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Letter

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Asymmetric Aerobic Oxidative Cross-Coupling of Tetrahydroisoquinolines with Alkynes

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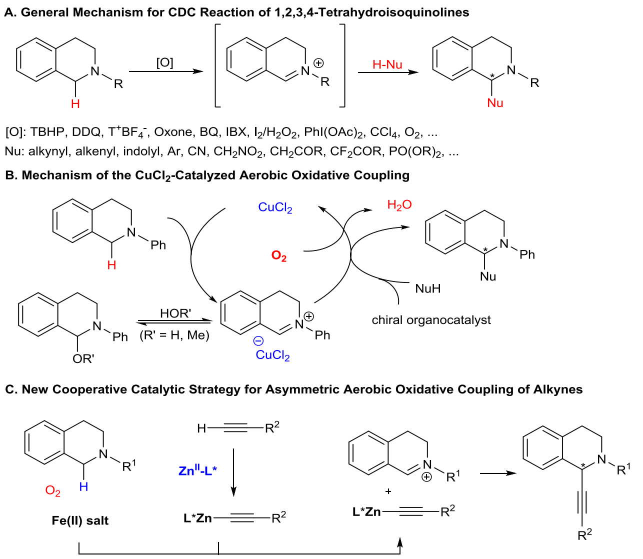
ABSTRACT: An efficient asymmetric aerobic oxidation of tetrahydroisoquinolines with terminal alkynes was realized under mild reaction conditions using O_2 as the sole oxidant. A chiral *N,N'*-dioxide/zinc(II)/iron(II) bimetallic cooperative catalytic system proves efficient for the formation of various α-alkynyl substituted tetrahydroisoquinolines in good to excellent yields and enantioselectivities. A primary mechanistic study supports an enantioselective electrophilic addition of zinc acetylide to the iminium intermediates, formed through a molecular O_2 involved oxidative process.

KEYWORDS: Aerobic oxidation, Alkynes, Cross-Coupling, Asymmetric catalysis, Cooperative catalysis.

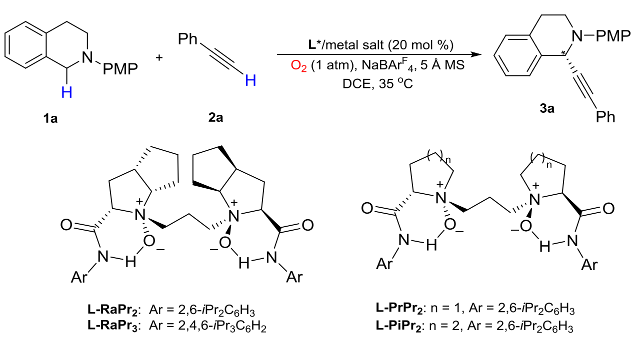
The direct coupling of two C-H bonds under oxidative condition is one of the most dynamic and synthetically powerful research areas in current organic synthesis.[1-3] Among them, the oxidation of C-H bonds adjacent to nitrogen coupling with a range of nucleophiles[4] attracted considerable attention. The general mechanism for cross-dehydrogenative coupling (CDC reaction) of tertiary amines is the formation of an intermediate iminium species in the presence of an oxidant, following Mannich-type reactions (Scheme 1, A). As a result, endeavors toward direct asymmetric oxidative coupling of amines, for example, tetrahydroisoquinoline (THIQ) derivatives, have been investigated because the related products represent one of the most prevalent scaffolds created by nature.[5] Chiral organocatalysts or chiral Lewis acid catalysts for the activation of nucleophiles,[6-8] proved to be successful strategies. Anion binding catalysis of the electrophile offers an alternative.[9] However, the current oxidative processes involve predominately synthetic oxidants, such as TBHP, DDQ, 2,2,6,6-tetramethylpiperidine *N*-oxide salt ($T^+BF_4^-$), etc. Economical and green aerobic oxidation with water as the only byproduct remains limitation in the asymmetric version. Although recent advances in Cu(II)/O_2 combination highlight opportunities to achieve selective aerobic oxidative functionalization of *N*-protected THIQs and others (Scheme 1, B),[10] there are only few examples to date that report on the asymmetric oxidative coupling of tertiary amines using O_2 as the sole oxidant.[7] One novel example from Wang's group is through the combination of $Cu(OTf)_2$ with chiral cinchona alkaloids using enone and acrylonitrile as the nucleophiles.



Scheme 1. Oxidative Coupling of THIQs and the Aerobic Oxidative Mechanism

We are interested in the asymmetric cross-coupling between THIQs and relatively weak nucleophiles of alkynes[8] because the corresponding products could be derived into structurally diverse and biologically active compounds, such as (+)-dysoxyline, homoprotoberberine, and emetine.[2i, 5] The previous examples about enantioselective alkynylation of THIQs involved the use of chiral PYBOX-Cu(I) complex catalysts and synthetic oxidants.[8a, 8d] Li group merged chiral QUINAP-Cu(I) and photoredox catalysis for this purpose and in one case O_2 was used as the terminal oxidant.[8e] In these cases, the formation of chiral copper(I) complex with acetylene might account for the enantioselection. However, to achieve enantioselective aerobic oxidative reaction with terminal alkynes as the nucleophiles and O_2 as the sole oxidant is difficult. As reported by Klussmann,[10a] in the $Cu(II)/O_2$ system, Cu(II) catalyst acts as the actual oxidant and the role of the terminal oxidant O_2 is the reoxidation of Cu(I) (Scheme 1, B).

Table 1. Optimization of the Reaction Conditions[a]



entry	metal salt	Ligand	yield (%)[b]	ee (%)[c]
1	$Cu(OTf)_2$	**L-RaPr$_3$**	59	0
2	$Zn(OTf)_2$	**L-RaPr$_3$**	30	88
3	$Co(BF_4)_2{\cdot}6H_2O$	**L-RaPr$_3$**	trace	ND
4	$Fe(OTf)_2$	**L-RaPr$_3$**	NR	ND
5	$Zn(NTf_2)_2$	**L-RaPr$_3$**	35	95
6	$Zn(NTf_2)_2$	**L-PrPr$_2$**	21	70
7	$Zn(NTf_2)_2$	**L-PiPr$_2$**	32	80
8	$Zn(NTf_2)_2$	**L-RaPr$_2$**	33	90
9[d]	$Zn(NTf_2)_2/Fe(OTf)_2$	**L-RaPr$_3$**	47	75
10[e]	$Zn(NTf_2)_2/Fe(OTf)_2$	**L-RaPr$_3$**	70	88
11[f]	$Zn(NTf_2)_2/Cu(OTf)_2$	**L-RaPr$_3$**	48	81
12[e,g]	$Zn(NTf_2)_2/Fe(OTf)_2$	**L-RaPr$_3$**	54	70
13[e,h]	$Zn(NTf_2)_2/Fe(OTf)_2$	**L-RaPr$_3$**	76	67
14[i]	$Zn(NTf_2)_2/Fe(OTf)_2$	**L-RaPr$_3$**	78	96
15[i,j]	$Zn(NTf_2)_2/Fe(OTf)_2$	**L-RaPr$_3$**	75	87

[a] Unless otherwise noted, all reactions were performed with **L**-metal salt (20 mol %, 1:1), **1a** (0.05 mmol), **2a** (1.2 equiv), $NaBAr^F_4$ (40 mol %) and 5 Å MS (30 mg) with oxygen balloon (1 atm) in DCE (0.5 mL) at 35 °C for 24 hours. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Zn(II)/Fe(II)/**L-RaPr$_3$** (20 mol %, 20:3:20). [e] Zn(II)/Fe(II)/**L-RaPr$_3$** (20 mol %, 20:2:22). [f] Zn(II)/Cu(II)/**L-RaPr$_3$** (20 mol %, 20:2:22). [g] Without 5 Å MS. [h] Without $NaBAr^F_4$. [i] Zn(II)/Fe(II)/**L-RaPr$_3$** (20 mol %, 20:3:23) in DCE (0.1 mL). [j] MeOH (1.0 equiv) was added. (PMP = 4-$MeOC_6H_4$; $NaBAr^F_4$ = $NaB[3,5\text{-}(F_3C)_2C_6H_3]_4$)

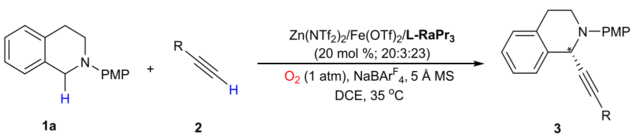
The incompatible actions of Cu(II)/Cu(I) species for the two coupling partners make the chiral copper-mediate asymmetric aerobic process a bit more complicate and impractical. Chiral organocatalyst/Cu(II) combination strategy seemed questionable for the reason that rare organocatalyst has interaction with alkynes. It is challenging and of interest to discover a new chiral catalytic system for the asymmetric version using dioxygen as the sole oxidant.

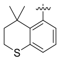
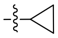
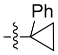
We envision a new Zn(II)/Fe(II) bimetallic cooperative system (Scheme 1, C) for the asymmetric aerobic oxidative coupling of THIQs with alkynes. It involves the asymmetric activation of alkynes with chiral zinc(II) complex which were effective in alkynylation reactions.[11-13] Although the Doyle group used $FeCl_3$ to promote the aerobic oxidation of tertiary anilines with several nucleophiles,[14] phenylacetylene did not undergo the coupling which might due to its weak nucleophilicity. Nevertheless, the aerobic oxidation of THIQs coupling with alkynes could be mediated by cheap and sustainable iron salt in our cooperative strategy.[15] The rich coordination chemistry and efficient enantiocontrol of chiral *N,N'*-dioxide ligands in catalytic asymmetric transformations[16] encourages us to extend their application in asymmetric activation of C-H bonds. In the presence of chiral *N,N'*-dioxide, the Zn(II)-Fe(II) heterobimetallic cooperative catalytic system allows facile enantioselective aerobic oxidative cross-coupling of THIQs with terminal alkynes. Optically active 1-alkynylated THIQ derivatives were obtained under mild reaction conditions.

Our investigation began with the coupling of ethynylbenzene **2a** with 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **1a** in 1,2-dichloroethane under one atmosphere of O_2 with cheap transition metal salts based on their propensity for C-H activation (Table 1). In the presence of chiral *N,N'*-dioxide **L-RaPr$_3$** ligand and $NaBAr^F_4$ additive, only $Cu(OTf)_2$ and $Zn(OTf)_2$ afforded the desired product **3a**, but the former gave higher reactivity without enantioselectivity (entry 1 vs entry 2). $Co(BF_4)_2{\cdot}6H_2O$ and $Fe(OTf)_2$ were inactive for the aerobic cross-coupling (entries 3 and 4). $Zn(NTf_2)_2$ as the metal salt precursor showed the highest enantioselectivity reaching 35% yield with 95% ee (entry 5). Evaluation of the structures of chiral *N,N'*-dioxides showed that **L-RaPr$_3$** outperformed the other ligands bearing varied amino acid backbone and amide substituent in terms of both reactivity and enantioselectivity (entries 5-8). We attempted to improve the yield via accelerating the formation of iminium species, and thus iron salt was added as the cocatalyst. It is interesting that $Fe(OTf)_2$ was more efficient than $Fe(OTf)_3$ in our cases, which differs from iron-catalyzed aerobic oxidative Mannich reaction.[2f, 14] The alkynylation product **3a** was isolated in a little higher yield but lower enantioselectivity after 3 mol % of $Fe(OTf)_2$ was added (entry 9). It is possible that the excessive metal salts might hamper the formation of chiral **L-RaPr$_3$**/Zn(II) complex catalyst which is crucial for the enantiocontrol. Optimization of chiral ligand loading showed delight result that the oxidative alkynylation reaction could achieve a 70% yield and 88% ee (entry 10). It implies that the formation of chiral **L-RaPr$_3$**/Fe(II) complex[15a] was compatible for both the aerobic oxidation and the enantioselection in coupling process. The cooperation effect of $Cu(OTf)_2$ was not obvious, and the product **3a** was obtained in 48% yield with 81% ee (entry 11). Moreover, 5 Å molecular sieves and $NaBAr^F_4$ were indispensable part of the catalytic system which is evident in entries 12 and 13. Pleasingly, with chiral Zn(II)/Fe(II)/**L-RaPr$_3$** cooperative catalytic system in higher concentration, the product could be isolated in 78% yield and 96% ee (entry 14). The addition of MeOH reduced the enantioselectivity (entry 15), thus it is too hard to further improve the yield but maintaining the enantioselectivity via the form of *N*-aryl hemiaminal assisted by alcohols.[8d, 10]

With the optimized conditions in hand (Table 1, entry 14), the substrate scope of the terminal alkynes was examined firstly. As shown in Table 2, substituted ethynylbenzenes underwent the reaction in good yields and enantioselectivities regardless of the electronic nature or position of the substituents on the aryl group (Table 2, entries 1-19;

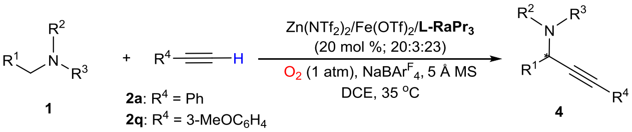
Table 2. Scope of Alkynes in the CDC Reaction[a]

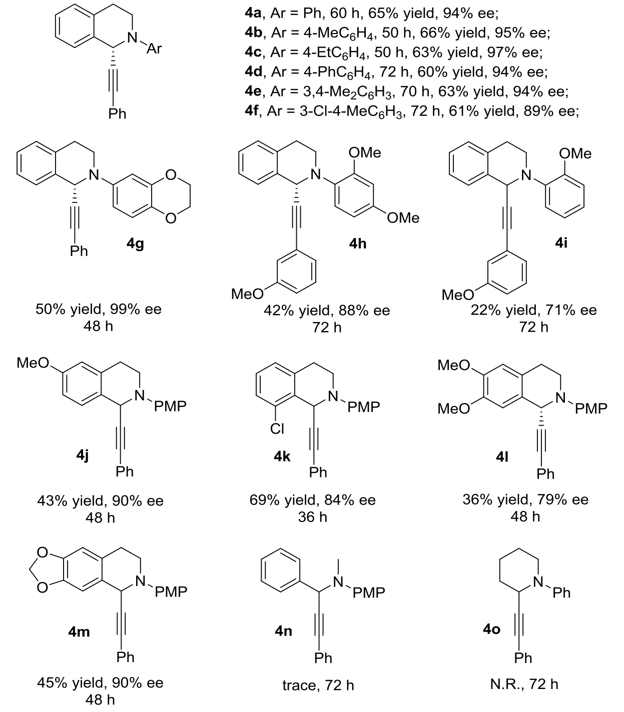


entry	R	time (h)	yield (%)	ee (%)
1[b]	Ph (**3a**)	24	70	93
2	4-ClC$_6$H$_4$ (**3b**)	40	74	96
3	4-BrC$_6$H$_4$ (**3c**)	50	73	99
4	4-MeC$_6$H$_4$ (**3d**)	24	74	92
5	4-EtC$_6$H$_4$ (**3e**)	24	76	95
6	4-^{n}PrC$_6$H$_4$ (**3f**)	24	72	95
7	4-^{n}BuC$_6$H$_4$ (**3g**)	24	73	96
8	4-^{n}PentC$_6$H$_4$ (**3h**)	24	68	96
9	4-MeOC$_6$H$_4$ (**3i**)	38	75	96
10	4-MeCO$_2$C$_6$H$_4$ (**3j**)	40	50	95
11	4-NCCH$_2$C$_6$H$_4$ (**3k**)	38	72	86
12	2-FC$_6$H$_4$ (**3l**)	72	65	90
13	2-ClC$_6$H$_4$ (**3m**)	72	68	85
14	3-FC$_6$H$_4$ (**3n**)	24	71	96
15	3-ClC$_6$H$_4$ (**3o**)	38	72	99
16	3-MeC$_6$H$_4$ (**3p**)	24	76	98
17	3-MeOC$_6$H$_4$ (**3q**)	24	82	93
18	3-O$_2$NC$_6$H$_4$ (**3r**)	24	45	95
19	3,5-F$_2$C$_6$H$_3$ (**3s**)	30	69	88
20	 S (**3t**)	48	75	88
21	1-naphthyl (**3u**)	28	75	95
22	2-thienyl (**3v**)	28	70	98
23	CH$_2$CH$_2$Ph (**3w**)	48	55	37
24	 (**3x**)	48	60	61
25	 Ph (**3y**)	24	77	20
26	^{n}C$_{10}$H$_{21}$ (**3z**)	48	40	20

[a] The reactions were performed with Zn(NTf$_2$)$_2$/Fe(OTf)$_2$/**L-RaPr$_3$** (20 mol %, 20:3:23), **1a** (0.05 mmol), **2** (1.2 equiv), NaBAr$^F{}_4$ (40 mol %) and 5 Å MS (30 mg) with oxygen balloon (1 atm) in DCE (0.10 mL) at 35 °C. Yields of isolated products. The ee values were determined by HPLC. [b] The reaction was carried out with **1a** (4.0 mmol), **2a** (5.0 mmol) and 5 Å MS (2.0 g) in DCE (8 mL).

Table 3. Scope of Amines in the CDC Reaction[a]



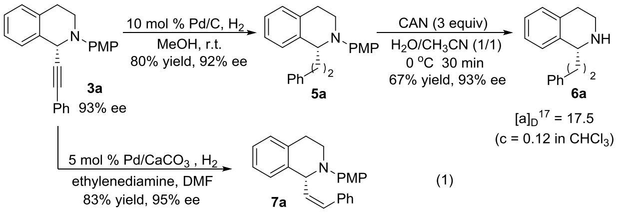


[a] The same as in Table 2.

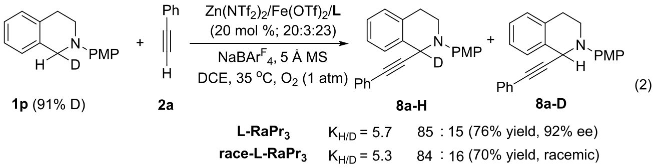
45-82% yield and 85-99% ee). In addition, heterocyclic sulfur-containing alkyne **2t** proceeded in 75% yield and 88% ee (Table 2, entry 20). Furthermore, 1-naphthyl substituted alkyne **2u** as well as 2-ethynylthiophene **2v** were also suitable candidates for the reaction, generating the related THIQ derivatives **3u** and **3v** in 75% yield and 95% ee, 70% yield and 98% ee, respectively (Table 2, entries 21 and 22). The reaction of alkyl substituted terminal alkynes performed smoothly, and moderate to good yields could be obtained but the enantioselectivity dropped a lot (Table 2, entries 23-26). It was possible owing to the weaker acidity of alkyl terminal alkynes and larger steric hindrance of the substituent. The CDC reaction of **1a** was enlarged to a gram scale under the optimized reaction condition, and gave the product **3a** in 70% yield with 93% ee (Table 2, entry 1).

Given the remarkable efficiency of the present catalytic system, various amine derivatives were also examined. As shown in Table 3, for the reaction with ethynylbenzene **2a**, THIQs with electron-donating substituent at the *para*-position of the *N*-aryl group proceeded the aerobic cross-coupling reaction smoothly, providing the products (**4a-4e**) in 60-66% yields with 94-97% ee. *N*-aryl groups bearing electron-withdrawing substituent at *meta*-position or electron-donating substituent at *ortho*-position were disadvantage to the enantioselectivity (**4f-4i**). The scope of substituted THIQs was next explored. Interestingly, when THIQ with an electron-withdrawing substituent could provide the desired product in higher yield than the ones with electron-donating substituents (**4j-4m**). When the catalytic condition was applied to *N*-benzyl aniline, *N*-phenyl piperidine and others failed (see SI for details; **4n-4o**).

The 1-phenylethynyl substituted THIQs could undergo useful transformations (eq 1). Reduction of **3a** gave phenethyl substituted **5a** in 80% yield and (*Z*)-styryl substituted **7a** in 83% yield without loss of enantioselectivity. *N*-PMP group of tetrahydroisoquinoline derivative could be easily removed by using CAN (ceric ammonium nitrate) in aqueous acetonitrile,[17] giving the *N*-unprotected tetrahydroisoquinoline derivative **6a** in good yield with excellent ee value, which is a valuable and versatile intermediate in organic synthesis.[5] The absolute configuration of **6a** was determined to be *R* by comparison the optical rotatory with the pervious report.[18] Thus, it allowed assignment of the absolute configuration of **3a** as *R*-isomer.[19]



To clarify the detailed reaction course, a kinetic isotope effect (KIE) experiment was then conducted (eq 2). Racemic monodeuternated substrate **1p** was subjected to the enantiomerically pure or racemic *N*,*N*'-dioxide/Zn(II)/Fe(II) catalytic system. Primary KIE value k_H/k_D of 5.7 and 5.3 were calculated for the two cases. This is in accordance with $CuCl_2/O_2$ catalytic process,[10a] indicating a rate-determining C-H bond cleavage. Under the optimal reaction conditions, the formation of [**L-RaPr**$_3$-Zn^{2+}-(NTf$_2$)$^-$]$^+$ and [**L-RaPr**$_3$-Zn-C≡CPh]$^+$ species was confirmed from ESI-HRMS analysis of the catalytic reaction system (for data and assignment see SI).



To elucidate the involved reactive oxygen species EPR spectroscopic measurements were performed (Figure 1). DMPO was employed as a probe for superoxide radical anion. A single radical was obviously trapped upon mixing $Zn(NTf_2)_2$, THIQ **1a** and DMPO in oxygen-saturated 1,2-dichloroethane. The spectrum and hyperfine coupling constants of the characteristic signal in Figure 1d is in agreement with the reported values, confirming the formation of adduct of $O_2^{\cdot-}$ with DMPO.[10b, 20] Nevertheless, complex EPR signals appeared if $Fe(OTf)_2$ was added (Figure 1, e and f), although the fine structure related to which is not identified, it indicates that iron accelerates the oxidation process. In addition, light has no obvious influence on the reaction process, and the signal remains even the test was carried out in dark (Figure 1, g).

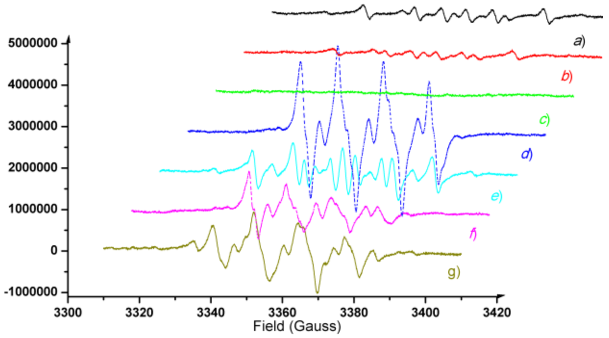
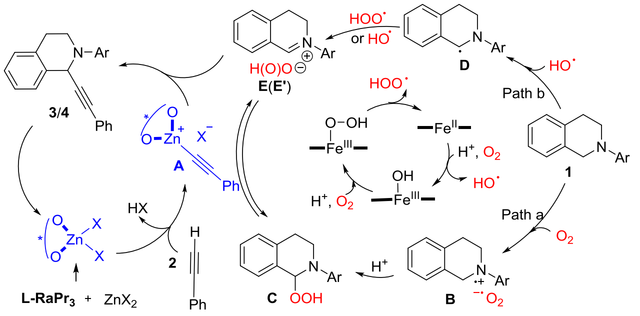


Figure 1. The electroparamagnetic resonance (EPR) spectra (X band, 9.43 GHz, rt. in oxygen-saturated DCE). (a) $Zn(NTf_2)_2$/DMPO; (b) **1a**/DMPO; (c) DMPO; (d) **1a**/$Zn(NTf_2)_2$/DMPO; (e) **1a**/$Fe(OTf)_2$/DMPO; (f) **1a**/$Zn(NTf_2)_2$/$Fe(OTf)_2$/DMPO; (g) **1a**/$Zn(NTf_2)_2$/DMPO in the dark. The concentration of each component is as follows: $Zn(NTf_2)_2$ (0.02 mol/L), DMPO (1.33 mol/L), $Fe(OTf)_2$ (0.003 mol/L), **1a** (0.1 mol/L).

Kinetic studies of the model CDC reaction in the Zn(II)/Fe(II)/**L-RaPr**$_3$ cooperative catalytic system with varied concentration were conducted to detect the initial rate of the reaction. The reaction showed clear first-order kinetic dependence on chiral **L-RaPr3**/Fe(OTf)2 complex and zero-order kinetic dependence on chiral **L-RaPr3**/Zn(NTf2)2 complex (for data and assignment see SI). The results were in agreement with the KIE experiment that oxidative step is involved in the rate-determining step.

On the basis of the above results and the literature reports,[10] the aerobic asymmetric CDC reaction promoted by Zn(II)/Fe(II)/*N*,*N*'-dioxide bimetallic cooperative catalysis was rationalized (Scheme 2). In the presence of a base (tetrahydroisoquinoline or basic anion generated in the oxidative process), chiral *N*,*N*'-dioxide-Zn(II) complex reacts with terminal alkynes to generate zinc acetylide intermediate **A** (confirmed by HRMS spectra). On the other side, without additional Fe(II) catalyst (path a), auto-oxidation of chemical substances results in the formation of **C** containing the amine radical cation of THIQ $1^{+\cdot}$ and superoxide radical anion $O_2^{\cdot-}$ (detected by EPR spectroscopy). H-abstraction way generates hydroperoxide THIQ-OOH **C** which is in equilibrium with the iminium species **E'**. In the presence of aerobic iron catalyst,[14, 21] Fenton-type reactions occur to generate Fe(III) species and HO$^\cdot$ radical, and the latter abstracts a H-atom from the substrate to give the corresponding C-radical **D** (path b). On the other hand, Fe(III) species convert into Fe(III)OOH species, following the homolysis of Fe-O bond to generate HOO$^\cdot$ radical, which benefits the formation of hemiaminal, providing a stabilizing reservoir for iminium species **E**. Finally, enantioselective alkynylation controlled by the chiral *N*,*N*'-dioxide-Zn(II) complex provides the cross-coupling products and regenerates the catalyst.



Scheme 2. Proposed Mechanism

In conclusion, the first catalytic asymmetric aerobic cross-dehydrogenative coupling of tetrahydroisoquinolines and terminal alkynes was established under mild reaction conditions. The merging of chiral *N*,*N*'-dioxide, zinc(II) and iron(II) catalysts allows an facile oxidative protocol with atom-efficient and environmentally-friend oxidant (O_2). The good level of yields with excellent enantioselectivities, broad substrate generality, operational simplicity, and mild reaction conditions highlighted the efficiency of this new cooperative catalytic system. In addition, this is also a breakthrough that chiral *N,N′*-dioxide-metal complex was used for the activation of unfunctionalized alkynes. We anticipate that it would bring new light for future efforts in the catalytic enantioselective C-H functionalization and aerobic oxidation with a wide range of transformations.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

Experimental details and analytic data (NMR, HPLC, EPR). This material is available free of charge at http://pubs.acs.org.

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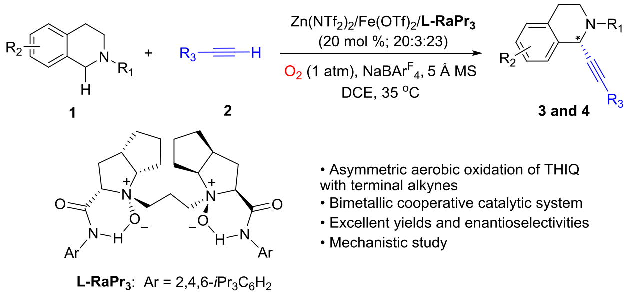

- Asymmetric aerobic oxidation of THIQ with terminal alkynes
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- Excellent yields and enantioselectivities
- Mechanistic study