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Directing-Group-Based Strategy Enabling Intermolecular Heck-Type Reaction of Cycloketone Oxime Esters and Unactivated Alkenes

Yi Deng,[#] Chunyang Zhao,[#] Yu Zhou,[#] Hongwei Wang, Xuexiang Li, Gui-Juan Cheng, and Junkai Fu*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00963 Read Online

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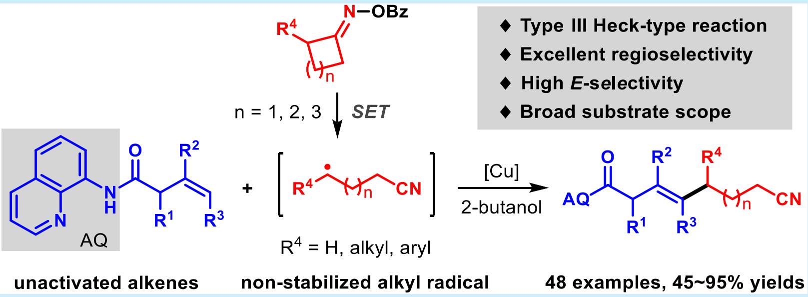


ABSTRACT: A new type of coupling between unactivated olefins and nonstabilized alkyl radicals was achieved, which enabled the first intermolecular Heck-type reaction of cycloketone oxime esters and unactivated alkenes. This directing-group-based strategy was compatible with various unactivated alkenes and cyclobutanone-, cyclopentanone-, and cyclohexanone-derived oxime esters. Density functional theory calculations showed that both excellent regioselectivities and good diastereoselectivities could be ascribed to the 2-butanol-assisted concerted H−OBz elimination of the conformationally strained metallacyclic transition state.

The Nobel Prize-winning Mizoroki−Heck reaction of aryl/vinyl (pseudo) halides and alkenes is considered as one of the most powerful methods in constructing $C_{sp2}-C_{sp2}$ bonds.[1] Recent advances show that alkyl electrophiles could serve as alternative partners to couple with alkenes and ultimately forge the $C_{sp2}-C_{sp3}$ bonds.[2] This Heck-type alkenylation typically relies on a single-electron transfer (SET) process of alkyl electrophiles to generate alkyl radical intermediates, which can avoid neither slow oxidative addition nor β-hydride elimination (Figure 1a).[3] Current research mainly focuses on the exploration of new catalytic systems or appropriate alkyl radical precursors to cooperate with activated alkenes, e.g., styrenes, acrylates, or vinyl ethers (type I).[4] In comparison, the intermolecular Heck-type reaction of alkyl electrophiles with unactivated olefins has received far less attention, with only a few cases using functionalized alkyl electrophiles bearing adjacent functionalities (type II). Dong,[5] Gevorgyan,[6] and Fu[7] have independently reported the Heck-type reaction of unactivated alkenes and α-cyano/ester alkyl radical intermediates, leading to the formation of γ,δ-unsaturated nitriles and esters. Various electrophilic trifluoromethylating reagents[8] and benzyl electrophiles[9] were successfully employed to couple with unactivated alkenes via either radical or ionic (due to no detachable β-hydrogens) pathways. However, to the best of our knowledge, the intermolecular Heck-type reaction of unactivated alkenes and nonstabilized alkyl radical intermediates without adjacent functionalities[10] has remained underexplored (type III). Without the stabilization by an adjacent functional group, the fleeting carbon radical intermediate is difficult to efficient capture with the already weakly reactive olefin partners. In addition, the control of both regio- and diastereoselectivities would be challenging due to the potential competing pathways for the final β-hydride elimination.[7]

Recently, the β-C−C bond cleavage of cycloketone oxime esters[11] has been demonstrated to be an efficient way to access nonstabilized alkyl radicals containing a distal cyano group via a SET process with transition metal catalysts[12] or photoredox catalysis.[13] This chemistry has been successfully applied to a variety of transformations of alkenes, including difunctionalizations,[14] couplings,[15] and type I Heck-like reactions[16] (Figure 1b). However, all of these reactions are restricted to activated alkene partners, presumably due to the difficulty in handling these highly reactive alkyl radicals without the stabilization modes.

In conjunction with our continuing efforts in directed copper-catalyzed functionalizations of unactivated alkenes,[7,17] we envisioned that a combination of cycloketone oxime esters and a directing-group-based strategy might be a potential solution to realizing type III Heck-type reaction. The weak N−

Received: March 16, 2020

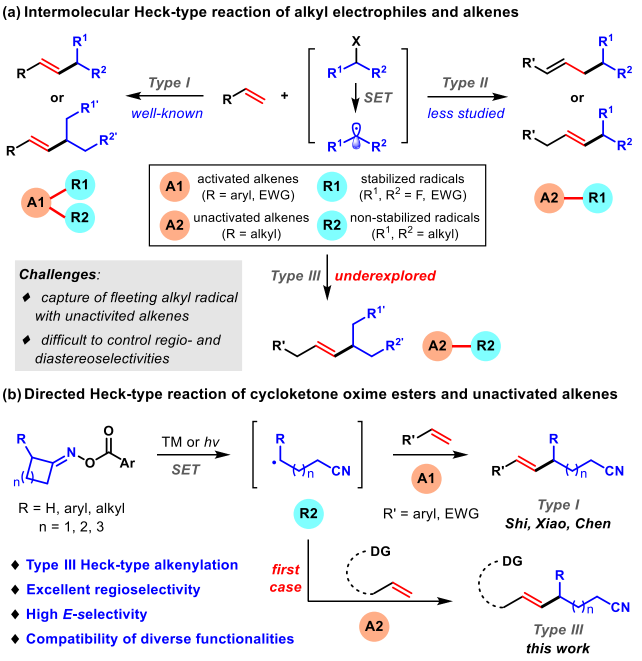
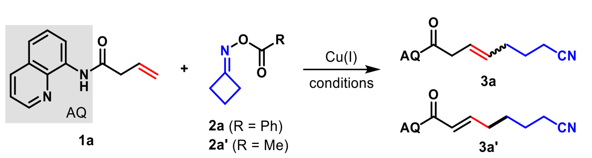
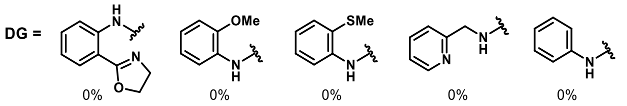


Figure 1. Intermolecular Heck-type reaction of alkyl electrophiles and alkenes.

Table 1. Optimization of the Reaction Conditions[a]





entry	catalyst	solvent	% yield (recovery of 1a)[b]	rr[c] (3a:3a′)	E:Z[c]
1	CuCl	DMSO	32 (46)	>20:1	1:1.2
2	CuI	DMSO	44 (32)	>20:1	1:1.8
3	$Cu(MeCN)_4PF_6$	DMSO	34 (47)	>20:1	1:1.4
4	$CuCl_2$	DMSO	35 (36)	>20:1	1:1.5
5	$Cu(OAc)_2·H_2O$	DMSO	48 (35)	>20:1	1:1.7
6	$Cu(OBz)_2$	DMSO	46 (40)	>20:1	1:1.5
7	$FeCl_2$	DMSO	0 (90)	–	–
8	$NiCl_2$	DMSO	0 (84)	–	–
9[d]	$Cu(OAc)_2·H_2O$	DMSO	trace (82)	–	–
10	$Cu(OAc)_2·H_2O$	THF	42 (35)	5:1	2.5:1
11	$Cu(OAc)_2·H_2O$	1,4-dioxane	34 (40)	5:1	2:1
12	$Cu(OAc)_2·H_2O$	toluene	25 (57)	<1:20	–
13	$Cu(OAc)_2·H_2O$	MeOH	45 (23)	>20:1	4:1
14	$Cu(OAc)_2·H_2O$	^{i}PrOH	60 (12)	>20:1	3:1
15	$Cu(OAc)_2·H_2O$	^{t}BuOH	31 (40)	13:1	1.5:1
16	$Cu(OAc)_2·H_2O$	2-butanol	68 (6)	>20:1	7.5:1
17	–	2-butanol	0 (81)	–	–
18[e]	$Cu(OAc)_2·H_2O$	2-butanol	56 (16)	>20:1	6:1

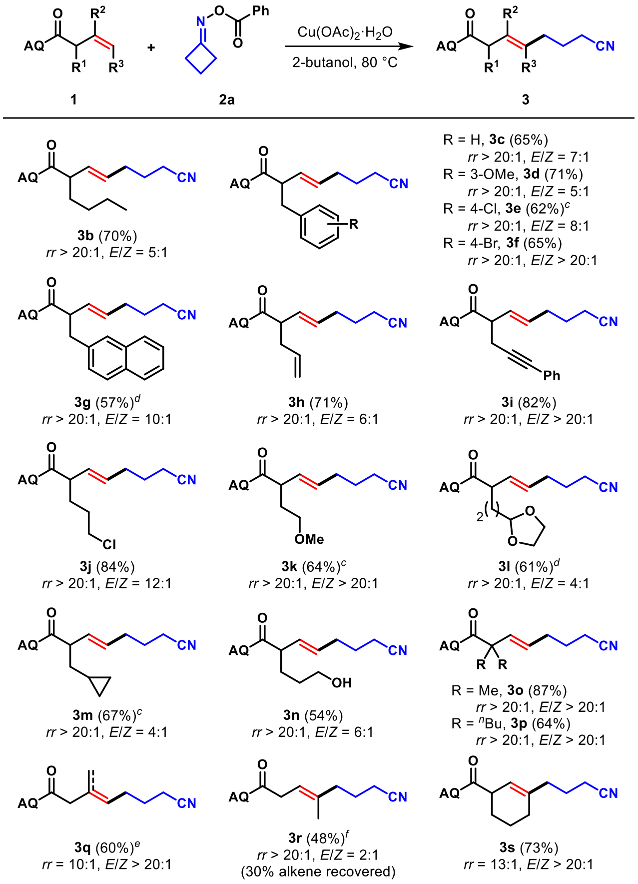
[a] Conditions: **1a** (0.20 mmol) and **2a** (0.50 mmol) in solvent (2.0 mL) with metal salt (0.04 mmol) at 80 °C. [b] Isolated yields of **3a** and **3a′**. [c] The rr values and E:Z ratios were determined by ^{1}H NMR. [d] With Cs_2CO_3 (0.20 mmol). [e] Replacement of **2a** with **2a′** (0.50 mmol).

O bond and ring strain make the cycloketone oxime esters easily undergo SET processes with the metal salts, especially these having a low oxidation−reduction potential, such as Cu(I), and therefore generate the nonstabilized alkyl radicals very fast. In the meantime, installation of a directing group might facilitate the intermolecular addition of a newly formed alkyl radical to an unactivated olefin moiety and control the regioselectivity via a kinetically favorable conformation of the metallacyclic intermediate.[18] This hypothesis ultimately enabled the development of the first case of type III Heck-type reaction of cycloketone oxime esters and unactivated alkenes, providing an efficient cyanide-free synthesis of diverse cyanoalkenes with excellent regioselectivities and good *E* selectivities.

For optimization of the reaction conditions, we used 3-butenoic acid masked as its 8-aminoquinoline (AQ)[19] amide **1a** and cyclobutanone *O*-benzoyl oxime **2a** as standard substrates (Table 1). Primary results demonstrated that running the reactions in the presence of copper salts in DMSO at 80 °C led to the formation of the desired coupled products (entries 1−6). Despite excellent regioselectivities, as expected, probably due to the assistance of DMSO,[7] these reactions suffered from inefficiency as well as low diastereoselectivities.[20] Other reductive metal salts, including Fe(II) and Ni(II), were shown to be ineffective (entries 7 and 8, respectively). Here we chose more readily available $Cu(OAc)_2$ for further screening of conditions, although $Cu(OBz)_2$ afforded a similar result. Contrary to expectation, addition of base, which was thought to be beneficial for the coordination of the directing group and metal salt, gave only a trace amount of the desired product (entry 9).[21] Switching the solvent to THF or 1,4-dioxane resulted in a dramatically decreased regioselective ratio, and only **3a′** was isolated in 25% yield when nonpolar toluene was used (entries 10−12). Further screening of solvents showed that the alcohols were crucial for controlling both regio- and diastereoselectivities (entries 13−16), with 2-butanol serving as the most effective solvent to afford **3a** in a yield of 68% with an excellent rr value (>20:1) and a good *E*:*Z* ratio (7.5:1) (as standard reaction conditions). A control experiment performed without $Cu(OAc)_2·H_2O$ demonstrated that a copper catalyst is essential for the reaction (entry 17). In addition, *O*-acetyl oximes **2a′** showed an inferior yield of 56% with a moderate *E*:*Z* ratio (entry 18), while other amide directing groups[22] all failed to give either **3a** or **3a′**.

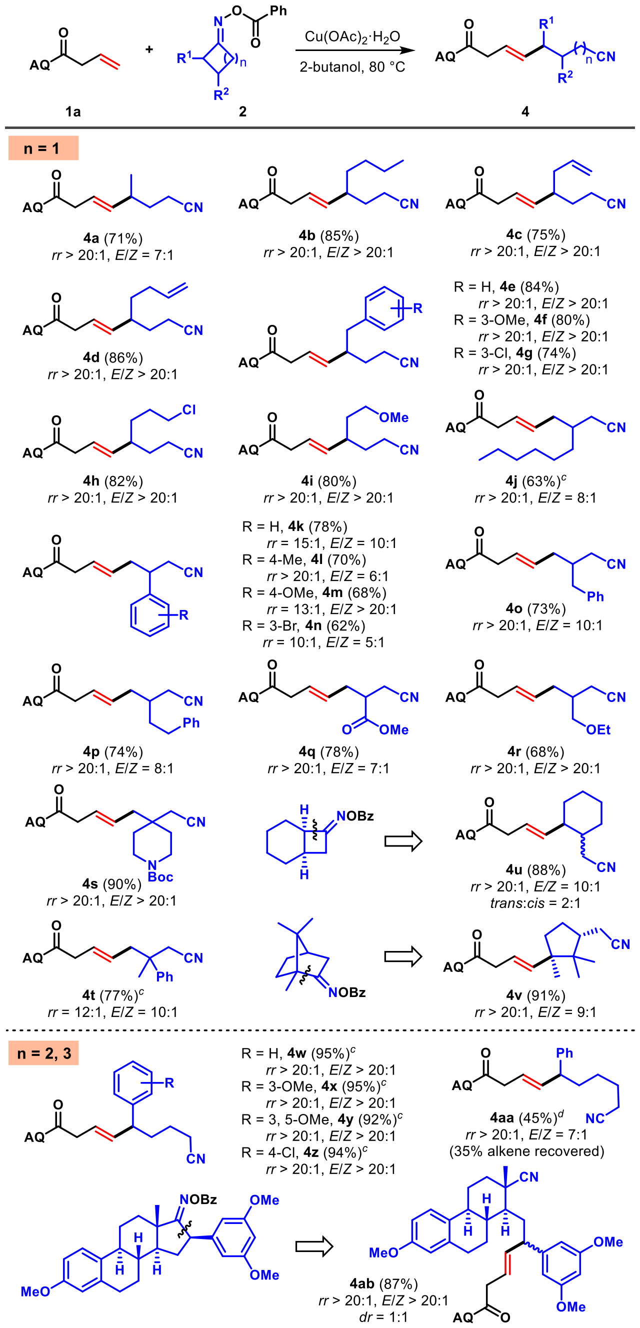
With the optimal reaction conditions established, we then investigated the substrate scope of unactivated alkenes (Scheme 1). A wide range of α-substituted terminal alkenes, including *n*-butyl, electronically diverse (−OMe, −Cl, and −Br) benzyl, and naphthyl forms, proved to be good partners to afford **3b−g** as single regioisomers with good to excellent *E*:*Z* ratios. It is noteworthy that the addition of 2,6-di-*tert*-butylpyridine in a mixed solvent improved the *E*:*Z* ratios for **3e** and **3g**.[23] The $\beta-\gamma$ double bond could be selectively functionalized in the presence of $\gamma-\delta$ olefin or acetylene moieties to produce **3h** and **3i**. The formation of **3j−n** demonstrated that this reaction was compatible with diverse functionalities, including halogen atom, ether, acetal, cyclopropyl, and even free hydroxyl groups. With regard to the sterically hindered α,α-dimethyl- or -dibutyl-substituted alkenes, the Heck-type reactions gave the corresponding products **3o** and **3p** as single regioisomers and *E* isomers. For the 1,1-disubstituted alkene, **3q** was obtained with a minor

Scheme 1. Substrate Scope of Unactivated Alkenes[a,b]



[a] Standard reaction conditions. [b] Isolated yields. [c] 2-Butanol/1,4-dioxane (2:1, 2.0 mL) as the solvent with 2,6-di-*tert*-butylpyridine (0.20 mmol) as the additive. [d] 2-Butanol/THF (2:1, 2.0 mL) as the solvent with 2,6-di-*tert*-butylpyridine (0.20 mmol) as the additive. [e] CuI (0.04 mmol). [f] CuI (0.08 mmol).

Scheme 2. Substrate Scope of Cycloketone Oxime Esters[a,b]



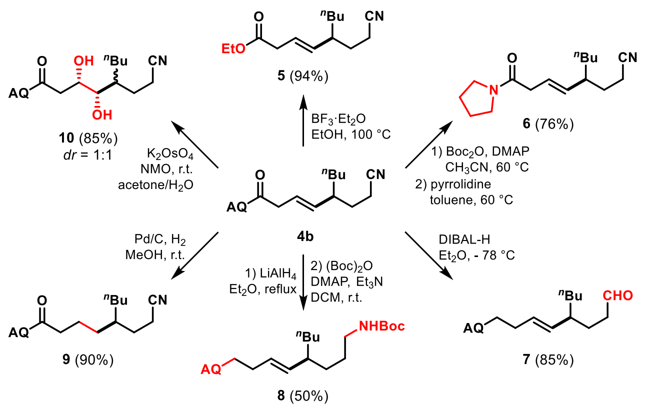
[a] Standard reaction conditions. [b] Isolated yields. [c] 2-Butanol/THF (2:1, 2.0 mL) as the solvent with 2,6-di-*tert*-butylpyridine (0.20 mmol) as the additive. [d] $Cu(acac)_2$ (0.04 mmol).

amount of regioisomer (rr = 10:1) that was most likely generated through the β-hydride elimination of a hydrogen on the methyl group. To our delight, internal alkenes were shown to be suitable substrates. The linear coupled product **3r** was isolated in a moderate yield of 48% (30% of alkene recovered; 2:1 *E*:*Z*), while cyclic **3s** was formed in 73% yield in a highly regioselective manner (rr = 13:1). However, as a limitation of this protocol, the substrate with a $\gamma-\delta$ double bond failed.[24]

Next, we continued to test the generality of the developed sequence by varying the structure of cycloketone oxime esters (Scheme 2). The nonsymmetrical cyclobutanone oxime esters with alkyl, olefin, substituted benzyl, haloalkyl, or ether groups at the C2 position all underwent ring-opening processes selectively at the more substituted carbon center, giving the corresponding products **4a−i** in good yields with both excellent rr values and *E*:*Z* ratios. For symmetrical mono- and disubstituted cyclobutanone oxime esters, including those with diverse functionalities (substituted phenyl, ester, ether, and amide groups), the internal alkenes **4j−t** were obtained in 62−90% yields with slightly inferior *E*:*Z* ratios compared to those of the C2-substituted oxime esters. Notably, the bicyclic oxime esters proved to be suitable partners. The bicyclo[4.2.0]-type oxime ester afforded *trans* product **4u** as a major product, while the oxime ester derived from camphor furnished **4v** in 91% yield. To our delight, the less strained cyclopentanone- and cyclohexanone-derived oxime esters could also undergo the desired reaction pathway in a highly regio- and diastereoselective manner. Products **4w−z** were obtained in superior yields (>90%), and a relatively low yield of 45% for **4aa** was found in the presence of $Cu(acac)_2$. Subjecting the estrone-based oxime derivative to the optimized reaction conditions produced **4ab** in 87% yield as a mixture of diastereoisomers, showing the potential application of this protocol in complex systems.

To demonstrate the synthetic applications, further transformations of the coupled product **4b** have been performed (Scheme 3). Treatment of **4b** with $BF_3\cdot OEt_2$ in ethanol could

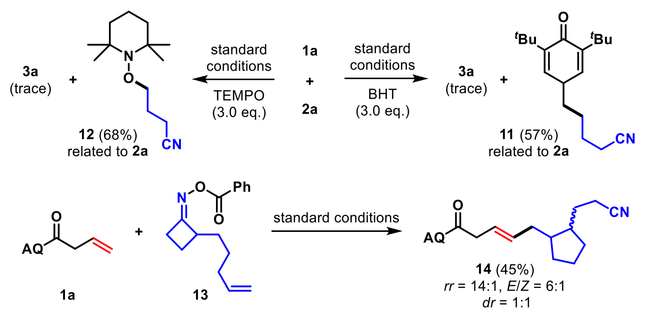
Scheme 3. Representative Derivatizations



convert the amide into corresponding ester **5** in 94% yield. A two-step approach via protection followed by substitution achieved the secondary amide transamidation to afford tertiary amide **6**. The cyano and amide groups could be reduced by diisobutyl aluminum hydride into aldehyde and secondary amine moieties, respectively, to give **7** in 85% yield. In comparison, diamine compound **8** was obtained when reduction of **4b** with lithium aluminum hydride in refluxing diethyl ether. Moreover, **4b** could be hydrogenated into cyanoamide **9** or undergo dihydroxylation to produce diol **10**.

Several control experiments were conducted to gain insight into the mechanism (Scheme 4). Addition of 3.0 equiv of either BHT or TEMPO to the reaction mixture completely suppressed the formation of desired product **3a**, and the cyanoalkyl−BHT and −TEMPO adducts **11** and **12** were isolated in 57% and 68% yields, respectively, based on the amount of oxime ester **2a**.[12f] Moreover, a radical clock experiment using oxime ester **13** as the substrate produced ring-closed product **14** in 45% yield as a mixture of diastereoisomers.[12b,d] These results indicate that the reaction may involve a cyanoalkyl radical species.

Scheme 4. Mechanistic Investigations



According to the aforementioned experimental results and previous reports,[25−27] we propose a plausible reaction mechanism. As shown in Figure 2, the disproportionation reaction of the Cu(II) catalyst generated a Cu(I) species.[28] Then species **M1** was generated through the coordination of Cu(I) salt with alkene **1a**. A SET process between **M1** and oxime ester **2a** would give the oxidized Cu(II)−OBz species **M2** and an iminyl radical **M3**, which underwent a fast selective *β*-C−C bond scission to generate cyanoalkyl radical **M4**. Subsequently, the nonstabilized radical species **M4** might be trapped in time by the environmental olefin moiety of **M2**, and the resultant carbon radical would recombine rapidly with the nearby Cu(II) species. This formal migratory insertion process afforded a putative directing-group-coordinated Cu(III) intermediate **M5**.[7,27,29] Eventually, H^a and H^b were distinguished during the concerted H^a−OBz (path a) or H^b−OBz (path b) elimination of the conformationally strained metallacyclic intermediate **M5**.[8b,18] Major product **3a** and minor one **3a′** were produced through the subsequent protodemetalation, along with the regeneration of Cu(I) salt. The screening conditions in Table 1 indicated that the solvent played a key role in controlling the reaction selectivities, with 2-butanol serving as the most effective one. Further DFT calculations performed at the SMD(2-butanol)/(U)M06/[6-31G(d,p)/LanL2DZ(Cu)] level (see Figure S1) showed that 2-butanol was involved in the transition state of the concerted H−OBz elimination process. The concerted H^a−OBz elimination is much more difficult than concerted H^b−OBz elimination ($\Delta\Delta G^\ddagger$ = 2.2 kcal/mol), and the barriers leading to the formation of *E*- and *Z*-**M7** were 19.0 and 20.5 kcal/mol, respectively. It was found that the slight preference for *E*-**M7** was attributed to the steric effect. In the transition state leading to the formation of *Z*-**M7**, the distance between the hydrogen of 2-butanol and the hydrogen of the substrate was only 2.2 Å. These calculated results were consistent with the experimental data of an excellent rr value and a good *E*:*Z* ratio.

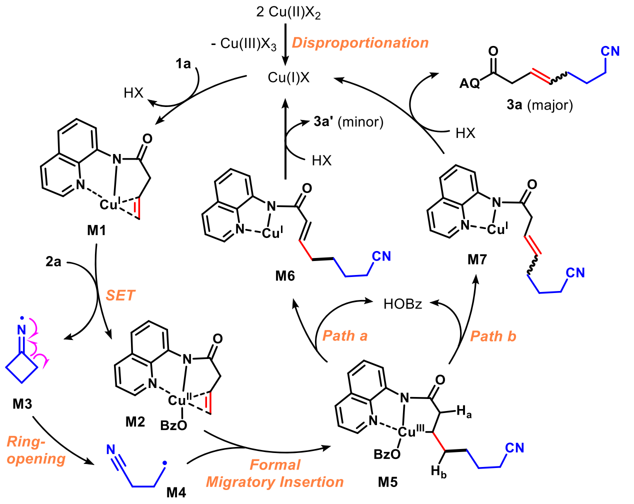


Figure 2. Proposed reaction mechanism.

In summary, a directed intermolecular Heck-type reaction of cycloketone oxime esters and unactivated alkenes was achieved for the first time, which represented a conceptually new type of coupling between the unactivated alkene and alkyl electrophile via nonstabilized alkyl radical species. All cyclobutanone-, cyclopentanone-, and cyclohexanone-derived oxime esters and a wide range of unactivated alkenes, including *α*-substituted, 1,1-disubstituted, and internal alkenes, were compatible. Further derivatization of the resultant cyanoalkenes showed the potential application prospect of this methodology in organic synthesis. Detailed mechanistic studies and DFT calculations disclosed that 2-butanol-assisted concerted H−OBz elimination of the conformationally strained Cu(III) cyclic transition state is the key to delivering the coupled products in excellent regioselectivities and good *E*:*Z* ratios.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00963.

Computational details, Figure S1, supplementary data, experimental procedures, and analytical data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Junkai Fu − *Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis, Department of Chemistry, Northeast Normal University, Changchun 130024, China;* orcid.org/0000-0002-7714-8818; Email: fujk109@nenu.edu.cn

Authors

Yi Deng − *Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis, Department of Chemistry, Northeast Normal University, Changchun 130024, China*

Chunyang Zhao − *Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis, Department of Chemistry, Northeast Normal University, Changchun 130024, China*

Yu Zhou − *Warshel Institute for Computational Biology, School of Life and Health Sciences, The Chinese University of Hong Kong (Shenzhen), Shenzhen 518172, China; School of Life Sciences, University of Science and Technology of China, 230027 Hefei, Anhui, China*

Hongwei Wang − *Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis, Department of Chemistry, Northeast Normal University, Changchun 130024, China*

Xuexiang Li − *School of Chemistry and Chemical Engineering, Northwestern Polytechnical University, Xi'an 710072, China*

Gui-Juan Cheng − *Warshel Institute for Computational Biology, School of Life and Health Sciences, The Chinese University of Hong Kong (Shenzhen), Shenzhen 518172, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00963

Author Contributions

#Y.D., C.Z., and Y.Z. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the NNSFC (21702027, 21971034, 21602175, and 21871221) and the Fundamental Research Funds for the Central Universities (2412019FZ017).

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