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Chromium(II)-Catalyzed Diastereoselective and Chemoselective Csp^2–Csp^3 Cross-Couplings Using Organomagnesium Reagents

Jie Li,* Qianyi Ren, Xinyi Cheng, Konstantin Karaghiosoff, and Paul Knochel*

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, Haus F, 81377 Munich, Germany.

ABSTRACT: A simple protocol for performing chromium-catalyzed highly diastereoselective alkylations of arylmagnesium halides with cyclohexyl iodides at ambient temperature has been developed. Furthermore, this ligand-free $CrCl_2$ enables efficient electrophilic alkenylations of primary, secondary and tetiary alkylmagnesium halides with readily available alkenyl acetates. Moreover, this chemoselective C–C coupling reaction with stereodefined alkenyl acetates proceeds in a stereoretentive fashion. A wide range of functional groups on alkyl iodides and alkenyl acetates are well tolerated, thus furnishing functionalized Csp^2–Csp^3 coupling products in good yields and high diastereoselectivity. Detailed mechanistic studies suggest that the in situ generated low-valent chromium(I) species might be the active catalyst for these Csp^2–Csp^3 cross-couplings.

INTRODUCTION

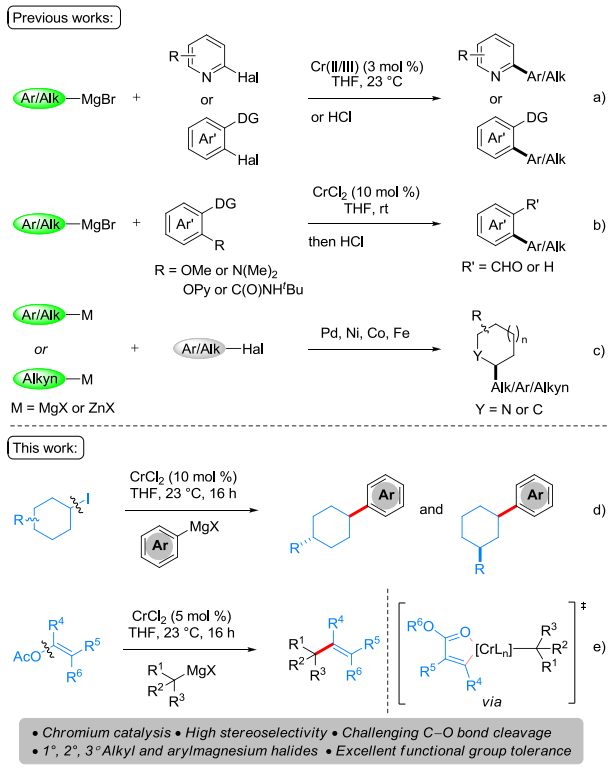
Transition-metal-catalyzed cross-couplings between Csp^2-centers and Csp^3-centers are important for the elaboration of complex organic molecules.[1,2] Whereas palladium- and nickel-catalysts are very useful, other first-row transition-metals,[2] such as Fe[3] or Co[4] have also found numerous applications. These metal-catalysts are especially important due to their low toxicity, low price and abundance. Recently, low-valent chromium salts have attracted considerable attention due to their natural abundance[5] and lower toxicity compared to iron.[6] We have shown that low-valent chromium-catalyzed cross-couplings between (hetero)aryl halides and aryl-[7] or alkyl-magnesium halides[8] proceeds very efficiently (Scheme 1a). Furthermore, Zeng also illustrated the chelation-assisted chromium-catalyzed aryl C–O or C–N bonds activation with Grignard reagents (Scheme 1b).[9]

Since Hiyama pioneered the stoichimetric chromium-mediated diastereoselective addition of allylic electrophiles to aldehydes,[10] an enantioselective 1,2-difunctionalization of 1,3-butadiene by chromium/cobalt-catalysis and stereoselectivie allylation of aldehydes by dual photoredox/chromium catalysis were recently reported by Zhang[11] and Glorius.[12] Despite these remarkable advances, chromium-catalyzed diastereoselective and chemoselective Csp^2–Csp^3 cross-couplings still have unfortunately thus far not been reported. The performance of diastereoselective cross-couplings catalyzed with transition metals of alkyl-, aryl- and alkynyl-magnesium or zinc reagents with secondary alkyl iodides or bromides has been reported using Fe,[13] Co[14] or Ni catalysts.[15] While the related transition-metal-catalyzed diastereoselective cross-couplings between alkenyl or (hetero)aryl iodides and alkyl-zinc or magnesium reagents largely rely on the use of Pd (Scheme 1c).[16] As a result, we have studied the chromium-catalyzed diastereoselective cross coupling between aryl Grignard reagents and functionalized alkyl halides (Scheme 1d).

On the other hand, easily accessible phenol and enol derivatives have been utilized as environmental friendly electrophiles (halide-free) for 3d transition-metal-catalyzed cross-couplings with organometallic reagents using iron- and nickel-catalysis, as were reported by Shi,[17] Garg,[18] Fürstner,[19] Martin[20] and others.[21] However, utilization of these more atom-economical and stable alkenyl acetates was rarely reported. Early reductive cross-couplings of vinylic acetates with aryl halides were developed by Gosmini, albeit with a limited substrate scope.[22] Thereafter, Ackermann has used alkenyl acetates for performing cobalt-catalyzed C–H activation of indoles.[23] The cross-couplings between alkenyl acetates and organometallic reagents were only recently reported by Jacobi von Wangelin and us using iron-[24] and cobalt-catalysis.[25] Also, the iron-catalyzed stereoselective cross-coupling using related enol carbamates and Grignard reagents was only recently described by Frantz.[26] Hence, we report herein a ligand-free chromium(II)-catalyzed cross-couplings between various functionalized alkenyl acetates and primary, secondary and tertiary alkylmagnesium halides under remarkably mild reaction conditions. It is

noteworthy that the chromium-catalyzed alkenylation with stereodefined alkenyl acetates occurred in a stereoretentive fashion (Scheme 1e).

Scheme 1. Low-valent chromium-catalyzed cross-couplings with Grignard reagents.



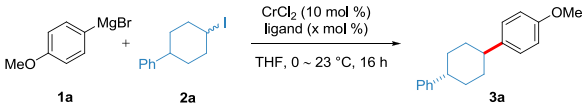
RESULTS AND DISCUSSION

We initiated our studies by testing different reaction conditions for the envisioned chromium-catalyzed diastereoselective Csp^2–Csp^3 cross-coupling between arylmagnesium reagents (**1a**) and 1,4-disubstituted cyclohexyl iodide (**2a**). Among various ligands (Table 1, entries 1–4), TMEDA gave a good yield and diastereoselectivity of desired product **3a** (70%, *dr*: 96:4). It is worth noting that omission of ligand led to a further yield of **3a** increase to 91%, with high diastereoselectivity (*dr*: 97:3; entry 5). Similar results were observed when using as low as 5 mol % of $CrCl_2$ (entry 6). Further, performing the reaction at 0 °C or switching the ratio of the starting materials resulted in significantly reduced yields (entries 7–8). Obviously, no reaction was observed in the absence of $CrCl_2$ (entry 9).

Thereafter, the optimized ligand-free chromium(II) catalyst was probed in a range of coupling reactions of various arylmagnesium halides **1** with functionalized cyclohexyl iodides **2** (Scheme 2). 1,4-Disubstituted cyclohexyl iodides **2a**–**2c** bearing phenyl, cyclohexyl, *tert*-butyl or methyl groups reacted smoothly with different arylmagnesium halides, furnishing the desired products **3a**–**3f** in 64–91% yield, albeit **3d** was obtained with a lower diastereoselectivity. Moreover, TBS-protected iodohydrin **2d** was also investigated and delivered the arylated products **3g**–**3i'** with good diastereoselctivity. The more synthetically useful amino-substituted cyclohexyl iodides **2e**–**2f** were identified as suitable substrates for the diastereoselective cross-couplings with functionalized arylmagnesium reagents, thereby providing the corresponding products **3j**–**3n** in 54–78% yield. Coupling of Grignard reagents with 1,3-disubstituted cyclohexyl iodides **2g**–**2j** gave the cyclohexane derivatives **3o**–**3r** in 63–89% yields. Remarkably, different steroid derivatives, such as cholesteryl and epiandrosterone iodides **2k**–**2m**, led to arylated steroids **3s**–**3u** in 53–75% (*dr* > 97:3) yield. It is noteworthy that a deuterated cholesteryl iodide **2n** underwent the arylation with (3-methoxyphenyl)magnesium bromide **1d** to afford the desired product **3v** with a slightly decreased yield.

Additionally, this Cr(II)-catalyzed cross-coupling was further applicable to functionalized secondary and primary iodides **2n**–**2q** to provide the corresponding arylated products **3w**–**3z** in moderate yields.

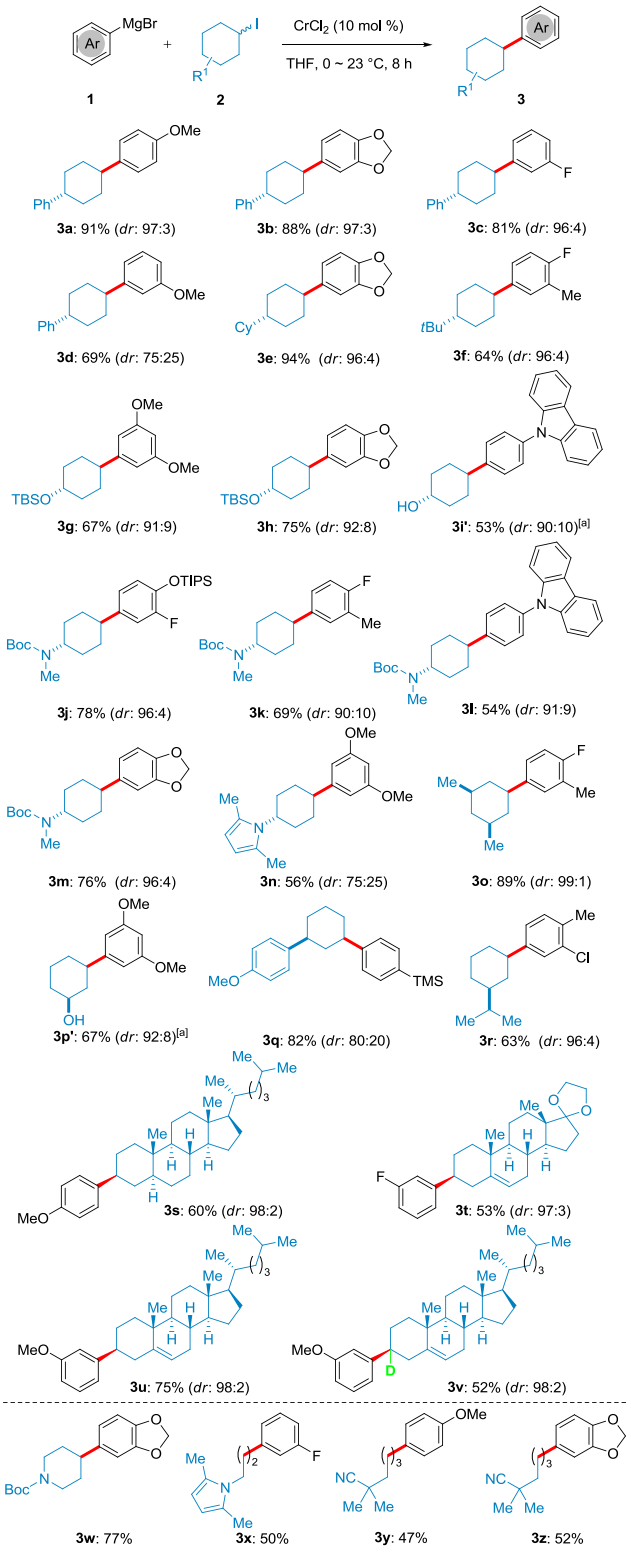
Table 1. Diastereoselective chromium(II)-catalyzed Csp^2–Csp^3 cross-coupling.[a]



entry	[Cr] (mol %)	ligand	yield (%)[b]
1	$CrCl_2$	dtbbpy (10 mol %)	16 (*dr*: 92:8)
2	$CrCl_2$	TMEDA (20 mol %)	70 (*dr*: 96:4)
3	$CrCl_2$	IPr•HCl (10 mol %)	14 (*dr*: 96:4)
4	$CrCl_2$	dppbz (10 mol %)	17 (*dr*: 93:7)
5	***$CrCl_2$***	--	***91 (dr: 97:3)***
6	$CrCl_2$	--	88 (*dr*: 96:4)[c]
7	$CrCl_2$	--	60 (*dr*: 96:4)[d]
8	$CrCl_2$	--	66 (*dr*: 96:4)[e]
9	--	--	0

[a] **1a** (0.45 mmol, 1.5 equiv), **2a** (0.3 mmol, 1.0 equiv), $CrCl_2$ (10 mol %), THF, 0~23 °C, 16 h. [b] Isolated Yield, *dr* value was determined by GC analysis. [c] $CrCl_2$ (5 mol %). [d] 0 °C, 16 h. [e] **1a** (0.3 mmol, 1.0 equiv), **2a** (0.45 mmol, 1.5 equiv), 12 h. dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine; TMEDA = *N,N,N',N'*-tetramethylethylenediamine; IPr•HCl = 1,3-Bis-(2,6-diisopropylphenyl)imidazolinium chloride; dppbz = 1,2-Bis(diphenylphosphino)benzene.

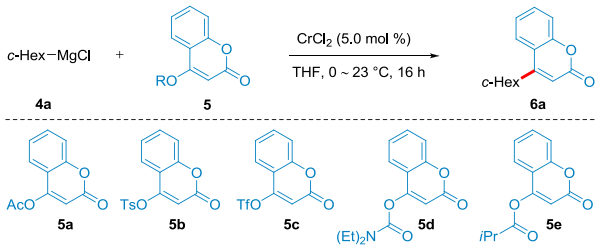
Scheme 2. Substrate scope of the chromium(II)-catalyzed diastereoselective arylation.



[a] After standard procedure, the residue was treated with TBAF (2.0 equiv) in CH_2Cl_2 (2.0 mL), 23 °C, 24 h.

In consideration of the high catalytic activity of this robust chromium(II) catalyst, we have further optimized the reaction conditions for the chromium-catalyzed olefination of alkylmagesium reagents (**4a**) with 4-acetoxy-2-chromenone (**5a**) through C–O bond cleavage. Among a set of representative ligands and additives, the alkylated product **6a** was obtained in 21–60% yields (Table 2, entries 1–5). However, 5.0 mol % $CrCl_2$ increased the yield of **6a** to 68% (entries 6) at 23 °C. No reaction was observed in the absence of chromium salts (entry 7). Replacement of $CrCl_2$ by using $CrCl_3$ or other typically transition-metal catalysts, such as $FeCl_3$, $CoCl_2$, $NiCl_2$, or $Pd(OAc)_2$ resulted in significantly reduced yields (entries 8–12). It is worth noting that related electrophiles, such as tosylate (**5b**), triflate (**5c**), carbamate (**5d**), as well as isobutyrate (**5e**), were also tested and led to inferior results (entries 13–16). Performing the reaction at 40 °C or in the presence of 10 mol % of $CrCl_2$ did not increase the yield of product **6a** (entries 17–18).

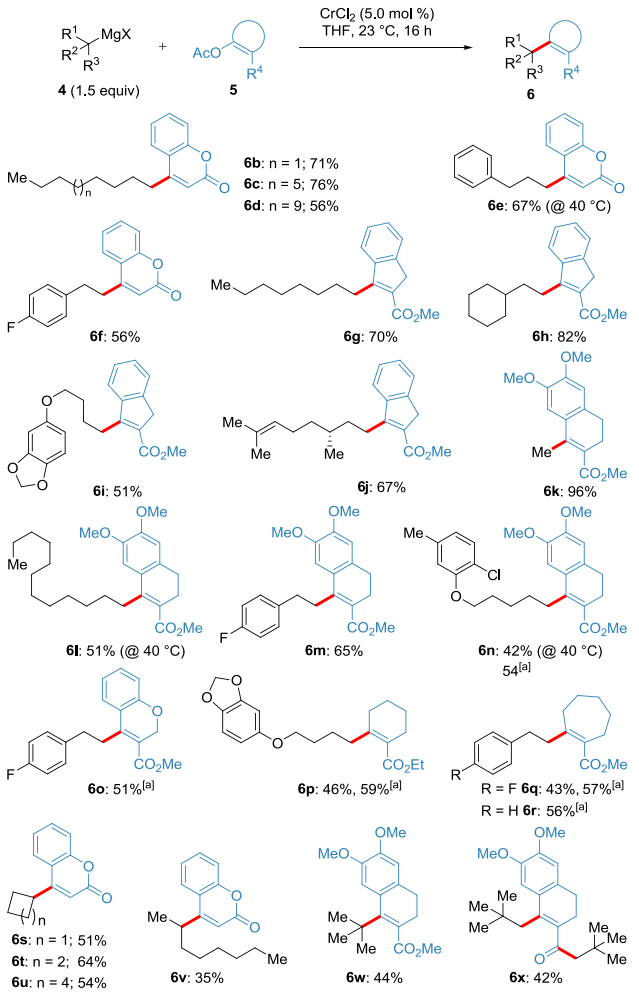
Table 2. Optimization for chromium(II)-catalyzed alkylation of 5 with cyclohexylmagnesium chloride (4a) through C–O bond cleavage.[a]



entry	modified conditions	yield (%)[b]
1	bpy (10 mol %) as ligand	21
2	TMEDA (20 mol %) as ligand	19
3	IMesHCl (10 mol %) as ligand	15
4	TMSCl (2.0 equiv)	44
5	NMP (2.0 equiv)	60
6	none	68[c]
7	without $CrCl_2$	0
8	$CrCl_3$ instead of $CrCl_2$	28
9	$FeCl_3$ instead of $CrCl_2$	53
10	$CoCl_2$ instead of $CrCl_2$	37
11	$NiCl_2$ instead of $CrCl_2$	24
12	$Pd(OAc)_2$ instead of $CrCl_2$	26
13	**5b** instead of **5a**	trace
14	**5c** instead of **5a**	17
15	**5d** instead of **5a**	50
16	**5e** instead of **5a**	49
17	under 40 °C	54
18	$CrCl_2$ (10 mol %)	66

[a] *c*-HexMgCl (**4a**, 0.45 mmol, 1.5 equiv), **5a** (0.3 mmol, 1.0 equiv), $CrCl_2$ (5.0 mol %), THF, 0 °C, 16 h. [b] Isolated Yield. [c] *c*-HexMgCl (0.45 mmol, 1.5 equiv), $CrCl_2$ (5.0 mol %), 23 °C, 16 h. bpy = 2,2'-bipyridine; IMesHCl = 1,3-bis(1,3,5-trimethylphenyl)imidazolium chloride.

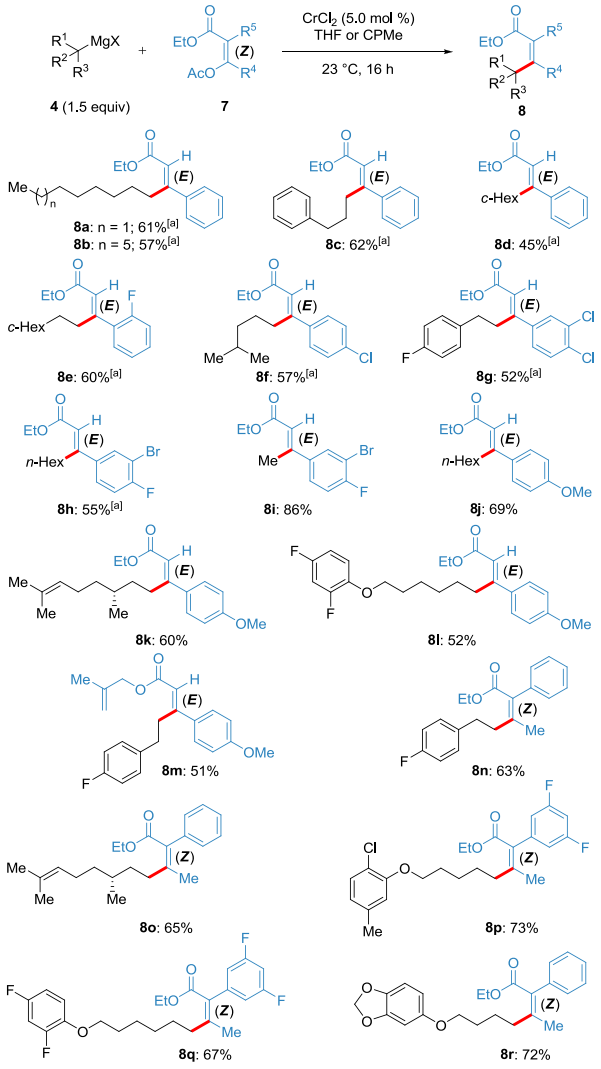
Scheme 3. Substrate scope of the chromium(II)-catalyzed alkylation of alkenyl acetates of type 5.



[a] $CrCl_2$ (10 mol %) was used in CPMe (CPMe = cyclopentyl methyl ether).

With the optimized chromium(II)-catalyst in hand, we have investigated the cross-coupling of various alkenyl acetates with alkylmagnesium halides (Scheme 3). All alkylmagnesium reagents were prepared from the corresponding alkyl bromides by Mg insertion in the presence of LiCl.[27] Notably, the 4-acetoxy-2-chromenone reacted smoothly with various primary alkylmagnesium derivatives leading to the alkylated chromenones **6b–6f** in 56–76% yields. Similarly, indenyl acetate, naphthalenyl acetate and chromenyl acetate underwent the desired cross-coupling reactions through C–O bond cleavage with functionalized Grignard reagents affording the corresponding products **6g–6o** in moderate to good yields. Among a set of alkylmagnesium derivatives, MeMgCl delivered the methylation product **6k** with high catalytic efficacy in 96% yield. Moreover, this cross-coupling was extended to acetoxycyclohexenylcarboxylate (**5i**) and acetoxycycloheptenylcarboxylate (**5j**). We were delighted to observe that the alkylated products **6p–6r** were smoothly generated, while better isolated yields were obtained when employing CPMe (cyclopentyl methyl ether) as solvent (56–59%). Importantly, secondary alkylmagnesium reagents proved to be viable nucleophiles as well, successfully participating in the alkenylation to produce the desired products **6s–6v**. We also found that *t*BuMgCl could be utilized for an alkenylation. A moderate yield of **6w** was obtained under our standard conditions. Interestingly, a two step reaction sequence consisting of the chromium-catalyzed electrophilic alkenylation, along with a nucleophilic addition/elimination occurred, when using neopentylmagnesium bromide as the nucleophile, yielding the bis-alkylated product **6x** in 42% yield.

Scheme 4. Chromium(II)-catalyzed stereoselective alkenylation with stereodefined alkenyl acetates of type 7.

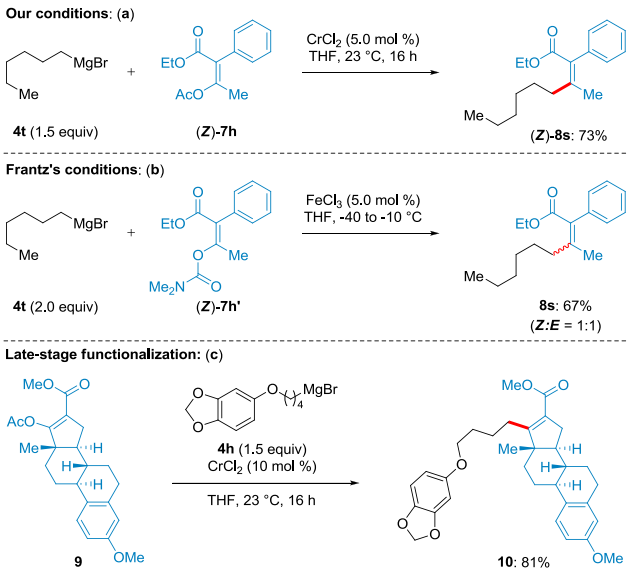


[a] $CrCl_2$ (10 mol %) was used in CPMe.

Thereafter, we further extended the substrate scope to well-stereodefined acyclic acetates of type **7** under otherwise identical reaction conditions (Scheme 4). Remarka-

bly, the chromium(II)-catalyzed electrophilic alkenylation using (*Z*)-alkenyl acetates **7** occurred in a stereoretentive mode. Indeed, no isomers of the desired functionalized olefins were observed by ^{1}H-NMR spectroscopy after purification of the reaction mixtures. Aryl acrylates bearing different valuable electrophilic substituents, such as fluoro-, chloro-, bromo-, methoxy-, as well as alkenyl-, ether-substitutents on the alkylmagnesium reagents were well tolerated under our standard conditions, thereby delivering the corresponding (*E*)-olefins **8a**–**8m** as the sole products. Beyond that, (*Z*)-diastereomers of tetrasubstituted acrylates **8n**–**8r** were also efficiently obtained through chromium(II)-catalyzed alkenylations between (*Z*)-alkenyl acetates and synthetic useful alkylmagnesium derivatives in good yields. It is noteworthy that the (*E*)-alkenyl acetates also delivered the stereoretentive products, which highlighted the unique versatility and stereoselectivity of this chromium(II)-catalysis, albeit the products were obtained in rather modest yields (see Scheme S10 in the Supporting Information for more details).

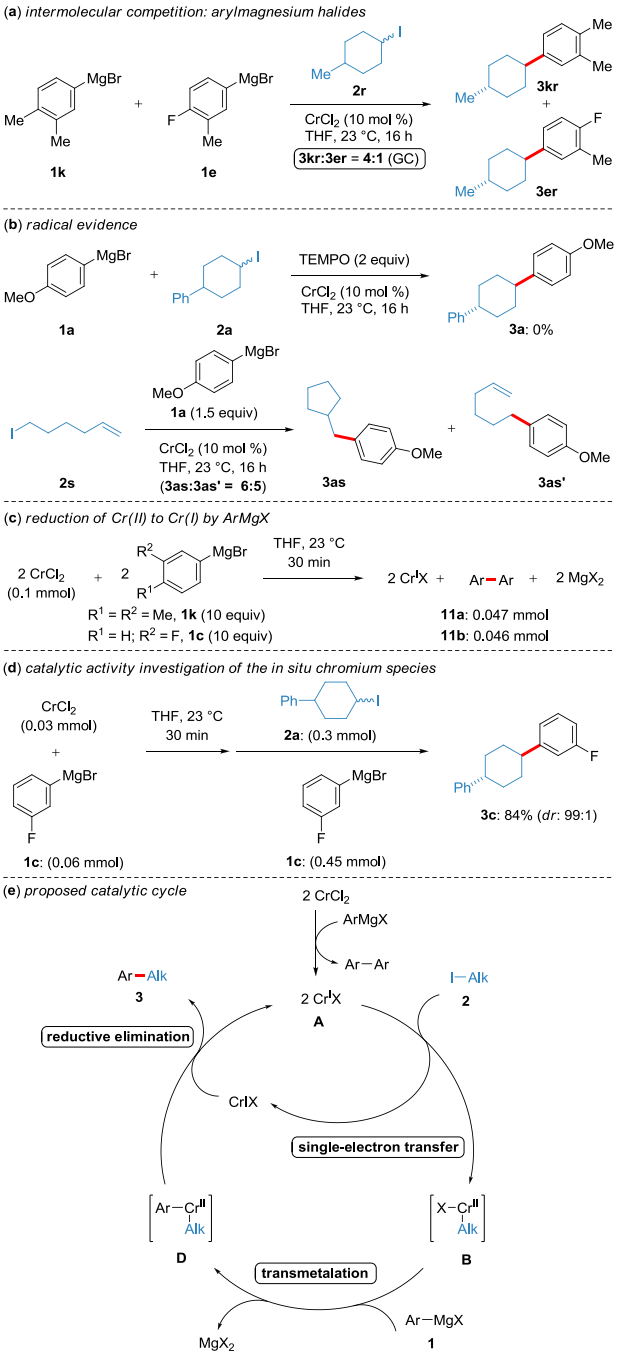
Scheme 5. Comparison experiments of regio-control between chromium- and iron-catalysis.



Furthermore, the results of comparison experiments between chromium(II)- and iron(III)-catalysis with (*Z*)-alkenyl acetate and (*Z*)-alkenyl carbamate highlighted the unique stereoselectivity of our current approach, since the chromium-catalyst delivered (*Z*)-**8s** as the single product (Scheme 5a), while the iron-catalyst ($FeCl_3$) provided a isomeric mixture of **8s** (*Z*:*E* = 1:1; Scheme 5b).[26] To illustrate the synthetic potency of this ligand-free chromium(II)-catalyzed alkylation protocol, a cross-coupling reaction between alkylmagnesium and pharmacologically relevant compound of estrone derivative (**9**)[25] was performed and delivered the alkylated steroid derivative **10** in 81% yield (Scheme 5c).

MECHANISM STUDIES

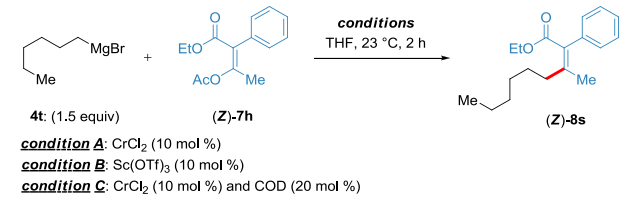
Scheme 6. Mechanistic studies for chromium-catalyzed diastereoselective arylation of functionalized iodides.

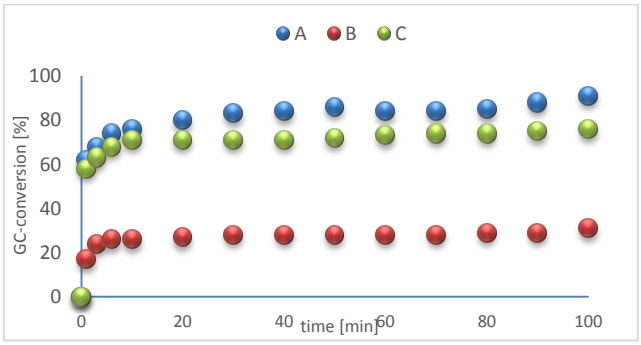


We performed detailed experiments to unravel the reaction mode of action. In this context, intermolecular competition experiments between the differently substituted arylmagnesium reagents (**1k** *vs* **1e**) showed that

electron-rich aryl groups react preferentially (Scheme 6a). This Cr(II)-catalyzed diastereoselective cross-coupling was inhibited by employing of stoichimetric quantities of TEMPO. Radical-clock experiment using 6-iodo-1-hexene **2s** as reaction partner was also performed and both ring-closed product **3as** and linear product **3as'** were detected (Scheme 6b). These results indicate that this cross-coupling may proceed by a single electron transfer (SET) process. Based on the previous mechanistic insights, an in situ low-valent Cr(0) was proposed as the catalytically active species.[9b] Therefore, we performed experiments of $CrCl_2$ (1.0 equiv) with excess of ArMgBr (**1k** or **1c**) under typical reaction conditions for 30 min. The reactions furnished the corresponding homo-product (**11a** or **11b**) in a near 0.5 equiv ratio to that of $CrCl_2$. These results support the formation of a Cr(I)-intermediate according to the stoichiometry shown in scheme 6c. Furthermore, we treated the $CrCl_2$ (0.03 mmol) with two equivalent of 3-FC_6H_4MgBr (**1c**, 0.06 mmol) at 23 °C for 30 min to form a tentative Cr(I)-species, followed by addition of the alkyl iodide **2a** (0.3 mmol) and another 0.45 mmol of **1c**. The desired product **3c** was obtained in 84% yield (Scheme 6d). These findings indicated that the in situ generated low-valent chromium(I)-species might be the active catalyst.

Scheme 7. Kinetic experiments with different Lewis acids.





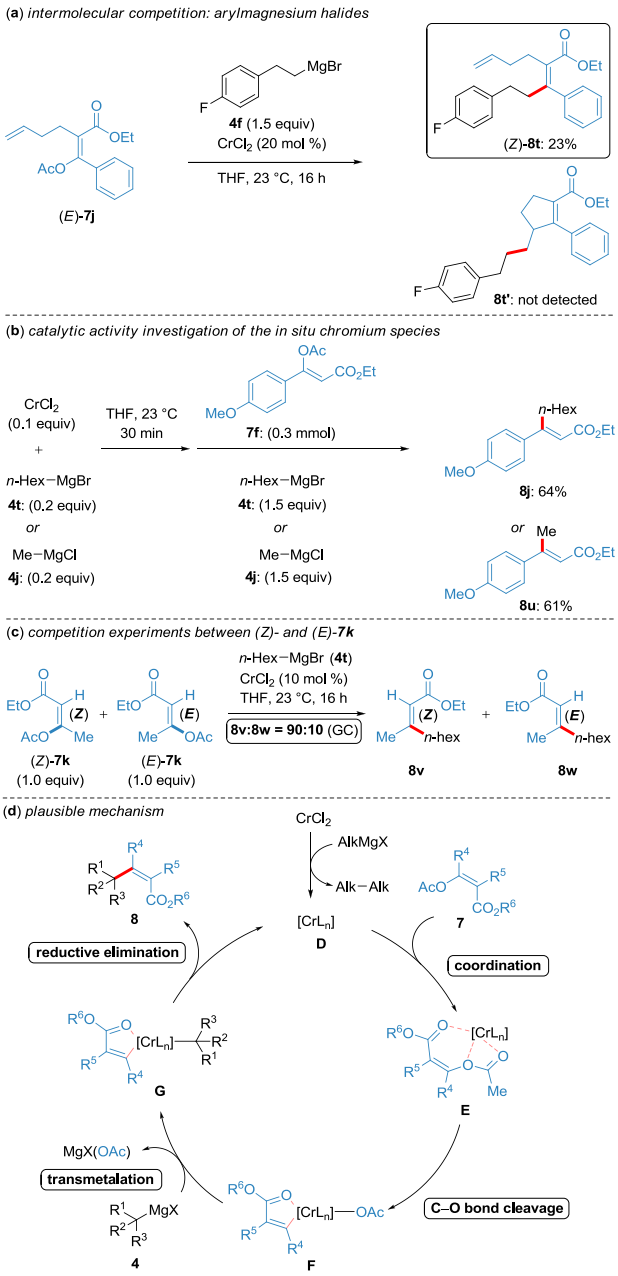
Based on our mechanistic studies, we propose a catalytic cycle for this chromium-catalyzed diastereoselective cross-coupling reaction (Scheme 6e). The reaction might start with the in situ formed Cr(I)-species (**A**), which reduces alkyl iodies (**2**) by SET and forms intermediate **B**, then followed by transmetalation with ArMgX (**1**) and reductive elimination deliver the desired product **3** and regenerate the active chromium(I)-catalyst.

On the other hand, in order to reveal the function of $CrCl_2$ in the cross-couplings between alkyl Grignard reagents and alkenyl acetates, a series of kinetic experiments using 10 mol % of $CrCl_2$, $Sc(OTf)_3$ or $CrCl_2$-COD as the metal complex were performed (Scheme 7). The transformation between *n*-hexylmagnesium bromide **4t** and acetate (*Z*)-**7h** occurred successful under standard conditions **A**, up to 90% conversion of the desired product (*Z*)-**8s** was detected by GC analysis after 100 min. However, 10 mol % of $Sc(OTf)_3$ only gave a sharp decreased conversion of 30%. Interestingly, different to the homogeneous catalysis of iron,[24] using COD (2.0 equiv) as the π-acceptor ligand of $CrCl_2$ resulted in a minor alteration of catalytic activity, which suggested that π-hydrocarbons could not coordinate to chromium species.[28]

Additionally, upon radical-clock experiment with substrate (*E*)-**7j** bearing a vinyl substituent, the stereoretentive product (*Z*)-**8t** was generated in 23% yield, while the ring-closing/cross-coupling compound **8t'** was not detected (Scheme 8a). With these findings, we propose this alkenylation undergoes a non-radical process. Similarly, we further performed the experiments to examine the catalytic activity of the in situ generated low-valent chromium species. A mixture of $CrCl_2$ (0.03 mmol) and two equivalent of *n*-hexMgBr (**4t**) or MeMgCl (**4j**) was stirred at 23 °C for 30 min and the low-valent chromium intermediate was generated (see Scheme S8 in the Supporting Information for more details). Substrate **7f** (0.3 mmol) and *n*-hexMgBr or MeMgCl (0.45 mmol) were subsequently added to the in situ generated chromium species solution and the reactions were continued for another 16 h. The corresponding products **8j** and **8u** were afforded in 61–64% yields.[28] These experimental results show again that the in situ formed low-valent chromium species enables the following C–O bond functionalization (Scheme 8b).[9] To further illustrate the effect of ester group, intermolecular competition experiments between the substrates (*Z*)-**7k** and (*E*)-**7k** were performed. A significant ratio (90:10) of **8v** and **8w** was detected by GC analysis, which verified the crucial importance of the ester directing group (Scheme 8c, see Scheme S9 in the Supporting Information for more details).

Given our mechanistic studies and previous mechanistic insights,[9] we propose the catalytic cycle involves an initial coordination of low-valent chromium species **D** and alkenyl acetate **7**. A subsequent C–O bond cleavage of **E** forms the intermediate **F**, which undergoes transmetalation with alkyl Grignard reagent **4** to generate the key intermediate **G**. Finally, reductive elimination liberates the desired Csp^2–Csp^3 coupling product **8** and regenerates the catalytically active chromium species (Scheme 8d).

Scheme 8. Mechanistic studies for chromium-catalyzed alkenylation through C–O bond cleavage.



CONCLUSION

In summary, we have reported efficient chromium-catalysis for diastereoselective and chemoselective alkylative and alkenylative Csp^2–Csp^3 cross-couplings. The ligand-free Cr-catalyzed alkylation of arylmagnesium halides with cyclohexyl iodides proceeded with high and predictable diastereoselectivity under mild reaction conditions. Beyond that, the C–C coupling also occurred with functionalized primary alkyl iodides. Furthermore, a simple Cr-catalyzed electrophilic alkenylation between various alkylmagnesium reagents and stereodefined alkenyl acetates proceeds under remarkably mild reaction conditions at 23 °C. Indeed, among a series of different C–O bonds, the more stable enol acetates shown the best reactivity, as compared to other activated esters, such as triflates, tosylates, carbamates and isopropylates. Notable features of this method are an unique stereoselectivity, less toxic and ligand-free chromium(II)-catalysis, user- and environmental-friendly reaction conditions, as well as an ample substrate scope and good functional group tolerance. The high-yielding preparation of arylated and alkylated steroids shows the potential of these methods for applications in medicinal chemistry. Detailed mechanistic studies demonstrated the in situ formed low-valent chromium-species might be the catalytically active catalyst.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI:

General remarks, optimization tables, additional experiments, representative procedures, X-ray of **3c**, characterization data of **3**, **6**, **8**–**10** and NMR spectra (PDF)

CCDC 1945146 contain the supplementary crystallographic data for this paper. This 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 containing The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax:+44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

E-mail: jjackli@jiangnan.edu.cn.
E-mail: paul.knochel@cup.uni-muenchen.de.

Notes

The authors declare no competing financial interest.

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SYNOPSIS TOC