Copper-Catalyzed Enantioselective [4π + 2σ] Cycloaddition of Bicyclobutanes with Nitrones

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Abstract:
The selective construction of bridged bicyclic scaffolds has garnered increasing attention due to their extensive use as saturated bio-isosteres of arene in pharmaceutical industry. However, in sharp contrast to their racemic counterparts, assembling chiral bridged bicyclic structures in an enantioselective and regioselective manner remains challenging. Herein, we describe our protocol for constructing chiral 2-oxa-3-azabicyclo[3.1.1]heptanes (BCHeps) by enantioselective [4π + 2σ] cycloadditions of bicyclo[1.1.0]butanes (BCBs) and nitrones taking advantage of a chiral copper(II) complex as Lewis acid catalyst. This method features mild condition, good functional group tolerance, high yield (up to 99%) and excellent enantioselectivity (up to 99% ee). Density functional theory (DFT) calculation elucidates the origin of the reaction's enantioselectivity and the mechanism of BCB activation by Cu(II) complex.

Arene rings are one of the most prevalent structures in bio-active molecules. However, in the developments of new drugs, arenes often bring undesired pharmaceutical properties, which has promoted medicinal chemists to seek for their bio-isosteres[1]. In recent years, three dimensional (3D) saturated bridged bicyclic scaffolds, such as bicyclo[1.1.1]pentanes (BCPs)[2], bicyclo[2.1.1]hexanes(BCHs)[3], and bicyclo[3.1.1]heptanes (BCHeps)[4] (Figure 1a), have been developed as surrogates of arene for their ability in mimicking the structural properties of arene rings and improving the physochemicals and pharmacokinetics of the corresponding drugs[5]. Among them, BCHeps present a fascinating structure with appropriate bond angles serving as mimetics of meta- or ortho-substituted arenes (Figure 1b). Various methods have been established to build BCHeps, among which the cycloadditions of bicyclo[1.1.0]butanes (BCBs) stand out for its efficiency and atom-economy[6]. In Baran's reports, the drugs whose arenes were replaced by saturated 3D bio-isosteres with opposite absolute configurations displayed distinct bioactivities[7], so enantioselective assembly of such structures is necessary[8].

Currently, the state-of-the-art strategies for constructing racemic BCHeps have been advanced by Molander[4c], Li[4e], Waser[4f] using photoredox or pyridine-boryl radical promoted open-shell chemistry and by Glorius[4i], Deng[4k] through dipolar-addition process. However, despite significant progress in racemic BCHeps synthesis, achieving enantioselective synthesis of chiral BCHeps remains challenging. Only Feng and Zhang published an example for enantioselective synthesis of chiral oxo-BCHeps by palladium-catalyzed ring-open of vinyl oxiranes followed by dipolar cycloaddition with BCBs, with excellent enantioselectivity but modest regioselectivity (up to 73:27) (Figure 1c)[4h]. On the other hand, Mykhailiuk's works showed that the inclusion of hetero-atoms in the 3D bio-isosteres of arenes leads to better water solubility, higher metabolic stability, and lower lipophilicity than their benzene and all-carbon bicyclic mimetics counterparts[9], which inspired our focus on the synthesis of aza- and oxo-BCHeps. In this context, nitrones were chosen to introduce N and O atoms into the BCHeps structure due to their excellent reactivity in cycloaddition reactions and ease of preparation and storage.[4k,10] Herein, we report Cu(II)-catalyzed enantioselective synthesis of 2-oxa-3-aza BCHeps via dipolar cycloaddition of BCBs with nitrones (Figure 1d). In the reaction, BCB coordinates with the copper catalyst to polarize and weaken the strained C–C σ bond, facilitating the nucleophilic attack of

nitrone to generate a Cu(II)-associated zwitterion intermediate, which then undergoes an enantio-determining ring-closing process to form chiral BCHep.

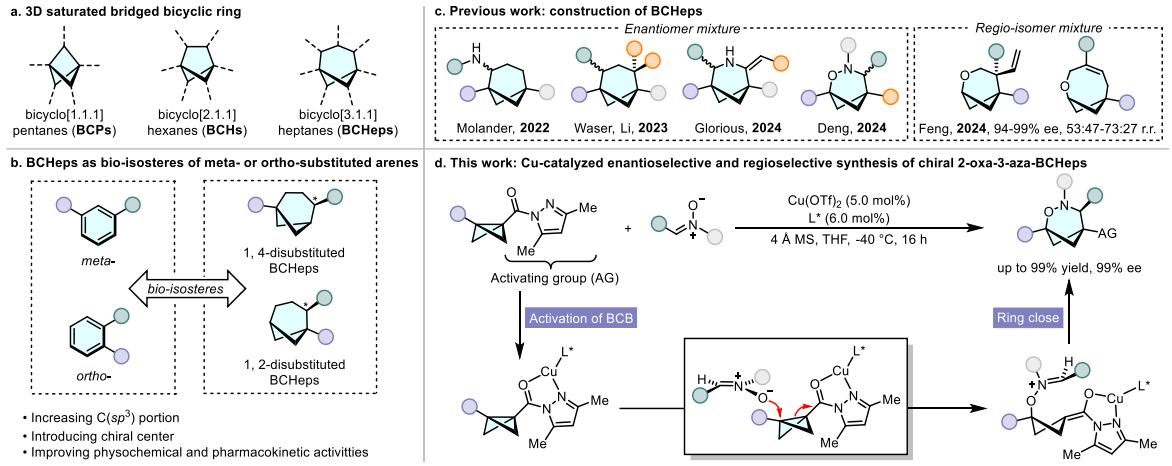
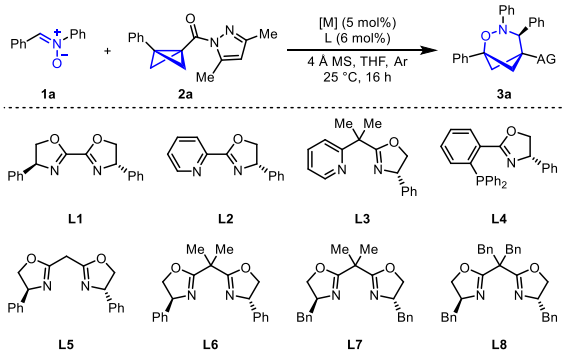


Figure 1. a. 3D saturated bridged bicyclic rings. **b.** Mimicking meta- and ortho-substituted arene with bicyclo[3.1.1]heptanes (BCHeps). **c.** Previous works on construction of BCHeps. **d.** This work: Cu(II)-catalyzed enantioselective and regioselective synthesis of chiral 2-oxa-3-aza-BCHeps.

To commence the investigation, we selected nitrone (**1a**) and the pyrazole amide substituted BCB (**2a**; Table 1; see Supplementary Information for details) as standard substrates to evaluate the reaction condition. Surprisingly, of the three Earth-abundant metals tested, copper was the sole catalyst capable of yielding 2-oxa-3-aza BCHep (**3a**) with an isolated yield of 67% (entry 1–3). Even more surprisingly, no ring-opening by-products were observed, highlighting the high chemoselectivity of the reaction. Next, chiral ligand was employed to control enantioselectivity of the reaction. Except **L5**, which is known to be a negatively charged ligand in the reaction, all the other electrically neutral ligands can improve the reaction yield (entry 4–11). To our delight, Evans bisoxazoline ligand **L6** presented a promising ee value of 71% (entry 9). Modification of bisoxazoline ligand revealed that one with four benzyl groups at the oxazoline ring and bridge carbon gave high ee value (89%, entry 11). Additionally, lowering the reaction temperature to –40 °C further increased the yield and enantioselectivity of the reaction (99%, 96% ee, entry 12).

Table 1. Optimization of reaction of BCB with nitrone[a]



entry	[M]	L	yield (%)[b]	ee (%)[c]
1	$Fe(OTf)_3$	none	n.d.	none
2	$Ni(OTf)_2$	none	n.d.	none
3	$Cu(OTf)_2$	none	67	none
4	$Cu(OTf)_2$	**L1**	99	11
5	$Cu(OTf)_2$	**L2**	99	0
6	$Cu(OTf)_2$	**L3**	99	0
7	$Cu(OTf)_2$	**L4**	99	0
8	$Cu(OTf)_2$	**L5**	n.d.	n.d.
9	$Cu(OTf)_2$	**L6**	89	71
10	$Cu(OTf)_2$	**L7**	82	82
11	$Cu(OTf)_2$	**L8**	79	89
12[d]	$Cu(OTf)_2$	**L8**	99	96

[a] Reaction condition: **1a** (0.1 mmol), **2a** (0.1 mmol), metal catalyst (0.005 mmol), ligand (0.006 mmol), THF (1 mL), 4 Å molecular sieves (40 mg), Ar atmosphere, 25 °C, 16 h. [b] Isolated yields. [c] The ee values were determined by chiral HPLC. [d] Reaction temperature –40 °C.

With optimal condition established, we then studied the substrate scope with respect to nitrone (Figure 2a). The nitrone substrates with methyl or trifluoromethyl group on the benzene ring of nitrones **1** all gave desired products with good yield and excellent enantioselectivity (**3a**–**3c**). The halogen substituents on the meta or para position of the benzene ring also didn't adversely affect the outcome of the reaction (**3e**–**3i**), which provides an opportunity for further cross-couplings. However, nitrone with an ortho-fluorophenyl gave lower ee value, perhaps due to the steric effect (**3d**). Moreover, the functional groups with potential for diverse synthetic transformation like nitro, cyano, ester, boric ester, acetoxyl, phenoxy, silyl and sulfonyl group (**3j**–**3q**) have no serious harm to the yield and enantioselectivity of the reaction. In addition, trifluoromethoxy (**3r**)[11] and trifluoromethylthio (**3s**)[12] groups which often show unusual bio-activities in drug molecules were compatible in the reaction. Except for substituted phenyl groups, the fused aryl rings and hetero-aryl rings in the nitrone substrates also have no negative effect, giving excellent enantioselectivity (**3t**–**3x**). Apart from the deviation of R^1, variations in the *N*-protecting aryl groups of BCB, including substitutions at the meta or para positions, showed minimal influence on both yield and enantioselectivity (**3y**–**3ab**). The substrate scope with respect to BCBs was explored (Figure 2b). Substitutions on the benzene ring of BCB, regardless of electron donating (**3ac** and **3ad**) or withdrawing (**3ae**–**3ag**) groups, all gave gratifying outcomes. Notably, a methyl-substituted BCB can also react with nitrone **1a** to form 2-oxa-3-aza BCHep **3ah** under standard conditions with high yield and enantioselectivity.

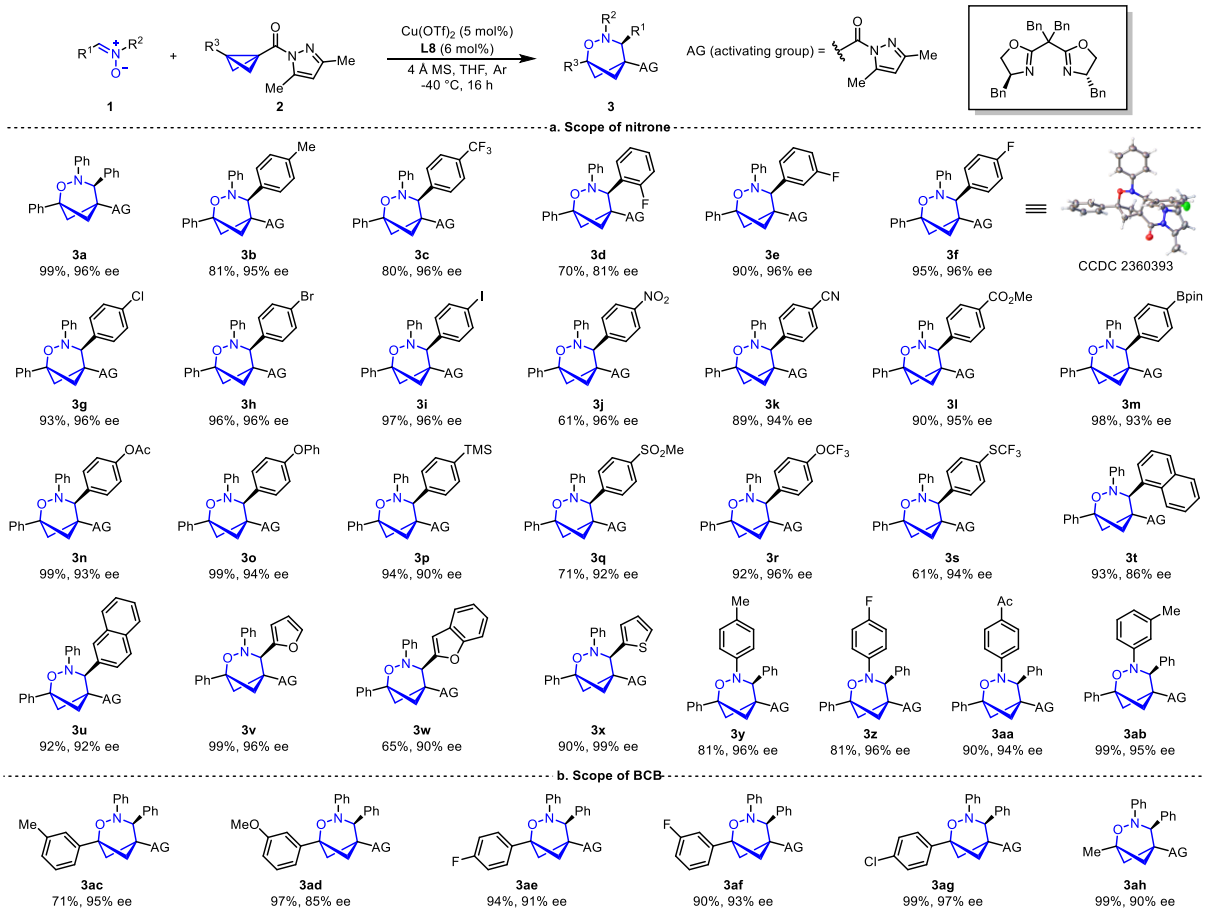


Figure 2. Enantioselective [4π+2σ] cycloaddition of BCBs with nitrones. **a**. Substrate scope of nitrone. **b**. Substrate scope of BCB.

To showcase the application potential of this method, we carried out mmol experiment with **1a** and **2a** under standard condition (Figure 3). At 1 mmol scale, **3a** was produced with undiminished yield and ee value, highlighting its scalability. Besides, pyrazole amide group of **3a** can be readily transformed into several valuable functional groups. Firstly, the $NaBH_4$ reduction of **3a** afforded primary alcohol with quantitative yield and unharmed ee value, facilitating subsequent connection through nucleophilic substitution or Mitsunobu reaction. Hydrolysis of **3a** produced carboxylic acid **5** with 81% yield and >99% enantio-specificity, granting convenience for further amidation or decarboxylative coupling[13]. Finally, the alcoholysis of **3a** converted the amide group to the ester group with 96% yield and 96% ee.

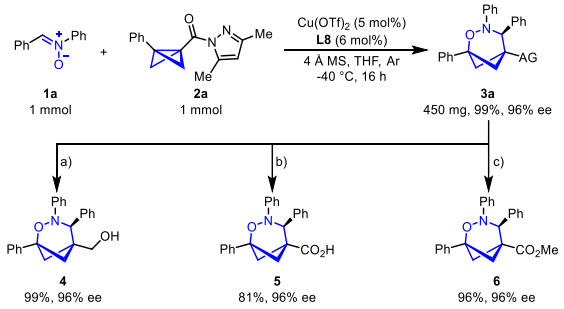


Figure 3. A mmol scale synthesis of **3a** and transformations. **a)** $NaBH_4$ (5.0 equiv.), THF/H_2O (4:1, 0.04 M), 0 °C-r.t., 3 h. **b)** LiOH (4.0 equiv.), THF/H_2O (1:1, 0.1 M), r.t., 16 h. **c)** DBU (1.1 equiv.), MeOH (0.1 M), r.t., 16 h.

In order to elucidate the reaction mechanism, control experiments were performed. Reaction of **2a** in the absence of nitrone resulted in >95% recovery of starting material with no observation of ring-opening by-products, thereby excluding the possibility of a copper-catalyzed ring-opened intermediate (Figure 4a). Ester substituted BCB **7** was then applied in the cycloaddition and yielded no product, revealing the chelation of bidentated pyrazole amide to copper is indispensable (Figure 4b). To gain a deeper insight into the activation effect of Cu(II) on pyrazole amide-substituted BCB, we perform DFT calculation to analyze the structural and electronic properties of several relevant species. As illustrated in Figure 4c, the bridgehead carbon adjacent to the phenyl substituent of the free BCB bears a certain amount of positive charge, showing its electrophilic nature. Without the coordination of Cu(II), the strained C–C σ bond of BCB has a bond length of 1.54 Å and a Mayer bond order of 0.64, indicating a weaker bond strength than typical open chained C–C single bond. However, upon coordination with a copper catalyst bearing a bisoxazoline ligand, the strained C–C σ bond of BCB elongated to 1.63 Å with a reduced bond order of 0.49, accompanied by an increased positive charge at the bridgehead carbon. These computational results showed that the coordination of copper(II) catalyst effectively activate BCB.

The ring-closing step which determines the enantioselectivity of the reaction was also studied by means of DFT calculations (Figure 4d, upper part). In this step, the Cu(II)-coordinated enol produced by the nucleophilic addition of nitrone and BCB connects its electronegative carbon to the electrophilic carbon of imine to form the BCHep scaffold. The Gibbs free energy of the transition state leading to (*S*)-**3a** (**TS-S**) is 1.7 kcal/mol lower than that leading to (*R*)-**3a** (**TS-R)**, resulting in the major product with (*S*)-configuration, which agrees with the experimental observations. To understand the origin of the energy difference between the two transition states, independent gradient model based on the Hirschfeld partition (IGMH) was employed to analyze the weak interaction[14]. As shown in Figure 4d (lower part), both transition states have multiple CH-π interactions between the bisoxazoline ligand and substrate. However, **TS-S** displays a greater number and stronger intensity of CH-π interactions (highlighted by red circles) compared to **TS-R**, indicating that enantioselectivity is primarily governed by non-covalent interactions.

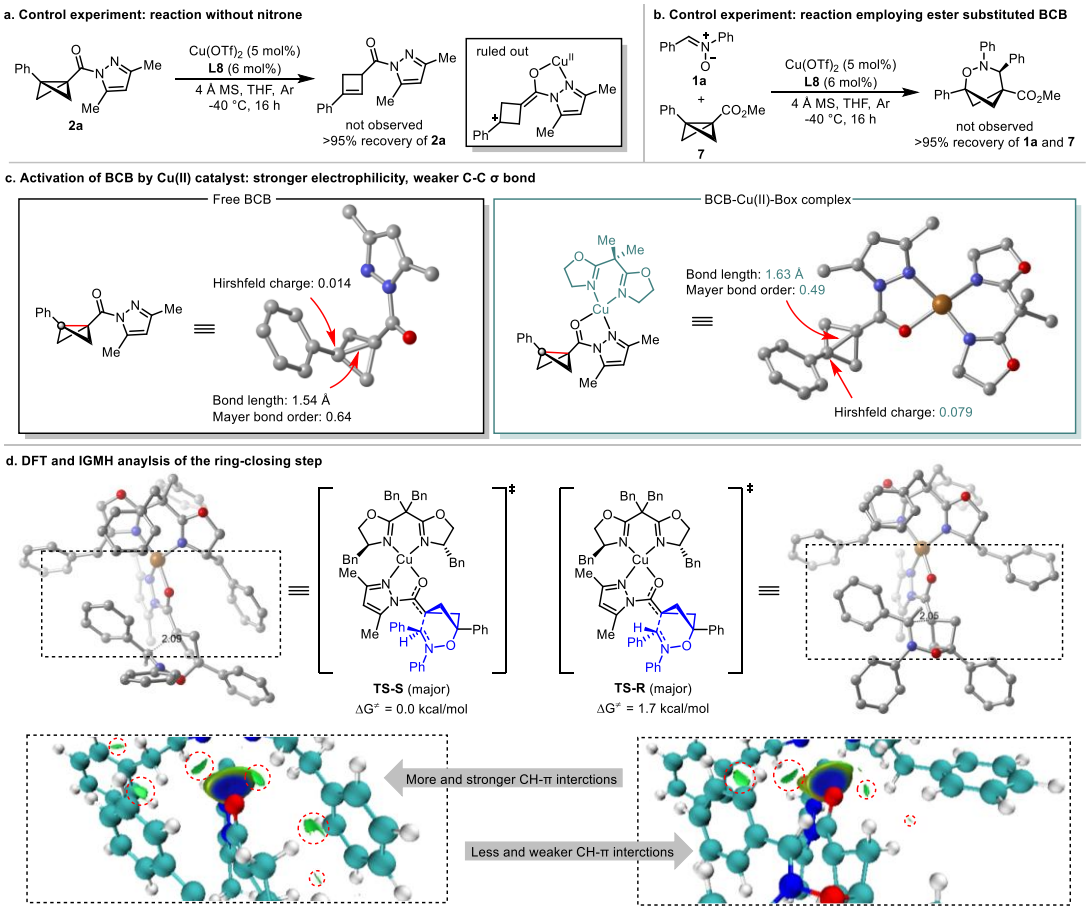


Figure 4. Control experiments and DFT calculations. **a.** Control experiment: reaction of BCB without nitrone. **b.** Control experiment: employing ester substituted BCB. **c.** Investigation of structural and electronic properties of BCBs by DFT calculations. **d.** DFT and IGMH analysis of ring-closing step.

In summary, we have established an enantio- and regio-selective method for the construction of chiral BCHeps through Cu(II)-catalyzed asymmetric cycloaddition of BCBs with nitrones. The reaction featured with mild condition, high yield, high selectivity, and broad substrate scope. The success of the reaction hinges on the activation of BCB by bisoxazolin-coordinated Cu(II) catalyst, which was verified by DFT calculations. Computational chemistry revealed that the origin of enantioselectivity arises from non-covalent interactions between the ligand and substrate, offering insights for constructing other types of saturated bridged bicyclic bio-isosteres of arenes. Future works will be focusing on the application of this catalytic system to the structurally divergent synthesis of bicyclic skeletons.

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