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Mild ketyl radical generation and coupling with alkynes enabled by Cr catalysis: stereoselective access to *E*-exocyclic allyl alcohols†

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The mild catalytic generation of ketyl radicals for organic transformations remains an unsolved issue, although it facilitates the discovery of metal-catalyzed reactions with the features of high functional group tolerance. Here, we report the generation of the ketyl radicals and coupling with alkynes that was enabled by cost-effective chromium catalysis, allowing for the formation of valuable *E*-exocyclic allyl alcohols with high stereo- and chemoselectivity. A broad range of synthetically useful functional groups that are sensitive to strong reductants are compatible with the catalytic system, providing access to diverse substituted *E*-exocyclic allyl alcohols under mild conditions. Appended hydroxyl groups in products are readily late-stage functionalized in accessing numerous derivatives, as well as the enantio-enrichment of exocyclic allyl alcohol using chiral ligands. Mechanistic studies suggest that bipyridine-ligated Cr(II) complex serves as a reactive catalyst enabling the generation of the ketyl radical for coupling, giving vinyl radical, followed by the combination of Cr and transmetalation with Cp_2ZrCl moiety in affording oxaziranium cycle. This reaction provides a new opportunity for the mild formation of transient ketyl radicals from widely accessible aliphatic aldehydes for coupling with Earth-abundant metal catalysis.

Introduction

Coupling reactions with transient radicals are one of the most powerful tools in the formation of C–C and C–heteroatom bonds in modern organic chemistry.¹ In this context, carbon-centered ketyl radicals or ketyl radical anions are valuable coupling intermediates, along with cross-coupling that enables the incorporation of important carbonyl groups to construct synthetically useful aliphatic alcohols.² However, because of the high reduction potential of carbonyl motifs,³ especially for reducing aliphatic carbonyls, stoichiometrically strong reductants, such as Na, K and Ti, are usually required for the generation of the ketyl radicals *via* the single electron transfer (SET) process.⁴ Alternatively, the thermodynamic barrier for ketyl formation can be overcome by the use of stoichiometric Kagan's reagent (SmI_2),^{2b,5} as well as by combining strong reductants of Zn/Hg in the catalytic formation of the ketyl radicals.⁶ Despite the progress in developing photoredox catalysis⁷ and reductive electrocatalysis,⁸ mild strategies using metal catalysis for the reduction of carbonyls to the ketyl radicals for couplings are

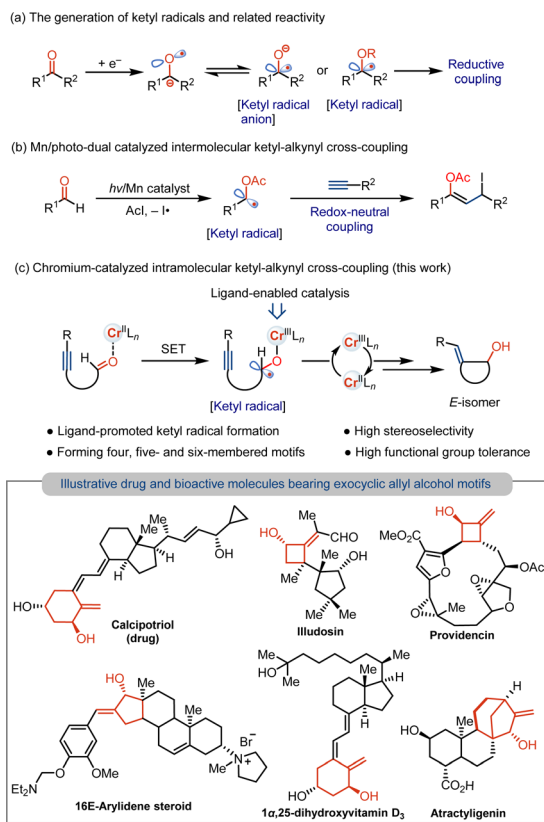
underdeveloped, particularly those that use earth-abundant 3d metal catalysts. In addition, to overcoming high reduction potential, chemoselectivity in metal-catalyzed reactions of the carbonyls without reducing resulting ketyl-coupled unsaturated adducts remains an issue. As a result, current studies focus on ketyl couplings with olefins to produce saturated products (Scheme 1a).⁹ Approaches that enable the formation of unsaturated motifs by catalytic formation of the ketyl radicals and selective couplings without over-reduction or over-addition would be value-addition to functionalized alcohol derivatives.

To address the selectivity problem, an impressive redox-neutral intermolecular coupling of the ketyl radicals with the alkynes has been reported by mechanisms involving atom-transfer radical addition (Scheme 1b).^{7f} We anticipate that an intramolecular coupling of aliphatic ketyl radicals generated *in situ* with the alkynes could be a possibility using appropriate 3d metal catalysts. This would need designing a mild reductive strategy to achieve the chemoselective formation of cyclic allyl alcohols and retain the vinyl group. In addition to overcoming the high reduction potential of aliphatic carbonyls, combining the vinyl radical with metals and regeneration of reactive catalysts remain unresolved issues. Herein, we report that a low-cost chromium(II) catalyst supported by a bipyridine ligand enables the mild formation of the ketyl radicals from unactivated aliphatic aldehydes, allowing for the intramolecular coupling with the alkynes under the mild conditions (Scheme 1c).¹⁰ This Cr-catalyzed ketyl coupling occurs by carbonyl reduction with Cr

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Scheme 1 Catalytic formation of the ketyl radicals and couplings with the alkynes.

catalyst and keeps the resulting vinyl functional group intact, achieving the stereo- and chemoselective formation of the *E*-exocyclic allyl alcohols that are ubiquitous structural motifs found in many pharmaceuticals and bioactive molecules.¹¹

Results and discussion

At the outset, we commenced our studies by the exploration of the formation of the ketyl radicals and intramolecular coupling by using alkynyl aliphatic aldehyde **1a** as a precursor (Fig. 1). Commercially available salt of CrCl₃ was chosen as a precatalyst in combination with 4,4'-di-*tert*-butyl-2,2'-dipyridyl (dtbpy) as the ligand, Mn as the reductant, and Cp₂ZrCl₂ with LiCl as the additive. We were pleased that the ketyl coupling occurs smoothly at ambient temperature, giving exocyclic allyl alcohol compound **2a** in 67% yield and excellent *E/Z*-selectivity (>99 : 1). The replacement of CrCl₃ by CrCl₂ remarkably increased the conversion to afford allylic alcohol **2a** in 87% yield. The reaction using Cr(acac)₃ led to the formation of **2a** in low yield. Nevertheless, a wide range of metal catalysts, such as FeCl₂, CoCl₂, NiCl₂, CuCl₂, AuCl₃, AgCl, VCl₃, MoCl₃, WCl₅ and RuCl₃, almost showed no efficiency in promoting the transformation under present conditions. However, relatively low stereoselectivity was obtained in these reactions. Further studies suggested that ligands play important roles in promoting the reactivity of Cr and stereochemistry of the conversion. In the absence of the

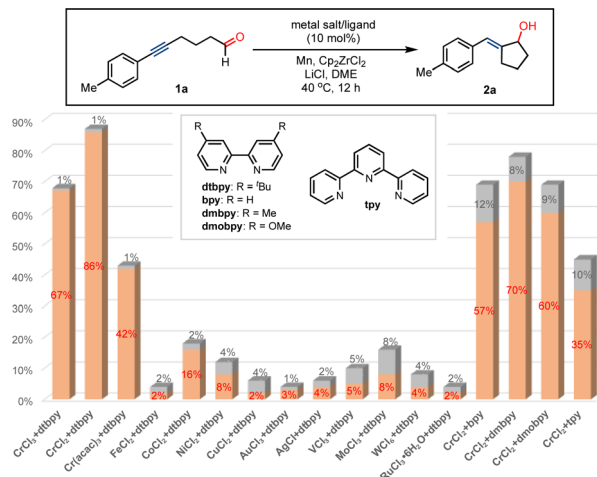
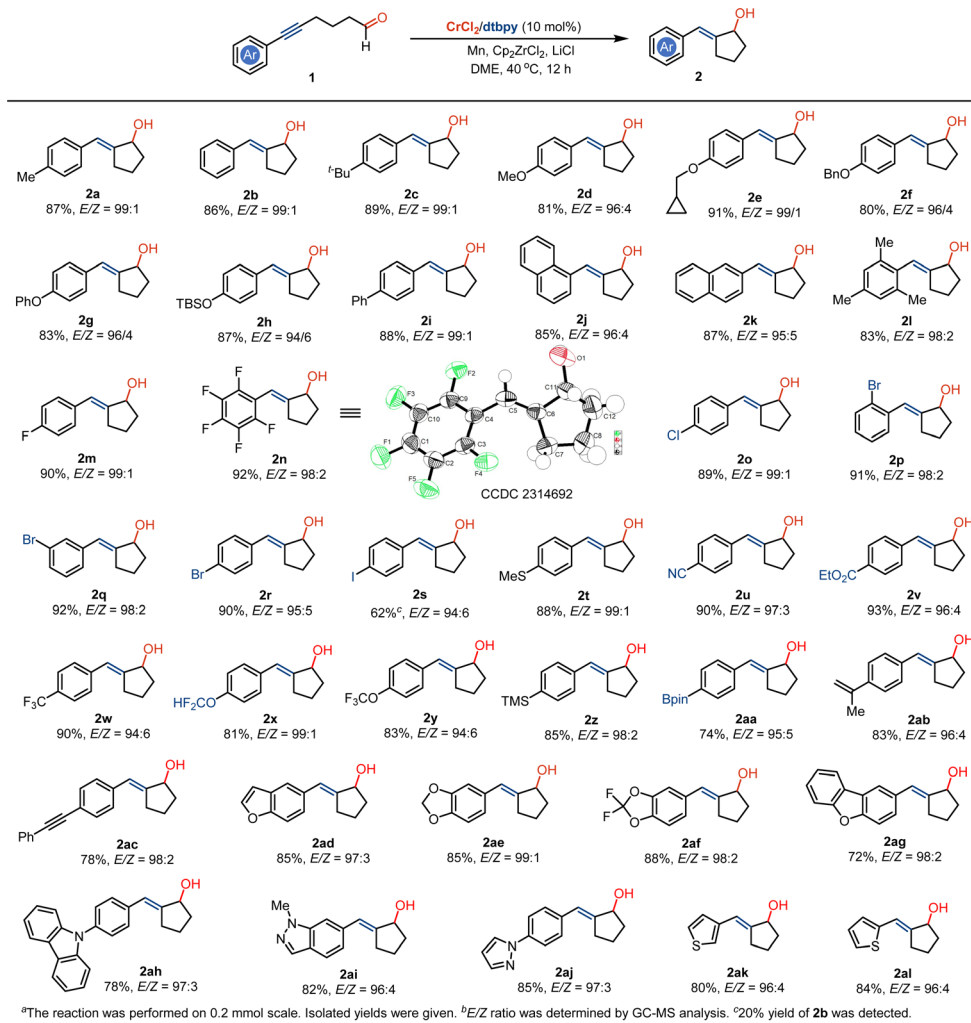


Fig. 1 Studying the effect of metal salts and ligands on ketyl coupling to produce *E*-exocyclic allyl alcohol.

dtbpy ligand, the ketyl radical coupling with the alkyne could almost not proceed with Cr catalysis. The use of bipyridine (bpy) as a ligand resulted in a relatively low conversion and *E/Z*-selectivity, as well as the replacement by ligands, such as 4,4'-dimethyl-2,2'-dipyridyl (dmbpy), 4,4'-dimethoxy-2,2'-dipyridyl (dmobpy) and terpyridine (tpy). In the absence of Mn or Cp₂ZrCl₂, the ketyl coupling reaction does not occur in almost complete recovery of **1a**, indicating their important roles in promoting the transformation. The reaction by the replacement of Mn by Zn or Mg produces product **2a** in low yields (see ESI[†]), whereas the conversion is completely inhibited using Al as a reductant.

Having optimal reaction conditions in hand, we examined the scope of the radical coupling using diverse substituted alkynyl aliphatic aldehydes. As shown in Scheme 2, the treatment of 5-hexynals that contain electron-donating substituents, such as *tert*-butyl, methoxy, cyclopropylmethoxy, benzyloxy, phenoxy and *tert*-butyldimethylsilyloxy on aryls by dtbpy-ligated Cr(II) catalysis enables the formation of annulated (*E*)-2-benzylidene-cyclopentanol motifs **2c-h** in 81–91% yields and 94 : 6–99 : 1 stereoselectivities. The incorporation of electron-withdrawing groups of phenyl and naphthyl into the alkynyl does not affect the coupling reaction and provides access to (*E*)-(biphenyl-4-ylmethylene)cyclopentanol **2i** and (*E*)-(naphthylmethylene)cyclopentanol (**2j** and **2k**) in good yields and high stereoselectivities. It was noted that the steric hindrance caused by the mesityl substituent around the alkynyl does not impede annulated coupling and produces the sterically congested compound **2l**. Due to the mild conditions with Cr(II) catalyst and manganese reductant, halogen substituents, such as fluoride, polyfluoride, chloride, bromide, and iodide can be effectively compatible with the coupling system, providing a valuable strategy in the preparation of various halide-bearing 2-methylenecyclopentanol (**2m–2s**). It was noted that the thio group on the aryl of 5-hexynal does not hinder the catalysis, offering a strategy in the synthesis of product **2t**. Using this methodology, 2-methylenecyclopentanol containing a range of

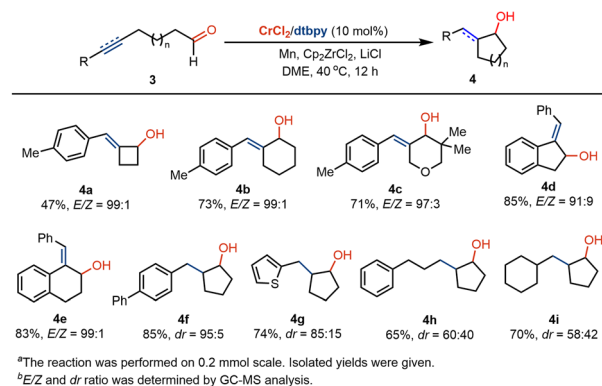


Scheme 2 Cr(II)-catalyzed ketyl radical coupling reactions with alkynyl aliphatic aldehydes.^{a,b}

synthetically useful groups, such as cyano, alkoxy, trifluoromethyl, trifluoromethoxy, trimethylsilyl, boronate ester, alkenyl and alkynyl groups can be readily accessible (**2u–2ac**). In addition, the reaction can be employed in the synthesis of methylenecyclopentanol derivatives that contain a range of heterocycle functional groups, such as benzofuranyl, dibenzo[*b,d*]furanyl, benzo[*d*][1,3]dioxol, 2,2-difluorobenzo[*d*][1,3]dioxol, 9*H*-carbazolyl, 1*H*-indazolyl, 1*H*-pyrazolyl and thiophenyl groups (**2ad–2al**).

Inspired by these results, we examined whether the radical coupling could be applied in the construction of four- and six-membered ring-containing cyclitols. Using 4-pentynal as a precursor, we were pleased that the four-member ring-based exocyclic butanol **4a** was obtained in moderate yields and high *E*-selectivity (Scheme 3). The treatment of 6-heptynal with Cr catalysis delivers six-membered (benzylidene)cyclohexanol in 73% yield and 99 : 1 *E/Z* selectivity (**4b**). The use of oxygen moiety as a linker in the radical coupling of alkynyl alcohol does not affect the conversion, offering a strategy in the formation of exocyclic tetrahydro-2*H*-pyranol **4c**. Moreover, benzylidene-based 2,3-dihydro-1*H*-indenol and 1,2,3,4-tetrahydronaphthol

motifs **4d** and **4e** can be prepared at ambient temperatures. In addition to the coupling with the alkyne, we wondered whether the ketyl radical coupling reaction with olefin could occur with Cr catalysis. By the use of alkenyl-substituted aliphatic

Scheme 3 Application in the formation of cyclobutanols, cyclopentanol and cyclohexanol derivatives.^{a,b}

aldehydes as precursors, we found that corresponding saturated five-membered cyclopentanol **4f–4i** were formed in moderate-to-good diastereoselectivity.

To gain insight into the reaction pathway, mechanistic experiments were performed. By the addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a radical scavenger into the reaction system, we found that the coupling was completely inhibited without the production of related compound **2a** (Fig. 2a). The analysis of the residue by the high-resolution mass spectrum (HRMS) technique suggested that the TEMPO-trapped compound **5a** or **5b** might be formed. Interestingly, the replacement of TEMPO by 1,1-diphenylethylene in the reaction led to the formation of dialkynyl-containing diol **6** in 20% yield, combined with a small amount of adduct **7** by the addition of aldehyde to olefin. These results indicate that the formation of the ketyl radicals could be considered in the reaction. The experiments of cyclic voltammetry (CV) were carried out to study the activation of carbonyl by Cr catalysis. A high reduction potential for 5-hexynal **1a** ($E_p = -2.46$ V) was observed (Fig. 2b). The coordination with the dtbpy ligand leads to the promotion of the reduction potential of CrCl_2 ($\text{CrCl}_2/\text{dtbpy}$; $E_p = -1.70$ V). Interestingly, the combination of the $\text{CrCl}_2/\text{dtbpy}$ complex with **1a** leads to a great decrease in the reduction potential of **1a**

($E_p' = -1.80$ V) with the increased potential of the complex ($E_p = -1.80$ V). It indicates that the coordination of $\text{CrCl}_2/\text{dtbpy}$ with **1a** might promote the reduction process in giving the related ketyl radical. Subsequently, we explored the source of hydrogen in the vinyl scaffold of **2a**. By the addition of 3.0 equivalent D_2O in the reaction, we found that the coupling occurs smoothly to afford the compound **2a** in 61% yield, with the incorporation of around 76% of deuterium into the vinyl group (Fig. 2c). The related metalated vinyl intermediate may be formed during the process. We explored related intermediates in the stoichiometric reaction by HRMS analysis (Fig. 2d). Both the vinylated chromate species **IN-4** that contained the Cp_2ZrCl moiety and oxazirconiumacycle **IN-5** were detected, indicating that the ketyl radical coupling with the alkynyl, followed by combination with dtbpy-Cr(II) , might be considered, which may undergo a transmetalation process by a further reaction with Cp_2ZrCl_2 in forming oxazirconiumacycle.

Based on the preliminary results and studies of Cr/Zr-catalyzed organic transformations,^{10e-k} we hypothesized that the reaction is initiated by a single electron transfer process between dtbpy-Cr complex and **1a**, resulting in the formation of ketyl radical **IN-1** (Scheme 4). It may deliver the related vinyl radical **IN-2** by the process of annulation and transmetalation with Cp_2ZrCl_2 to produce **IN-3** and the $(\text{dtbpy})\text{Cr(III)}$ complex. The reactive Cr(II) catalyst can be regenerated by reduction with manganese and combination with vinyl radical by transmetalation between $(\text{dtbpy})\text{Cr(III)}$ and Zr species to produce oxazirconiumacycle **IN-5**. Exocyclic *E*-allyl alcohol compound **2a** is formed by following the work-up process.

The Cr-catalyzed ketyl radical coupling reaction can be conducted on a gram-scale without loss of efficiency, giving exocyclic *E*-allyl alcohol products with high stereoselectivity (Scheme 5a). We investigated the late-stage functionalization of the resulting exocyclic allyl alcohol in the preparation of valuable motifs. By oxidation using the Dess–Martin reagent, α,β -unsaturated ketone **8** can be easily accessed, which reacts with vinyl Grignard reagent to afford vinylcyclopentanol **9** in good

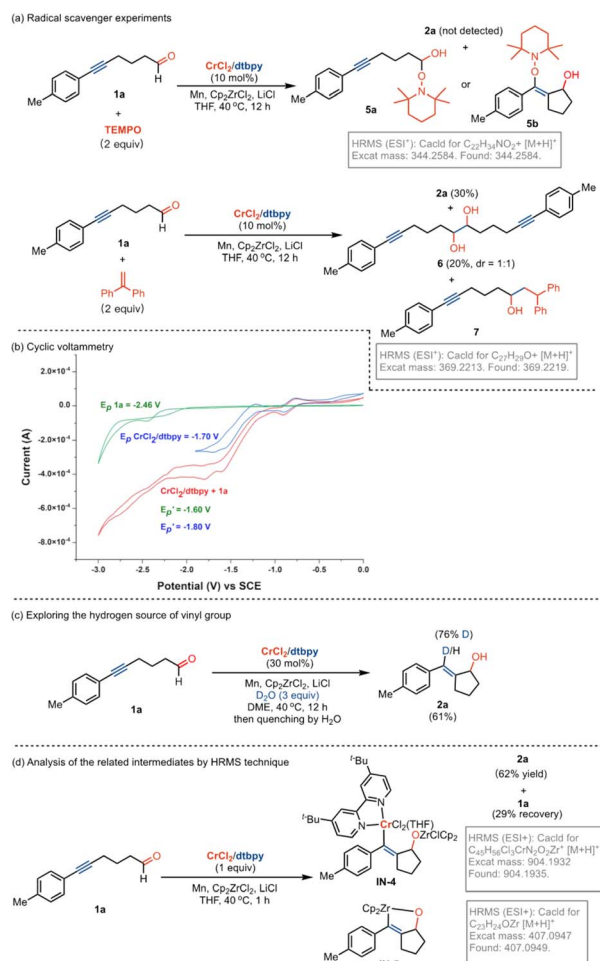
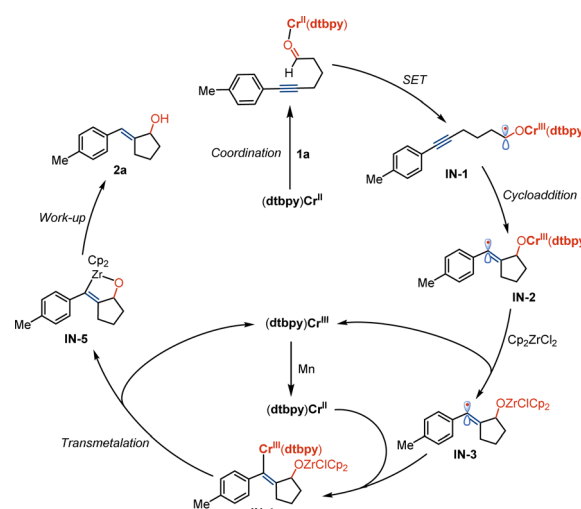
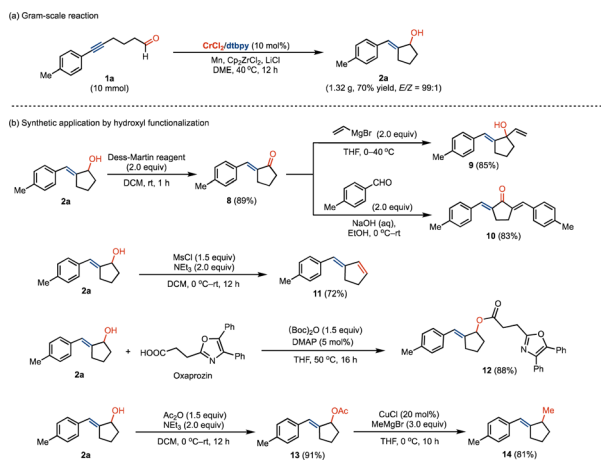


Fig. 2 Mechanistic studies.



Scheme 4 Presumed reaction pathway.





Scheme 5 Gram-scale reaction and late-stage functionalization.

yields (Scheme 5b). The reaction of **8** with benzaldehyde led to the formation of functionalized bis(benzylidene)cyclopentanone motif **10**. By the elimination of the hydroxyl group, the related 1,3-diene compound **11** could be obtained in 72% yield. The hydroxyl scaffold can be facilely functionalized in accessing the pharmaceutical compound of oxaprozin (**12**) by esterification. In addition, the transformation of the hydroxyl group by sequential esterification and methylation allowed us to prepare the methylated derivative **14**.

Chiral exocyclic pentanols are synthetically intriguing motifs that serve as core structures and are widely found in numerous biologically active molecules and pharmaceuticals.¹¹ As a result, the development of asymmetric catalysis in the stereoselective construction of these motifs is of significant interest.¹² To probe the possibility of developing the Cr-catalyzed asymmetrical ketyl radical coupling, we studied the effect of chiral ligands on the transformation of enantioselective formation of chiral exocyclic allyl alcohols. As shown in Scheme 6, the use of chiral *tert*-butyl-

substituted bis(oxazoline) ligand of **L1**, we found that the ketyl radical coupling occurs smoothly, leading to the formation of the product (**R**)-**2a** in 62% yield and 48% value of enantiomeric excess (ee). The replacement of dimethyl substituents by cyclopropanyl or methylbenzyl in the linker does not strongly promote enantioselectivity with Cr catalysis (**L2** and **L3**). The reaction used phenyl-substituted bis(oxazoline) **L4** to form the product (**R**)-**2a** with a good yield and ee value. Further studies suggested that the change of substituents of the linker and oxazolanyl groups did not greatly improve the transformation (**L5**–**L13**). While the incorporation of quinolinyl or pyridinyl as coordination groups into oxazoline (**L14** and **L15**) led to relatively low conversions and enantioselectivity.

Conclusions

In summary, we have developed a chromium-catalyzed ligand-enabled ketyl radical formation in coupling with the alkynes. This reaction was initiated by a bipyridine-supported Cr(II) catalyst for the generation of the ketyl radicals for alkyne hydrofunctionalization, offering a stereo- and chemoselective strategy in the synthesis of valuable *E*-exocyclic allyl alcohols. Because of mild catalytic conditions, a range of synthetically useful functionalities, including iodide, bromide, chloride, fluoride, cyano, amino, alkoxy-carbonyl, alkynyl, and olefin groups, can be compatible with reaction systems. Compared with previous reports using strong reductants, this reaction employs (dtbbpy)Cr(II) catalyst as a mild reagent to reduce aldehydes to the ketyl radicals, by the annulation and transmetalation with Cp₂ZrCl motif in giving oxazirconiumacycle species. Formed exocyclic allyl alcohol derivatives can be modified by hydroxyl functionalization in the construction of various synthetically useful molecules. Further improvement is underway in the enantioselectivity for the development of asymmetric ketyl radical coupling reaction by Cr catalysis.

Data availability

Experimental details and characterization of the products are available in the ESI.†

Author contributions

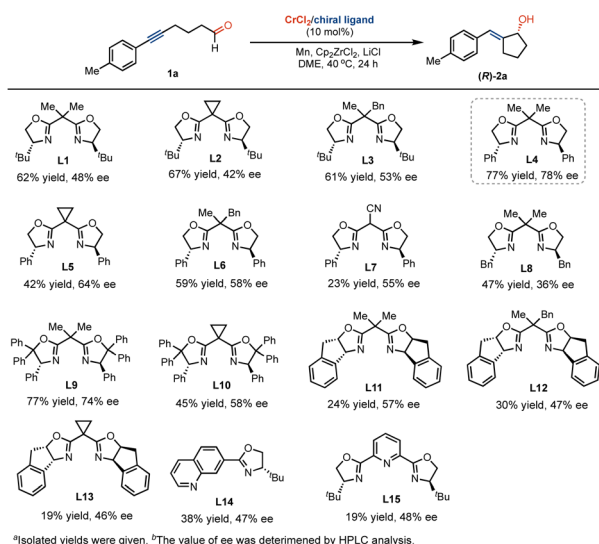
X. Zeng conceived and directed the overall research project. Z. Luo, X. Zhang, and Z. Li designed and conducted the experimental studies. Z. Luo, M. Luo, and X. Zeng analyzed the data and contributed to the preparation of the manuscript. X. Zeng wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Scheme 6 Exploration of Cr-catalyzed asymmetric ketyl radical coupling reaction.^{a,b}

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