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6-Azabicyclo[3.2.1]octanes *via* Copper-Catalyzed Enantioselective Alkene Carboamination

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Abstract: Bridged bicyclic rings containing nitrogen heterocycles are important motifs in bioactive small organic molecules. An enantioselective copper-catalyzed alkene carboamination reaction that creates bridged heterocycles is reported herein. Two new rings are formed in this alkene carboamination reaction where *N*-sulfonyl-2-aryl-4-pentenamines are converted to 6-azabicyclo[3.2.1]octanes using the complex [Ph-Box-Cu](OTf)$_2$ or related catalysts in the presence of manganeses dioxide (MnO_2) as stoichiometric oxidant in moderate to good yields and generally excellent enantioselectivities. Two new stereocenters are formed in the reaction, and the C–C bond-forming arene addition is a net C–H functionalization.

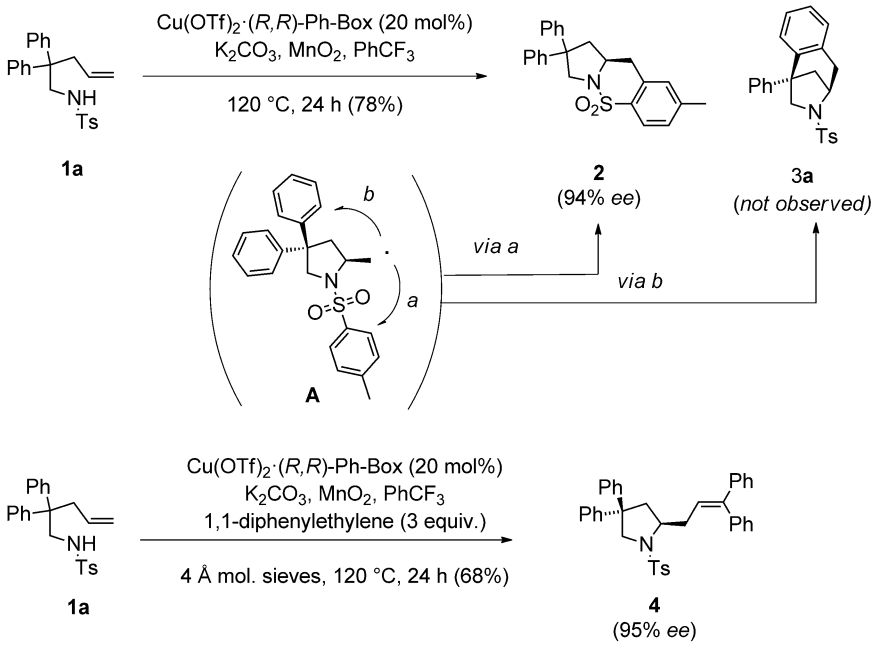
Keywords: 6-azabicyclo[3.2.1]octanes; alkaloids; carboamination; copper-catalyzed reactions; enantioselectivity

Bridge-containing organic compounds are attractive molecular scaffolds due to their relative rigidity and ability to precisely display functional groups in three dimensions.[1] The azabicyclo[3.2.1]octane skeleton is at the core of important biologically active natural products such as cocaine, aphanorphine, and securinine.[2] In addition, synthetic analogs have demonstrated promising therapeutic potential for the treatment of drug addiction and pain.[3] Although a number of methods for their synthesis have been developed,[4] few form two rings in one step,[5] and of these latter examples, none provide azabicyclo-[3.2.1]octanes enantioselectively through asymmetric catalysis.[5e,f] This report describes the synthesis of 6-azabicyclo[3.2.1]octanes *via* copper-catalyzed enantioselective alkene carboamination.

We have previously shown that *N*-tosyl-2,2-diphenyl-4-pentenamine **1a** can undergo copper-catalyzed enantioselective alkene carboamination to form the chiral bicyclic sultam **2** with 94% *ee* (Scheme 1).[6a] The new N–C bond is thought to be set by an enantioselective aminocupration step. Subsequent C–Cu(II) bond homolysis is thought to occur, forming intermediate **A**. Carbon-carbon bond formation *via* intramolecular addition of the primary carbon radical of **A** to the pendant arylsulfonyl group followed by oxidation/rearomatization provides sultam **2**. More recently, we reported that in the presence of 1,1-diphenylethylene, the same carbon radical intermediate can undergo an intermolecular C–C bond formation to give chiral pyrrolidine **4** with 95% *ee*.[7] In both examples, formation of the bridged bicyclic carboamination product **3a** *via* path b (Scheme 1) is possible but was not observed.

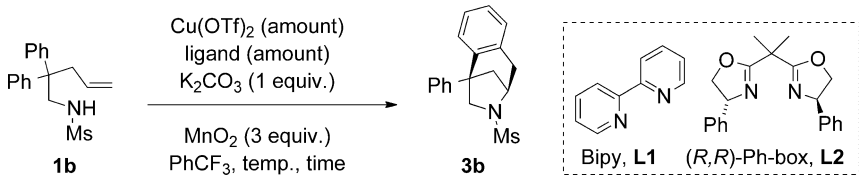
We hypothesized that in the absence of all other radical acceptors (tosyl, 1,1-diphenylethylene), 2-arylpentenamines **1** could undergo intramolecular carboamination reactions to give 6-azabicyclo[3.2.1]octanes **3**. To our delight, we found that this process could indeed occur using *N*-mesyl-2,2-diphenylpentenamine **1b** as the model substrate (Table 1, entry 1). Furthermore, the reaction could be rendered enantioselective to give **3b** with 67% *ee* using the commercially available (*R,R*)-Ph-Box ligand complexed with Cu(OTf)$_2$ (Table 1, entry 2). Addition of activated 4 Å molecular sieves led to a higher and more reproducible level of enantioselectivity (91% *ee*, Table 1, entry 3), presumably due to sequestration of adventitious water, which is deleterious to the reaction's efficiency and selectivity. We were able to reduce the catalyst loading to 15 mol%, the temperature to 110 °C, and the reaction time to 12 h without loss of efficiency or enantioselectivity (Table 1, entry 4).

The scope of the enantioselective alkene carboamination reaction was examined (Table 2) using either the conditions from Table 1, entry 3 [120 °C, 20 mol% Cu(OTf)$_2$], or Table 1, entry 4 [110 °C, 15 mol% Cu(OTf)$_2$]. *N*-2-(Trimethylsilylethane)sulfonyl-4-pentenamine **1c** gave 78% of the bicyclic adduct **3c** with



Scheme 1. Possible carboamination pathways.

Table 1. Optimization of reaction conditions.[a]



Entry	$Cu(OTf)_2$ (amount)	Ligand (amount)	Temperature, time	Yield [%][b]	*ee* [%][c]
1	30 mol%	**L1** (40 mol%)	120 °C, 24 h	84	–
2	20 mol%	**L2** (25 mol%)	120 °C, 24 h	78	67
3[d]	20 mol%	**L2** (25 mol%)	120 °C, 24 h	81	91
4[d]	15 mol%	**L2** (19 mol%)	110 °C, 12 h	76	95
5[d,e]	10 mol%	**L2** (13 mol%)	110 °C, 12 h	72	66

[a] *Conditions:* $Cu(OTf)_2$ was combined with **L1** or **L2** under argon and heated in dry $PhCF_3$ (0.8 mL) for 2 h in a sealed tube. Substrate **1b** (50.0 mg, 0.158 mmol), K_2CO_3 (0.158 mmol), MnO_2 (0.473 mmol) and $PhCF_3$ (0.8 mL) were added and the mixture was heated and stirred.
[b] Isolated yield following flash chromatography on silica gel.
[c] Enantiomeric excess determined by chiral HPLC analysis.
[d] Activated flame-dried molecular sieves (20 mg mL^{-1}) were used.
[e] Reaction did not go to completion.

90% *ee*. This sulfonyl group is attractive as it is easily removed with fluoride reagents such as TBAF. The *N*-benzylsulfonyl pentenamine **1d** gave 83% of **3d** with 80% *ee*. The *N*-3,5-*tert*-butyl-4-methoxybenzenesulfonyl substrate **1e** gave 76% of **3e** with 95% *ee*. This arylsulfonyl group's *ortho* positions are hindered by its *meta*-*tert*-butyl groups, rendering formation of the fused ring sultam analogous to **2** (Scheme 1) less favorable. Electron-rich (OMe, SMe) and more electron-deficient (Cl, F) *para*-substituents on the substrate's backbone aryl rings had little effect on the reaction efficiency and selectivity (Table 2, entries 5–8). The 2,2-bis(2-methylphenyl)-substituted 4-pentenyl sulfonamide **5e** underwent the enantioselective carboamination uneventfully, despite the added steric hindrance on the aryl acceptor, giving adduct **6e** in 81% yield and 93% *ee* (Table 2, entry 9). *N*-Mesyl-4-methyl-4-pentenamine **7**, a 1,1-distubstituted alkene, gave adduct **8** bearing two fully substituted chiral carbons in 69% yield with 92% *ee* (Table 2, entry 10). The internal alkene substrates **9a** and **9b**, however, reacted poorly, producing intractable mixtures of sub-

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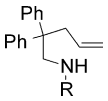
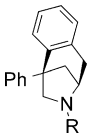
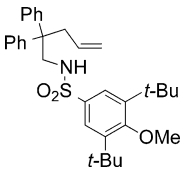
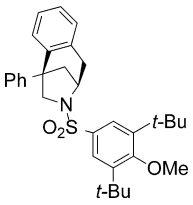
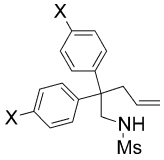
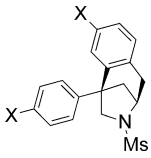
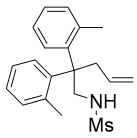
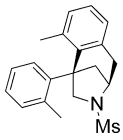
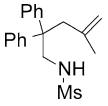
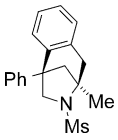
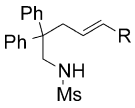
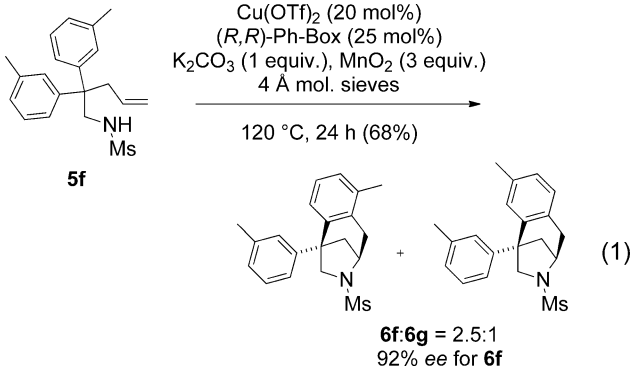
Table 2. Scope of the enantioselective carboamination.

Entry	Substrate		Product		Yield [%]	*ee* [%]
1[a]		**1b**, R = Ms		**3b**	76	95
2[b]		**1c**, R = SES		**3c**	80	90
3[b]		**1d**, R = SO_2Bn		**3d**	83	80
4[b]		**1e**		**3e**	76	95
5[a]		**5a**, X = OMe		**6a**	83	95
6[a]		**5b**, X = SMe		**6b**	80	93
7[a]		**5c**, X = Cl		**6c**	80	90
8[a]		**5d**, X = F		**6d**	68	95
9[b]		**5e**		**6e**	81	93
10[b]		**7**		**8**	69	92
11[b]		**9a**, R = Me			–	–
12[b]		**9b**, R = Ph			–	–

[a] Conditions from Table 1, entry 4.
[b] Conditions from Table 1, entry 3.

strate and unidentified products under the reaction conditions (Table 2, entries 11 and 12).

An *N*-mesyl-2,2-diaryl-4-pentenamine bearing *meta* substitution on its aryl rings produced a 2.5:1 ratio of regioisomers favoring the more hindered *ortho* isomer **6f** [Eq. (1)]. The level and direction of regioselectivity is consistent with addition of a carbon radical to the arene (e.g., path b, Scheme 1)[6b,c,8] as electrophilic aromatic substitution would be expected to favor the less hindered *para* product **6g**.[9]



(1)

The absolute configuration of **3b** was confirmed by its X-ray structure (Figure 1) and all other enantioenriched products were assigned by analogy to **3b**.

We next examined the desymmeterization reactions of bis(2-allyl) substrates **10a** and **10b** (Scheme 2). The use of our standard conditions (Table 1, entry 3) with the (*R,R*)-Ph-Box ligand gave **11a** in 30% yield with a disappointing 35% *ee* (not shown), thus we turned to the (4*R*,5*S*)-*cis*-diphenylbis(oxazoline) ligand,

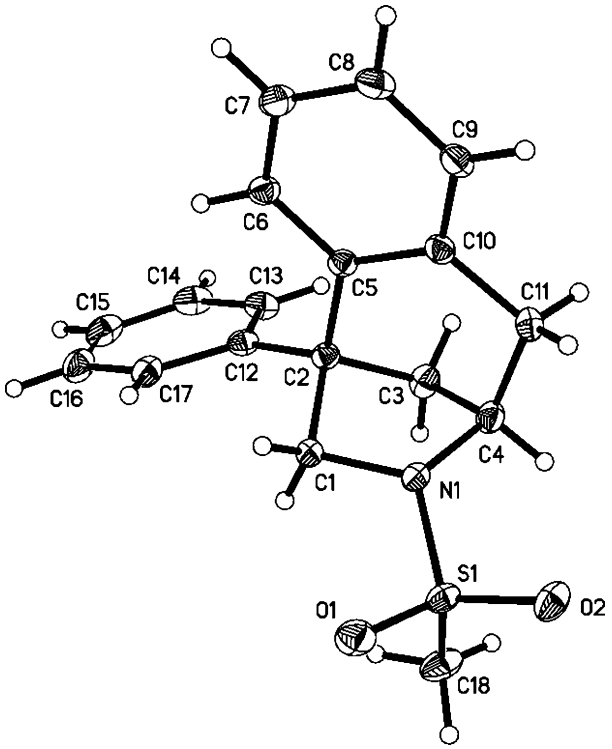
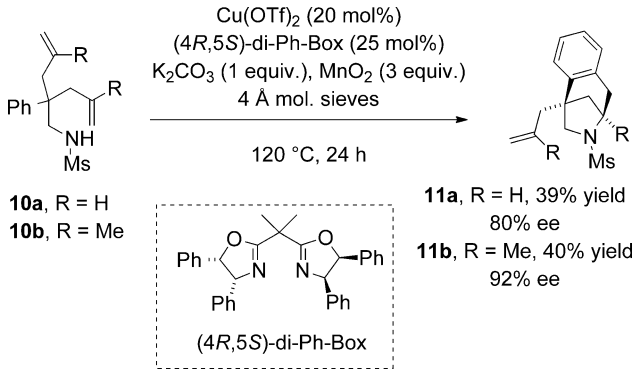


Figure 1. X-ray crystal structure of **3b** (CCDC 991873 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif).



Scheme 2. Desymmetrization reactions.

which has demonstrated superior enantioselectivity in challenging cases in copper catalysis.[10] Encouragingly, **11a** was formed in 39% yield and 80% *ee* using this ligand. We were also able to achieve enantioselective desymmeterization using the bis(2-methylallyl) substrate **10b**, which gave **11b** in 40% yield, with 92% *ee*. The reduced yield in these reactions is likely due to the additional demand for diastereoselectivity in the N–C bond forming step, although we were unable to isolate and identify minor products from these reactions.

The proposed catalytic cycle is given in Scheme 3. The stereoselectivity of the reaction is achieved in the *cis*-aminocupration step, where the the phenyl rings on the chiral ligand are "*trans*" to the substrate's mesyl and alkene groups to avoid steric interaction.[11] The resulting organocopper(II) intermediate undergoes homolysis to form a primary carbon radical which adds across the pyrrolidine ring to the aryl group it is *cis* to. Oxidation of the resulting aryl radical under the reaction conditions provides the azabicyclic product **3**. It should be noted that analogous transannular additions of carbon radicals to alkenes have been reported,[12] but transannular radical additions to arenes are more rare.[8b,13]

In conclusion, the copper(II)-catalyzed enantioselective alkene carboamination reaction is an efficient method to prepare a variety of chiral 6-azabicyclo-[3.2.1]octanes. Further investigations into the scope and utility of this method for its application in organic synthesis will be reported in due course.

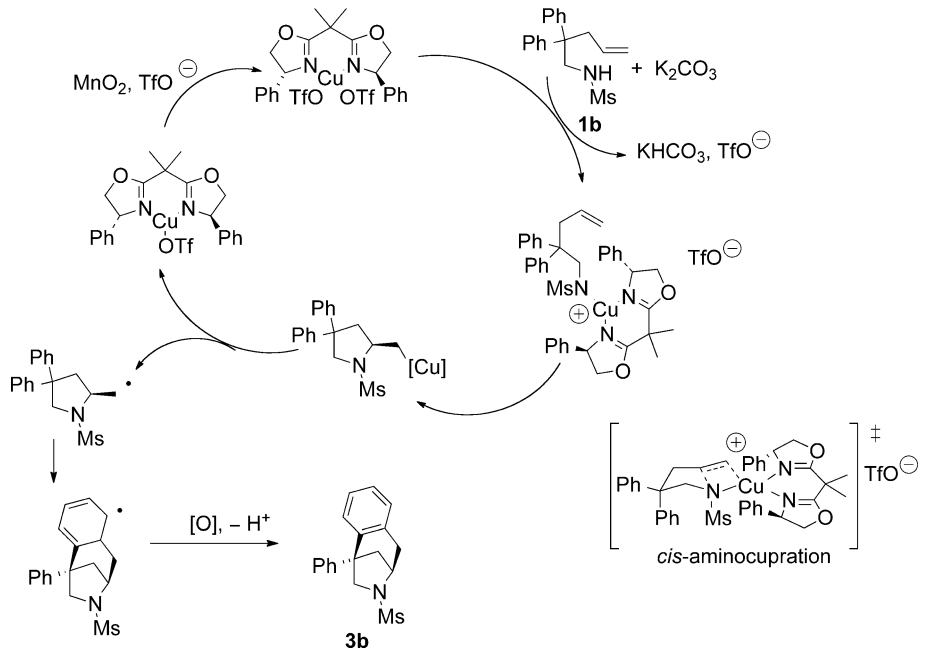
Experimental Section

For experimental details and spectral data for all new compounds, see the Supporting Information.

Representative Procedure for the Enantioselective Carboamination: (1*S*,4*R*)-3-(Methylsulfonyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-methanobenzo[*d*]-azepine (3b)

$Cu(OTf)_2$ (8.5 mg, 0.024 mmol, 15 mol%), (*R,R*)-Ph-Box (10.0 mg, 0.030 mmol, 19 mol%) and dry $PhCF_3$ (0.8 mL) were placed in a flame-dried glass reaction tube under argon. The tube was capped and the reaction heated at 60 °C for 2 h. After cooling, sulfonamide **1b** (50.0 mg, 0.158 mmol), K_2CO_3 (21.8 mg, 0.158 mmol, 1 equiv.), MnO_2 (41.1 mg, 0.473 mmol, 3 equiv.) and $PhCF_3$ (0.8 mL) were added. Flame-dried molecular sieves (4 Å, 35 mg) were added to the reaction mixture, the tube was flushed with argon, capped and the mixture was heated at 110 °C for 12 h. Upon cooling, the mixture was diluted with EtOAc and filtered through a pad of silica gel. The filtrate was concentrated under vacuum and the crude residue was purified by flash chromatography on silica gel, providing 6-azabicyclo[3.2.1]octane **3b** as a white solid; yield: 38 mg (76%).

Compound **3b** was further purified *via* HPLC and found to be in 95% enantiomeric excess as determined by analysis on chiral HPLC [Chiralpak AD-RH, 50% CH_3CN/H_2O, 0.5 mL min^{-1}]: t(minor) = 15.93 min, t(major) = 18.63 min], $[\alpha]_D^{23}$: −88.3° (*c* 0.6, $CHCl_3$); mp 209–211 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.28 (m, 5H), 7.16–7.13 (m, 2H), 7.01–6.95 (m, 1H), 6.53 (d, J = 8.4 Hz, 1H), 4.58–4.54 (m, 1H), 3.88 (ABq, J_{AB} = 9.0 Hz, $\delta\nu$ = 17.0 Hz, 2H), 3.30 (d, J = 17.1 Hz, 1H), 3.18 (dd, J = 17.1, 2.4 Hz, 1H), 2.80 (s, 3H), 2.61 (d, J = 11.1 Hz, 1H), 2.30 (ddd, J = 12.0, 5.8, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 142.2, 132.7, 129.5, 127.6, 127.3, 126.8, 126.2, 61.0, 57.0, 51.3, 40.6,



Scheme 3. Proposed catalytic cycle.

38.5, 36.5; IR (neat, thin film): $\nu = 3061$, 3031, 2955, 2868, 1485, 1450, 1331, 1157, 1061 cm^{-1}; HR-MS (ESI): $m/z =$ 314.1219, calcd. for $C_{18}H_{19}NO_2S$ $[M+H]^+$: 314.1209.

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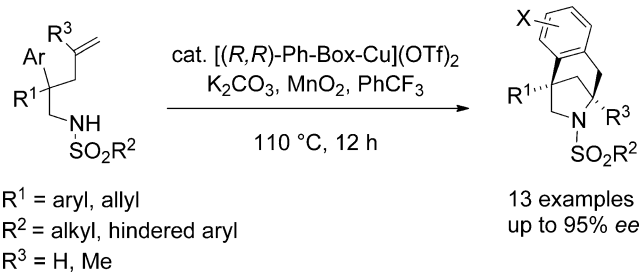

R^1 = aryl, allyl
R^2 = alkyl, hindered aryl
R^3 = H, Me

13 examples
up to 95% *ee*

7

