ACS Catalysis

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Cr-Catalyzed Regio-, Diastereo-, and Enantioselective Reductive Couplings of Ketones and Propargyl Halides

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Cite This: *ACS Catal.* 2023, 13, 3170−3178 Read Online

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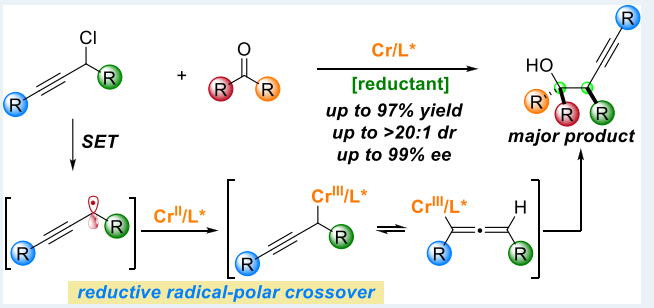
ABSTRACT: Enantioconvergent reductive couplings of racemic alkyl halides with carbonyl compounds provide efficient access to valuable chiral alcohols, especially those bearing vicinal stereocenters. However, limited success has been achieved due to the challenging reactivity and stereoselectivity control. Herein, we developed the Cr-catalyzed asymmetric reductive coupling of racemic propargylic chlorides and ketones, affording valuable chiral tertiary alcohols bearing vicinal stereocenters. These reactions proceed efficiently under mild conditions in a radical−polar crossover manner with good regio-, diastereo-, and enantioselectivity control. Preliminary mechanistic studies, including radical trapping, nonlinear effect, and UV−vis spectroscopy, provide insights into the radical-involved catalytic cycle. DFT calculations suggest that the regio- and stereoselectivity are determined by the Zimmerman−Traxler-type ketone addition transition states under Curtin−Hammett conditions.



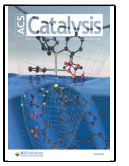
KEYWORDS: *radical−polar crossover, enantioconvergent coupling, asymmetric propargylation, chromium catalysis, chiral tertiary alcohol*

Transition-metal-catalyzed enantioconvergent cross-couplings of racemic alkyl electrophiles emerged as pivotal strategies in organic synthesis and pharmaceuticals.[1] During the past two decades, great breakthroughs have been achieved in the asymmetric cross-couplings of sp^3 carbons with predominantly late-3d transition-metal catalysts, including Ni, Cu, Co, Fe, etc. (Figure 1a).[1a,b,2,3] These cross-couplings provide facile access to sp^3-hybridized stereocenters from readily available starting materials. Mechanistically, transient alkyl radicals are involved in the reaction process. Despite the potential difficulty in reactivity and selectivity control, the radical nature could endow these reactions with the ability to construct complex molecules in an enantioconvergent manner under mild conditions.[4] Carbonyl compounds are readily available and broadly applied in organic synthesis. Practically, the catalytic enantioconvergent reductive couplings of alkyl electrophiles with carbonyl compounds represent attractive strategies, providing efficient access to chiral alcohols bearing vicinal stereocenters (Figure 1a). However, despite recent elegant reports on radical-involved carbonyl additions,[5] only limited success has been achieved. Significant challenges are as follows: (1) direct alkyl radical addition to a carbonyl group is thermodynamically disfavored due to the generation of an unstable oxygen-centered radical and (2) simultaneously controlling the diastereoselectivity and enantioselectivity during this carbon−carbon bond construction remain a prominent challenge.

Radical−polar crossover recently emerged as a powerful strategy in synthetic chemistry.[6] This strategy features an elementary step of turning the radical intermediate into an electrophile or nucleophile via further single-electron transfer and thus could combine the advantages of both radical and two-electron chemistry.[6a] Notably, it provides a potential solution for the asymmetric reactions between alkyl radicals and carbonyl compounds via the formation of a nucleophilic chiral alkyl metal complex (Figure 1a). In this context, precise control of the reactivity of the proposed alkyl metal complex and the stereoselectivity of the nucleophilic addition to carbonyl compounds must be achieved. As such, further endeavors toward catalytic asymmetric reactions via radical−polar crossover could find broad applications in efficient chiral alcohol synthesis and thus are in high demand.

Chiral tertiary alcohols and their derivatives widely occur in complex natural products and pharmaceuticals (Figure 1b).[7] Consequently, extensive efforts have been devoted to their synthesis.[8] Specifically, asymmetric nucleophilic addition to ketones represents one of the most straightforward and privileged strategies. However, ketones typically exhibit increased steric hindrance and attenuated electrophilicity compared to aldehydes. Additionally, when synthesizing chiral

Received: January 12, 2023
Revised: February 11, 2023
Published: February 17, 2023



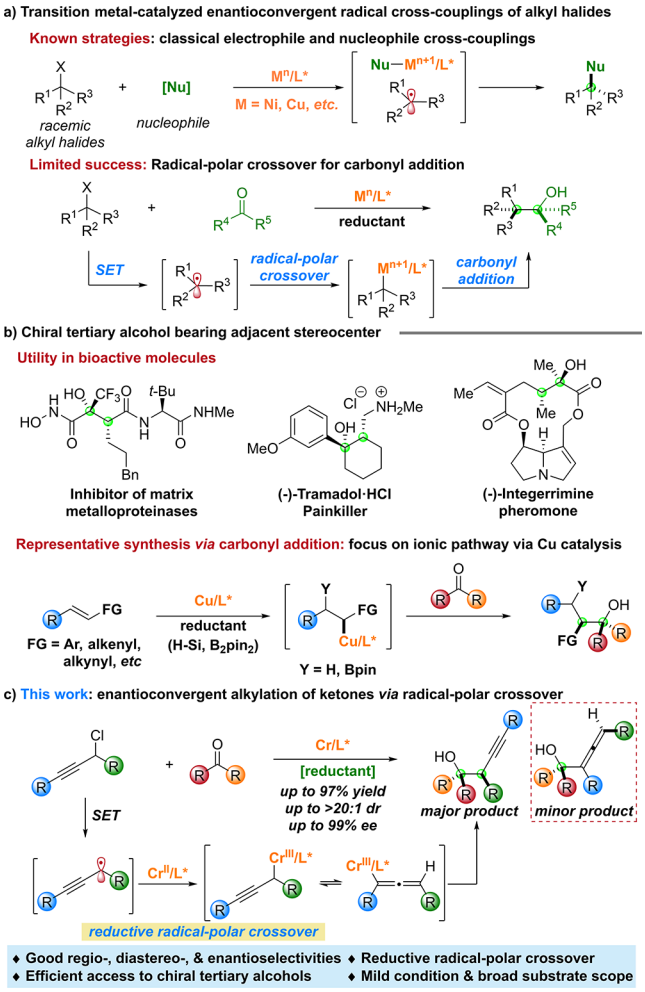
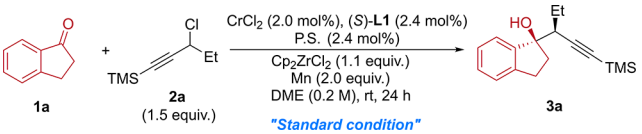


Figure 1. Research background.

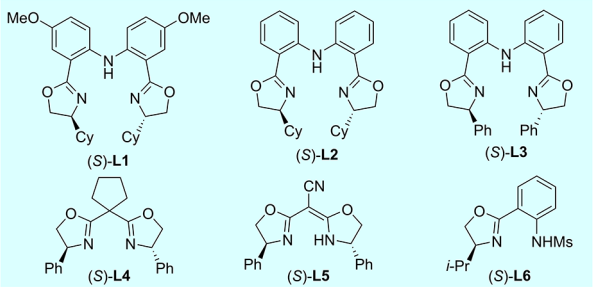
tertiary alcohols bearing vicinal stereocenters, the diastereoselectivity control raises the challenge immensely. Early reports mainly focused on asymmetric addition to ketones with stoichiometric amounts of organometallic reagents via chiral auxiliaries or Lewis acid catalysis and typically constructed a single stereocenter.[8a−c] Recently, elegant methods were developed, especially the Cu-catalyzed reductive couplings of olefins with ketones, to achieve the efficient construction of vicinal stereocenters (Figure 1b).[9,10] However, these reactions primarily proceed via a two-electron pathway. In sharp contrast, the radical-involved method of synthesizing tertiary alcohols bearing vicinal stereocenters remains elusive. In spite of the transient nature, radical chemistry proves to be privileged for the efficient construction of complex molecules stereoselectively under mild conditions. In this context, radical-involved asymmetric carbonyl additions could significantly expand the chemical space of chiral tertiary alcohols.

We recently became interested in the development of radical-involved asymmetric carbonyl additions via Cr-catalyzed radical−polar crossover.[11] With the success of secondary alkyl radical-involved asymmetric additions to aldehydes, we anticipate that ketones might act as suitable substrates in these catalytic systems. Indeed, elegant reports from the Sigman, Chen, and Connell groups described the Cr-catalyzed asymmetric allylation or propargylation of ketones to afford enantioenriched tertiary alcohols.[12,13] However, these studies predominantly focused on using primary alkyl halides

Table 1. Effect of Reaction Parameters on the Enantioconvergent Propargylation of Ketones



Entry	Variation from "Standard condition"	Yield (%)[b]	dr[b]	ee (%)[c]
1	none	98	>20:1	99
2	no $CrCl_2$	<3	-	-
3	no ligand	39	>10:1	rac.
4	no P.S.	88	>20:1	93
5	2.4 mol% NEt_3, instead of P.S.	92	>20:1	99
6	1.0 mol% $CrCl_2$, 1.2 mol% (*S*)-**L1**, 2.4 mol% P.S.	94	>20:1	99
7	(*S*)-**L2**, instead of (*S*)-**L1**	77	>20:1	91
8	(*S*)-**L3**, instead of (*S*)-**L1**	40	>20:1	71
9	(*S*)-**L4**, instead of (*S*)-**L1**	95	7:1	50
10	(*S*)-**L5**, instead of (*S*)-**L1**	<3	-	-
11	(*S*)-**L6**, instead of (*S*)-**L1**	87	4:1	12
12	1.1 equiv. TMSCl, instead of Cp_2ZrCl_2	48	>20:1	98
13	Zn, instead of Mn	93	>20:1	6
14	THF, instead of DME	88	>20:1	98
15	MeCN, instead of DME	45	2:1	83
16	0.1 M, instead of 0.2 M, in DME	96	>20:1	99
17	1.0, instead of 1.1 equiv. Cp_2ZrCl_2	96	>20:1	99
18	1.2, instead of 1.5 equiv. **2a**	96	>20:1	95
19	1.0 mL air, added through syringe	73	>20:1	99
20	with 1.0 equiv. H_2O	<3	-	-



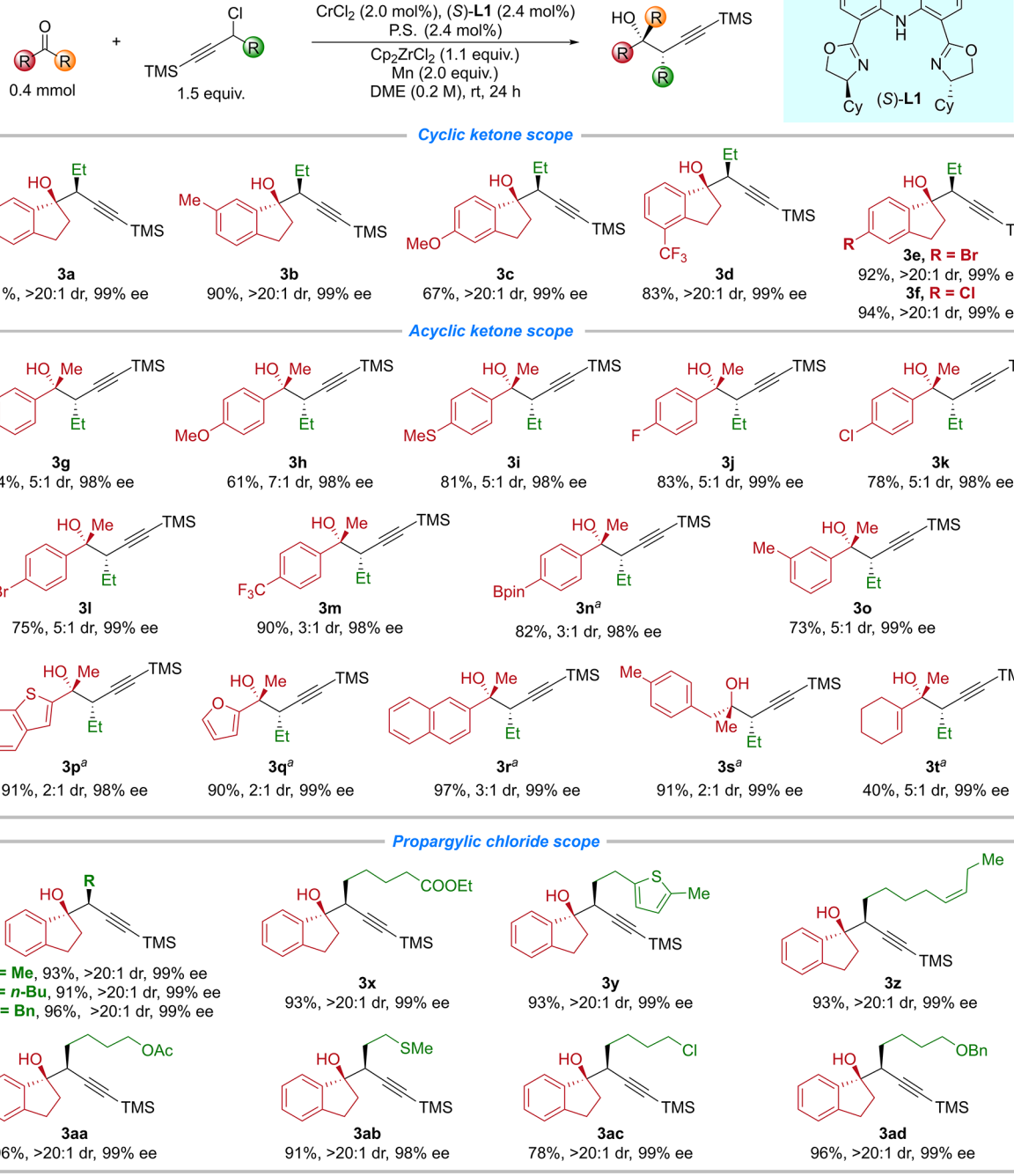
[a]Reactions were performed under a N_2 atmosphere, and conditions are as follows: **1a** (0.2 mmol), **2a** (0.3 mmol), 1.0 mL of DME, $CrCl_2$ (2.0 mol%), ligand (2.4 mol%), proton sponge (P.S.) (2.4 mol%), Cp_2ZrCl_2 (0.22 mmol), and Mn (0.4 mmol). [b]Yield and dr were determined *via* ^1H NMR analysis of the reaction mixture with CH_2Br_2 as the internal standard. [c]ee was determined *via* HPLC analysis.

for single-stereocenter construction. Notably, secondary alkyl electrophiles are easily accessible, and their reaction with ketones provides efficient access to tertiary alcohols bearing vicinal stereocenters. Nevertheless, the decreased stability of secondary alkyl Cr complexes and the difficulty in controlling the stereoselectivity of the vicinal stereocenters restrict further development in this direction. Herein, we describe the Cr-catalyzed enantioconvergent reductive couplings of ketones with racemic propargyl chlorides via a radical−polar crossover manner (Figure 1c). Distinct from the previous report,[11a] homopropargylic alcohols, rather than allenols, are afforded in good regio-, diastereo-, and enantioselectivities. This methodology features mild conditions, a broad substrate scope, and good functional group compatibility.

We initially explored the reductive coupling of 1-indanone (**1a**) and the propargylic chloride **2a**. After evaluating various

https://doi.org/10.1021/acscatal.3c00177
ACS Catal. 2023, 13, 3170−3178

Scheme 1. Substrate Scope of Ketones and Propargylic Chlorides[b]

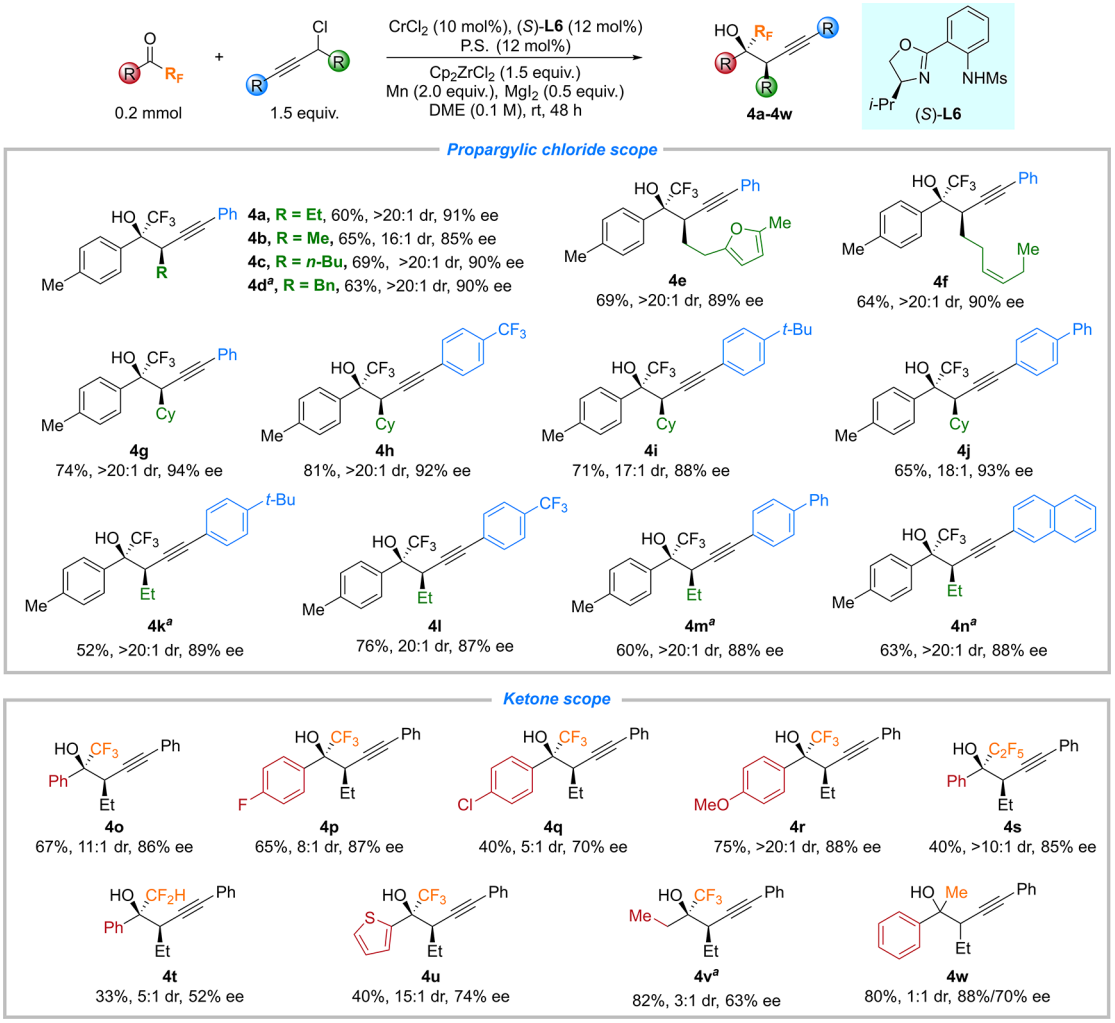


[a]48 h reaction time. [b]All the data are the averages of two experiments, and the yields are the sums of both diastereomers (<10:1 dr). The dr's are determined *via* ^{1}H NMR analysis of the crude material.

reaction parameters, we determined that a chiral chromium/diarylamine bis(oxazoline)[14] **L1** in a 2 mol% loading could achieve the stereoselective homopropargylation of ketones in a good yield and high regio-, diastereo-, and enantioselectivities at room temperature with Mn dust as the reductant and Cp_2ZrCl_2 as the dissociation reagent (98% yield, >20:1 dr, 99% ee, Table 1, entry 1). Control experiments revealed that both $CrCl_2$ and **L1** were critical for this enantioconvergent propargylation (entries 2 and 3, respectively). The proton sponge could facilitate the coordination of **L1** to chromium. The reaction proceeded with a slight decrease in efficiency in the absence of the proton sponge (entry 4). Additionally, triethylamine could be used as the base instead of the proton sponge (entry 5). Notably, the model reaction proceeded smoothly with 1.0 mol% catalyst loading in high stereoselectivity (entry 6). Using diarylamine bis(oxazoline) ligands **L2** and **L3**, the desired chiral alcohol **3a** was afforded in a decreased yield with lower enantioselectivity (entries 7 and 8, respectively). Other families of nitrogen-containing chiral ligands were also tested,[15] but they were not effective for

https://doi.org/10.1021/acscatal.3c00177
ACS Catal. 2023, 13, 3170−3178

Scheme 2. Substrate Scope of Fluorinated Ketones and Propargylic Chlorides[b]



[a]The reaction was performed with 1.0 equiv of MgI_2 in a 0.2 M concentration. [b]All the data are the averages of two experiments, and the yields are the sums of both diastereomers (<10:1 dr). The dr's are determined *via* ^{1}H NMR analysis of the crude material.

this transformation under similar conditions (entries 9−11). Using TMSCl as the dissociation reagent led to a diminished yield (entry 12). Using Zn as the reductant resulted in poor enantioselectivity control (entry 13). The reaction also performed well in THF, with a comparable yield and stereoselectivity (entry 14), but was inefficient in CH_3CN, with a moderate yield and poor diastereoselectivity (entry 15). It is noteworthy that the outcome is only modestly diminished if 1.0 equiv of Cp_2ZrCl_2 or 1.2 equiv of **2a** is used or 1.0 mL of air is added (entries 16−18, respectively).

With optimal conditions in hand, we next evaluated the substrate scope of this enantioconvergent propargylation of ketones (Scheme 1). A broad array of indanone derivatives and acyclic ketones serve as suitable reaction partners, providing the chiral tertiary alcohols bearing vicinal stereocenters in high yields and good regio-, diastereo-, and enantioselectivities (**3a**−**3t**). Various functional groups are compatible under the optimal conditions, including an aryl halide (*e.g.*, F, Cl, and Br), thioether, boronate, benzothiophene, furan, naphthalene, and cyclohexene. We found that using acyclic ketones generally led to diminished diastereoselectivity compared to indanone derivatives, probably due to the increased flexibility of acyclic ketones and difficulty in differentiating the stereoface. With respect to alkyl halides, the scope is also fairly broad (**3u**−**3ad**). Various racemic propargylic chlorides bearing different functionalized alkyl chains reacted efficiently with 1-indanone to furnish the desired chiral alcohols in high yields and excellent stereoselectivities. Notably, the terminal substituent on the alkyne is critical for the reaction efficiency and stereoselectivity. Under the optimal condition, increasing the steric hindrance (e.g., switching to TES or TBS) was detrimental to the reaction yield, and using terminal alkyl or aryl substituents decreased the enantioselectivity (see Scheme S1 in the Supporting Information for details).

Fluorine-containing compounds have broad applications in pharmaceuticals, agriculture, and material science primarily due to the unique property of fluorine atoms.[16] Thus, there has been growing interest in synthesizing fluorinated organic molecules, especially in a stereoselective manner.[17] With this context, we next tested trifluoromethyl ketones under the optimal condition in Table 1, which could afford the desired homopropargylic alcohols high regioselectively but in moderate yield and ee. Upon further condition optimization (see Table S2 in the Supporting Information for details), we determined that a chromium complex with the Kishi-type ligand **L6** could catalyze the reductive coupling of propargylic

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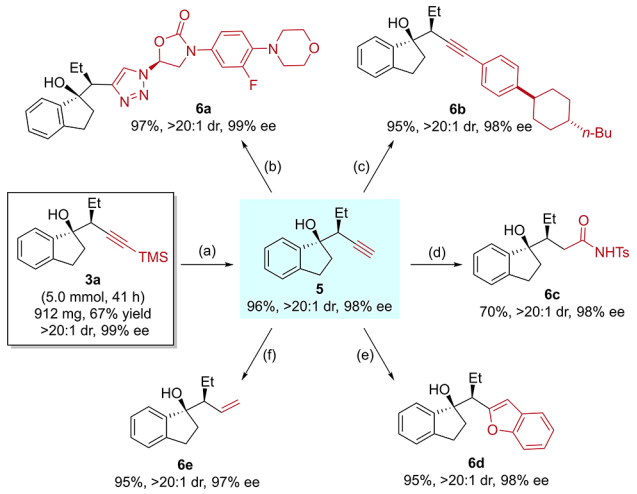

Figure 2. Representative product transformation. (a) K_2CO_3 (5.0 equiv.), MeOH, rt, 3 h. (b) CuTC (0.1 equiv.), (*S*)-5-azido-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (1.1 equiv.), toluene, 50 °C, 16 h. (c) 1-((1*S*,4*R*)-4-Butylcyclohexyl)-4-iodobenzene (1.3 equiv.), $Pd(PPh_3)Cl_2$ (0.04 equiv.), CuI (0.2 equiv.), TMG (3 equiv.), toluene, 80 °C, 12 h. (d) TsN_3 (1.2 equiv.), H_2O (2.5 equiv.), CuI (0.1 equiv.), NEt_3 (1.2 equiv.), $CHCl_3$, rt, 12 h. (e) *o*-Iodophenol (1 equiv.), $Pd(PPh_3)Cl_2$ (0.04 equiv.), CuI (0.2 equiv.), TMG (3 equiv.), 80 °C, 13 h. (f) H_2, $Pd/CaCO_3$ (0.05 equiv.), quinoline (1.4 equiv.), hexane, rt, 3 h.

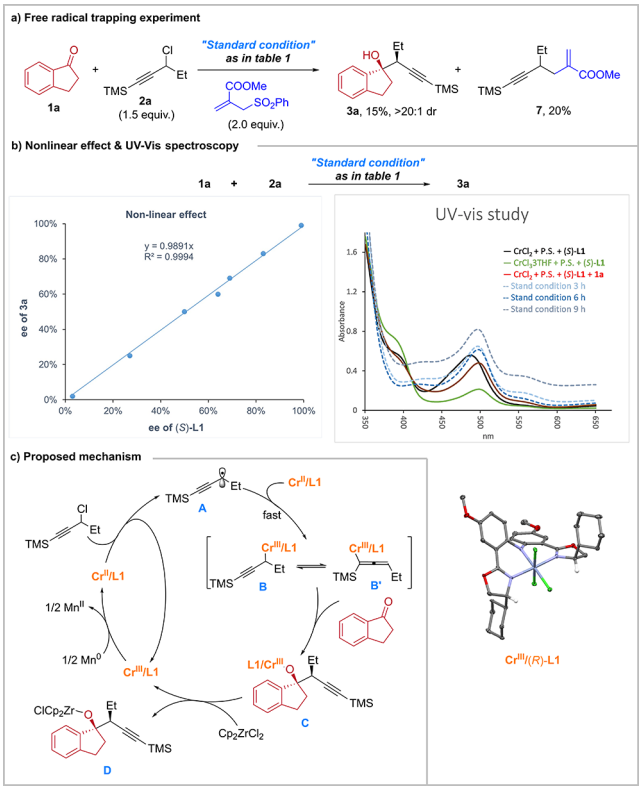

Figure 3. Preliminary mechanistic study and proposed catalytic cycle

chlorides and trifluoromethyl ketones efficiently in moderate to good yields and stereoselectivities (Scheme 2). The regioselectivity is excellent, with the predominant formation of homopropargylic alcohols, instead of allenols, bearing vicinal stereocenters. The substrate scope is relatively broad and possesss good compatibility with various functional groups, including furan, thiophene, internal olefin, CF_3, and naphthalene. Furthermore, with respect to the propargyl chlorides, the alkyl chain could also vary in steric hindrance from Me, Et, and Bn to Cy (**4a**, **4b**, **4d**, and **4g**, respectively). However, switching the terminal aryl group of propargylic chlorides to TMS, *n*-Bu, or H is detrimental to the stereoselectivity (see Scheme S2 in the Supporting Information for details). When exploring the ketone scope, we found that using aryl trifluoromethyl ketone with a *para*-electron-withdrawing substituent led to attenuated stereoselectivity (**4q**). Varying the CF_3 to CF_2H or C_2F_5 in the ketone could afford the desired propargylation product but in a diminished yield and ee (**4s** and **4t**), probably due to the electron property change of the carbonyl group. Trifluoromethyl alkyl ketones also demonstrate good reactivity under optimal conditions with moderate dr and ee (**4v**). However, when using acetophenone as the reaction component, the desired product **4w** was isolated in a good yield and regioselectivity but poor diastereoselectivity, which indicated the essential role of CF_3 for stereoselectivity control in these reductive couplings. Despite these issues in the substrate scope study, this method provides efficient access to complex chiral tertiary alcohols bearing a CF_3 from readily available starting materials, might find related applications in pharmaceuticals and inspire asymmetric synthesis in a radical−polar crossover manner.

The chiral products were readily converted into other useful families of enantioenriched compounds to demonstrate their synthetic utility (Figure 2). Alkynes serve as highly privileged synthons that are easily elaborated into a broad array of valuable functionalized structures.[18] The model reaction in Table 1 could be directly scaled up in good efficiency (0.912 g, 67% yield, >20:1 dr, 99% ee). After removing the TMS protecting group under basic conditions, the terminal alkyne **5** could be engaged in [3 + 2] cycloaddition[19] (**6a**) or a Sonogashira reaction (**6b**), transformed into an amide (**6c**)[20] or a benzofuran derivative (**6d**),[21] or reduced to an alkene (**6e**). Notably, all these transformations proceeded efficiently without the loss of diastereomeric or enantiomeric excess.

Mechanistic experiments were conducted to provide insights into the reaction pathway (Figure 3). The addition of 2.0 equiv of allyl sulfone to the model reaction under optimal conditions resulted in a racemic adduct **7** in 20% yield, also with the isolation of desired product **3a** in a 15% yield, which indicated the generation of a propargyl radical during the reaction process (Figure 3a). Next, a linear relationship was observed between the enantiopurity of the ligand **L1** and that of the corresponding chiral tertiary alcohol, which suggests that only a monomeric chromium complex bearing a single chiral ligand is involved in the stereodetermining step (Figure 3b, left). An X-ray crystallographic study of $Cr^{III}Cl_3$/(*R*)-**L1** disclosed an octahedral chromium complex (Figure 3b). The UV−vis spectrum of $CrCl_3$·3THF/(*S*)-**L1**/proton sponge dissolved in DME exhibited an absorption feature at 498 nm, which was slightly different from that of the Cr^{II} complex (487 nm). Additionally, the UV−vis spectrum of the coupling reaction in progress reveals a similar absorption feature as that of Cr^{III}/(*S*)-**L1**, which suggests that the predominant resting state of the catalyst might be a Cr^{III} complex (Figure 3b, right). Based on these preliminary results and previous reports,[11a,22] a plausible catalytic cycle is proposed (Figure 3c). The halogen atom transfer between Cr^{II}/**L1** and the propargyl chloride initiates the reaction, which generates the corresponding reactive propargyl radical **A**. Subsequent radical capture via

https://doi.org/10.1021/acscatal.3c00177
ACS Catal. 2023, 13, 3170−3178

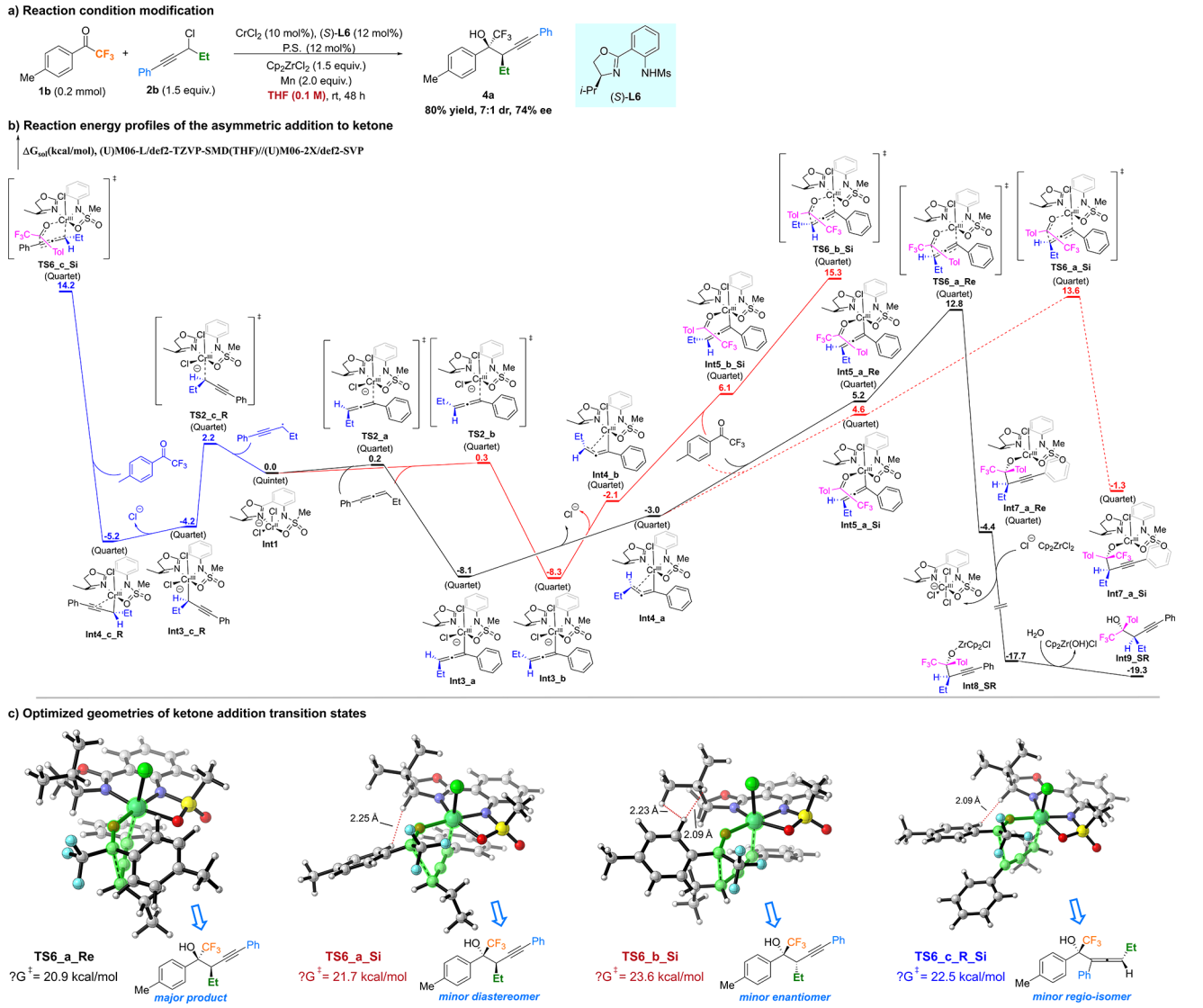

Figure 4. DFT-calculated Gibbs free-energy profiles of the Cr-catalyzed reaction between ketone **1b** and propargyl chloride **2b** at the (U)M06-L/def2-TZVP-SMD(THF)//(U)M06-2X/def2-SVP level of theory.

single-electron reduction by Cr^{II}/**L1** furnishes the nucleophilic propargyl Cr^{III}/**L1** complex **B**, which is proposed to be in equilibrium with allenyl Cr^{III}/**L1** complex **B′** via isomerization or a C−Cr bond homolysis and radical recombination process.[23] The distinct propargylation regioselectivity might be largely due to the increased steric hindrance and decreased electrophilicity of ketones in comparison to aldehydes. Thus, the nucleophilic attack to 1-indanone from intermediate **B′** affords the enantioenriched propargylation adduct **C**, and this elementary step is believed to proceed via a six-membered cyclic transition state. The dissociation of the Cr−O bond in intermediate **C** by Cp_2ZrCl_2 generates **D**, which is driven by the formation of a strong Zr−O bond. Further Zr−O bond hydrolysis in **D** provides the desired chiral tertiary alcohol. The reduction of Cr^{III}/**L1** by manganese powder regenerates Cr^{II}/**L1** and closes the catalytic cycle.

To further explore the origins of the regio- and stereoselectivity control, density functional theory (DFT) calculations were carried out to study the free-energy profiles of the reaction between **1b** and **2b** with (*S*)-**L6** as the chiral ligand (see the Supporting Information for computational methods). To simplify the DFT calculation, we adjusted the optimal conditions in Scheme 2. We found that the reaction proceeded with slightly lower efficiency in the absence of MgI_2 (see Table S2 in the Supporting Information for details). We speculate that MgI_2 might serve as a Lewis acid to activate the ketone in the asymmetric propargylation step. However, related control studies were inconclusive. This reductive propargylation was also operable in THF without MgI_2 (80% yield, 7:1 dr, 74% ee), which was used for DFT calculations (Figure 4a). Consistent with the proposed mechanism in Figure 3c, the four calculated reaction pathways all feature a radical−polar crossover mechanism and asymmetric ketone addition (Figure 4b). Our calculations reveal that the interconversion among the allenyl and propargyl Cr complexes (**Int3_a**, **Int3_b**, **Int4_a**, **Int4_b**, **Int3_c_*R***, and **Int4_c_*R***) is kinetically facile. Thus, under the Curtin−Hammett conditions, the regio-, diastereo-, and enantioselectivity are determined by the nucleophilic ketone addition transition states (Figure 4b). Further calculations on the ketone addition step led to the Zimmerman−Traxler-type transition states with optimized geometries (see the Supporting Information for details).

https://doi.org/10.1021/acscatal.3c00177
ACS Catal. 2023, 13, 3170−3178

These results suggest that regio- and stereoselectivity might originate from the interaction between the substrates and the chiral ligand, especially the steric repulsion between the ketone and (*S*)-**L6** (Figure 4c). No apparent interaction related to the CF_3 group was identified in these transition states. We believe that CF_3 could increase the electrophilicity of the carbonyl group, and its steric hindrance also matters during the nucleophilic addition step.

In summary, we have described the Cr-catalyzed enantioconvergent propargylation of ketones with racemic propargylic chlorides, affording valuable chiral tertiary alcohols bearing vicinal stereocenters. The reaction proceeds efficiently under mild conditions in a radical−polar crossover manner with good regio-, diastereo-, and enantioselectivity. This method also exhibits good functional group compatibility. Preliminary mechanistic studies, including radical trapping, nonlinear effect, and UV−vis spectroscopy, provide insights into the catalytic cycle. DFT calculations support that the regio- and stereoselectivity are determined by the Zimmerman−Traxler-type ketone addition transition states under Curtin−Hammett conditions. Given the importance of chiral tertiary alcohols and the growing interest in radical chemistry, we anticipate that our protocol will find application in organic synthesis and facilitate current endeavors toward radical-involved asymmetric transformations.

■ ASSOCIATED CONTENT

Data Availability Statement

Crystallographic data for compounds **3w**, **3n**, **4c**, and Cr^{III}/(*R*)-**L1** is available free of charge from the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/) under reference numbers 2207684, 2207686, 2207687, and 2207691. All other data are available from the authors upon reasonable request.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c00177.

Data relating to the materials and methods, experimental procedures, HPLC/SFC spectra, mechanism research, and NMR spectra (PDF)

Crystallographic data for compound **4c** (CIF)

Crystallographic data for compound **3n** (CIF)

Crystallographic data for compound Cr^{III}/(*R*)-**L1** (CIF)

Crystallographic data for compound Cr^{II}/(*R*)-**L6** (CIF)

Crystallographic data for compound **3w** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Natural Science Foundation of China (22171231), the Leading Innovative and Entrepreneur Team Introduction Program of Zhejiang (2020R01004), and Westlake University. We thank the Instrumentation and Service Center for Molecular Science and Physical Science and the HPC Center at Westlake University for the assistance in measurement and data interpretation. We thank Professor Lei Sun (Westlake University) for helpful discussions on the mechanistic study.

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