ChemComm

COMMUNICATION

Check for updates

Cite this: Chem. Commun., 2019, 55, 14291

Received 15th October 2019, Accepted 4th November 2019

DOI: 10.1039/c9cc08077e

rsc.li/chemcomm

Visible light-induced palladium-catalyzed ring opening β-H elimination and addition of cyclobutanone oxime esters†

Wei-Long Xing,^a Rui Shang, 🛈 *^{ab} Guang-Zu Wang^a and Yao Fu 🛈 *^a

A palladium catalyst under visible light irradiation activates cyclobutanone oxime ester through single electron transfer to induce radical ring opening to generate hybrid cyanoalkyl Pd(I) radical species. Hybrid cyanoalkyl Pd(I) radical species can undergo either β -H elimination to deliver (*E*)-4-arylbut-3-enenitrile or undergo radical addition with silyl enol ether and enamide to generate δ -cyano ketones. A dual ligand system composed of two phosphine ligands is essential for the high reactivity.

Palladium-catalysis in its photoexcitation state by absorbing visible light energy has received increasing attention recently.¹ Palladium phosphine complexes exhibit a blend of radical and organometallic reactivity after photo-excitation.^{1a} It was recently reported that photoexcited palladium(0) phosphine complexes activate alkyl halides² and alkyl N-(acyloxy)phthalimide³ to generate a putative hybrid alkyl Pd(1) radical species that allows alkyl Heck reaction,⁴ desaturation,⁵ and even C-H functionalization reactions⁶ in high efficiency. Single electron oxidative addition and generation of hybrid alkyl Pd(1) species effectively overcomes several long standing problems encountered in thermal palladium-catalyzed alkylation, such as oxidative addition to tertiary alkyl electrophiles and suppression of undesired β -H elimination in nonproductive steps. However, the electrophile substrates amenable in excitation state palladium catalysis are still limited. Herein, we found that cyclobutanone oxime esters,⁷ a class of electrophile easily accessed from cyclobutanone,8-10 can be activated by a phosphine ligated Pd(0) complex under mild irradiation conditions to generate hybrid cyanoalkyl Pd(I) radical species. The generated hybrid cyanoalkyl Pd(1) radical species can either undergo β -H elimination to deliver (E)-4-arylbut-3-enenitrile

or undergo radical addition with silyl enol ether and enamide to generate δ -cyano ketones by tuning the ligand system that is composed of two types of phosphine (Fig. 1).^{3,4a,5a,6c} The photoinduced palladium-catalyzed ring opening process compares differently with the palladium-catalyzed two-electron oxidative addition process under thermal conditions reported by Nishimura and Uemura in terms of reactivity and selectivity (Fig. 1).¹¹ Although the ring-opening addition of cyclobutanone oxime esters has been reported extensively by using photoredox catalysis¹² and transition-metal catalysis¹³ our work reported herein presents a new reactivity of the palladium catalyst to active cyclobutanone oxime esters. The reactivity control of hybrid cyanoalkyl Pd(1) radical species by tuning the dual ligand system offers guidance to design and to discover new catalytic reactivity of palladium under visible light irradiation.

The optimized conditions for ring-opening elimination and addition with silyl enol ether are shown in Scheme 1a and b, respectively. Use of a combination of a bidentate phosphine ligand and a monodentate phosphine ligand is essential for both the transformations to proceed in high efficiency (see ESI[†] for more details about reaction optimization).

In the elimination reaction, the desired product could be obtained in 89% isolated yield under the optimal conditions.



Fig. 1 Activation of cyclobutanone oxime ester by the palladium catalyst (1) under thermal conditions through oxidative addition and (2) under irradiation conditions through the formation of hybrid alkyl Pd(i) radical species.

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^a Hefei National Laboratory for Physical Sciences at the Microscale, CAS Key Laboratory of Urban Pollutant Conversion, Anhui Province Key Laboratory of Biomass Clean Energy, iChEM, University of Science and Technology of China, Hefei 230026, China. E-mail: fuyao@ustc.edu.cn

^b Department of Chemistry, School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: rui@chem.s.u-tokyo.ac.jp

 $[\]dagger$ Electronic supplementary information (ESI) available. See DOI: 10.1039/ c9cc08077e



Scheme 1 Key reaction parameters: (a) ring opening elimination, reaction conditions: oxime ester (0.5 mmol), Pd(OAc)₂ (5 mol%), Xantphos (6 mol%), PPh₃ (10 mol%) and i-Pr₂NH (0.5 mmol) in dioxane (3 mL) at room temperature under irradiation with blue LEDs (Kessil, 40 W, 440 nm). (b) Addition with silyl enol ether, reaction conditions: oxime ester (0.2 mmol), silyl enol ether (0.3 mmol), PdCl₂ (5 mol%), dppf (6 mol%), PPh₃ (10 mol%) and Na₂HPO₄ (0.2 mmol) in dioxane (2 mL) at room temperature under irradiation with blue LEDs (Kessil, 40 W, 456 nm). Yield determined by GC with diphenylmethane as an internal standard. TMS = trimethylsilyl. Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. BINAP = (+/-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl. 1,10-Phen = o-phenanthroline. dppf = 1,1'-Bis(diphenylphosphino)ferrocene. dppp = 1,3-Bis(diphenylphosphino)propane. DPEphos = Bis(2-diphenylphosphinophenl)ether.

Control experiments revealed that the dual ligand system and irradiation are essential for the ring-opening elimination reactivity. The wavelength of the light source was also crucial for high efficiency. Compared with the result using 440 nm blue LEDs, irradiation sources of other irradiation wavelengths (390 nm, 427 nm and 456 nm) resulted in reduced yields (see ESI[†] for details). For ring opening addition with silvl enol ether (Scheme 1b), control experiments revealed that the combination of dppf and PPh₃ is essential for the high catalytic efficiency. The desired product could only be obtained in a moderate yield when dppf was used alone. Irradiation also played a crucial role in ring opening addition, and it was found that 456 nm LEDs were the optimal irradiation source (Schemes 1b, 1). Oxime esters other than trifluoromethyl benzoate were also investigated (Scheme 1b, 2), benzoate, 4-methoxybenzoate, and pentafluorobenzoate were all amenable to deliver the desired product, but with lower efficiency. The results of testing other bidentate phosphine ligands and bidentate nitrogen ligands showed that dppf was the most suitable ligand for ring opening addition with silyl enol ether.

With the optimal reaction conditions established, we evaluated the reaction scope of the ring-opening elimination

Table 1 Scope of ring-opening elimination of α -arylated cyclobutanone oxime esters^a



^{*a*} Reaction conditions: oxime ester (0.5 mmol), Pd(OAc)₂ (5 mol%), Xantphos (6 mol%), PPh₃ (10 mol%) and i-Pr₂NH (0.5 mmol) in dioxane (3 mL) at room temperature under irradiation with blue LEDs (Kessil, 40 W, 440 nm) for 12 h. Yields of isolated products were reported.

of α -arylated cyclobutanone oxime ester (Table 1). Several 2-aryl substituted cyclobutanone oxime esters with both electron-donating (3, 4) and electron-withdrawing substituents (5, 8) were suitable substrates for providing (*E*)-4-arylbut-3-enenitrile products in 54–87% yields. 2-Thienyl (6) and 2-naphthyl (7) substituted cyclobutanone oxime esters were amenable substrates. 2-Alkyl substituted cyclobutanone oxime esters were not suitable substrates under the optimized reaction conditions.

The reaction scope for ring opening addition with silyl enol ether with respect to different cyclobutanone oxime esters is demonstrated in Table 2. Cyclobutanone oxime esters bearing various functional groups, such as ester (9) and protected amine (10) at the 3-position, were well tolerated to afford the expected products in good yields. The cyclobutanone oxime esters derived from spiro-cyclobutanones containing a piperidine ring also showed comparable reactivity (11, 87% yield). Furthermore, heterocyclobutan-3-one oxime esters (O, S, N) participated in the reaction well to deliver products with good yields (12-15, 65-77% yields). Cyclobutanone oxime esters possessing substituents at the 2-position delivered the ring opening addition products with carbon-carbon bond cleavage occurring selectively at the more hindered position (16-21). This ring opening selectivity suggested a radical process rather than a pure organometallic mechanism through β -carbon elimination. In addition, benzocyclobutenone derivatives also worked well under the standard conditions to deliver benzonitrile products (22) in 78% yields. Ring strain is the main driving force for the radical ring opening process, as less-strained substrates turned out to be unreactive, such as cyclopentanone oxime ester. 2-Aryl substituted cyclobutanone oxime esters were not suitable substrates for ring-opening addition with silvl enol ether, probably because of the stability of the generated benzylic radical species after ring-opening.

The scope with respect to functional group tolerance on trimethyl((1-phenylvinyl)oxy)silane for ring opening addition is summarized in Table 3. Both *para-* and *meta-*substituents

Table 2Reaction scope with respect to oxime esters for ring openingaddition with silyl enol ether*



^{*a*} Reaction conditions: oxime ester (0.5 mmol), $PdCl_2$ (5 mol%), dppf (6 mol%), PPh₃ (10 mol%) and Na₂HPO₄ (0.5 mmol) in dioxane (4 mL) at room temperature under irradiation with blue LEDs (Kessil, 40 W, 456 nm) for 12 h. ^{*b*} Enol silyl ether (2 equiv.). Boc = *tert*-butoxycarbonyl. Cbz = benzyloxycarbonyl. i-Pr = isopropyl. Yields of isolated products were reported.

were tolerated (23, 24). An *ortho*-substituent on trimethyl((1phenylvinyl)oxy)silane (25) slightly lowers the reactivity. Functional groups such as methyl sulfide (26), ether (27), trifluoromethyl (28), halides (29–32), ester (33), and sulfone (35) were well tolerated. α -Heteroaryl silyl enol ethers, including thienyl (37), pyridyl (38), and furanyl (39) were also reactive to afford the desired products in good yield.



In addition to the enol-type substrate, we found that *N*-acetyl protected enamine also reacted with oxime esters (eqn (1)) to give δ -cyanoketone as a product after hydrolysis.

Based on our experimental evidence and the literature, ^{3,4a,5a,6c} a proposed mechanism that accounts for the palladiumcatalyzed ring opening β -H elimination and ring-opening addition of cyclobutanone oxime esters is depicted in Fig. 2. The palladium(0) complex **A** coordinated with both bidentate

Table 3Reaction scope with respect to silyl enol ether for ring-opening
additional



^{*a*} Reaction conditions: oxime ester (0.5 mmol), $PdCl_2$ (5 mol%), dppf (6 mol%), PPh₃ (10 mol%) and Na_2HPO_4 (0.5 mmol) in dioxane (4 mL) at room temperature under irradiation with blue LEDs (Kessil, 40 W, 456 nm) for 12 h. Yields of isolated products were reported.

phosphine and monodentate phosphine ligand activates oxime esters through light-induced single electron transfer to form a hybrid iminyl radical Pd(I) intermediate B. Intermediate B undergoes ring-opening cleavage of the carbon-carbon bond to generate a hybrid cyanoalkyl radical Pd(1) intermediate C. For ring opening addition with silvl enol ether, intermediate C interacts with silyl enol ether to produce a new hybrid benzyl radical Pd(I) species **D**, which is prone to undergo benzyl association to form benzyl-Pd(II) species (E) with the dissociation of PPh₃. β-H elimination on E generates F. Rebinding of PPh₃ to **F** releases alkylated silyl enol ether, which generates a ketone product after hydrolysis, and regenerates A for the next catalytic cycle. The process of C to G to H shown in pale color demonstrates the mechanism of forming the ring opening elimination product. Xantphos showed a better efficacy for ring opening elimination compared with dppf (20% GC yield of 1) probably because radical recombination to Pd in hybrid intermediate C is facilitated by using Xantphos as a supporting ligand. From the proposed mechanism, the two phosphine ligands work synergistically to facilitate inner-sphere single electron transfer from Pd(0) to substrates and also stabilize the generated hybrid iminyl and alkyl radical Pd(I) intermediates (B and C).



In summary, cyclobutanone oxime esters can be activated by a photo-excited Pd(0) complex to induce radical ring opening/ carbon–carbon cleavage to generate hybrid cyanoalkyl Pd(1) radical species. By utilizing this reactivity, we developed irradiationinduced palladium-catalyzed ring opening β -H elimination and addition reaction to silyl enol ether of cyclobutanone oxime esters under mild conditions, to deliver β -aroyl hexanenitriles and (*E*)-4-arylbut-3-enenitriles, respectively. A dual phosphine ligand system, in which a bidentate phosphine ligand and a monodentate phosphine ligand work synergistically through an association/dissociation process, was found to be the key enabler for the high reactivity. This work presents a new synthetic application of the increasing repertoire of visible light induced excitation state palladium catalysis.

We are grateful for the support from National Key R&D Program of China (2018YFB1501600), National Natural Science Foundation of China (21572212, 21732006, 51821006, 51961135104), Strategic Priority Research Program of CAS (XDB20000000), HCPST (2017FXZY001), and KY (2060000119).

Conflicts of interest

The authors declare no competing interests.

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