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Asymmetric Coupling of Carbon-Centered Radical Adjacent to Nitrogen: Copper-Catalyzed Cyanation and Etherification of Enamides

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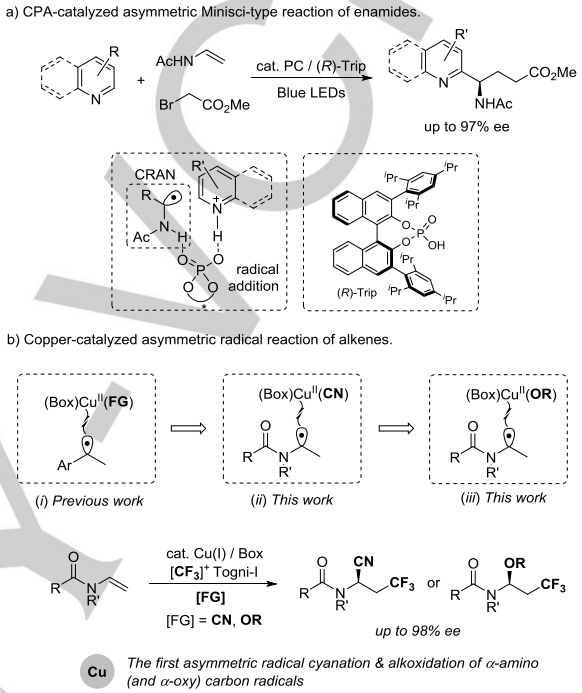
Dedication to the celebration of 70th anniversary of SIOC

Abstract: The first copper-catalyzed asymmetric cyanation and etherification of enamides have been established, where a carbon-centered radical adjacent to a nitrogen atom (CRAN) is enantioselectively trapped by a chiral copper (II) species. Moreover, the asymmetric cyanation of vinyl esters was disclosed as well. These reactions featuring very mild reaction conditions and high functional group tolerance give a series of chiral α-cyano amides, α-cyano esters and α-hemiaminals in good yields with excellent enantioselectivities, in which chiral α-cyano amides can be easily converted into enantio-enriched 1,2-diamines and amino acids.

Optically pure amines and amides represent not only one of most privileged moieties frequently found in natural products and drugs, but also act as useful synthons in organic synthesis.[1] Therefore, much effort has been devoted to their synthesis and many well-established methods have been documented,[2] such as asymmetric hydrogenation,[3] hydroboration,[4] Michael addition,[5] and so on. Owing to highly reactive radical species, difunctionalization of alkenes via radical pathways recently serves as a powerful tool in organic synthesis.[6] Among them, reactions of enamides present an attractive method for the concise and efficient synthesis of amides, where a carbon radical adjacent to a nitrogen atom (CRAN) is considered as a key intermediate.[7] To survey the possible asymmetric reaction, the enantioseletive capture of CRAN becomes an inevitable problem.[8] Recently, Phipps developed the first CPA-catalyzed asymmetric decarboxylative Minisci-type reaction, where a chiral phosphoric acid (CPA) catalyst could promote highly enenatioselective radical addition of CRAN to pyridines via a hydrogen-bonding process.[9] Later on, Studer and coworkers untilized this strategy to disclose the elegant asymmetric radical difunctionation of enamides (Scheme 1a).[10]

As our ongoing research interest in asymmetric radical transformations (ATRs),[11] our group has developed a series of copper-catalyzed asymmetric difunctionalizations of styrenes, such as cyanation, arylation and alkynylation reactions, where a benzylic radical intermedaite generated by radical addition across styrenes could be efficiently and enantioselectively trapped by the corresponding chiral (Box)Cu(II) species (Box = bisoxazoline), leading to the formation of a chiral C-C bond (Scheme 1b, *i*).[11a, 12] However, when



Scheme 1. Asymmetric radical difunctionalization of enamides.

aliphatic alkenes were employed as substrate, these reactions involving a non-benzylic radical intermediate furnished the corresponding products with low enantioselectivities. Although benzylic,[12a-b,13] allylic[14] and propargylic radicals[15] could be efficiently and enantioselectively trapped by chiral (Box)Cu(CN)$_2$ species to deliver enantioenriched organonitriles, the asymmetric cyanation of alkyl-substituted carbon-centered radicals yielding the dialkyl-substituted organonitriles with low levels of enantioselective induction still remains a big challenging issue, presumably due to the less stabilities of the transiently generated alkyl-substituted carbon-centered radical. It is well known that a carbon-centered radical can be stablized by heteroatoms adjacent to the radical such as nitrogen,[16] thus promoting us to survey the enantioselective enantioselective cyanation of CRAN generated by radical addition to enamides; in addition, a coordination of the carbonyl group in the enamide to a copper center woud be highly beneficial to the enantioselective induction (Scheme 1b, *ii*). Moreover, Stahl and coworkers recently reported a copper-catalyzed etherification of benzylic C-H bonds.[17] However, employing chiral Box ligand failed to achieve an enantioselective reaction, yielding racemic oxygenation products. The significantly different properties between CRAN and benzylic radicals also intrigued us to investigate the asymmetric coupling of CRAN to alcohols (Scheme 1b, *iii*). However, it is noteworthy that CRAN can be easily over oxidized to an iminium cation,[18] making the enantioselective coupling reaction more challenging. Herein, we communicate the first copper-catalyzed asymmetric cyanation of enamides, involving highly enantioselective capture of CRAN by chiral L*Cu(CN)$_2$ species. Moreover, the enantioselective coupling of enamides to alcohols is also realized by the same strategy (Scheme 1b). In addition, our method features excellent functional group compatibility and provides an easy and

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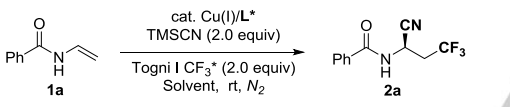
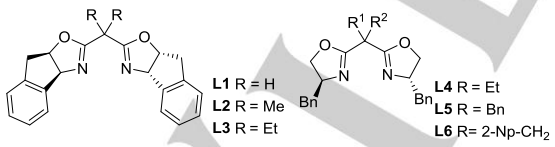
efficient access to a wide array of enantiomerically enriched CF_3-containing amides.

To test the above hypothesis, we initially focused on the asymmetric cyanation of enamides as the mode reaction. First, the reaction of *N*-vinyl benzamide **1a** with Togni-I reagent was surveyed, using 5 mol% $Cu(CH_3CN)_4PF_6$ and 6 mol% privileged Box ligand in our previous reports.[12a] As shown in Table 1, the Box ligand **L1** with the indane moiety yielded the desired product **2a** in 53% yield with poor enantioselectivity (19% ee, entry 1). To our delight, the enantioselectivity of **2a** could be significantly improved by introducing substituents into the Box ligands at the *gem*-carbon position (**L2**-**L3**), but a yield of **2a** was dramatically decreased (entries 2-3); for instance, the reaction with ligand **L3** provided **2a** in 18% yield with 76% ee. The Box ligands **L4**-**L6** with benzyl groups on the oxazoline rings were also investigated, and **L4** exhibited a slightly lower enantioselectivity; using **L6** led to similar results as using **L3** (entries 4-6). In the presence of **L3**, copper catalyst screening revealed that CuOAc exhibited the best reactivity to provide **2a** in **64**% yield, albelt with 69% ee (entry 7, for details, see SI). Moreover, solvents also played a key role in the reaction, and methyl *tert*-butyl ether (MTBE) proved to be the best to afford **2a** in 98% yield with 87% ee (entry 9). Notably, 1,2,4,5-tetrafluorobenzene gave **2a** with a better enantioselectivity but in a moderate yield (entry 8). Decreasing the reaction temperature resulted in better enantioselectivities without loss of the reaction efficiency. The reaction performed at -20 °C and using **L3** as ligand in MTBE provided 2a **in** 98% yield with 96% ee as the best results (entries 10-12). Again, **L6** and **L3** exhibited similar reactivities under the optimized reaction conditions (entries 12-13).

Table 1. Condition Screening[a]



Entry	Ligand	Cu catalyst	Solvent	**2a** yield (ee)[b]
1	**L1**	$Cu(CH_3CN)_4PF_6$	CH_2Cl_2	53% (19%)
2	**L2**	$Cu(CH_3CN)_4PF_6$	CH_2Cl_2	20% (35%)
3	**L3**	$Cu(CH_3CN)_4PF_6$	CH_2Cl_2	18% (76%)
4	**L4**	$Cu(CH_3CN)_4PF_6$	CH_2Cl_2	35% (62%)
5	**L5**	$Cu(CH_3CN)_4PF_6$	CH_2Cl_2	13% (70%)
6	**L6**	$Cu(CH_3CN)_4PF_6$	CH_2Cl_2	18% (74%)
7	**L3**	CuOAc	CH_2Cl_2	64% (69%)
8	**L3**	CuOAc	$C_6H_2F_4$	58% (94%)
9	**L3**	CuOAc	MTBE	98% (87%)
10	**L3**	CuOAc	MTBE	98% (92%)[c]
11	**L3**	CuOAc	MTBE	98% (95%)[d]
12	**L3**	CuOAc	MTBE	98% (96%)[e]
13	**L6**	CuOAc	MTBE	98% (92%)[e]



[a] Reaction condtions: **1a** (0.1 mmol), Cu salt (5 mol%), ligand (6 mol%), Togni-I (0.2 mmol) and TMSCN (0.2 mmol) in solvent (1 mL) under a nitrogen atmosphere at room temperature; [b] Yields were determined by crude ^1H NMR with CH_2Br_2 as an internal standard, and enantiomeric excess (ee) value was determined by HPLC on a chiral stationary phase; [c] At 0 °C. [d] At -10 °C. [e] At -20 °C.

With the optimized reaction conditions in hand, the substrate scope with respect to enamides was then explored, and these results were summarized in Table 2A. *N*-Vinyl benzamides with various substituents on the aromatic ring were suitable for the reaction to provide the corresponding products **2a**-**2h** in excellent yields (85%-98%) with excellent enantioselectivities (92%-98% ee). In addition, reactions of *N*-vinyl-amides with 1- or 2-naphthalenyl groups also proceeded very well to give products **2i** in 90% yield (93% ee) and **2j** in 93% yield (92% ee), respectively. Moreover, substrates derived from alkyl carboxylic acids were also suitable, and the reactions provided **2k** and **2l** in 92-97% yields with 93-94% ee. Interestingly, reactions of *N*-vinyl Boc-amides also worked nicely to furnish **2m** in 72% yield with 98% ee, which is considered as a valuable synthon in organic synthesis. Notably, *N*-vinyl benzamides, in which the N-H bond was protected by phenyl or Boc groups, also proved amenable to the reaction, yielding products **2n-2o** in good yields with excellent enantioselectivities (86-93% ee). *N*-vinyl phthalimde and *N*-vinly lactams could also be employed as substrate to afford the corresponding products **2p-2r** in excellent yields with 87-90% ee. More importantly, the compatiblity of various heteroarenes (furan, thiophene and pyridine) was examined under the current reaction conditions, and the corresponding products **2s-2u** were furnished in 70-94% yields with 93-96% ee. Unfortunately, *β*-substitued *N*-vinyl amides as substrate failed to deliver tetra-substituted product (**2v**). Notably, the reaction of **1a** could be performed on a 10 mmol scale without loss of reaction efficiency and enantioselectivity. The absolute structure of (*S*)-**2a** was unambiguously determined by the X-ray crystallography.[19].

A carbon-centered radical adjacent to oxygen has been extensively studied, and its properties were similar to CRAN. We then turned our attention to testing the asymmetric cyanation of the carbon-centered radicals adjacent to an oxygen atom. To our delight, the asymmetric trifluoromethylcyanation reaction of **3a** indeed worked, in the presence of **L6** (Table 2B, for the optimization of the reaction conditions, see SI), giving the product **4a** with excellent enantioselectivity (90% ee), and a series of enantioenriched α-cyano esters were successfully synthesized. Both vinyl aryl esters and vinyl alkyl esters yielded the corresponding products **4a**-**4e** in good to excellent yields (70-99%) with excellent enantioselectivities (87-91% ee). Notably, the reaction displays high functional group tolerance, such as methoxyl, chloro and trifluoromethyl moieties were compatible with the current reaction conditions. More importantly, substrates bearing heterocycles such as indole and thiophene, were suitable for the reaction to delivere the desired product **4f-4g** in good to excellent yields (70-90%) with excellent enantioselectivities (89-90% ee). When chiral vinyl amino acid ester **3h** was employed as substrate, to our delight, the desired product **4h** was obtained in good yields with excellent diastereoselectivities (d.r. = 10:1). Lastly, other various vinyl esters as substrate were tested, vinyl phosphinate **3i** gave product **4i** in 86% yield with 92% ee, while the reaction of vinyl-OTs **3j** just afforded **4j** in 65% yield with moderate enantioselectivity (60% ee).

Above results demonstrated that the generated CRAN could be enantioselectively trapped by chiral copper(II) cyanide. Inspired by these results, then we turned our attention to testing the asymmetric coupling of CRAN with alcohols. Under the cyanation reaction conditions, $(MeO)_4Si$ instead of TMSCN was initially employed as a methoxide source, the reaction of enamide **1a** with $(MeO)_4Si$ afforded the desired trifluoromethoxylation product **6a** in 37% yield with 53% ee, in the presence of 10 mol% $Cu(CH_3CN)_4PF_6$/12 mol% **L3**, and 51% yield and 67% ee were obtained when 10 mol% $Cu(CH_3CN)_4PF_6$/12 mol% **L6** were used. After systematic screening, 10 mol% $Cu(CH_3)_4PF_6$/12 mol% **L7** as catalyst provided a better performance to give **6a** in 59% yield with 89% ee. Gratifyingly, simple MeOH could be directly applied to the reaction, providing **6a** in 84% yield with 94% ee as the best results (for details, see SI).

After having established the optimal reaction conditions, the substrate scope of the oxygenation of enamides was also explored under the optimized reaction conditions, and the results were summarized in Table 3. The reaction showed excellent functional group tolerance, *N*-vinyl benzamides with various substituents on the aromatic ring such as electron-donating groups (methyl, methoxyl) and electron-deficient groups (halogen, phenyl, cyano, trifluoromethyl) were suitable for the reaction to provide the corresponding products **6a-6j** in moderate to excellent yield (55-91%) with excellent enantio-selectivities (84%-96% ee). Notably, the *ortho*-substituted substrate exhibited slightly lower enantioselectivity (**6i**, 86% ee). In addition, *N*-vinyl-amides bearing 1- or 2-naphthalenyl groups could also give products **6k** in 65% yield (98% ee) and **6l** in 74% yield (84% ee), respectively. Enamide substrates derived from alkyl carboxylic acids

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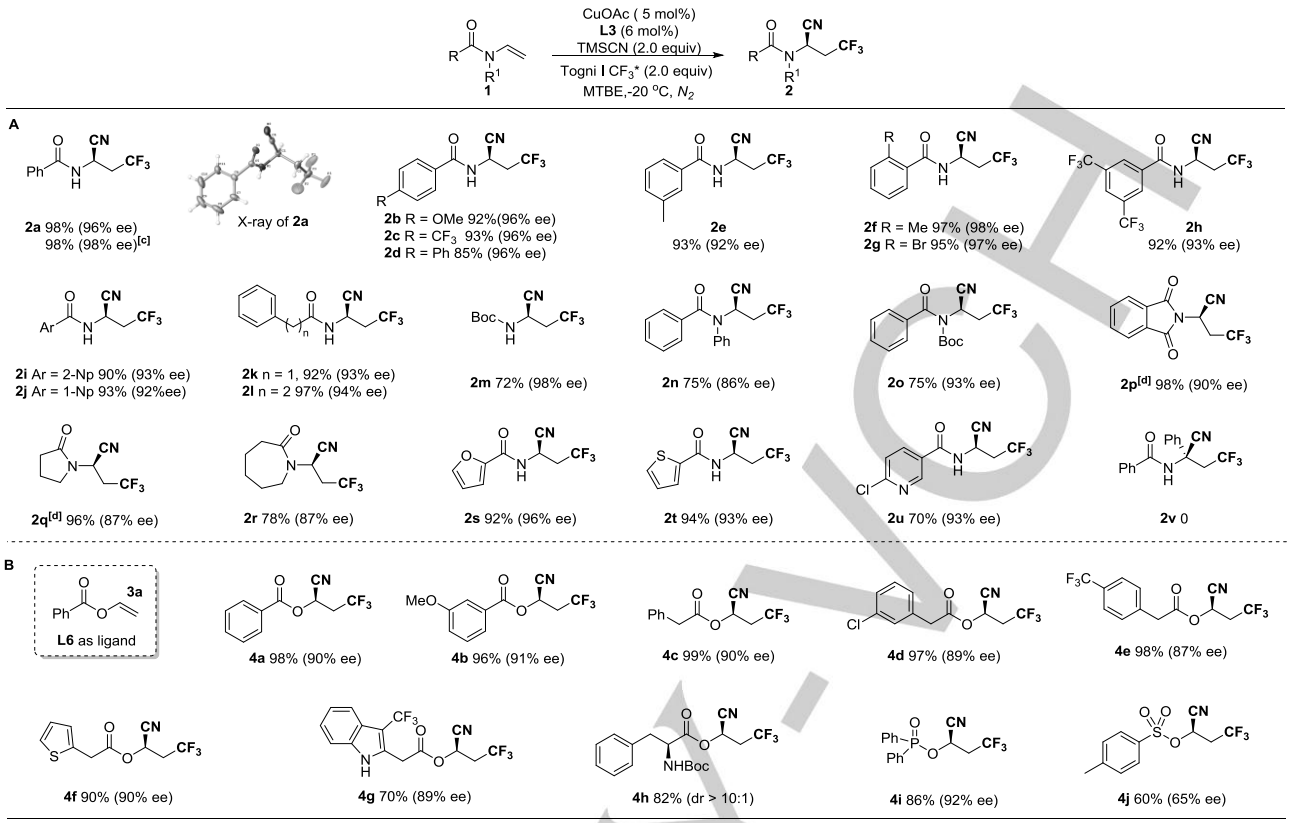
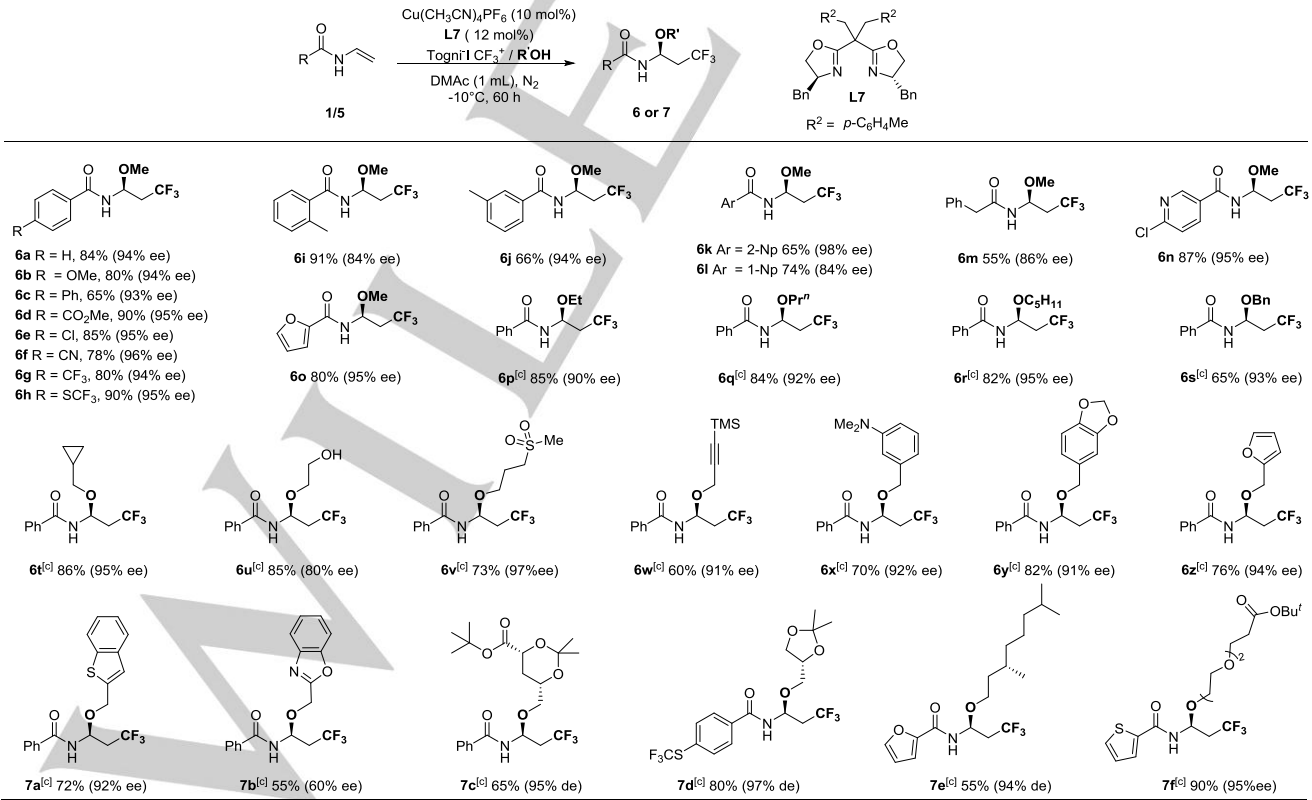
Table 2. Scope of enamides and vinyl esters.[a,b]



[a] All reactions were run on a 0.2 mmol scale in MTBE (2 mL) under a nitrogen atmosphere. [b] Isolated yields, and enantiomeric excess (ee) values were determined by HPLC on a chiral stationary phase. [c] On a 10 mmol scale. [d] Using **L6**.

Table 3. Scope of enamides and alcohols.[a,b]

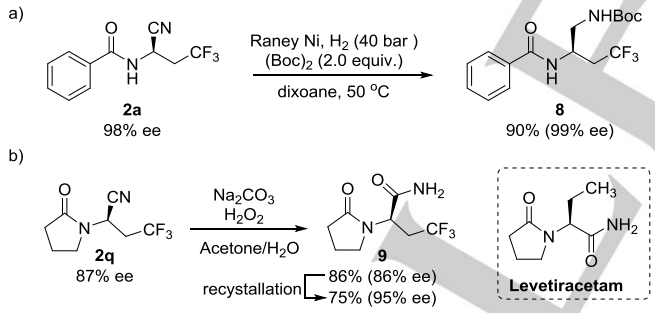


[a] All reactions were run on 0.2 mmol scale in DMAc (1 mL) under a nitrogen atmosphere. [b] Isolated yields, and enantiomeric excess (ee) values determined by HPLC on a chiral stationary phase. [c] Reaction at -20 ℃.

were also suitable for reaction to give **6m** in 55% yield with 86% ee. Moreover, enamides bearing heterocycles, such as pyrridine and furan, were also compatible with the reaction conditions to deliver products **6n** and **6o** in good yields (80-87%) with excellent enantioselectivities (95% ee).

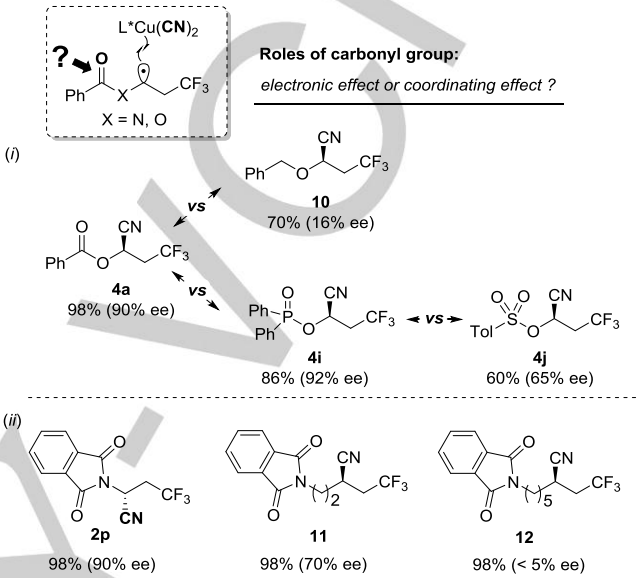
Lastly, a series of alcohols as coupling partners were investigated. Reactions of simple alcohols, such as ethanol, propanol, pentanol and benzyl alcohol, proceeded smoothyl to yield corresponding products **6p**-**6s** with excellent results. Notably, the oxygenation reaction of CRAN also featured high functional group tolerance, a series of alcohols containing various functional groups such as cyclopropanyl (**6t**), diol (**6u**), sulfonyl (**6v**), alkynyl (**6w**), aniline (6x) and methylenedioxybenzene (**6y**) were subjected to the reaction conditions, giving the desired products in 60-86% yields with 80-97% ee. Moreover, reactions of alcohols bearing heteroarenes including furan and thiophene also proceeded very well to afford **6z**-**7a** in good yields with excellent enantioselectivities, except that the reaction of alcohol with benzoxazoline gave product **7b** with moderate enantioselectivity (60% ee). In addition, reactions of enamides with chiral alcohols also furnished the products **7c**-**7e** in good yields with high levels of diastereoselective induction (94-97% de). Alcohols with a long chain (**7f**) also proved amenable to the asymmetric etherification.

In order to showcase the synthetic utility of the method, further transformations of the trifluoromethylcyanation products were investigated (Scheme 2). Optically pure 1,2-diamine **8** could be readily prepared through the hydrogenation of **2a** using Raney nickel catalyst in 90% yield with 99% ee. Moreover, **2q** could be transformed into amide **9** in 86% yield with 86% ee, the core structure of which is similar to that of antiepileptic drug Levetiracetam;[20] Interestingly, further recrystallization of product **9** in isopropanol yielded a small amount of precipitate only, and we were delighted to find that the enantioselectivity of **9** in solution was accumulated to 95% ee in 75% yield.



Scheme 2. Synthetic applications.

Some control experiments revealed that the reactions involves a radical pathway (for details, see SI). In addition, compared to vinyl enolate **3a**, the reaction of vinyl benzyl ethers yielded the desired product with low enantioselectivity (**10**, 16% ee, Scheme 3, *i*), indicating that the carbonyl groups in vinyl substrates were essential for the asymmetric coupling. There are two possible roles for the carbonyls: (1) decreasing the electron density of a carbon-centered radical and thus avoiding its overoxidation to a carbocation; and (2) acting as a coordinating site for chiral copper(II) species to facilitate the asymmetric coupling of the chiral copper(II) species with carbon-centered radicals. For vinyl phosphite (**3i**) and sulfonate (**3j**) bearing a stronger electron-withdrawing group than the carbonyl group in **3a**, the reaction of **3i** led to slightly higher enantioselectivity than **3a**, while the reaction of **3j** gave product **4j** with much lower ee value (Scheme 3, *i*). We reasoned that these outcomes might be attributed to the order of the chelating ability of groups: phosphinyl > acyl > sulfonyl. Moreover, compared to the CRAN generated from substrate **1p** (90% ee), when two more carbon atoms were added to the carbon-centered radical connecting to a nitrogen atom, the cyanation product **11** was produced with lower enantioselectivity (70% ee), and increasing the carbon atoms resulted in even worse enantioselectivity (<5% ee, **12**) (Scheme 3b, *ii*). Based on these studies, we concluded that the carbonyl group coordinating to chiral Cu(II) species played an essential role in the asymmetric radical coupling step.



Scheme 3. Preliminary mechanistic studies.

In conclusion, we have developed the first copper-catalyzed asymmetric cyanation and oxygenation of enamides proceeding through a highly enantioselective capture of CRAN by a chiral copper complex; and the asymmetric cyanation of vinyl esters was illustrated as well. These methods allow for the straightforward and efficient synthesis of various α-cyano amides, α-cyano ethers and hemiaminals in good yields with excellent enantioselectivities under very mild conditions. Preliminary mechanistic studies reveal that the carbonyl group in the enamides plays a crucial role in achieving high levels of enantioselectivities in the asymmetric cyanation and etherification of the carbon-centered radicals adjacent to a heteroatom.

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Keywords: asymmetric radical reaction • copper catalysis • cyanation • etherification • enamides

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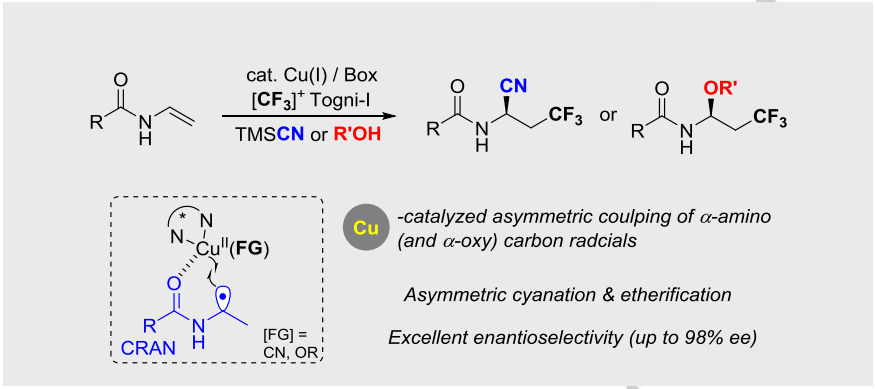

The first copper-catalyzed asymmetric cyanation and etherification of enamides have been established, where a carbon-centered radical adjacent to a nitrogen atom (CRAN) is enantioselectively trapped by a chiral copper (II) species. The asymmetric cyanation of vinyl esters was illustrated as well. The reactions featuring very mild reaction conditions and high functional group tolerance give a series of chiral α-cyano amides, α-cyano esters and hemiaminals in good yields with excellent enantioselectivities.

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Asymmetric Coupling of Carbon-Centered Radical Adjacent to Nitrogen: Copper-Catalyzed Cyanation and Etherification of Enamides