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# Anionic Bisoxazoline Ligands Enable Copper-Catalyzed Asymmetric Radical Azidation of Acrylamides

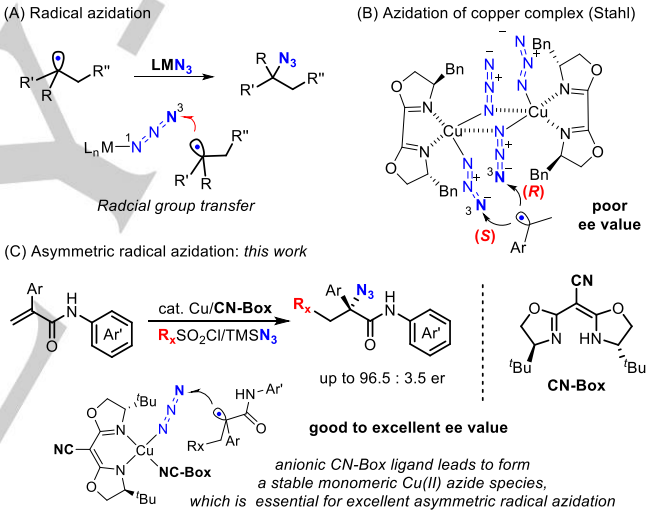
Lianqian Wu,[†a] Zhihan Zhang,[†b] Dunqi Wu,[†c] Fei Wang,[a] Pinhong Chen,[a] Zhenyang Lin,*[b] and Guosheng Liu*[a,c]

**Abstract:** Asymmetric radical azidation for the synthesis of chiral alkylazides remains a tremendous challenge in organic synthesis. We report here an unprecedented highly enantioselective radical azidation of Acrylamides catalyzed by 1 mol% of copper catalyst, and arrays of substrates were converted to the corresponding alkylazides in high yield with good to excellent enantioselectivities. Notably, employing anionic cyano-bisoxazoline (CN-Box) ligand is crucial, which generates a monomeric Cu(II) azide species, rather than a dimeric Cu(II) azide intermediate, for this highly enantioselective radical azidation.

Organic azides play irreplaceable roles in organic synthesis, chemical biology, drug discovery, and materials science,[1,2] thus motivating the continuing development of efficient methods for their preparation.[1,3] Despite great progress in this field, the catalytic synthesis of optically pure alkylazides remains elusive.[4,5] Radical azidation represents a powerful tool for the synthesis of alkylazides.[3d-3g,6] However, nearly all the present protocols lead to the racemic targets,[7] which results from notorious difficulty as the following reasons: (1) the ready generation of the azidyl radical could result in the undesired side reactions, which would depletes the desired radical coupling with carbon-centered radicals;[8] (2) transition metal-catalyzed radical azidation reactions were demonstrated as efficient tools for the alkylazide synthesis,[3g,6-7,9] where the C-$N_3$ bonds are generated from a *outer sphere pathway* with carbon radical attacking at terminal $N^3$ atom (Scheme 1A). Thus, the relatively far away of reaction site to catalyst chiral center make enantioselective radical azido-transfer even more challenging.

To address this issue, we became interested in developing efficient asymmetric radical azidation reaction based on our recent works on the copper-catalyzed asymmetric radical transformations.[10-11] Distinct from our previous reactions involving a proposed Cu(III) intermediates, however, the azidation reaction are proposed to undergo the *radical group transfer (outer sphere) pathway* for the C–$N_3$ bond formation. More importantly, Stahl and coworkers recently reported a radical azidation of benzylic C-H bond, in which a copper-azide dimer having neutral bisoxazoline (Box) ligands was involved, and both bridging and terminal azides can be attacked by the carbon centered radical to lead to two opposite azidation enantiomers, which compromise the enatioselectivity and result in poor er values (Scheme 1B, for details, see the supporting information of ref. 3g).

Based on above analysis, the enantioselective radical azido-transfer is extremely challenging, and quite rare examples were documented to date. Thus, exploration of the appropriate chiral ligands and/or reaction modes for the asymmetric radical azidation reactions is highly demanded. Here we describe an unprecedented highly enantioselective radical azidation of acrylamides via copper-catalyzed radical relay (Scheme 1C). Interestingly, different from the commonly used neutral Box ligands giving poor enantioselectivity, the anionic cyano-bisoxazoline (CN-Box) ligands show much higher enantioselecitivity, which derived from a novel monomeric Cu(II) azide species stabilized by two CN-Box ligands.




**Scheme 1.** Asymmetric azidation of alkenes..

We began our investigation by choosing acrylamide **1a** as the model substrate, $TMSN_3$ as the nucleophilic azide source, and Togni-I reagent as the radical precursor, to optimize the reaction conditions in the presence of Box/Cu(I) catalyst. However, similar to the Stahl's results, the neutral Box ligands (e.g., **L1**-**L3**) afforded poor enantiomeric induction (Table 1A). Interestingly, further ligand screening revealed that the anionic ligand CN-Box exhibited much better enantioselectivity than the neutral Box ligands, where CN-Box **L4** with a sterically hindered *tert*-butyl group showed the best performance to give **2a** in 88.5:11.5 enantiomeric ratio (er). However, switching the bulky *tert*-butyl to less hindered isopropyl (**L5**) or phenyl (**L6**) led to a remarkably diminished enantiomeric ratio (Table 1A).

The remarkably different enantioselectivities between the neutral Box **L1** and the anionic CN-Box **L4** triggered us to investigate the insight of these ligands. Considering the versatile bridging modes of azide in copper complexes, neutral Box (e.g., **L1**) coordinated monomeric **(L1)Cu(II)** azide species could simultaneously dimerize to give a azide bridged **(L1)Cu(II)** dimer, which was supported by our DFT calculation at the $\omega$B97X-D level of theory ($\Delta G$ = -13.6 kcal/mol, see Fig. S2).[3g,12]

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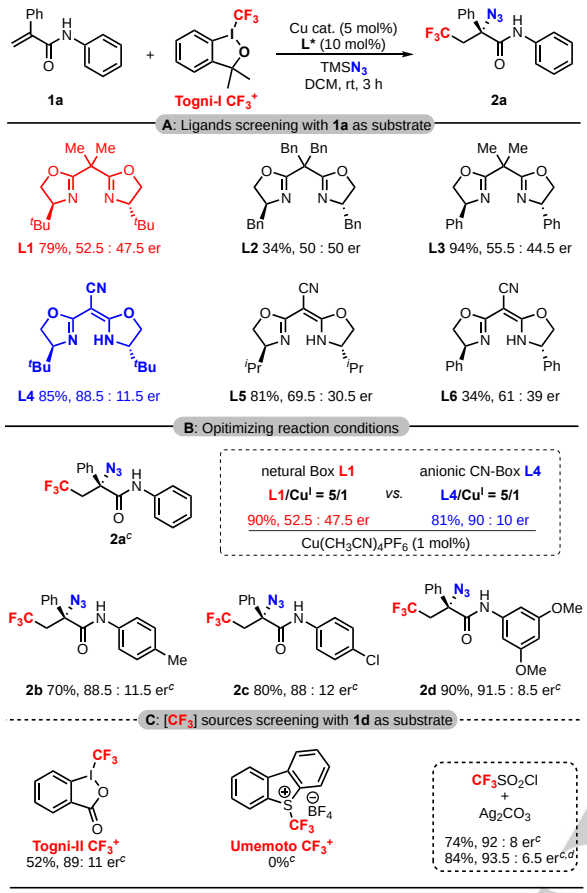
**Table 1.** Optimization of the conditions.[a,b]




[a] All reactions were conducted in 0.1 mmol scale with $Cu(CH_3CN)_4PF_6$ (5 mol%) and Chiral ligand (10 mol%) in dichloromethane (DCM, 0.1 M). [b] Yield was determined by $^{19}F$-NMR of the crude mixture using $CF_3$-DMA as an internal standard, and enantiomeric ratio (er) were determined by HPLC on a chiral stationary phase. [c] $Cu(CH_3CN)_4PF_6$ (1 mol%), Chiral ligand (5 mol%). [d]0.2 mmol scale (0.01 M).

In view of the high thermodynamic driving force, the azide bridged **(L1)Cu(II)** dimer should be overwhelmingly dominant and be likely responsible for the radical azidation to give poor enantioselectivity (see Scheme 1B, and the result of **L1** in Table 1A).

In contrast, our DFT results in Fig. 2 indicate that the anionic CN-Box ligand (e.g., **L4**) coordinated Cu(II) azide complex **(L4)Cu-1** also shows tendency to undergo dimerization to generate **(L4)Cu-2** species (ΔG = -3.8 kcal/mol), but to a much lesser extent with a significantly smaller endergonicity. With the anionic CN-Box **L4**, the dimer **(L4)Cu-2** does not contain terminal azides. More importantly, when excessive amount of **L4** was added, **(L4)Cu-1** transforms to a thermodynamically stable monomeric complex **(L4)Cu-3** (ΔG = -4.6 kcal/mol), in which the neutral form of **L4** (the proton does not ionize) acts as a better nitrile donor, and substitutes $CH_3CN$ via a ligand substitution process. These calculation results indicate that the extra CN-Box significantly increases the stability of a monomeric copper azide, shifting the equilibrium from the dimer to the monomer and providing an opportunity for better enantioselectivity. In fact, the conclusion made here on the basis of DFT calculations was indeed supported by the experimental results, where the obvious effect of the **L4**/Cu(I) ratio on the enantioselectivity was observed. When the amount of **L4** was increased from 1 to 5 equivalents in the presence of 1 mol% $Cu(CH_3CN)_4PF_6$, the enantioselective ratio was dramatically improved from 68:32 to 90:10 (Fig. 1). Notably, the similar ligand effect on the enantioselectivity was not observed in the cases of neutral Box **L1**.

To gain further insights into the enantio-determining C-$N_3$ bond formation, the initial DFT calculations were carried out to survey the

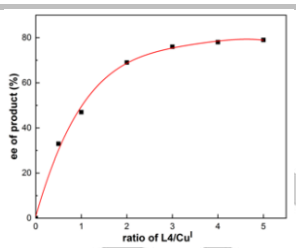



**Figure 1.** Extraneous ligand effect on the enantioselectivity (ee value of product **2a** versus the ratio of **L4**/$Cu^I$).

reaction of the monomeric complex **(L4)Cu-1** with benzylic radical, and the results suggested that the benzylic radical favors attacking the terminal $N^3$ position instead of the more congested internal $N^1$ position (for details, see the Fig. S3), which was consistent with the results reported by Groves[7] and Stahl[3g].

We then investigated/calculated how the various chiral (**L4**)Cu(II) azide species reacts with the carbon centered radicals. As shown in Fig. 2, the monomeric complex **(L4)Cu-3** is the most stable species, which is taken as the energy reference point. The reaction of monomeric complex **(L4)Cu-1** with benzylic radical exhibits the highest energy barriers, while the monomeric complex **(L4)Cu-3** gives the lowest energy barriers. Thus, we concluded that the monomeric complex **(L4)Cu-3** should act as the truly active species for the asymmetric radical azidation in the presence of excess amount ligand (e.g. **L4**:Cu = 5:1). The calculated barrier difference is 1.5 kcal/mol between $\mathbf{TS3R_{L4}}$ and $\mathbf{TS3S_{L4}}$ (see Fig. 2 and Fig. S4), which agrees well with the experimental results ($\Delta\Delta G^{\ddagger}$ = 1.5 kcal/mol for **2a**, 92 : 8 er).

In the similar process using dimer complex **(L4)Cu-2**, the corresponding barrier difference was calculated to be 0.8 kcal/mol (Fig. 2), but with an opposite enantioselective induction to give major (*S*)-isomer. We reasoned that, in the case of less ligand (e.g., **L4**:Cu = 1:1), the equilibrium should be existed between the monomer **(L4)Cu-3** and the dimer **(L4)Cu-2**. The minor dimer **(L4)Cu-2** in the catalytic system generates the major (*S*)-isomer to compromise the enantioselectivity derived from the major **(L4)Cu-3**, resulted dramatically in the ruined ee value (see Fig. 1). Above analysis indicates that the monomeric **(L4)Cu-3** should act as an active species, rather than the dimer species **(L4)Cu-2**, to account for the excellent enantioselective radical azidation.

As discussed above, excessive amount of ligand **L4** is required to achieve high enantiomeric induction. Then, substrates with various *N*-substituted anilines were further evaluated in the presence of extraneous ligands (**L4**/Cu = 5), and we found that acrylamide **1d** performed the best to give **2d** in 91.5:8.5 er (Table 1B). Finally, various $[CF_3]^+$ sources were also evaluated, and the Togni-II and Umemoto reagents gave inferior results (Table 1C). To our delight, when $CF_3SO_2Cl$ was employed as a $CF_3$ radical precursor, the enantiomeric ratio was slightly elevated to 92:8 er in the presence of $Ag_2CO_3$. Alkylsulfonyl chlorides are commercially available and inexpensive, and allow us to incorporate diverse haloalkyl groups into the target molecules.[13] Further lowering the reaction concentration could slightly increase the er value to 93.5 : 6.5 (Table 1C).

After identifying the optimized reaction conditions, the substrate scope for the asymmetric radical azidation was next examined. Table 2A shows that substrates with a range of substituents on the phenyl ring that connected with the double bond were suitable for the reaction to provide the desired products **3-8** in good to excellent yields with excellent enantiomeric ratios. Among them, the sterically hindered substrates containing *ortho*-substitutents (**6-8**) were also tolerated, and the reactions exhibited a slightly better enantioselectivity. Similarly, substrate with a naphthalene moiety (**9**) also performed well to furnish the target alkylazide in 62% yield with 94:6 enantiomeric ratio.

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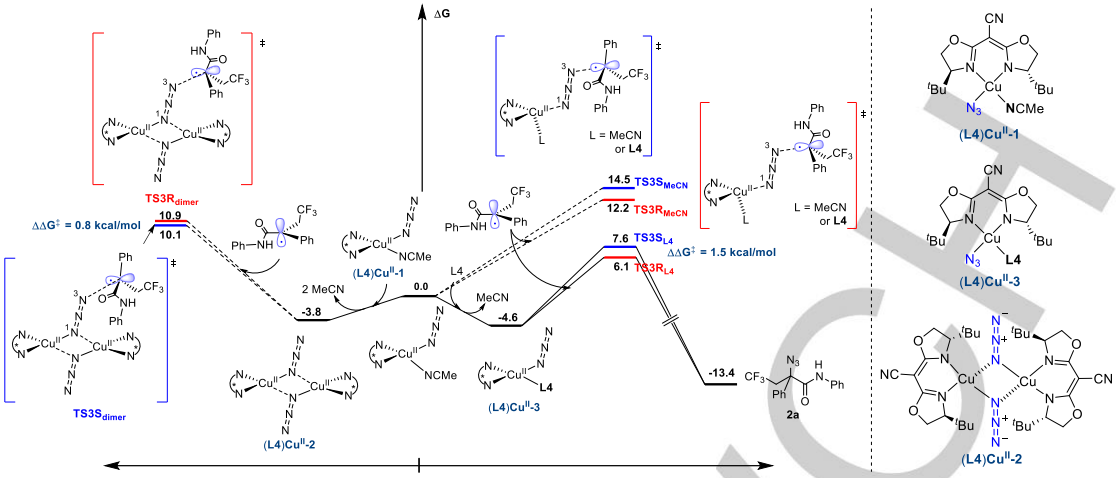
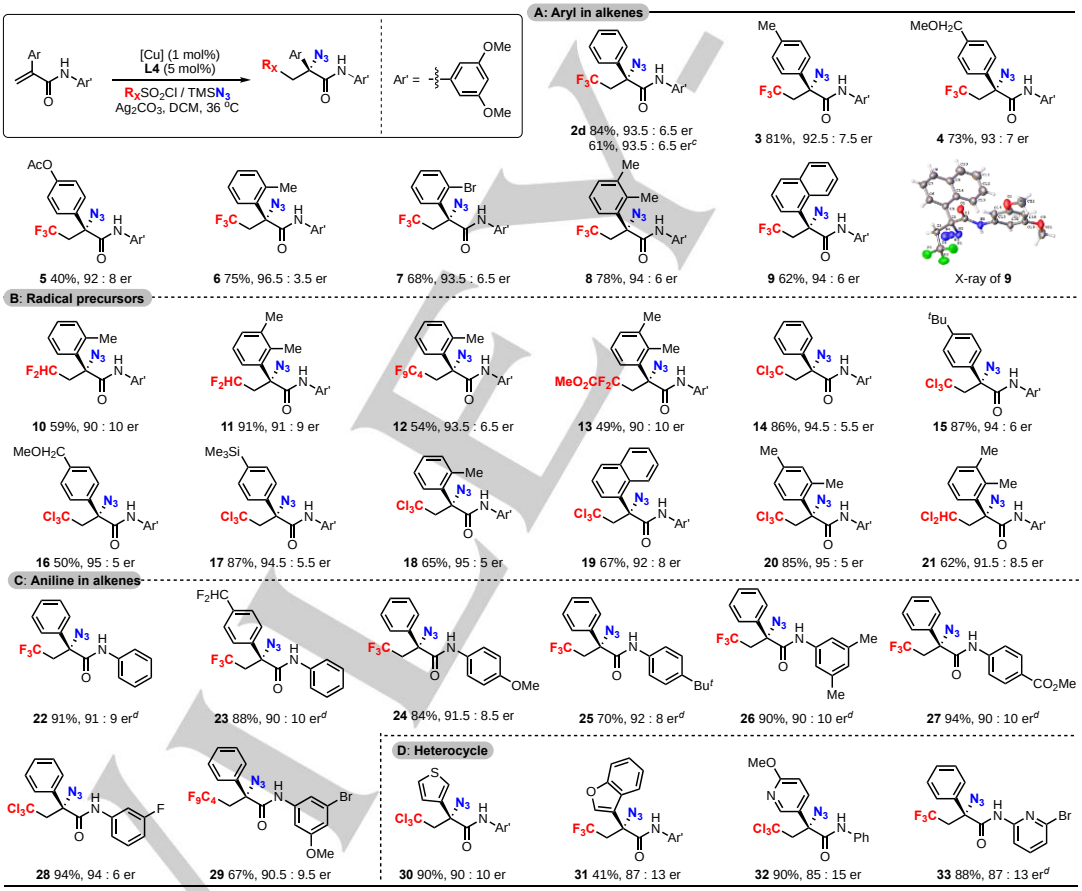



**Figure 2.** The energy profiles calculated for the reactions of benzylic radical with the various chiral (**L4**)Cu$^{II}$ azide species by means of DFT calculations at the $\omega$B97X-D level of theory. The relative free energies are given in kcal/mol at 298 K.

**Table 2.** Substrate scope[a, b]




[a] Reaction conditions: **1** (0.2 mmol), $R_XSO_2Cl$ (0.4 mmol), $TMSN_3$ (0.4 mmol), $Cu(CH_3CN)_4PF_6$ (0.002 mmol), **L4** (0.01 mmol), $Ag_2CO_3$ (0.24 mmol) in DCM at 36 °C. [b] Isolated yield, and enantiomeric excess (ee) were determined by HPLC on a chiral stationary phase. [c] **2d** (0.90 g) was obtained in 4.0 mmol scale. [d] Reaction conditions: **1** (0.2 mmol), Togni-I (0.3 mmol), $TMSN_3$ (0.4 mmol), $Cu(CH_3CN)_4PF_6$ (0.002 mmol), **L4** (0.01 mmol) in DCM at 25 °C.

Owing to the easy availability of the alkylsulfonyl chlorides, other radical precursors were then evaluated under the current reaction condition to afford structurally diverse and potentially useful optically active halogen-substituted alkylazides. To our delight, this method is not limited to $CF_3SO_2Cl$, and a range of haloalkylsulfonyl chlorides could also serve as the radical precursors under the identical reaction conditions (Table 2B). A diverse array of fluoroalkyl and chloroalkyl groups, such as $CF_2H$ (**10**-**11**), $C_4F_9$ (**12**), $CF_2CO_2Me$ (**13**), $CCl_3$ (**14**-**20**), $CCl_2H$ (**21**), could be easily incorporated into the desired alkylazides in good yields with excellent enantioselectivities. Unfortunately, alkylsulfonylic chlorides (e.g., $MeSO_2Cl$, *c*-$HexSO_2Cl$) were unsuitable, possibly because this reagent failed to initiate the SET process.

Moreover, acrylamides bearing various aniline moieties were further tested. The results show that either electron-rich (**22**-**26**) or electron-deficient (**27**-**29**) substituent groups could all be installed into the anilines, which do not compromise the efficiency and

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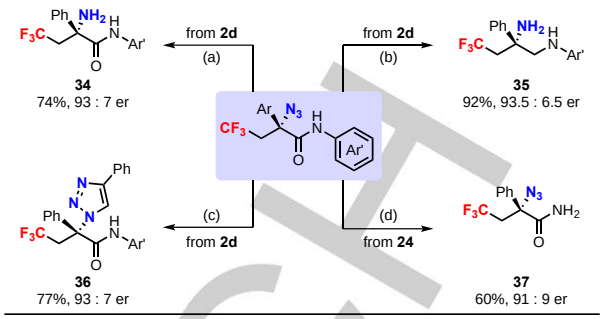
enantioselectivities of the current process, and all give chiral azides in good to excellent enantioselectivity (Table 2C). However, the acrylamides with *N*-alkyl groups and acryl esters were proven to be unsuitable for the current asymmetric azidation reactions (see SI).

Notably, different heteroaromatic rings were also tolerated (Table 2D), such as thiophene, benzofuran and pyridine, delivering the desired products with good yield and satisfactory enantioselectivity (**30**-**33**). The protocol also shows modest functional group tolerance. For example, ether, halide, ester and silyl groups are all compatible with the reaction conditions. Finally, the enantioselective C-$N_3$ cross-coupling can be conducted on a gram scale with a similar outcome (61% yield, and 93.5 : 6.5 er). The absolute configuration of the optically active **9** was unambiguously determined to be ***R*** by X-ray crystallography.

Finally, we moved our attention to the product transformation to further highlight the anticipated synthetic utility of this asymmetric radical protocol (Scheme 2). We found that the enantio-enriched alkylazides could be converted into other families of compounds without any erosion of the enantioselectivity. For example, the straightforward reduction of azide **2d** delivered the optically active 1,2-diamine **35**, which is a common structure moiety in natural products and pharmaceutical agents.[14] On the other hand, the copper-catalyzed Huisgen cycloaddition was also employed to transform sterically demanding azide **2d** into the corresponding triazole **36** in excellent yield. Moreover, the amide **24** could be treated by oxidant CAN to give α-azidyl free amide **37** in good yield with the retention of enantioselectivity.

**Scheme 2.** Product derivatization.[a]




[a] Reaction conditions: (a) $LiAlH_4$ (1.2 equiv), THF, 0 °C, 12 h. (b) $LiAlH_4$ (5.0 equiv), THF, 60 °C, 12 h. (c) CuI (1.0 equiv), phenylacetylene (3.0 equiv), sodium ascorbate (1.0 equiv), $CH_3CN/H_2O$, 110 °C, 6 h. (d) CAN (3.0 equiv), $CH_3CN/H_2O$, 50 °C, 6 h.

In conclusion, we have developed a protocol for the facile synthesis of enantioenriched alkylazides, specifically, copper-catalyzed asymmetric radical azidation of acrylamides. The success of this reaction relies on the use of anionic cyano-bisoxazoline ligands (CN-Box), which are expected to have less tendency to form dimeric species and then lead to improved enantioselectivities. The generality of this process has beenstrongly supported by the low catalyst loading (1 mol%) and good substrate scope. Future efforts will be focused on further detailing the mechanistic underpinnings of this process and discovering other synthetically useful asymmetric transformations based on the anionic type ligands.

## Acknowledgements

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Conflict of interest

The authors declare no competing financial interest.

**Keywords:** Asymmetric azidation • Copper-catalyzed • Anionic bisoxazoline • Radical • acrylamides

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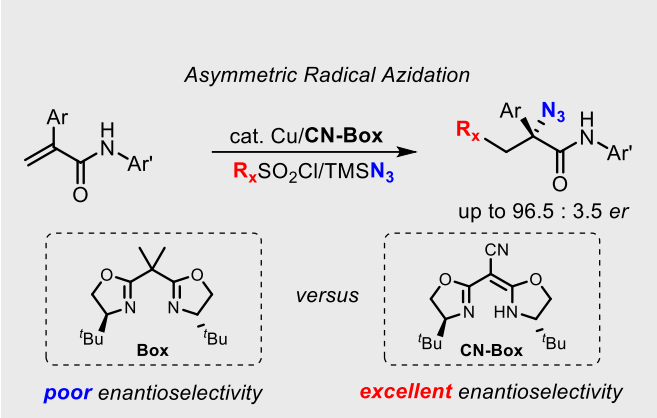


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**Anionic Bisoxazoline Ligands Enable Copper-Catalyzed Asymmetric Radical Azidation of Acrylamides**

Asymmetric radical azidation for the synthesis of chiral alkylazides remains a tremendous challenge in organic synthesis. We report here an unprecedented highly enantioselective radical azidation of acrylamides promoted by 1 mol% of copper catalyst, and arrays of acrylamides were converted to the corresponding alkylazides in high yield with good to excellent enantioselectivities. Notably, employing anionic cyano-bisoxazoline (CN-Box) ligand is crucial, which generates a monomeric Cu(II) azide species, rather than a dimeric Cu(II) azide intermediate, for this highly enantioselective radical azidation.