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Iron-catalysed cross-coupling of halohydrins with aryl aluminium reagents: a protecting-group-free strategy attaining remarkable rate enhancement and diastereoinduction†

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Non-protected halohydrins are cross-coupled with aryl aluminium reagents to produce aryl alkanols in the presence of the iron–bisphosphine catalysts. Remarkable reaction rate enhancement and diastereoinduction are realized by the *in situ* generated aluminium alkoxides, offering a new method for the reactivity and selectivity control of the iron-catalysed cross-coupling reaction.

The directing effect of non-protected hydroxyl groups (called *neighbouring group participation* when the directing group is near the reaction centre) is recognised as a classical, yet powerful chemical tool in organic synthesis for controlling stereo-, regio-, and chemoselectivities as well as reaction rate.[1] This synthetic control may also be expected to be operative in cutting-edge cross-coupling technology,[2] but there have been very few reports on attempts to actively implement it in designing such reactions.[3] In addition to the paucity of systematic research efforts, the increasing interest in protecting-group-free syntheses[4] prompted us to investigate the cross-coupling reactions of protected/non-protected halohydrins to eventually find the novel reactivity of organoaluminium reagents for iron-catalysed cross-coupling reactions. Herein, we report a new cross-coupling reaction of *non-activated* alkyl chlorides and aryl aluminium reagents, in which the free hydroxyl group, or more precisely, *in situ* generated aluminium-alkoxide, facilitated the reaction and enhanced the diastereoselectivity.

We have reported previously that the cross-coupling reactions of alkyl halides with various organometallic reagents proceed efficiently in the presence of the iron–bisphosphine catalysts ($FeCl_2$–SciOPPs, Fig. 1).[5][‡a] However, we did not observe sufficient reactivity of the catalyst when a free hydroxyl group was present in the coupling substrates or when a free alcohol substrate was added to the reaction mixture. We assumed that catalyst poisoning resulted from the formation of inert iron-alkoxide species.[5a]

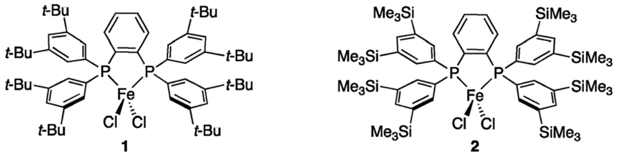
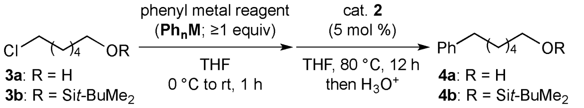


Fig. 1 $FeCl_2$(SciOPP) **1** and $FeCl_2$(TMS–SciOPP) **2**.

In contrast to the previous observations, we found unexpectedly that the iron-catalysed cross-coupling reaction of a non-protected chlorohydrin proceeded readily when using aryl aluminate as the nucleophile. It should be noted that primary alkyl chlorides usually show low reactivity in iron-catalysed cross-coupling reactions (regardless of the presence of a free hydroxyl group), and require certain elaborate catalysts.[6] Thus, we first reinvestigated the iron–bisphosphine-catalysed cross-coupling of various phenyl metal nucleophiles by using 6-chloro-1-hexanol **3** as a model substrate, in order to confirm the unexpected unique reactivity of aryl aluminates (Scheme 1 and Table 1).

As shown in entry 1, PhMgBr (**5a**)[5b,c,7] gave the desired cross-coupling product **4a** in only 4% yield, along with the formation of 5-hexen-1-ol and 1-hexanol in *ca.* 30% combined yield. The reaction with diphenylzinc, $Ph_2Zn{\cdot}2MgCl_2$ (**5b**),[8] was sluggish, giving **4a** in 6% yield (entry 2). Triphenylzincate ($Ph_3Zn{\cdot}MgBr$, **5c**)[8] gave the product in a higher yield than the neutral diphenylzinc; however, the yield and selectivity of the reaction were both low (entry 3). When diphenylborate ($Ph_2B(pin)Li$, **5d**)[5a] was used, no desired product was obtained (entry 4). While neutral phenyl aluminium ($Ph_3Al{\cdot}3MgCl_2$, **5e**)[9] resulted in almost complete recovery of halohydrin **3a**, the reaction with phenyl aluminate ($Ph_4Al{\cdot}MgCl$, **5f**)[9] proceeded smoothly and selectively to give the desired **4a** in 91% yield (entries 5 and 6).[‡b,c] We suspected that the efficient reaction might be explained by the formation of a heteroleptic aluminate species (*e.g.* $Ph_3AlOR{\cdot}MgCl$), which generates an anionic iron (ferrate) or Fe–Al mixed cluster species that exhibits the unprecedented reactivity (see mechanistic discussion).[10]



Scheme 1 Iron-catalysed cross-coupling reaction of protected or non-protected halohydrins with various phenyl metal reagents.

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Table 1 Reactivity differences between various phenyl metal reagents and effect of protection of hydroxyl group on the reactivity

			Yield[b] (%)			
Entry[a]	Halide	Ph_nM (equiv.)	**4a** or **4b**[c]	Alkene	Alkane	RSM (%)[b]
1	**3a**	**5a** (2.0)	4	12	17	63
2	**3a**	**5b** (1.0)	6	0	0	89
3	**3a**	**5c** (1.0)	13	23	20	30
4[d]	**3a**	**5d** (1.0)	0	9	0	91
5	**3a**	**5e** (1.0)	0	0	0	> 99
6[e]	**3a**	**5f** (1.0)	91	6	0	0
7	**3b**	**5f** (1.0)	20	1	20	52

[a] Reactions were carried out at 80 °C for 12 h. [b] The yields were determined by ^1H NMR analysis and confirmed by GLC analysis. [c] The cross-coupling products **4a** and **4b** were obtained in entries 1–6 and 7, respectively. [d] 20 mol% $MgBr_2$ was added as a co-catalyst. [e] The reaction of phenyl aluminate prepared by transmetalation from $AlCl_3$ and PhMgBr gave the same result as that prepared from PhMgCl.

The reaction of the protected chlorohydrin **3b** with phenyl aluminate, thus, gave a 1 : 1 mixture of the coupling product and the alkane by-product in only 40% combined yield (entry 7), and the results of the reactions using the other phenyl metal reagents were almost the same as those reported previously.[6]‡[d]

For the further study of the influence of alkoxide in the reaction, 1-hexanol was added to the iron-catalysed cross-coupling reaction of the protected halohydrin **3b** with phenyl aluminate **5f**. Although the reactions in the absence of alcohol gave the cross-coupling product in low yield (Table 1, entry 7), stoichiometric or even 20 mol% 1-hexanol dramatically improved the reaction to give the desired product in high yield. The *in situ* generated aluminium alkoxide did not cause any catalyst poisoning, but enhanced the reaction.‡[e] This observation also clearly indicates that the formation of aluminium-alkoxide species is a key to the observed high catalytic activity.

Fig. 2 shows a plausible catalytic cycle inferred from the above-mentioned results and previous reports published by us and others. In the initial step, the precatalyst complex $FeCl_2$(TMS–SciOPP) is transformed into intermediate **A** through transmetalation with an aryl aluminate ($Ar_3AlOR·MgX$).‡[f] The intermediate **A**, which is reminiscent of the bis(μ-oxo)phenyl-aluminium–phenyltitanium complex[11] and iron chloride–aluminium-*tert*-butoxide complexes,[12] is proposed here as a catalytically active species because of its expected high reactivity towards non-activated alkyl chlorides.[6,13] Subsequently, homolytic cleavage of the C–Cl bond proceeds to give an alkyl radical and the ferrate intermediate **B**.‡[g] This is followed by the recombination of the resulting elusive alkyl radical with the aryl group on intermediate **B**, which occurs in a solvent cage to give the cross-coupling product and intermediate **C**.[6]

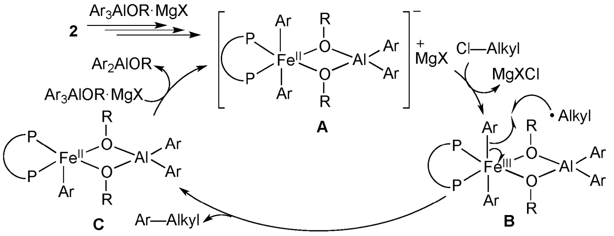


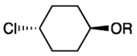
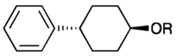
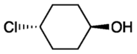
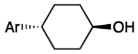
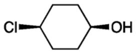
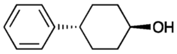
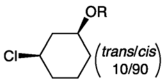
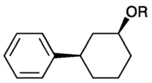
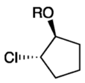
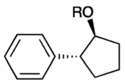
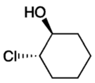
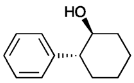
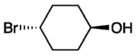
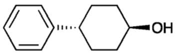
Fig. 2 Plausible catalytic cycle.

Finally, intermediate **A** is regenerated by transmetalation between intermediate **C** and the aryl aluminate.

We next focused on the stereoinduction by the hydroxyl group in the electrophilic coupling partner. González-Bobes–Fu[3a] and Yorimitsu–Oshima[3b] reported the catalytic diastereoselective cross-coupling reactions of protected cyclic 2-halohydrins using nickel and cobalt catalysts, respectively. In addition, Knochel *et al.* recently reported the iron-mediated diastereoselective cross-coupling reaction of *tert*-butyldimethylsilyl-protected cyclic 2-iodohydrins.[3c] A protected hydroxyl group near the reaction centre is thus known to induce diastereoselectivity in Ni- and Co-catalysed as well as Fe-mediated cross-coupling reactions. However, it was unknown whether a non-protected hydroxyl group, *i.e.*, a metal alkoxide generated *in situ*, could give rise to such stereoinduction.

We first compared the diastereoselectivities of the reactions of non-protected and acetyl-protected *trans*-4-chlorocyclohexanols with phenyl aluminate **5f** (Table 2, entries 1 and 2). While the reaction of the protected halohydrin afforded an almost 1 : 1 mixture of diastereomers, that of the non-protected substrate produced the *trans*-isomer in 94% yield with high diastereoselectivity (93/7). Although the bulkiness of the silyl protecting groups may have affected the diastereoselectivity slightly,

Table 2 Diastereoselective cross-coupling of cyclic halohydrins

Entry[a]	Halide	Product		Yield[b] (%) (*trans*/*cis*)
1			R = H	94 (93/7)
2			R = Ac	96 (55/45)
3			R = $SiMe_2{}^tBu$	96 (70/30)[c]
4			Ar = 4-FC_6H_4	75 (90/10)
5			Ar = 4-$MeOC_6H_4$	93 (89/11)
6			Ar = 2-MeC_6H_4	85 (93/7)
7			Ar = 2-naphtyl	93 (92/8)
8			Ar = 4-biphenyl	94 (93/7)
9			Ar = mesityl	16 (100/0)
10				91 (92/8)[c]
11	 (*trans*/*cis* 10/90)		R = H	83 (25/75)
12			R = Ac	88 (40/60)
13			R = H	67 (90/10)
14			R = Ac	20 (69/31)[c]
15				39 (85/15)[c]
16				91 (92/8)[c]

[a] Reactions were carried out at 80 °C for 12 h on 0.5 mmol scale. [b] Isolated yield. The diastereoselectivity of the product was determined by ^1H NMR and confirmed by GLC analysis. [c] The yields were determined by ^1H NMR analysis.

high-level diastereoinduction was not observed‡[h] (entry 3). Various aryl aluminates possessing electron-rich, electron-deficient, and sterically demanding aromatic groups could participate in the reaction, and gave the product with high diastereoselectivities (entries 4–8).‡[i] The reaction of mesityl aluminate gave the desired product with excellent diastereoselectivity, albeit in low yield,‡[j] showing that the steric demand of the nucleophile also contributes to the high diastereoselectivity (entry 9). The reaction of *cis*-4-chlorocyclohexanol also gave the *trans*-isomer of the cross-coupling product, as in the case of *trans*-4-chlorocyclohexanol, suggesting that the stereochemistry at the newly formed C–C bond is controlled by that of the *in situ* generated alkoxide moiety in the radical recombination step (entry 10). With *cis*-3-chlorocyclohexanol, the *cis*-isomer was obtained as the major product (entries 11 and 12). Acetylated *trans*-2-chlorocyclopentanol gave the desired product in low yield with low diastereoselectivity, whereas *trans*-2-chlorocyclopentanol gave the product in good yield with high diastereoselectivity (entries 13 and 14). With *trans*-2-chlorocyclohexanol, the product was obtained with high diastereoselectivity, but in low yield because of the side reaction that gave cyclopentyl-(phenyl)methanol (entry 15).[14] *trans*-4-Bromocyclohexanol gave essentially the same result as that of the corresponding chloride (entry 16). Because high diastereoselectivities have been observed when a bulky substituent, such as *tert*-butyl[7e] or siloxyl[3a,c] groups, is in the cyclic alkyl halide substrates, we consider that the observed diastereoselective induction is caused by the bulkiness of aluminium alkoxide: it is likely to exist in the form of an aluminium alkoxide oligomer, thereby acting as a sterically demanding substituent.[15]

In summary, we have demonstrated the unique iron-catalysed cross-coupling reaction between halohydrins and aryl aluminates.

The aluminium alkoxide generated *in situ* through deprotonation of the hydroxyl group of halohydrin by aryl aluminate did not cause the expected catalyst poisoning; instead, in contrast to the initial expectation, the reaction rate was enhanced, and high-level diastereoselectivity was induced, thus providing a first illustration of the synthetic potential of this protective-group-free strategy in catalytic cross-coupling reactions.

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Notes and references

‡ (a) SciOPP is the abbreviation for Spin-Control-Intended *Ortho*-Phenylene bisPhosphine. (b) We interpreted that the reactivity difference between **5f** and **5e** is derived from whether or not the reactive ferrate species **A** in Fig. 2 is formed with the organoaluminate species. (c) A study to find effective dummy ligands on aryl aluminate is ongoing, see ESI.† (d) The result of the reaction of phenyl metal reagents is shown in ESI.† (e) See details in ESI.† (f) Neutral $FeAr_2$–SciOPPs, which are the reactive species in the cross-coupling of alkyl halides previously reported by us (ref. 5), showed poor reactivities toward primary alkyl chlorides. (g) Radical clock experiments are described in ESI.† (h) The aluminum alkoxide did not improve the diastereoselectivity as shown in ESI.† (i) Further studies to reduce the amounts of aryl ligands by screening of dummy ligands and the use of functionalized aryl aluminum reagents are currently underway. (j) The starting material was recovered (*ca.* 80%).

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