantioselectivity.

A crystal structure of benzylamine **3h** enabled assignment of the absolute configuration of the chiral center as the (*S*)-enantiomer (see SI). The configurations of the other products were assigned *S* by analogy to **3h**. Unsubstituted phenol displayed modest reactivity and gave adduct **3j** in 30% yield in excellent *ee* (96%). Even electron-deficient 3,5-dibromophenol gave adduct **3k** in a modest yield (26%) but good enantioselectivity. 2,3-Dimethoxyphenol, an ortho-substituted phenol, gave benzyl amine **3l** in good yield but poor enantioselectivity, implying sensitivity of the catalyst for 1,2-disubstituted phenols. 1,3,5-Trimethoxybenzene reacted with the imine to give 25% yield of the racemic adduct **3m**, suggesting the phenol likely binds to the copper catalyst in the enantioselective transition state (vide infra, Figure 1).

An expanded scope of alkyl aldimines was next investigated in the aza-Friedel–Crafts reaction (Scheme 3). Products **3n**, **3o**, and **3r** were all formed smoothly and with high *ee*'s. The reaction to form **3n** was run on 1 mmol scale of **2b**. Benzylic amine **3n** was formed in lower but acceptable yield (63%), and no reduction in enantioselectivity was observed. The 2-bromo-hydrocinnamal-dehyde imine from products **3p** and **3s** gave good yields for both nucleophiles, as well as excellent *ee*'s. A reaction of 3-bromo-5-methoxyphenol and 4-*N*-tosyl-benzyloxybutyl imine provided two regioisomeric products **3q**; the product of imine addition between the oxygens of the nucleophile was formed in excellent enantioselectivity, while the other regioisomer suffered slightly in the same respect. Even *N*-tosyl acetaldehyde imine gave moderate reactivity (50% yield) and a good *ee* (86%), implying an extended chain off the aldimine is not necessary to achieve high enantioselectivity. TBDPS-protected *N*-tosyl-3-hydroxy-propylimine underwent reaction to give product **3u** in moderate yield and excellent enantioselectivity. Results of aza-Freidel–Crafts to form products **3v**, **3w**, and **3x** indicated the effect of alkyl imine sterics profoundly affected reactivity. Reaction of a phenyl acetaldehyde imine to give benzylamine **3v** using the standard conditions occurred in good yield, but poor enantioselectivity (6%, see SI). Changing the ligand from (*S*)-Ph-Box to (*S*)-*i*Pr-Box afforded adduct **3v** in 39% yield and 89% *ee*. Adding a methyl group to the *β*-position to the imine significantly reduced the reactivity, yet excellent product enantioselectivity was maintained (**3w**, 12% yield, 94% ee). The isobutyraldehyde imine was unreactive (**3x** was not obtained).

The enantioselective aza-Friedel–Crafts reactions of aryl aldimines were next investigated. 3,5-Dimethoxyphenol was found to be the only phenol sufficiently reactive in this transformation, unfortunately. While the (*S*)-Ph-Box-derived catalyst demonstrated poor regioselectivity and enantioselectivity with *N*-tosyl aryl imines, the (*R*)-Bn-Box-derived catalyst provided higher regioselectivity (see SI for optimization table), and the reaction temperature was reduced to 0 °C to obtain optimal enantioselectivity. A range of *N*-sulfonyl aryl imines functionalized with both electron-donating and electron-withdrawing groups underwent reaction with 3,5-dimethoxyphenol (Scheme 4). *N*-Tosyl, *N*-benzenesulfonyl, and *N*-nosyl benzylimines all underwent the reaction efficiently and selectively to give products **5a**–**c** (Scheme 4). A crystal structure of the bis(aryl)methylsulfonamide **5d** was obtained,

and the absolute configuration was established as *R* (see SI). The absolute configurations of all other benzylamine adducts **5** were assigned by analogy.

In order to rationalize the observed enantioselectivity of the transformation, we invoked transition states where the *N*-sulfonyl aldimine is bound to the [Cu(II)]-bis(oxazoline)] complex via a 1,3-binding mode at the nitrogen and an oxygen of the sulfonyl (Figure 1).[26] The oxygen of the phenol is bound directly to the metal, and due to the sterics of the ligand, ortho-selective phenol addition is preferred on the *Re*-face for alkyl aldimine addition using (*S*)-Ph-Box and the *Si*-face using (*R*)-Bn-Box for aryl aldimine addition. A steric match between aryl imine/alkyl-Box or alkyl imine/aryl-Box appeared optimal from the ligand screening data (Table 1 and optimization table in SI). The imine sulfonyl group was expected to be very sterically demanding; thus, its placement on the same face as the closest (cis) chiral ligand substituent was avoided. Hydrogen bonding between the phenol hydrogen and the other sulfonyl oxygen as drawn (Figure 1) could add additional activation and structure at the transition state.

The synthetic utility of the alkyl aldimine aza-Friedel–Crafts reaction was demonstrated by synthesizing a dual orexin receptor antagonist in its enantioenriched form for the first time (Scheme 5).[3,4] Phenolic benzyl amine $\mathbf{3q_1}$ was *O*-methylated, followed by hydrogenation to both hydrodebrominate the aromatic ring and cleave the benzyl ether, affording alcohol **7**.[23] Oxidative cyclization utilizing pyridinium dichromate gave the 5-aryl-*N*-tosyl amide **8**.[24] Tosyl deprotection using lithium-naphthalenide[25] and *N*-alkylation provided the dual orexin receptor antagonist (–)-**11**.

Additionally, benzylamine **3s** was converted to 2-aryltetrahydroquinoline **13** (Scheme 6). *O*-Methylation of phenolic benzylamine **3s** provided **12**. Palladium-catalyzed intramolecular cyclization/coupling[26] of the pendant amine to the aryl bromide of **12** then efficiently formed the *N*-tosyl-2-aryl-tetrahydroquinoline **13**.

In conclusion, we have developed a catalytic enantioselective aza-Friedel–Crafts reaction between phenols and aldimines using a copper(II)-bis(oxazoline) catalyst. Good to excellent ee’s were observed for alkyl aldimines and aryl aldimines. The synthetic utility of the products was displayed by the enantioselective synthesis of a known dual orexin receptor antagonist, as well as a chiral 2-aryltetrahydroquinoline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the National Institutes of Health (GM078383) for financial support of this work. We acknowledge Dr. William W. Brennessel and the Crystallography Facility at the University of Rochester for obtaining the X-ray structures of **3i** (CCDC 1588079) and **5d** (CCDC 1588080). We thank Dr. Valerie Frerichs (UB instrument center) for help with the chiral HPLC.

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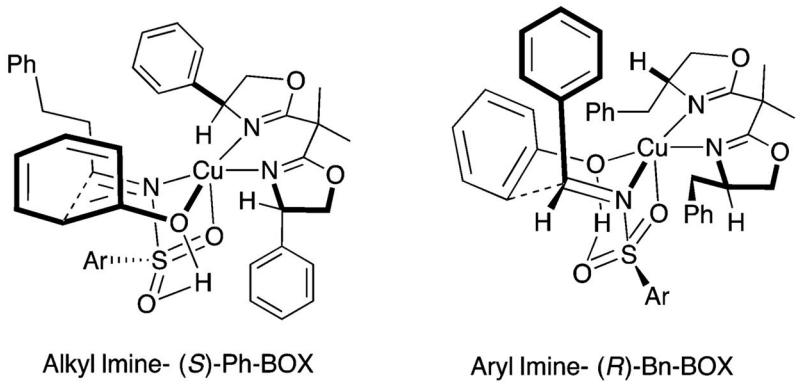
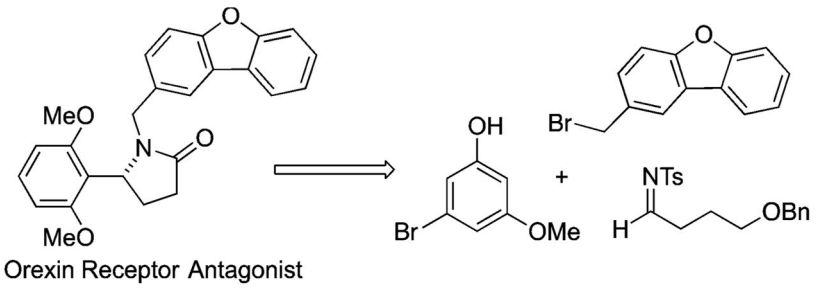
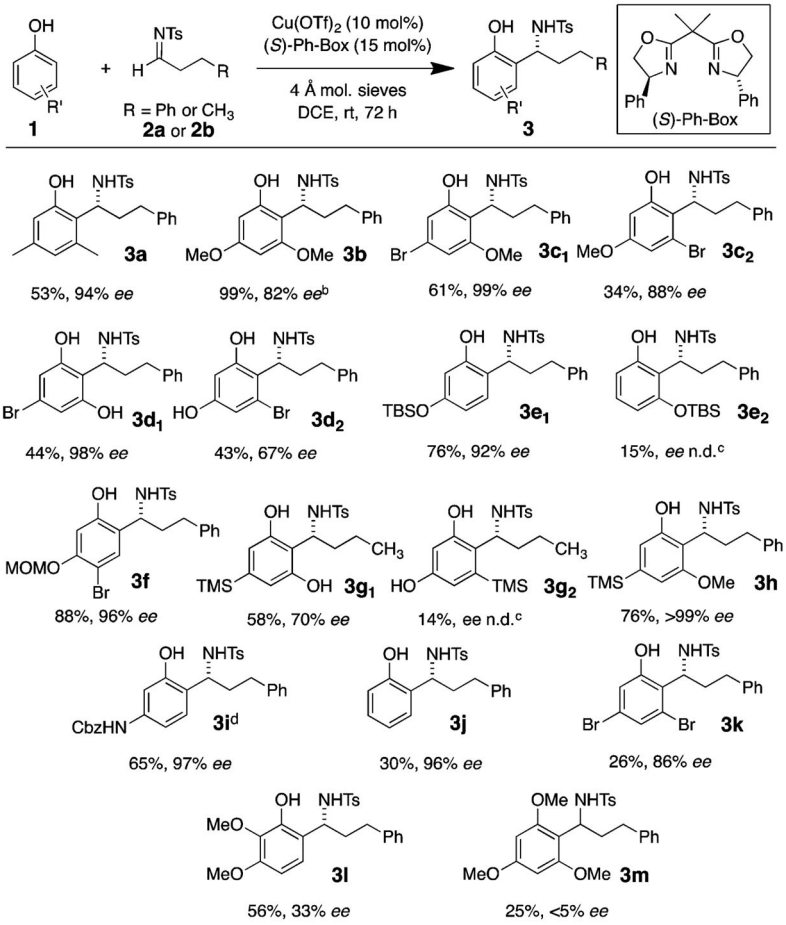


Figure 1.
Proposed major transition states.

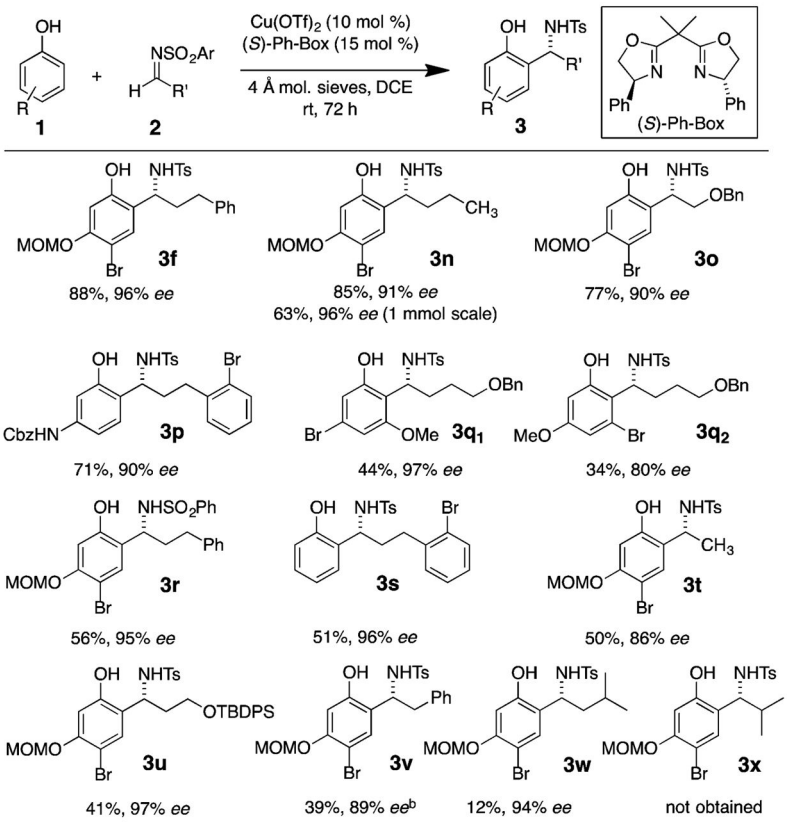


Scheme 1.
Retrosynthetic Analysis of a Bioactive Benzylic Amine



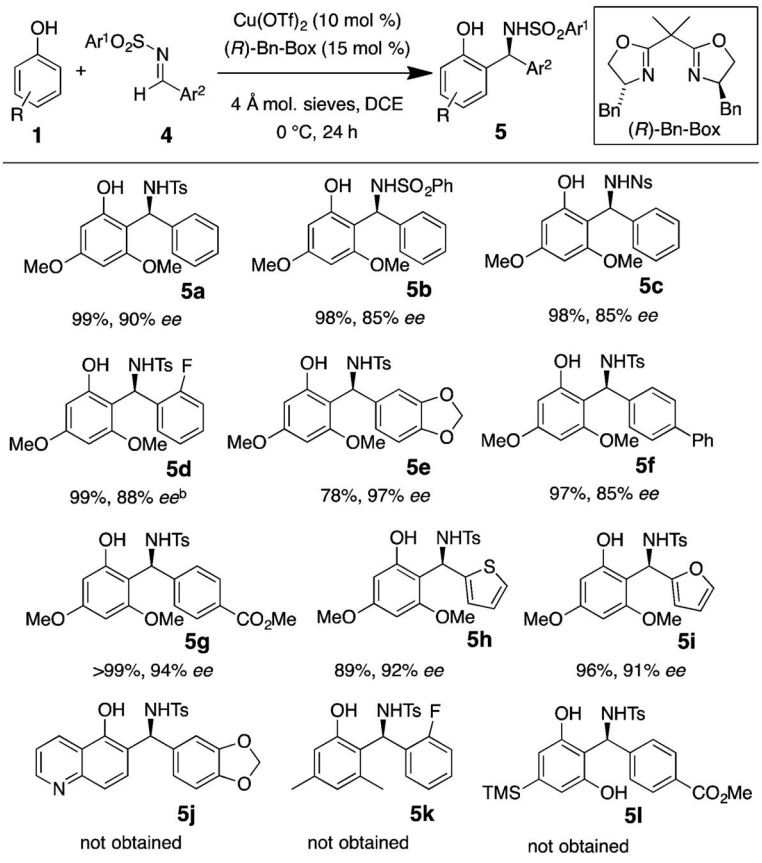
Scheme 2. Phenol Scope[a]

[a]Reaction conditions: imine **2** (0.20 mmol) and phenol **1** (0.30 mmol) and flame-dried 4 Å mol. sieves were added to a solution of $Cu(OTf)_2$ (0.020 mmol) and (*S*)-Ph-Box (0.03 mmol) in 1 mL of DCE, and the reaction was allowed to stir at rt for 72 h, unless otherwise noted. [b]Reaction performed at 0 °C for 24 h. [c]n.d. = not determined. [d]Absolute configuration determined by X-ray crystallography (see SI). All others were assigned by analogy.



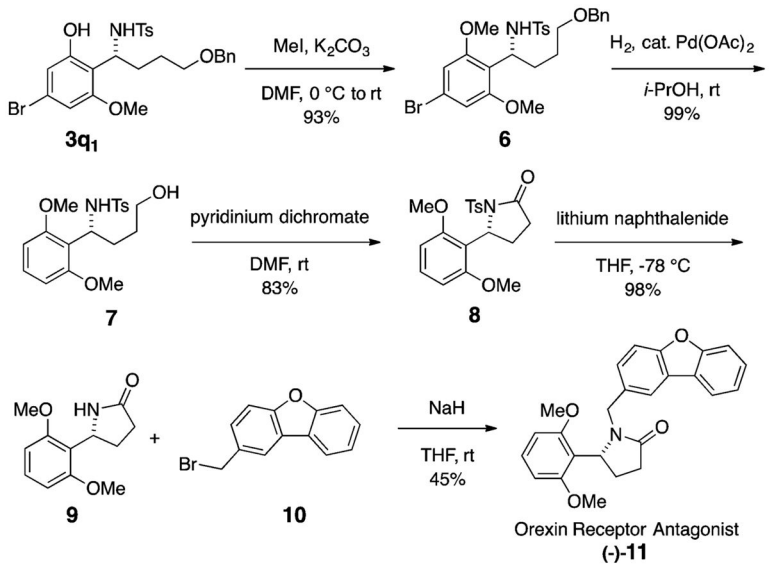
Scheme 3. Alkyl Imine Scope[a]

[a]Reaction conditions: imine **2** (0.20 mol) and phenol **1** (0.03 mmol) and flame-dried 4 Å mol. sieves were added to a solution of $Cu(OTf)_2$ (0.020 mmol) and (*S*)-Ph-Box (0.030 mmol) in 1 mL of DCE and allowed to stir at rt for 72 h unless otherwise noted. [b](*S*)-*i*Pr-Box used instead of (*S*)-Ph-Box.

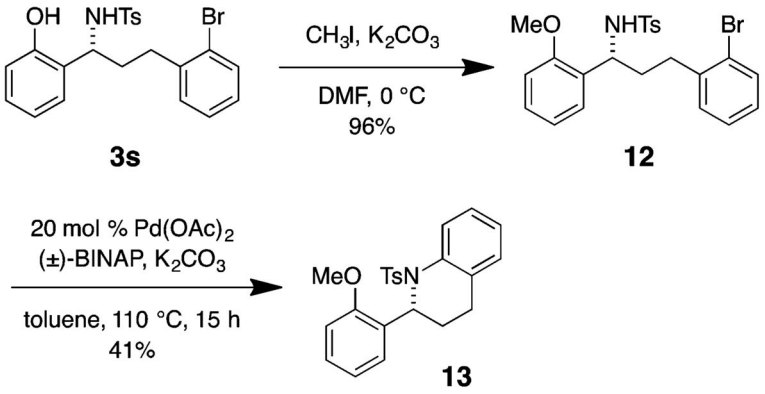


Scheme 4. Aryl Imine Aza-Friedel–Crafts Scope[a]

[a]Reaction conditions: imine (0.20 mmol) and phenol (0.30 mmol) and flame-dried 4 Å mol. sieves were added to a solution of $Cu(OTf)_2$ (0.020 mmol) and (*R*)-Bn-Box (0.030 mmol) in 1 mL of DCE at 0 °C, and the mixture was stirred 24 h. [b]Absolute configuration determined by X-ray crystallography (see SI).



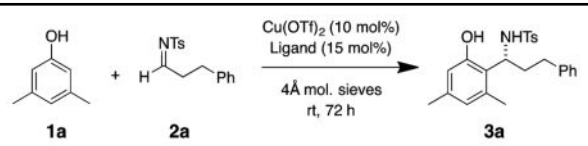
Scheme 5.
Enantioselective Synthesis of an Orexin Receptor Antagonist



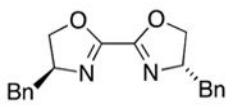
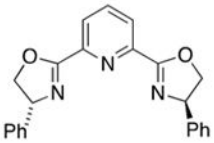
Scheme 6.
Synthesis of a Tetrahydroquinoline

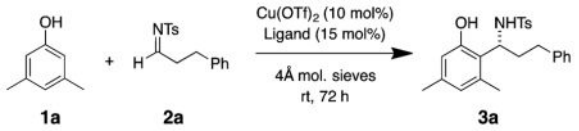
Table 1

Aza-Friedel–Crafts Alkyl Imine Optimization[a]



1a **2a** **3a**

entry	solvent	ligand	phenol (equiv)	yield (%)	ee (%)
1	CH_2Cl_2	(*R*)-Bn-Box	5	19	−43
2	CH_2Cl_2	(*S*)-*i*-Pr-Box	5	23	69
3	CH_2Cl_2	(*S*)-*t*-Bu-Box	5	5	37
4	CH_2Cl_2	(*S*)-Ph-Box	5	54	84
5	CH_2Cl_2		5	28	<5
6	CH_2Cl_2		5	5	−5
7	CH_2Cl_2	(4*R*,5*S*)-bis-Ph-Box	5	7	91
8	DCE	(*S*)-*i*-Pr-Quinox	1.5	57	<5
9	CH_2Cl_2	(*S*)-Ph-Box	1.5	38	84
10	xylenes	(*S*)-Ph-Box	1.5	24	66
11	THF	(*S*)-Ph-Box	1.5	11	94
12	toluene	(*S*)-Ph-Box	1.5	16	75
13	**DCE**	**(*S*)-Ph-Box**	**1.5**	**53**	**94**
14	$PhCF_3$	(*S*)-Ph-Box	1.5	6	63
15	EtOAc	(*S*)-Ph-Box	1.5	36	94
16[b]	DCE	(*S*)-Ph-Box	1.5	66	76



entry	solvent	ligand	phenol (equiv)	yield (%)	ee (%)
17[c]	DCE	(*S*)-Ph-Box	1.5	49	92
18[d]	DCE	(*S*)-Ph-Box	1.5	26	83
19[e]	DCE	(*S*)-Ph-Box	1.5	39	87
20[f]	DCE	(*S*)-Ph-Box	1.5	0	—

[a] Reaction conditions: imine **2a** (0.20 mmol) and phenol **1a** (0.30 mmol) and flame-dried 4 Å mol. sieves were added to a solution of $Cu(OTf)_2$ (0.020 mmol) and ligand (0.030 mmol) in 1 mL of solvent, and the mixture was stirred at rt for 72 h unless otherwise noted.

[b] Reaction run at 40 °C.

[c] Reaction performed at 0.3 M with respect to imine.

[d] Reaction performed for 24 h.

[e] Reaction performed for 48 h.

[f] Reaction performed without $Cu(OTf)_2$.