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A Rare Ruthenium(II)-Catalyzed Inert C-H Bond Activation Assisted by a Chiral Transient Directing Group

Guozhu Li, Qinzhe Liu, Laxmaiah Vasamsetty, Weicong Guo, and Jun Wang*

Abstract: *A ruthenium(II)-catalyzed asymmetric intramolecular hydroarylation assisted by a chiral transient directing group has been developed. A series of 2,3-dihydrobenzofurans bearing chiral all-carbon quaternary stereocenters have been prepared in remarkably high yields (up to 98%) and enantioselectivities (up to >99% ee). By this methodology, a novel asymmetric total synthesis of CB2 receptor agonist MDA7 has been successfully developed.*

Transition-metal-catalyzed asymmetric reactions involving inert C-H activation is one of the most challenging research frontiers in modern organic chemistry, which attracts increasing attention of researchers.[1] It features high atom- and step-ecomomy. Various high-value-added enantioenriched chiral compounds could be prepared from structurally simple chemicals. So far, many transition metal catalysts have proved competent to this task, especially with the palladium[2] and rhodium[3] catalysts being the most powerful. To our surprise, however, the comparatively inexpensive ruthenium catalysts are seldom seen in literatures on the asymmetric inert C-H activation,[4] despite great success having been achieved in the corresponding non-asymmetric inert C-H activation.[5]

Notably, since Yu's pioneering work in 2016,[6] the chiral transient directing group (TDG)-assisted,[7] palladium-catalyzed asymmetric inert C-H activation has been emerging as an efficient tool in organic synthesis.[8] The major characteristics of this strategy is that the chiral TDG assisting the C-H activation and enantiocontrol can form and decompose automatically in situ. In addition, the amount of chiral reagent (typically amino acid) to form the chiral TDG is substoichiometric.

In the early 2019, we introduced the chiral TDG strategy into the rhodium(III)-catalyzed asymmetric C-H activation for the first time,[9] in which a chiral primary aliphatic amine and an achiral $CpRh^{III}$ were used (Cp means cyclopentadienyl ligand). It is noteworthy that $CpRh^{III}$ catalyst features a piano stool geometry with three open coordination sites, which is quite distinct from the palladium complex taking a square planar geometry with four open coordination sites. It is maybe due to this reason that the bidentate chiral TDG from the related palladium chemistry is found no longer compatible with $CpRh^{III}$ catalyst. Instead, the mono-dentate chiral TDG was found effective. In view of the resemblance of Ru^{II}(*p*-cymene) species to the $CpRh^{III}$ in geometry, it was speculated that the chiral TDG strategy might be also suitable for Ru^{II}(*p*-cymene) catalyst. According to this idea and with our continuous interest in asymmetric C-H activation reactions,[9-10] we launched this study with the purpose of exploring a solution to the mainly underdeveloped ruthenium-catalyzed asymmetric inert C-H activation (Figure 1a).

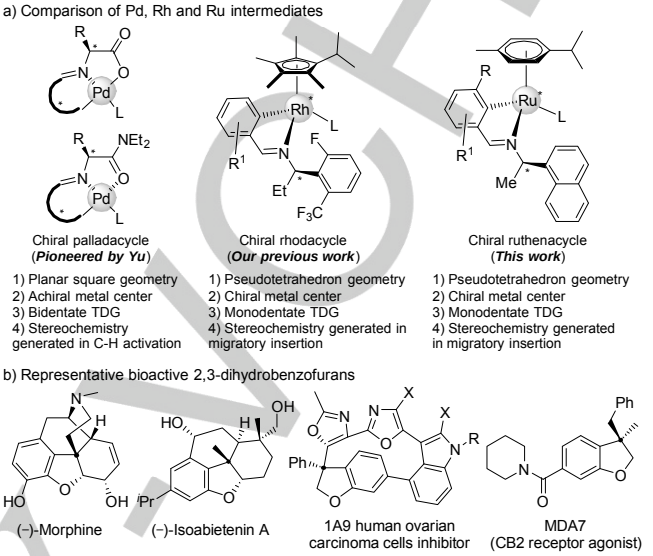
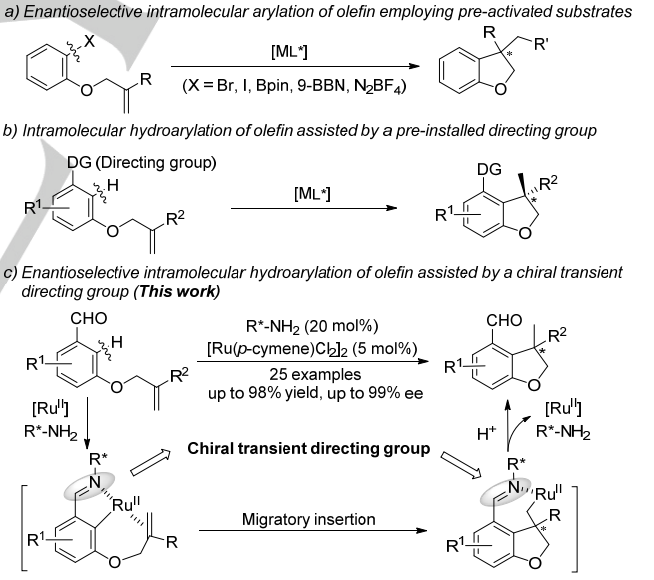


Figure 1. Comparison of Pd, Rh and Ru intermediates and representative bioactive 2,3-dihydrobenzofurans.



Scheme 1. Enantioselective synthesis of 2,3-dihydrobenzofuran.

The chiral 3,3-disubstituted 2,3-dihydrobenzofuran skeleton bearing an all-carbon quaternary stereogenic carbon center exists in many natural products and bioactive molecules, such as morphine, isoabietenin A, 1A9 human ovarian carcinoma cells inhibitor,[11] and cannabinoid type 2 (CB2) receptor agonist MDA7[12] (Figure 1b). However, construction of this structural motif as well as its associated enantiocontrol is highly challenging.[13] Recently, some elegant progress has been achieved by transition-metal-catalyzed asymmetric intramolecular annulations with various pre-activated substrates such as olefin-tethered aryl halides,[14] diazonium salts,[15] and boronic reagents[16] (Scheme 1a). Intriguingly, the analogous asymmetric annulations have been realized by the directing

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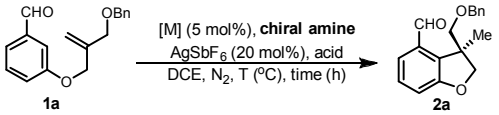
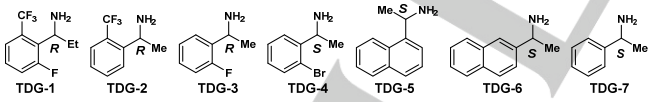
group-assisted C-H activation promoted by either rhodium(I)[17] or rhodium(III)[18] catalyst (Scheme 1b).[19] Herein, we described a ruthemium-catalyzed enantioselective synthesis of chiral 3,3-disubstituted 2,3-dihydrobenzofuran by the TDG strategy (Scheme 1c). [20] A series of 2,3-dihydrobenzofurans with chiral all-carbon quaternary stereocenters were obtained in high yields (up to 98%) and high enantioselectivities (up to >99% ee) promoted by catalytic amounts of [Ru(*p*-cymene)Cl_2]$_2$ and a cheap chiral amine. Furthermore, this methodology was successfully applied to the asymmetric total synthesis of CB2 receptor agonist MDA7.

Table 1. Optimization of reaction conditions[a]



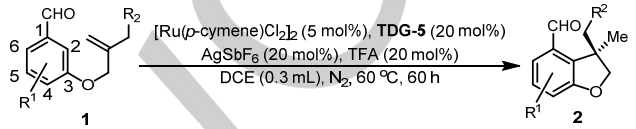
entry	[M]	chiral amine	acid (mol%)	yield (%)	ee (%)
1	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-1**	PivOH (50)	64	56
2	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-1**	PivOH (0)	trace	ND
3	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-2**	PivOH (50)	30	87
4	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-3**	PivOH (50)	11	80
5	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-4**	PivOH (50)	21	91
6	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-5**	PivOH (50)	21	96
7	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-6**	PivOH (50)	2	74
8	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-7**	PivOH (50)	trace	71
9	[Cp*$RhCl_2$]$_2$	**TDG-5**	PivOH (50)	60	83
10	[Cp*$IrCl_2$]$_2$	**TDG-5**	PivOH (50)	trace	ND
11[b]	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-5**	PivOH (50)	43	98
12[b]	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-5**	TFA (50)	61	98
13[b,c]	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-5**	TFA (50)	96	98
14[b,c]	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-5**	TFA (20)	86	98
15[b,d]	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-5**	TFA (20)	**96**	**98**
16[b,d,e]	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-5**	TFA (20)	92	98
17[b,d,f]	[Ru(*p*-cymene)Cl_2]$_2$	**TDG-5**	TFA (20)	80	98

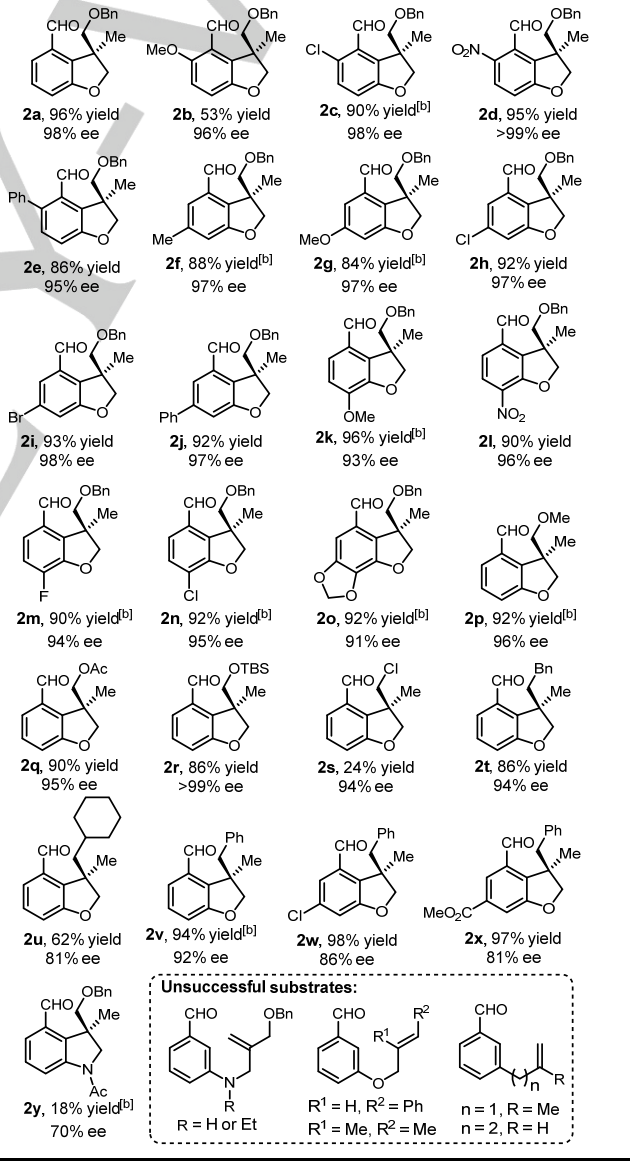
[a] Under nitrogen atmosphere, **1a** (0.1 mmol, 1.0 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%), $AgSbF_6$ (20 mol%), chiral amine, acid, DCE (0.3 mL), at 70 °C for 24 h. [b] At 60 °C. [c] 48 h. [d] 60 h. [e] [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%). [f] [Ru(*p*-cymene)Cl_2]$_2$ (1 mol%).



To commence our study, the olefin-tethered aldehyde **1a** was prepared from readily available 3-hydroxybenzaldehyde. Initial investigations revealed that the desired product **2a** could be obtained in 64% yield with 56% ee in the presence of of [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%), $AgSbF_6$ (20 mol%), chiral amine **TDG-1** (40 mol%), and pivalic acid (PivOH, 50 mol%) in DCE at 70 °C for 24 h (Table 1, entry 1). It should be mentioned that when L-*tert*-leucine was used instead, no reaction occurred. In addition, the reaction did not proceed in the absence of acid (entry 2). Screening a series of chiral amines indicated **TDG-5** was the best, furnishing the product **2a** in 21% yield and 96% ee (entries 3-8). Interestingly, [Cp*$RhCl_2$]$_2$ gave inferior results, and [Cp*$IrCl_2$]$_2$ proved inactive (entries 9−10). Lowering the reaction temparature to 60 °C could improve both the yield and enantioselectivity (entry 11). Examining various acids indicated trifluoroacetic acid (TFA) was the best (entry 12). Prolonging the reaction time to 48 h led to an exceptional result of 96% yield and 98% ee (entry 13). Gladly, both the loading of **TDG-5** and that of TFA could be reduced to 20 mol%, giving the product in a slightly decreased yield (86%) with 98% ee (entry 14). To our delight, the yield restored to 96% by simply extending the reaction time to 60 h (entry 15). Reducing the loading of [Ru(*p*-cymene)Cl_2]$_2$ led to slightly lower yields (entries 16-17). For more detailed optimization of reaction conditions, please refer to Supporting Information (SI, Tables S1-S6).

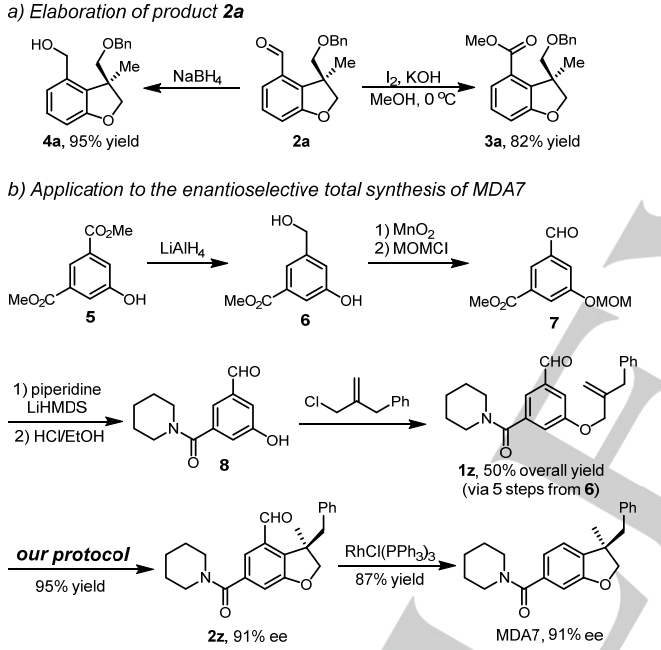
Table 2. Substrate scope.[a]





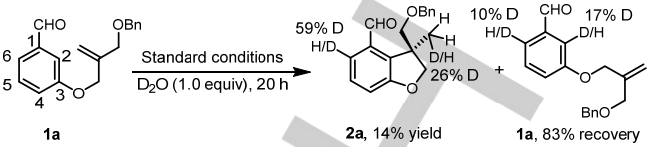
[a] Under nitrogen atmosphere, **1a** (0.1 mmol, 1.0 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), chiral amine (20 mol%), acid (20 mol%), DCE (0.3 mL), at 60 °C for 60 h. [b] **TDG-5** (40 mol%), TFA (40 mol%), 60 °C, 60 h.

Under the optimized reaction conditions, the substrate scope was explored (Table 2). It was found that the substrate **1** bearing either electron-withdrawing or electron-donating substituent on the arene ring was tolerable, giving the desired products in high yields and excellent enantioselectivities (**2a–o**). Besides, substrates bearing diverse allyl groups were also found compatible with the reaction conditions (**2p−x**). However, attempt to extend this methodology to the corresponding indoline synthesis proved less successful, for instance, affording the N-Ac indoline **2y** in 18% yield with 70% ee. Some unsuccessful substrates were also shown in Table 2. To check the practicability of this protocol, the model reaction was performed on a 5.0 mmol scale. The product **2a** was obtained in 94% yield (1.33 g) with 98% ee, which could be facilely transformed into potential useful intermediates such as ester **3a** (82% yield) and alcohol **4a** (95% yield) via I_2-mediated oxidation[21] and $NaBH_4$ reduction, respectively (Scheme 2a).



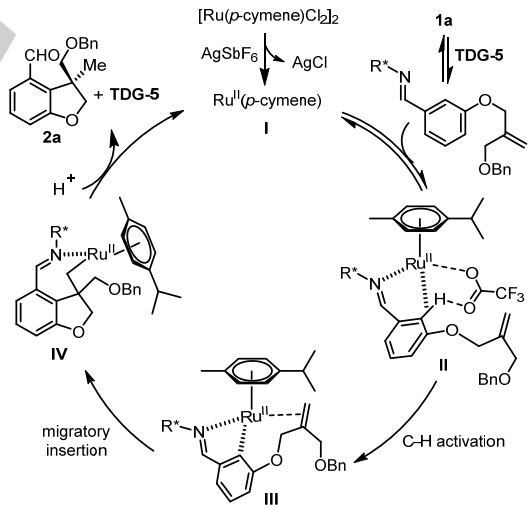
Scheme 2. Elaborations of product **2a** and enantioselective total synthesis of CB2 receptor agonist MDA7.

Significantly, by taking advantage of this methodology, a novel asymmetric total synthesis of CB2 receptor agonist MDA7 was explored and got successful (Scheme 2b). First, the alcohol **6** was prepared by partial reducing the readily available diester **5**. Upon sequential oxidation by MnO_2, phenolic hydroxy protection with MOMCl, aminolysis of ester by piperidine, deprotection of MOM group and then allylation, **6** was transformed to the substrate **1z** in 50% overall yield via five steps. Conveniently, no purification was needed until the final step. Then, **1z** was subjected to our standard catalytic conditions to afford the desired product **2z** in 95% yield with 91% ee. Lastly, removal of the formyl group in **2z** by Tsuji-Wilkinson decarbonylation gave the CB2 receptor agonist MDA7 in 87% yield with 91% ee. It should be noted that either enantiomer of **2z** could be respectively preapred by employing (*R*) and (*S*)-configured chiral amine.



Scheme 3. H/D Exchange experiment.

To gain some mechanistic insights, the hydroarylation of **1a** was carried out in the presence of D_2O (1.0 equiv) for 20 h. The product **2a** was isolated in 14% yield together with 83% of the recovered starting material **1a** (Scheme 3). The significant deuterium rates at the *ortho* positions of the formyl groups in **2a** (59% D) and the recovered **1a** (10% and 17% D) suggest the C-H activation process is reversible. Moreover, for the recovered **1a**, the higher deuterium rate at the 2-position (17% D) than that at the 6-position (10% D) implies higher reactivity of the former position towards C-H activation, which might be attributed to its more electronrichness. Moreover, the deuterium rate (59% D) at the *ortho* position of the formyl group in **2a** is much higher than that in the recovered **1a**. It indicates that if the C-H activation occurs at the 6-position (unproductive way), the resulting ruthenium intermediate can rapidly reverse to imine-ruthenium complex by protonation and redirect the C-H activation onto the 2-position (productive way). This whole process shoud proceed faster than the imine decomposition. Otherwise, the deuterium rate at the *ortho* position of the formyl group in **2a** would be comparable to that in **1a** (about 10% D). In addition, incorporation of 26% of D into the 3-methyl group in **2a** implies the existence of a RCH_2-Ru intermediate in the catalytic cycle.



Scheme 4. Proposed reaction mechanism.

Based on the above results and previous studies,[9, 22] a plausible reaction mechanism is proposed (Scheme 4). First, dechlorination of $[Ru(p\text{-cymene})Cl_2]_2$ by $AgSbF_6$ generates the catalytically active species **I**. The imine generated from substrate **1a** and the chiral amine **TDG-5** coordinates to the ruthenium in

the species **I** to form the intermediate **II**. With the assistance of trifluoroacetate, the *ortho* C-H bond is cleaved possibly via a concerted metalation-deprotonation (CMD) mechanism to give the ruthenacycle **III**. Coordination of the tethered olefin followed by migratory insertion provides the intermediate **IV**. After protonation of C-Ru bond and hydrolysis of imine, the product **2a** is delivered together with the recovery of the ruthenium species **I** and the chiral amine **TDG-5**.

In summary, we describe a rare ruthenium-catalyzed inert C-H bond activation assisted by a chiral transient directing group. A series of chiral 3,3-disubstituted 2,3-dihydrobenzofurans bearing all-carbon quaternary stereogenic carbon centers have been constructed in high yields and high enantioselectivities. The synthetic utility of this methodology has been demonstrated by its successful application in the asymmetric total synthesis of CB2 receptor agonist MDA7. A plausible reaction mechanism is depicted.

Acknowledgements

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Keywords: asymmetric catalysis • C-H activation • ruthenium(II) • CB2 receptor agonist • chiral transient directing group

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[20] A relevant study on the synthesis of indolines by Cui and coworkers (ref. 4d) appeared when we were preparing our manuscript. It is worth noting that in Cui's work a chiral carboxylic acid (30 mol%) was also used, which is crucial to achieve satisfied yields and enantioselectivities.

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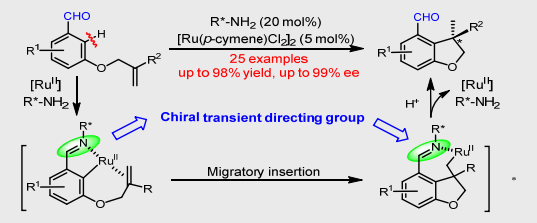

Assisted by a chiral transient directing group, a highly enantioselective ruthenium-catalyzed intramolecular hydroarylation via inert C-H activation process has been realized in up to 98% yield and 99% ee using a readily available and inexpensive metal catalyst [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%) and a chiral primary amine (20 mol%).

*G. Li, Q. Liu, L. Vasamsetty, W. Guo, Prof. Dr. J. Wang**

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A Rare Ruthenium(II)-Catalyzed Inert C-H Bond Activation Assisted by a Chiral Transient Directing Group