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Chromium-Catalyzed Asymmetric Dearomatization Addition Reactions of Halomethyl Heteroarenes

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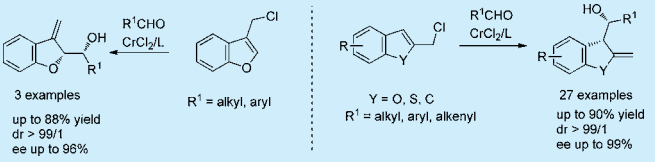
Supporting Information

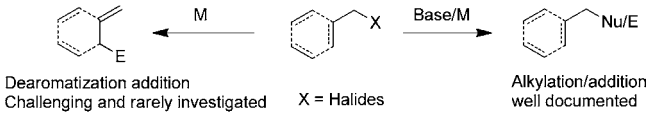
ABSTRACT: The first asymmetric dearomatization addition reaction of halomethyl arenes including benzofuran and benzothiophene was enabled by chromium catalysis. A variety of aldehydes served as suitable electrophiles under mild reaction conditions. Molecular complexities are quickly increased in a highly diastereo- and enantioselective manner.



Dearomatization reactions are attractive methods to quickly build complex and diverse molecular architectures from simple, flat aromatic molecules.[1] More importantly, the resulting alicyclic systems are frequently observed in bioactive natural products and pharmaceuticals. In recent years, catalytic asymmetric dearomatization (CADA) reactions have drawn broad research interest and have become a powerful synthetic method.[2,3] Thanks to efforts from many research groups, excellent enantiomeric excess values have been achieved through substrate design and exquisite subtle control of the stereoselectivities in many elegant catalytic dearomatization reactions such as hydrogenation of heteroarenes,[2b] oxidative dearomatizations,[3a,c,d,f,i,j,m] and alkylative[3g,l] and arylative dearomatizations.[3b,h,n,o]

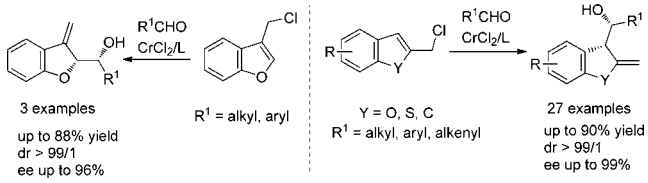
Among various aromatic materials, halomethyl arenes are one class of important building blocks which are widely utilized in alkylation related transformations. However, to the best of our knowledge, catalytic dearomative addition occurring at its γ position, i.e. electrophile added on arenes, has been rarely investigated, not to mention the enantioselective version.[4] The major challenge to realize this dearomative reactivity is to circumvent the direct benzylic addition upon metal activation (Scheme 1).Undoubtedly, a new strategy to address this issue would be synthetically useful and mechanistically interesting, not only opening new possibilities for these stock chemicals but also adding a valuable variant to the fast growing asymmetric dearomatization research field.

Scheme 1. Reactions of Halomethyl Arenes



Chromium mediated Grignard-type addition of carbohalides to aldehyde, well-known as the NHK (Nozaki–Hiyama–Kishi) reaction when Ni salt cocatalyzes, has proven to be one of the most powerful synthetic methods for carbon–carbon bond formation.[5] In line with our own interests in chromium-catalyzed asymmetric transformations with functionalized carbohalides,[6] we envisioned the feasibility of dearomatization of halomethyl arenes upon chromium catalysis for two reasons. First, the fact that allyl-chromium reagents prefer to react at its γ end might offer a chance to overcome the aromaticity of halomethyl arenes.[5f] Second, the fixed *E* olefin geometry of halomethyl arenes leads to the favored configuration of allylchromium species for *anti*-products through a cyclic Zimmermann–Traxler-type chair transition state.[11c] Herein, we wish to report our preliminary results on chromium-catalyzed highly stereoselective dearomatization addition reactions of halomethyl hetereoarenes with aldehydes (Scheme 2).

Scheme 2. CADA Addition of Halomethyl Arenes with Aldehydes



At the outset, 2-(chloromethyl)benzofuran was selected as a model substrate to test this hypothesis; we chose benzofuran not only because of its relatively weak resonance stabilization which facilitates the dearomatization but also because of the fact that 5-membered hetereoarenes represent one class of privileged structural units in organic syntheses. We first investigated the reaction of 2-(chloromethyl)benzofuran and dihydrocinnamaldehyde under standard NHK conditions without a ligand, i.e. a catalytic amount of $CrCl_2$, stoichiometric

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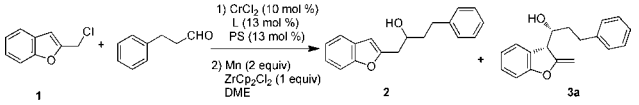
amount of Mn as reductant, and TMSCl as dissociating reagent.[7] To our delight, a small amount of desired dearomatized coupling compound **3a** did form together with benzylic adduct **2** as a major product (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions



entry[a]	ligand	solvent	temperature	yield[b] (%) of **2**	yield[b] (%) of **3a**	ee[c] (%) of **3a**
1[d]	–	THF	rt	40	5	–
2	–	THF	rt	55	20	–
3	**L1**	THF	rt	9	81	89
4	**L2**	THF	rt	12	66	30
5	**L3**	THF	rt	6	79	69
6	**L4**	THF	rt	10	85	95
7	**L5**	THF	rt	9	80	91
8	**L6**	THF	rt	14	68	82
9	**L4**	CH_3CN	rt	10	75	86
10	**L4**	DME	rt	–	92	95
11[e]	**L4**	DME	rt	–	80	92
12	**L4**	DME	0 °C	–	93	96
13	**L4**	DME	−10 °C	–	90	98
14	**L4**	DME	−20 °C	–	74	97
15[f]	**L4**	DME	−10 °C	–	82	97
16[g]	**L4**	DME	−10 °C	–	89[h]	99

[a]The reactions were carried out at 0.2 mmol scale; $ZrCp_2Cl_2$ was employed unless noted otherwise. [b]Measured by ^1H NMR analysis using 1,1,2,2-tetrabromoethane as internal standard. [c]Determined by chiral HPLC analysis. [d]TMSCl instead of $ZrCp_2Cl_2$ was employed. [e]$CrCl_3$ was employed. [f]5 mol % $CrCl_2$ and 7 mol % **L4** were employed. [g]1 mmol of aldehyde was used. [h]Isolated yield. TMS = trimethylsilane; Cp = cyclopentadienyl; PS = proton sponge (N1,N1,N8,N8-tetramethylnaphthalene-1,8-diamine).

Notably, only one diastereomer of **3a** was observed. TMSCl was changed to well-behaved $ZrCp_2Cl_2$, and a much improved yield of **3a** was obtained (Table 1, entry 2).[8] Encouraged by this result, we tested asymmetric catalysis of the coupling reaction using modified Nakata ligand **L1** (Figure 1).[6,9]

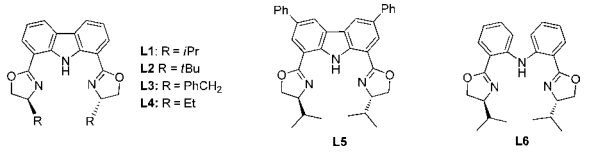


Figure 1. Tested ligands.

Delightfully, the coupling reaction proceeded even better with much less formation of **2** (9% yield) and more of **3a** (81% yield), and the ee of **3a** was determined to be 89% by chiral HPLC analysis; again, only one diastereomer was observed (Table 1, entry 3). The following ligand screening showed that less-hindered **L4** with the ethyl substitution was the most effective one, giving **3a** in 85% yield with 95% ee (Table 1, entry 6). Ligand **L2** with the sterically demanding *t*Bu group was not effective for this reaction; **3a** was obtained in 66% yield with 30% ee (Table 1, entry 5).

Ligand **L3** with benzyl groups gave a much lower enantioselectivity (69% ee). For more information, ligands **L5** reported by Nakada[9] and **L6** by Guiry[10] were both tested, providing **3a** in 80% yield with 91% ee and 68% yield with 82% ee, respectively (Table 1, entries 7 and 8). The above results indicated the rigid ligand backbone benefits the overall efficiency.[11] Using **L4** as the ligand, a few solvents were then examined. DME gave the best result, affording **3a** in 92% yield with 95% ee; notably, the formation of **2** was minimized to a negligible amount (Table 1, entry 10). Air-stable $CrCl_3$ was also tested, giving the product in 80% yield with comparable 92% ee (Table 1, entry 11). Lowering the temperature to −10 °C further improved the reaction; the product **3a** was obtained in 90% yield with 98% ee, and **2** was not detected by crude NMR (Table 1, entry 12). A significant amount of aldehyde remained unreacted when the reaction occurred at −20 °C, but the enantioselectivity was essentially the same (Table 1, entry 14). The impact of various deviations from the standard reaction conditions was also evaluated. A lower catalyst loading ($CrCl_2$ 5 mol %, **L4** 7 mol %) resulted in a decreased yield and ee (82% yield, 97% ee, Table 1, entry 15). No extra additives are necessary for this reaction, which significantly simplified the reaction setup. Notably, the reaction scale could be increased to 1 mmol with maintenance of the efficiency, giving **3a** in 99% ee (Table 1, entry 16).

The absolute configuration of the product **3a** (>97% ee) was unambiguously identified to be (*R*,*R*) by single crystal X-ray diffraction analysis.[12] Based on this experimental result, a possible transition state was suggested to account for the preferential formation of the (*R*,*R*)-enantiomer of the product (Figure 2).

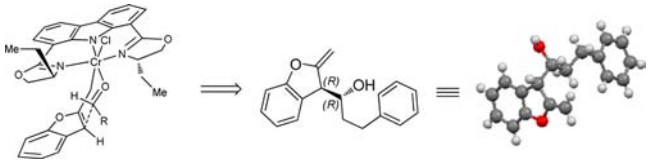


Figure 2. Proposed transition state.

With the optimized reaction conditions in hand, the substrate scope was promptly investigated. We first checked the dearomative coupling of 2-(chloromethyl)benzofuran with various aldehydes; moderate to good yields (65%−91%) and excellent diastereoselectivity (>99/1) and enantioselectivity (92−98% ee) were obtained (Scheme 3). Aliphatic aldehydes including cyclopropyl carboxyaldehyde and 5-chloropentanal participated in the coupling reaction efficiently; the corresponding dearomative products **3b** and **3c** were isolated in good yield with excellent enantiomeric excess (96% and 95% ee respectively). A range of *α*,*β*-unsaturated aldehydes such as cinnamaldehyde, (*E*)-3-(4-fluorophenyl)acrylaldehyde, and (*E*)-hex-2-enal also reacted well, providing dearomatized products **3d**−**3f** in high enantiomeric excess (97%−98% ee). It is worth noting that this dearomatization addition protocol works equally well with aryl aldehydes including benzaldehyde and thiophene-2-carbaldehyde, producing the corresponding arylated secondary alcohols **3g**−**3h** in moderate yields with excellent enantiomeric excess (92% ee and 96% ee). These optimal conditions can also be expanded to reactions with 2-(chloromethyl)benzothiophene, and an even higher enantioselectivity ranging between 91% and 99% ee was observed (Scheme 3). Aliphatic aldehydes including dihydrocinnamaldehyde, 5-chloropentanal, cyclohexyl carboxyaldehyde,

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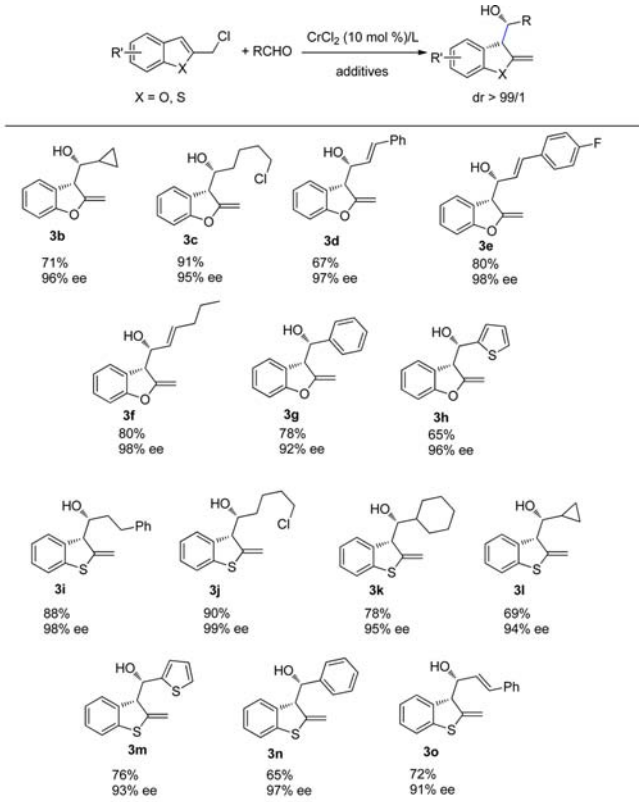
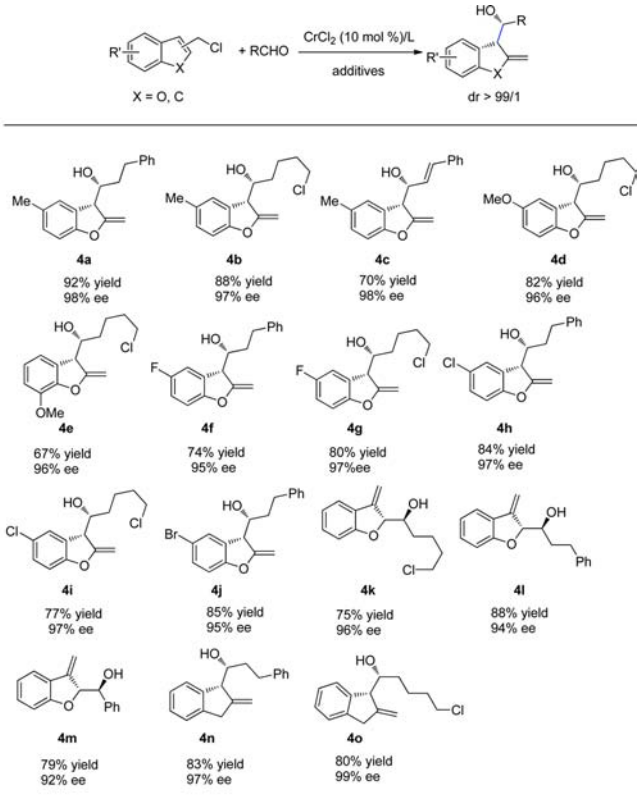
Scheme 3. Substrate Scope Studies[a]



[a]All reactions carried out at 0.2 mmol scale under the standard conditions; ligand (*S*)-**L4** was used unless otherwise noted. The absolute configurations of products were assigned by analogy.

Scheme 4. Substrate Scope Studies[a]



[a]All reactions carried out at 1 mmol scale under the standard conditions; ligand (*S*)-**L4** was used unless otherwise noted. The absolute configurations of products were assigned by analogy.

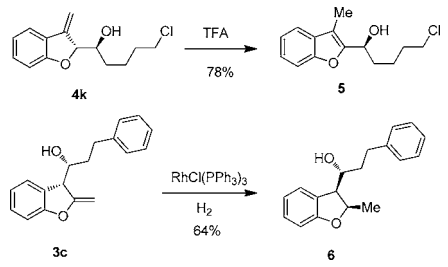
heptaldehyde, and cyclopropyl carboxyaldehyde all reacted well; the resulting **3i**–**3l** were isolated in high yields with excellent enantiomeric excess (91% ee to 99% ee). Again, both benzaldehyde and thiophene-2-carbaldehyde are suitable substrates for this reaction as well, giving products **3m** and **3n** in 76% yield with 94% ee and 65% yield with 97% ee, respectively. Reaction of cinnamaldehyde proceeded smoothly to give product **3o** in 72% yield with 91% ee.

The benzene ring of 2-(chloromethyl)benzofuran could be freely functionalized (Scheme 4). 2-(Chloromethyl)-5-methylbenzofuran performed slightly better than its unmethylated counterpart; the corresponding products **4a**–**4c** by coupling with 5-chloropentanal, dihydrocinnamaldehyde, and cinnamaldehyde were obtained in moderate to good yields with excellent ee (97%–98%). A stronger electron-donating group, a methoxy group, was compatible under current reaction conditions. Notably, changing the position of the methoxy on the phenyl ring did not impose an evident influence on the yield and enantioselectivity since 5- and 7-substituted substrates offered the corresponding products **4d** and **4e** with the same enantioselectivities (96% ee each). Halides including F, Cl, and Br were well tolerated under the standard conditions; the corresponding product **4f**–**4j** were obtained in moderate to good yields and high ee (95% –97%). A preinstalled bromo-group on benzene ring allows further functionalization through standard cross-coupling reactions. To our delight, 3-(chloromethyl)-benzofuran proved to be a suitable substrate for this dearomatization addition reaction as well. Excellent ee's (92% to 96%) of the elaborated products **4k**–**4m** were obtained from the reactions of 3-(chloromethyl)-benzofuran with 5-chloropentanal, cinnamaldehyde, and cyclohexyl carboxyaldehyde.

For comparison, 2-chloromethyl indene was also prepared and subjected to the standard conditions; to our delight, the coupling with dihydrocinnamaldehyde and 5-chloropentanal proceeded smoothly to give highly functionalized benzene ring-fused cyclopentane in good yields with excellent ee (97% and 99%).

The highly functionalized products could be further elaborated. As shown in Scheme 5, treatment of dearomatized

Scheme 5. Synthetic Utilities of Dearomatized Products



product **4k** with trifluoroacetic acid gave the rearomatized compound **5** with a disubstituted benzofuran segment which is frequently present in bioactive natural products and synthetic molecules.[13] Compound **3c** could undergo facile hydrogenation in the presence of Wilkinson's catalyst to produce compound **6** which contains three contiguous stereogenic centers; notably, only one diastereomer was observed from this reaction.

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In summary, the first asymmetric dearomatization addition reaction of readily available halomethyl heteroarenes with a broad range of aldehydes was realized under chromium-catalyzed conditions, leading to optically pure elaborated molecules with two adjacent stereogenic centers. Remarkable features of the reaction include the mild reaction conditions and excellent chemo-, regio-, diastereo-, and enantioselectivities. Future work will focus on expanding this catalytic system to other halomethyl arene systems and applying this protocol to the syntheses of complex molecules with biological and medicinal significance.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00559.

Experimetal procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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