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Chromium-Catalysed Asymmetric Dearomatization Addition Reactions of Bromomethylnaphthalenes

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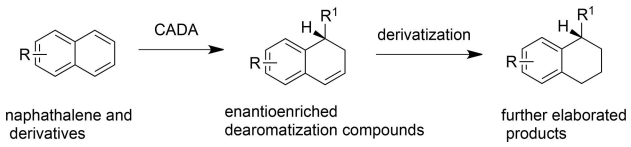
Abstract: The asymmetric dearomatization and addition reaction of bromomethylnaphthalenes with aldehydes proceeded smoothly in the presence of carbazole-based bisoxazoline $CrCl_2$ complex to give the corresponding enanioenriched hydroxylated dearomatization products. The excellent chemo-, regio-, diastereo- and enantioselecitivity are remarkable. Furthermore, hydrogenation of the product led to highly elaborated compound containing three contiguous stereogenic centers.

Keywords: symmetric; Dearomatization; Chromium catalysis; Naphthalene; Aldehyde

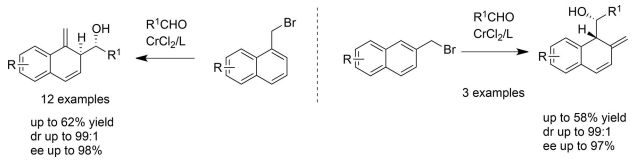
Development of efficient methods for the synthesis of optically pure alicyclic compounds constitutes one of the most active and important topics in synthetic organic chemistry due to the wide occurrence and broad applicability of chiral aliphatic carbocycle molecules. Among the methods established, the dearomatization reactions of arenes has become a straightforward and powerful tool since the aromatic compounds are stable and widely available.[1] Over the past several years, Catalytic Asymmetric DeAromatization (CADA) reaction has developed into a reliable synthetic method and quite a few aromatic systems underwent dearomatization reactions in a highly diatereoselective and enantioselective manner.[2,3] several elegant asymmetric dearomatization of naphthalenes have been reported to construct a variety of benzocyclohexane derivatives which occurs widely as an important structural core in complex natural products and pharmaceuticals agents (Scheme 1).[3d,i,j,n] Halomethyl naphthalenes are one class of important building blocks leading to alkylated products. Dearomatization-type reaction of halomethylnaphthalenes have been scarcely investigated in palladium catalysed coupling reactions[4] and Grignard reaction with aldehyde.[5] To the best of our knowledge, the asymmetric version remains an unmet challenge. Undoubtedly, new strategy to address this issue would be synthetically useful and mechanistically interesting, not only opening new possibilities for this stock chemicals but also offering a facile and potent entry to enantioenriched cyclohexane and derivatives.[6a]



Scheme 1. Reactions of Halomethyl Arenes.

We recently reported the first asymmetric dearomatization addition reactions of halomethyl heteroarenes with broad range of aldehydes under the chromium-catalyzed conditions leading to highly functionalized heterocycles.[6a] In line with our continuing interest on asymmetric chromium catalysis,[6] herein, we wish to report our preliminary results on the successful expansion of this novel strategy to bromomethylnaphthalenes. A series of optically pure highly functionalized dearomatization products can be readily accessed under chromium-catalyzed reaction conditions (Scheme 2).

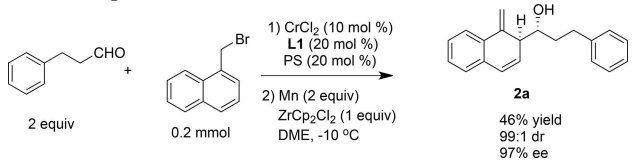
At the outset of this study, commercially available 1-(bromomethyl)naphthalene was selected as model substrate to test this idea. We first investigated the reaction of 1-(bromomethyl)naphthalene and dihydrocinnamaldehyde under standard NHK conditions without ligand (i.e., a substoichiometric amount of $CrCl_2$, stoichiometric amount of Mn as reductant, TMSCl as dissociating reagent).[7] To our delight, a



Scheme 2. CADA Addition of Bromomethyl Naphthalene with Aldehydes.

small amount of desired dearomatized coupling compound **2a** did form with only one diastereomer was detected by ^{1}H NMR. In addition, no benzylic adduct was observed (Table 1, entry 1). TMSCl was changed to well-behaved $ZrCp_2Cl_2$, a much improved yield of **2a** was obtained (Table 1, entry 2).[8] Encouraged by this result, we tested asymmetric catalysis of the coupling reaction using modified Nakada ligand **L1**.[6,9] Delightfully, the coupling reaction proceeded even better (40% yield), and the ee of **2a** was determined to be 60% by chiral HPLC analysis; again, only one diastereomer was observed (Table 1, entry 3). The following ligands screening showed that Ligand **L2** and **L3** with sterically demanding Ph group and iBu group were not effective for this reaction; **2a** was obtained with marginal ee (<10%) (Table 1, entry 4 and entry 5).less-hindered **L4** with the ethyl substitution was less effective, giving **2a** in 39% yield with 30% ee (Table 1, entry 6; Figure 1).

Table 1. Optimization of the Reaction Conditions.



Entry[a]	Ligand	Solvent	Temp	Yield[b] [%]	ee[c] [%]
1[d]	–	THF	rt	5%	–
2	–	THF	rt	20	–
3	**L1**	THF	rt	40	60
4	**L2**	THF	rt	30	10<
5	**L3**	THF	rt	25	10<
6	**L4**	THF	rt	39	30
7	**L5**	THF	rt	40	40
8	**L1**	CH_3CN	rt	<10%	–
9	**L1**	DME	rt	45	89
10	**L1**	DME	0 °C	46	93
11	**L1**	DME	−10 °C	46	97
12	**L1**	DME	−20 °C	14	-
13[e]	**L1**	DME	−10 °C	47	97

[a] The reactions were carried out at 0.2 mmol scale, $ZrCp_2Cl_2$ was employed unless noted otherwise.
[b] isolated yield.
[c] Determined by chiral HPLC analysis.
[d] TMSCl instead of $ZrCp_2Cl_2$ was employed.
[e] 0.5 mmol of bromide was used. TMS = trimethylsilane; Cp = cyclopentadienyl; PS = proton sponge (N1, N1, N8, N8 – tetramethylnaphthalene – 1, 8-diamine).

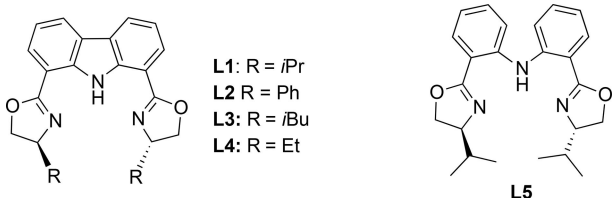


Figure 1. Tested ligands.

For more information, ligand **L5** by Guiry[10] was tested, providing **2a** in 40% yield with 40% ee (Table 1, entry 7). [11] Using **L1** as ligand, a quite few solvents were then examined, DME gave the best result, affording **2a** in 45% yield with 89% ee (Table 1, entry 9). Lowering the temperature to −10 °C further improved the reaction, the product **2a** was obtained in 46% yield with 97% ee (Table 1, entry 11). Notably, the reaction scale could be increased to 0.5 mmol with maintenance of the efficiency, giving **2a** in 97% ee (Table 1, entry 13). The moderate yield was due to the decomposition of the unstable dearomized product during the work-up which is in accord with the observations in a literature precedent.[5]

Relying on a single crystal X-ray analysis in previous dearomatization of 2-chloromethyl benzofuran study[6a] and a proposed working transition model (Figure 2), the configuration of the product **2a** (>97% ee) was tentatively assigned to be (*S*, *R*) (Figure 2).

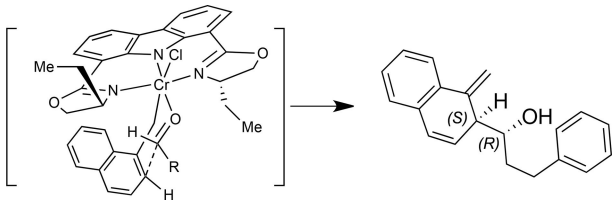
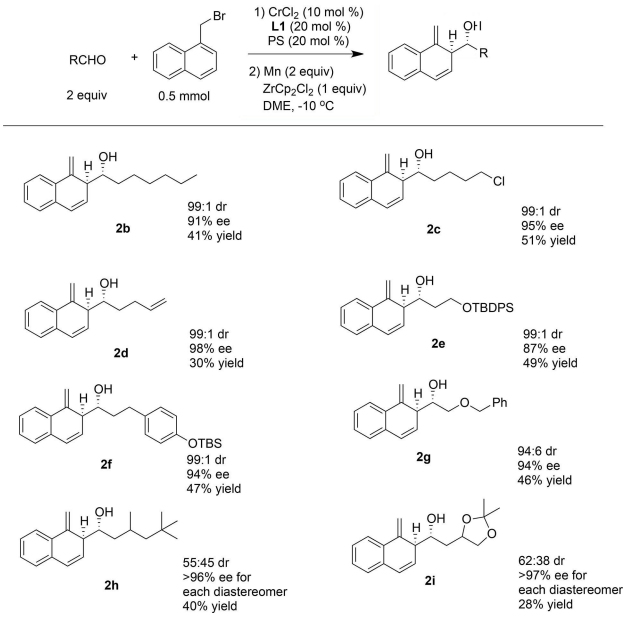


Figure 2. Proposed transition state.

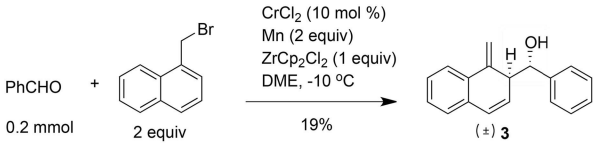
With the optimized reaction conditions identified, the coupling of various aldehydes with 1-(bromomethyl)naphthalene was explored (Scheme 3). Linear aliphatic aldehyde, heptanal participated in coupling reaction efficiently, the corresponding dearomative products **2b** was isolated in good yield with excellent enantiomeric excess 91% ee.

A terminal chloro group was well tolerated under the standard conditions, as 5-chloropentanal reacted well, giving the desired **2c** in 51% yield with 95% ee. Aldehyde **1d** bearing a terminal double bond was



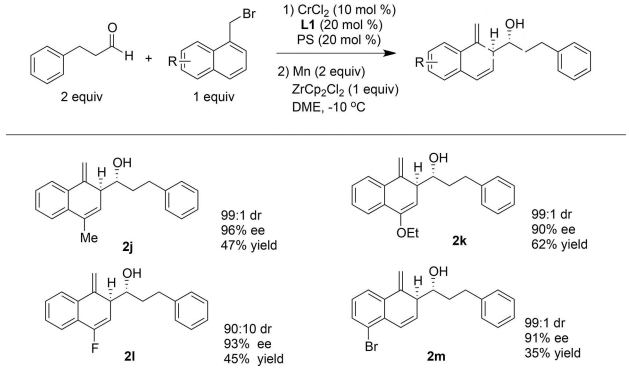
Scheme 3. Substrate Scope Studies.

suitable substrate for this reaction, product **2d** was isolated in 30% yield with 98% ee. A range of hydroxyl protecting groups such as TBDPS, TBS and benzyl were examined, providing dearomatized products **2e**–**2g** in high enantiomeric excess (87%–94% ee). The reaction of naturally occurring aldehyde racemic citronellal proceeded well, affording product **2h** as a mixture of two inseparable diastereomers in 55:45 ratio and over 96% ee for each diastereomer. A sensitive ketal moiety was compatible under current reaction conditions, as **2i** was obtained in 28% yield as a mixture of two diastereomers at the ratio of 62:38 with both highly enantioenriched (>97% ee each). Aryl aldehydes and α, β-unsaturated aldehydes were also examined, after numerous trials, unfortunately, we could not obtain enough amount of products for characterization due to the quick decomposition of the dearomatized products under weak acidic conditions. Interestingly, in the absence of the chiral ligand, coupling of 1-(bromomethyl)naphthalene and benzaldehyde did proceed to provide the racemic **3** as a single diastereomer (Scheme 4).



Scheme 4. Substrate Scope Studies.

The effect of naphthalene substituents was examined next. To our delight, naphthalene ring of 1-(bromomethyl)naphthalene could be freely functionalized (Scheme 5), rendering this methodology with added synthetic value. A weak electron donating methyl group could be introduced at the 4 position of 1-(bromomethyl)naphthalene, an equal level of reaction efficiency in terms of product yield and enantioselectivity (96% ee) was observed.

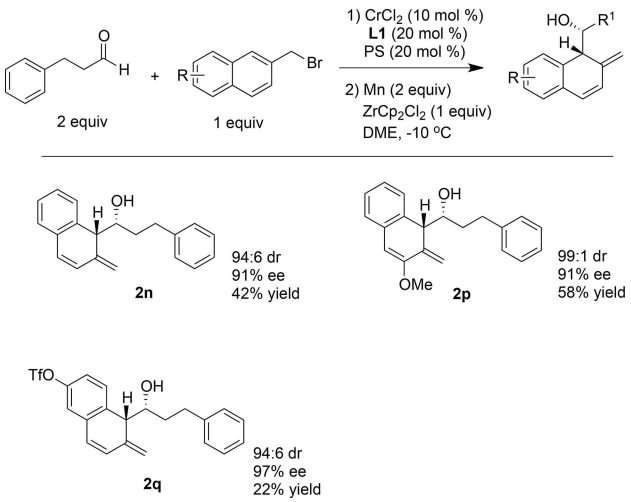


Scheme 5. Substrate Scope Studies.

A strong electron donating ethoxy group at the 4 position didn't significantly impact the dearomatization addition process on yield and stereoselectivity, in this case, a slightly dropped enantioselectivity 90% ee but better isolation yield was identified. Interestingly, a pharmaceutically useful fluorine functionality could be installed at the same position, product **2l** was obtained in moderate diastereoselectivity (90/10 dr) and good enantioselectivity (93% ee). Furthermore, a bromo substitution was allowed which provides a platform for facile derivatization through traditional transition-metal-catalyzed cross coupling reactions.

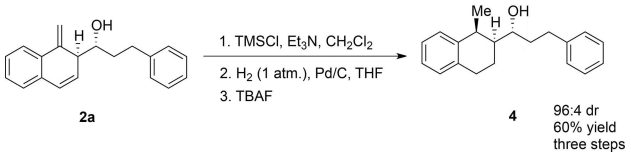
This dearomatization addition protocol could be extended to 2-(bromomethyl)-naphthalene and derivatives (Scheme 6). The reaction of 2-(bromomethyl)-naphthalene with dihydrocinnamaldehyde proceeded smoothly to give the **2n** in useful level of yield with slightly decreased diastereoselectivity and good enantioselectivity. To our delight, a methoxy group could be introduced at the 3 position to give the highly functionalized product **2p** in good yield with excellent dr and ee. In addition, a triflate group could be allowed at the 6-position of naphthalene which serves as a surrogate to halide for further functionalization transformations.

The highly functionalized products could be further elaborated. As shown in Scheme 7, compound **2a** could undergo a three-step sequence procedure, TMS protection, global hydrogenation and desilylation to afford product **4** which contains three contiguous



Scheme 6. Substrate Scope Studies.

stereogenic centers, notably, only one diastereomer was observed from this reaction.



Scheme 7. Synthetic Utilities of Dearomatized Products.

In summary, the first asymmetric dearomatization addition reaction of readily available halomethylnaphthalene and derivatives with a variety of aldehydes was realized under chromium-catalysed conditions, leading to optically pure elaborated molecules with two adjacent stereogenic centers. The mild reaction conditions, excellent chemo, regio, diastereo and enantioselectivities are remarkable. 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.

Experimental Section

Typical procedure for the dearomatization of bromomethyl naphthalene.

To a mixture of anhydrous chromium(II) chloride (6.1 mg, 0.05 mmol), 1,8-bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-9H-carbazole (L-2, 25.0 mg, 0.07 mmol) and Proton sponge (13.9 mg, 0.07mmol) was added DME (2.0 ml) under an nitrogen atmosphere. The mixture was stirred vigorously at room temperature for 2 h before it was transferred into a vessel charged with $Zr(Cp)_2Cl_2$ (146 mg, 1.0 mmol), and Manganese powder (54 mg, 1.0 mg), and Bromomethyl Naphthalene (0.05 mmol). Then aldehyde (1.0 mmol) was added. The resulting suspension was left stirred at −10 °C for 24 hrs. After the full consumption of Bromomethyl Naphthalene, the reaction mixture was diluted with solvent of ethyl acetate (10 mL) and Et_3N (0.2 mL). Then resulting suspension was filtered over a pad of silica gel using cosolvent (Hexane: EA = 2:1) as eluent. Volatiles were evaporated *in vacuo*. The residue was purified by Et_3N basified chromatography to afford the final product.

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