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Enantioselective Radical Ring-Opening Cyanation of Oxime Esters by Dual Photoredox and Copper Catalysis

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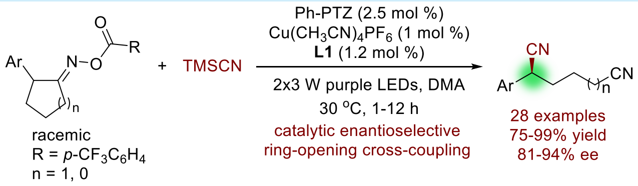
Supporting Information

ABSTRACT: Catalytic enantioselective chemical reactions involving highly reactive radical species remain largely unexplored. We report herein for the first time a novel enantioselective radical ring-opening cyanation of redox-active oxime esters by dual photoredox and copper catalysis. This mild protocol shows good functional group tolerance and broad substrate scope, producing a wide range of optically active alkyl dinitriles with high yields and excellent enantioselectivities, which are difficult to access traditionally.



Radical chemistry has been established as a potentially powerful synthetic platform for the construction of organic molecules because of a unique profile of reactivity mode and selectivity that is complementary to the traditional ionic chemistry.[1,2] Despite significant advances in this area, the control of enantioselectivity remains a formidable challenge and has been largely unsolved for many classes of radical transformations. Among numerous efforts in subverting this challenge, transition-metal-catalyzed radical cross-coupling (RCC) in the presence of chiral ligands represents a conceptually new strategy. In a typical catalytic cycle (Scheme 1A), the in situ-formed chiral metal complexes are explored as radical traps to intercept open-shell carbon-centered radicals to form high-valent metal complexes and thus control the following reductive elimination in an enantioselective manner.[3]

Inspired by the works of Fu on the nickel- and copper-catalyzed enantioselective RCC reactions with various aliphatic electrophiles as alkyl radical precursors,[4] Liu et al. developed a novel Cu(I)/Box-catalyzed radical relay strategy for generation of various benzylic radicals through hydrogen atom abstraction of C(sp^3)−H bonds, photocatalyic decarboxylation, or radical addition to styrenes.[5] These radical species then intermolecularly combine with the catalytically formed Cu(II) nucleophile to form highly reactive chiral Cu(III) complexes, followed by reductive elimination to form new carbon−carbon bonds with excellent enantioselectivity. Depending on the properties of the nucleophiles, a range of asymmetric functionalizations at the benzylic positions could be achieved, including cyanation,[6] arylation,[7] and alkynylation.[8] Meanwhile, the groups of Buchwald[9] and Liu[10] independently disclosed that a range of alkenes bearing pendant nucleophilic groups (e.g., carboxylic acid, alcohol, oxime, urea) could undergo radical addition/intramolecular cross-coupling with excellent enantioselectivities, when using a Cu(I)/(*S*,*S*)-^{t}BuBox or Cu(I)/chiral phosphoric acid dual-catalytic system. These methods enabled synthesis of diverse enantioenriched oxygen and nitrogen heterocycles under mild conditions.

Recently, Fu and Ito independently extended the RCC strategy to Ni(II)- and Cu(I)-catalyzed asymmetric borylation of racemic electrophilic benzyl chlorides.[11] Despite being powerful, in the majority of alkene-based RCC reactions, the spectrum of radical classes is usually restricted to these small functional organic radical precursors, such as Togni reagent, NFSI, $TMSN_3$, and *O*-acylhydroxlamines. Therefore, it is highly desirable to explore other new radical precursors to generate diversely functionalized benzylic radicals and their analogues, which would provide access to more structurally complex and useful molecules.

We and others have recently described a variety of photoredox- or metal-catalyzed ring-opening/functionalization reactions of these redox-active substrates.[12,13] To date, progress in this field has been limited to non-enantioselective trapping of the key cyanoalkyl radicals (Scheme 1B). Expanding the profile of trapping reagents to include chiral metal-complexed nucleophiles such as **L***Cu(II)Nu would probably enable enantioselective RCC reaction of cyanoalkyl radicals. For example, with use of TMSCN as a nucleophilic coupling partner, the achievement of this reaction would provide a practical approach to valuable chiral alkyl dinitriles,[14] which are difficult to access traditionally (Scheme 1C). Herein, we report the development of a novel enantioselective ring-opening radical cyanation of oxime esters for the first time by merging photoredox and asymmetric copper catalysis.[15]

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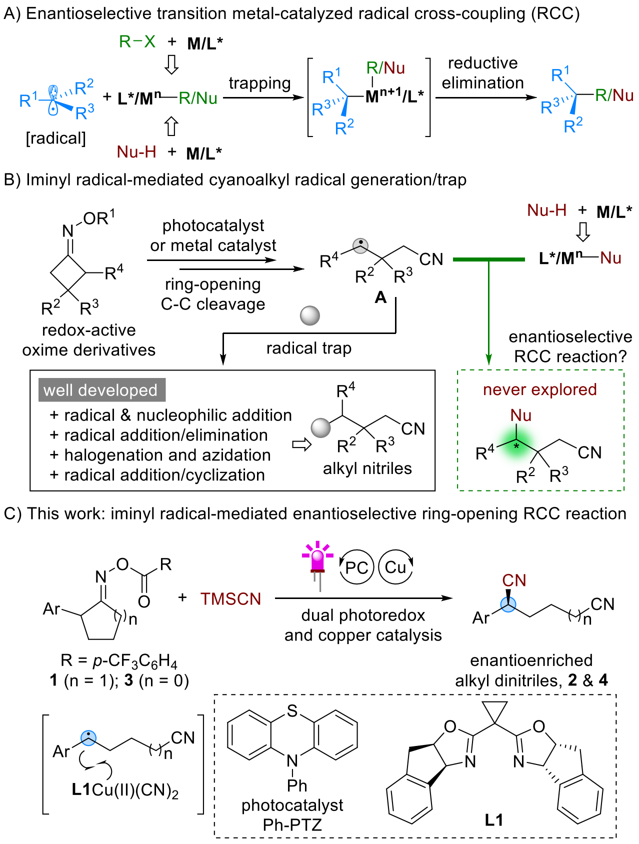
Scheme 1. Background of the Methodology Development

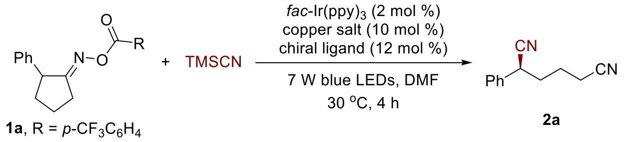


We began our investigation by examination of the reaction of less-strained 2-phenylcyclopenta-1-one-derived oxime ester **1a** with TMSCN as the cyanide source using photocatalyst *fac*-Ir(ppy)$_3$ and Cu(CH$_3$CN)$_4$PF$_6$ combined with a series of chiral bisoxazoline ligands in DMF under irradiation of 7 W blue LEDs at room temperature (Table 1).[16] To our delight, the combination of Cu(CH$_3$CN)$_4$PF$_6$ (10 mol %) and Box-type ligand **L1** (12 mol %) furnished the desired product **2a** in 43% yield with 89% ee (entry 1). A brief further screen of ligands revealed that chiral ligands have an important role in the reaction efficiency and enantioselectivity. Though bisoxazoline ligands **L2**−**L5** led to somewhat improved efficiency, inferior enantioselectivity was obtained (5−61% ee, entries 2−5). With **L1** identified as the best chiral ligand, we further evaluated a series of commonly used Cu(I) and Cu(II) salts and found that Cu(CH$_3$CN)$_4$PF$_6$ is still the best one of choice in terms of yields (entries 6−8). With Cu(CH$_3$CN)$_4$PF$_6$/**L1** as the best chiral catalyst, we examined a series of solvents and confirmed that DMA afforded **2a** in 90% ee though with somewhat lower yield (entry 9). An extensive screening of catalyst loading demonstrated that use of only 0.5 mol % of *fac*-Ir(ppy)$_3$ together with 1 mol % of Cu(CH$_3$CN)$_4$PF$_6$ and 1.2 mol % of **L1** resulted in a significant increase of yield, leading to **2a** in 73% yield with 91% ee (entry 10). Notably, the use of commercially available organic photocatalyst 10-phenylphenothiazine (Ph-PTZ)[17] (2.5 mol %) further increased the reaction efficiency, furnishing **2a** in 92% yield with 91% ee (entry 11). A series of control experimental results confirmed that each component is essential for the target reaction.[16]

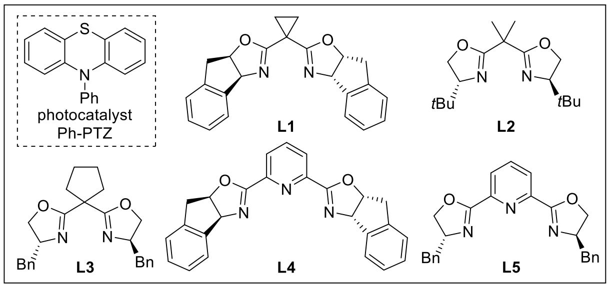
With the optimal reaction conditions established, we then examined the substrate scope of oxime esters (Scheme 2). A wide range of oxime esters that can be easily prepared from 2-aryl-substituted cyclopentanones were well-tolerated (Scheme 2A). Aside from **1a**, substrates **1b**−**j** with various either electron-donating (e.g., OMe, ^{t}Bu, TMS, Ph) or electron-withdrawing (e.g., F, Cl, Br, CO$_2$Me, SO$_2$Me) groups at the para-position of the aromatic ring all proved to be suitable candidates, and the corresponding products **2b**−**j** were obtained with excellent yields (90−99%) and enantiomeric excess (81−94% ee). Halide groups (**2f**−**h**) remained intact after the reaction, thereby providing an easy handle for additional synthetic elaborations. The reaction of **1k** and **1l** with synthetically useful amide and Bpin functionalities at the para-position of the phenyl ring also worked well to give **2k** and **2l** in satisfactory yields with excellent ee values. As shown in the cases of **2m**−**p**, variation of the substitution pattern and steric hindrance of the phenyl ring has no deleterious effect on the reaction efficiency and enantioselectivity. In addition, substrates **1q**−**t** containing extended aromatic systems (e.g., 2-naphthyl), heterocycle-fused rings, or pyridine all underwent the enantioselective ring-opening cyanation efficiently, affording products **2q**−**t** with 82−93% yields and 81−92% ee.

The current catalytic system could also be successfully extended to 2-aryl-substituted cyclobutanone-derived oxime esters **3** (Scheme 2B). Oxime esters **3a** and **3b**−**e** with methyl or halides (F, Br, I) at the para-position of the aromatic ring reacted well with TMSCN. The desired alkyl dinitriles **4a**−**e** were isolated in high yields with 90−94% ee. Furthermore, as shown

Table 1. Condition Optimization[a]

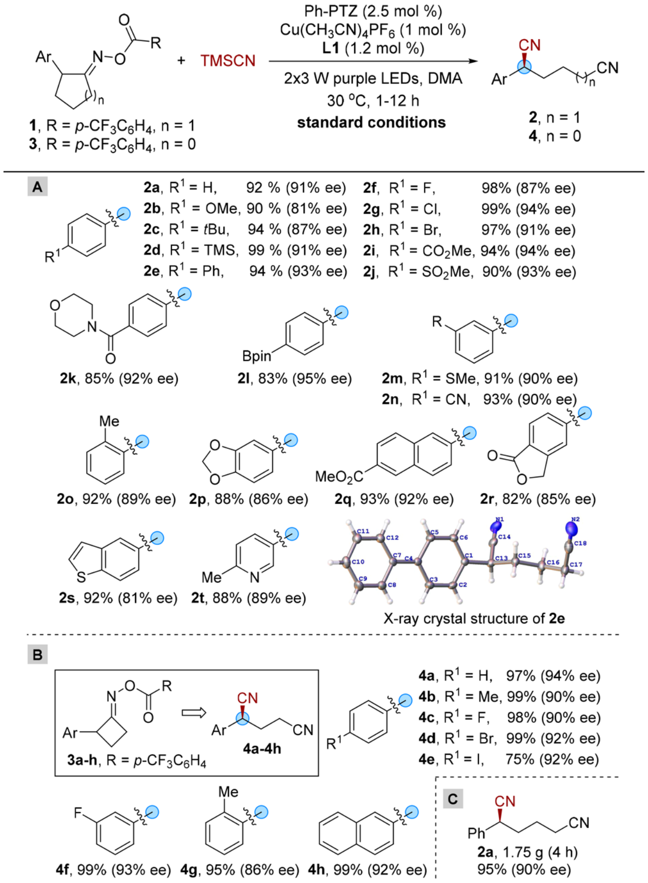


entry	copper salt	ligand	yield (%)[b]	ee (%)[c]
1	Cu(CH$_3$CN)$_4$PF$_6$	**L1**	43	89
2	Cu(CH$_3$CN)$_4$PF$_6$	**L2**	45	-32
3	Cu(CH$_3$CN)$_4$PF$_6$	**L3**	50	-61
4	Cu(CH$_3$CN)$_4$PF$_6$	**L4**	97	5
5	Cu(CH$_3$CN)$_4$PF$_6$	**L5**	75	-13
6	CuCl	**L1**	34	89
7	Cu(OAc)$_2$	**L1**	36	88
8	Cu(OTf)$_2$	**L1**	35	89
9[d]	Cu(CH$_3$CN)$_4$PF$_6$	**L1**	33	90
10[d,e]	Cu(CH$_3$CN)$_4$PF$_6$	**L1**	73	91
11[d,f]	Cu(CH$_3$CN)$_4$PF$_6$	**L1**	99(92)	91



[a] **1a** (0.1 mmol) and TMSCN (0.3 mmol) were used. [b] Yields were determined by GC analysis, with isolated yield in parentheses. [c] The ee values were determined by HPLC on a chiral stationary phase. [d] With 2.0 mL of DMA. [e] 0.5 mol % of *fac*-Ir(ppy)$_3$, 1 mol % of Cu(CH$_3$CN)$_4$PF$_6$, and 1.2 mol % of **L1**. [f] 2.5 mol % of Ph-PTZ, 1 mol % of Cu(CH$_3$CN)$_4$PF$_6$, and 1.2 mol % of **L1** under irradiation of 2 × 3 W purple LEDs for 1 h.

Scheme 2. Scope of the Cycloketone Oxime Esters^{a,b,c}

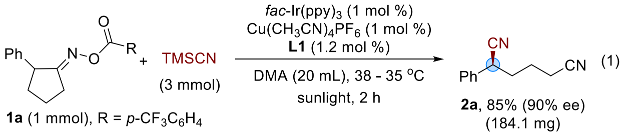


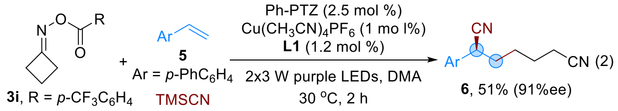
^{a}**1** or **3** (0.2 mmol), TMSCN (0.6 mmol), and DMA (4.0 mL) were used. ^{b}Isolated yields. ^{c}The ee values were determined by HPLC on a chiral stationary phase.

in the reactions of **3f** and **3g**, the change of the position of substituent has no obvious effect on the reaction, with the corresponding products **4f** and **4g** being obtained in quantitative yields with 93 and 86% ee, respectively. Oxime ester **3h** with a 2-naphthyl group also proved to be suitable for the reaction, giving rise to **4h** with 92% ee.

Notably, the reaction of **1a** and TMSCN performed on 10.0 mmol scale also worked well to furnish the product **2a** in 95% yield (90% ee) within 4 h, when using only 1.25 mol % of Ph-PTZ, 0.5 mol % of Cu(CH$_3$CN)PF$_6$, and 0.6 mol % of ligand **L1** (Scheme 2C). The photocatalyst Ph-PTZ could also be recovered with 97% yield. Suitable crystals of compound **2e** were obtained, and a single-crystal analysis revealed the configuration to be *S*.

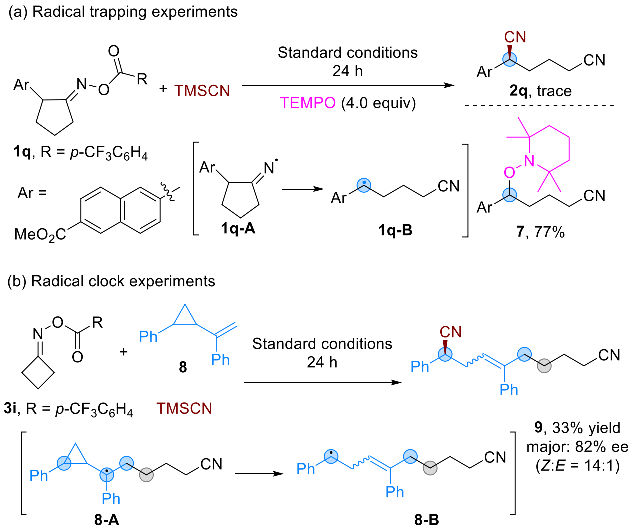
Moreover, the model reaction of **1a** and TMSCN carried out on 1.0 mmol scale proceeded smoothly to give **2a** with 85% yield (184.1 mg) and 90% ee, when replacing Ph-PTZ with *fac*-Ir(ppy)$_3$ under only 2 h of sunlight exposure (eq 1). Preliminary efforts have established that the current catalytic system could also be applied to a three-component enantioselective ring-opening cross-coupling of oxime esters. It was found that the reaction of cyclobutanone oxime ester **3i**, para-phenyl-substituted styrene **5**, and TMSCN worked well under the standard conditions, giving alkyl dinitrile **6** in synthetically useful yield with 91% ee (eq 2). Further optimization studies to improve the yield of this reaction are ongoing.





To gain some insight into the working proposal, we first performed a control experiment with **1q** and TMSCN (Scheme 3a). Upon addition of stoichiometric TEMPO (4.0 equiv), complete suppression of the formation of the desired product **2q** was observed, and the corresponding TEMPO-trapping product **7** was isolated in 77% yield. Moreover, the ring-opening product **9** was obtained in the reaction of radical clock substrate **8** (Scheme 3b), which should result from a radical cross-coupling of radical intermediate **8-B** with TMSCN. These results suggest the involvement of cyanoalkyl radical **1q-B** and a benzylic radical such as **8-A**.

Scheme 3. Mechanistic Studies



As the Ph-PTZ and *fac*-Ir(ppy)$_3$ demonstrated comparable results, we then investigated the luminescence quenching of *fac*-Ir(ppy)$_3$ with excitation at 355 nm by **1a**, CuCN/**L1**, and TMSCN.[16] The Stern–Volmer plot results revealed that **1a** could more significantly quench the excited state of the photocatalyst than CuCN/**L1** or TMSCN (Figure 1).

The excited-state photocatalyst *Ph-PTZ is reported to be a very strong reductant ($E_{1/2}$[Ph-PTZ$^{\bullet+}$/Ph-PTZ*] = −2.1 V vs SCE in CH$_3$CN).[17] The redox potential of **1a** was determined to be −1.69 V vs SCE in DMA,[16] suggesting that an SET event between **1a** and *Ph-PTZ was presumably engaged in the reaction to enable SET reduction of **1a**. On the other hand, the oxidized state Ph-PTZ$^{\bullet+}$ is a strong oxidant ($E_{1/2}$[Ph-PTZ$^{\bullet+}$/Ph-PTZ] = 0.68 V vs SCE in CH$_3$CN) capable of oxidizing **L1***Cu(I)CN to **L1***Cu(II)CN ($E_{1/2}$[Cu(II)/Cu(I)] = +0.36 V vs SCE in CH$_3$CN).[6b] We determined the quantum yield of the reaction of **1a** and TMSCN to be 0.509. A value below unity suggests that the reaction should proceed by a sequential redox process rather than a radical chain pathway. Finally, a study of the impact of the ee of ligand **L1** on the ee of the product **2a** did

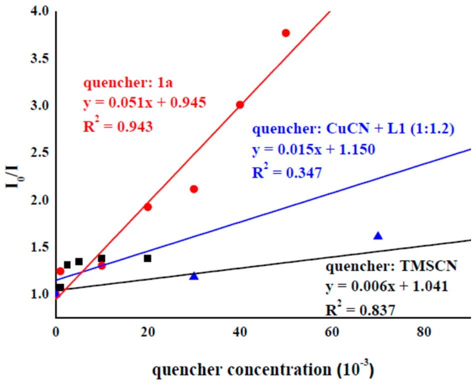
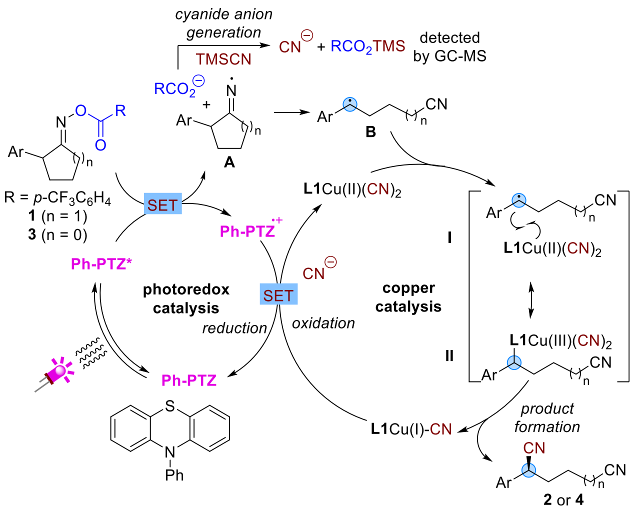


Figure 1. Stern–Volmer plot for the emission quenching of excited photocatalyst *fac*-Ir(ppy)$_3$ in toluene by different quenchers.

not demonstrate an obvious nonlinear effect, suggesting that a copper complex should contain one ligand **L1**.[16]

Finally, we proposed a dual photoredox and copper-catalyzed pathway for the present enantioselective radical ring-opening cross-coupling reaction (Scheme 4). The reaction begins with SET reduction of redox-active oxime ester **1** or **3** by the photoexcited Ph-PTZ*, followed by fragmentation to give iminyl radical **A** and carboxylic anion (RCO$_2^-$). Next, iminyl radical **A** undergoes a selective β-C–C bond cleavage to generate cyanoalkyl radical **B**. On the other hand, the resultant carboxylic anion (RCO$_2^-$) could facilitate the formation of a cyanide anion from TMSCN, which undergoes ligand change with copper(I) salt to form the **L1**Cu(I)CN species. Notably, the side product RCO$_2$TMS was indeed detected by GC-MS. Then, the strongly oxidizing Ph-PTZ$^{\bullet+}$ could oxidize the **L1**Cu(I)CN complex to active species **L1**Cu(II)(CN)$_2$ after trapping another molecule of the cyanide anion from TMSCN with regeneration of ground-state Ph-PTZ. Subsequently, the **L1**Cu(II)(CN)$_2$ complex could capture relatively stable prochiral cyanoalkyl radical **B** to generate chiral Cu(III) complex **II** via intermediate **I**. Finally, intermediate **II** undergoes reductive elimination to give the product **2** or **4**, with regeneration of the **L1**Cu(I)CN complex, closing the copper catalysis cycle.

Scheme 4. Proposed Mechanism



In conclusion, we have developed a novel enantioselective radical ring-opening cyanation of oxime esters by dual photoredox and copper catalysis. This protocol demonstrates broad substrate scope, producing various optically active alkyl dinitriles with high yields and excellent enantioselectivities, which are difficult to access traditionally. This work has also established a platform to explore cyanoalkyl radicals derived from cycloketone oxime esters in catalytic asymmetric radical cross-coupling chemistry. Further expansion of this dual catalytic system to other carbon- and heteroatom-based nucleophiles is currently in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03970.

Experimental procedures, full analysis data for new compounds, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1956493 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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