CHEMISTRY
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Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201900762

Link to VoR: http://dx.doi.org/10.1002/chem.201900762

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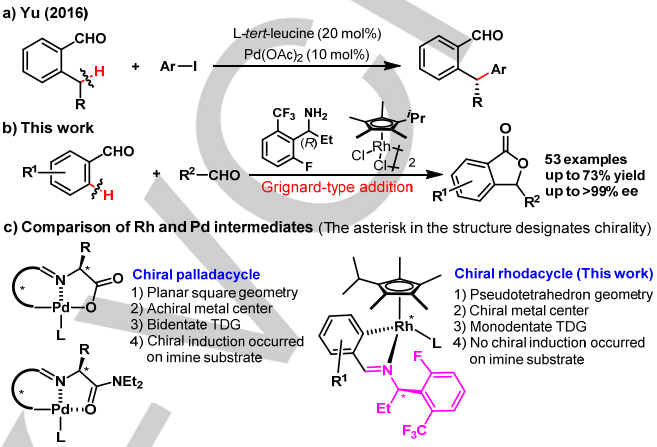
Introducing Chiral Transient Directing Group Strategy to Rhodium(III) Catalyzed Asymmetric C-H Activation

Guozhu Li, Jijun Jiang, Hui Xie, and Jun Wang*

Abstract: The chiral transient directing group (TDG) strategy has been successfully introduced to the rhodium(III) catalyzed asymmetric C-H activation. In the presence of a catalytic amount of a chiral amine and an achiral rhodium catalyst, various chiral phthalides were synthesized from simple aldehydes in high chemoselectivity, regioselectivity, and enatioselectivity (53 examples, up to 73% yield and >99% ee). It is noteworthy that the chiral induction model is different from the previously reported chiral TDG system using amino acid derivatives and palladium salts. The imino group generated in situ from chiral amine and aldehyde acts as the monodentate TDG to promote the C-H activation, stereoselectively generating the chiral rhodacycle bearing a chiral metal center. Moreover, the stereogenic center of the product is created and stereo-controlled during the Grignard-type addition of C-Rh bond to aldehyde, rather than during the C-H activation step.

Over the past two decades, transition-metal catalyzed C-H bond activation has attracted much attention of chemists and achieved tremendous progress.[1] This strategy features high atom-economy and step-economy. Remarkably, it has found great utility in the synthesis of complex organic molecules by being able to provide shorter synthetic routes starting from simpler starting materials.[2] Among various strategies to achieve inert C-H bond activation, the most intensively studied one should be the directed C-H activation using directing group (DG) to coordinate to the transition-metal of a catalyst to facilitate C-H activation.[3] Although great success has been achieved, the most notable drawback associated with this strategy might be having to pre-install DG beforehand and remove it after the reaction.[4] Encouragingly, this problem is partially overcome by the strategy of using transient directing group[5] (TDG) pioneered by Jun and coworkers[6], in which the DG is installed (typically in a small amount) and removed in situ automatically during the reaction process. Moreover, as it could be easily imagined, if a chiral transient directing group is introduced, it is possible to achieve an asymmetric catalytic C-H activation reaction. However, it is a very challenging task. It was not until 2016 that the first example of asymmetric C-H activation reaction employing chiral TDG was achieved by Yu and coworkers,[7] in which the chiral amino acid L-*tert*-leucine was used to form a bidentate TDG in situ to assist the $Pd(OAc)_2$ catalyzed enantioselective benzylic $C(sp^3)$–H arylation of aldehydes (Scheme 1a). Similar catalyst systems have later been applied to other asymmetric C-H activation reactions.[8] However, despite those achievements, using chiral TDG to achieve the



Scheme 1. Asymmetric C-H Activation with Chiral Transient Directing Group

asymmetric C-H activation is still very rare. And especially, the reported catalyst systems are only limited to the combined use of chiral amino acid derivatives and palladium catalyst. Therefore, it is highly desirable to develop both new chiral catalyst systems and new transformations to enrich the chemistry of chiral TDG strategy.

It is well konwn that CpRh(III) catalyzed C-H activation has achieved great success,[9] where Cp is cyclopentadienyl ligand. Notably, the asymmetric CpRh(III) catalyzed C-H activation has also been realized by various strategies, including designing artificial metalloenzyme,[10] employing chiral Cp ligands,[11] combining achiral CpRh(III) catalyst with an external chiral anion[12] or acid[13], and using chiral substrate[14]. But to the best of our knowledge, asymmetric CpRh(III) catalyzed C-H activation by chiral TDG strategy is still unkonwn.[15] In 2013, Seayad[16] reported a synthesis of phthalides[17] by the $[Cp^*RhCl_2]_2$ catalyzed Grignard-type addition[18] of C-H bonds to aldehydes with 4-trifluoromethyl aniline as the TDG forming reagent. To make this reaction enantioselective, we developed and describe herein an efficient chiral TDG catalyst system consisting of a chiral amine and an achiral rhodium(III) catalyst. Various chiral phthalides (53 examples) have been prepared from simple aldehydes in up to 73% yield and >99% ee (Scheme 1b). It is noteworthy that the chiral induction mechanism is quite different from that of the previously reported chiral TDG system using amino acid derivatives and palladium salts (Scheme 1c). Firstly, assisted by a monodentate chiral TDG, the rhodacycle generated via the C-H activation is chiral at metal owing to the pseudotetrahedral geometry of rhodium(III) complex. Secondly, the stereogenic center of the product is created and stereo-controlled during the Grignard-type addition of C-Rh bond to aldehyde, rather than in the C-H activation step.

To commence our research, the rhodium(III) catalyzed homocoupling reaction of benzaldehyde was selected as the

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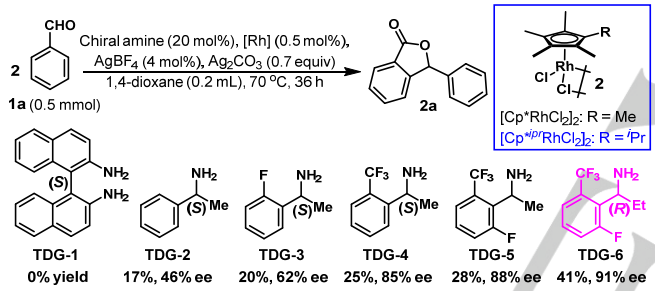
model reaction (Table 1). It was assumed that the key to achieve our research goal is to find out a suitable chiral amine. According to Seayad's study,[16] only electron-deficient aromatic amine was effective for this reaction, whereas aliphatic amine such as cyclohexylamine only gave trace amount of product. Therefore, with $[Cp^*RhCl_2]_2$ as the catalyst, the chiral aromatic amine (*S*)-1,1'-binaphthyl-2,2'-diamine **TDG-1** was examined first, but unfortunately no desired product was detected. Considering the actuality that chiral aliphatic amines are much more readily available than chiral aromatic amines, we still decided to take a chance to attempt some chiral aliphatic amines. Gratifyingly, the chiral aliphatic amine (*S*)-1-phenylethylamine **TDG-2** offered a promising result of 17% yield and 46% ee. Based on this clue, more than 30 chiral amines analogous to (*S*)-1-phenylethylamine were screened (Table S5). Selected results were shown in Table 1. Finally, the self-made chiral amine **TDG-6** was identified as the best. The reason might be that the fluoro and trifluoromethyl groups at 2- and 6-positions of phenyl ring could properly adjust the steric hidrance and basicity of the chiral amine. And they could also prevent the C-H activation from occurring on its own phenyl ring of chiral amine. Investigation of rhodium(III) catalyst with diverse cyclopentadienyl ligand was also conducted (Table S5), indicating $[Cp^{*ipr}RhCl_2]_2$ was the optimal (64%, 92% ee).

Table 1. Optimization of Reaction Conditions



After optimizing other reaction conditions (Tables S1-7), the optimal were identified as $[Cp^{*ipr}RhCl_2]_2$ (1 mol%), $AgBF_4$ (8 mol%), Ag_2CO_3 (0.7 equiv), **TDG-6** (20 mol%), in 1,4-dioxane and at 70 °C, under which the substrate scope of homocoupling reaction of aromatic aldehyde was examined (Table 2). In general, both electron-poor and electron-rich aldehydes were applicable. Various functional groups were well tolerated. Notably, for *meta*-substituented aldehyde, the reaction occurred regioselectively at the less hindered C-H bond (e.g., **2c**, **2d**, **2e**).

Subsequently, we turned to the heterocoupling reaction of two different aldehydes, which is more challenging because four possible products may be produced. To our surprise, when 4-methylbenzaldehyde and 3,5-difluorobenzaldehyde were subjected to the optimal homocoupling reaction conditions, only two types of products were detected. The major one was the heterocoupling product **2p**, and the minor one was the homocoupling product **2f**. The yield and enantioselectivity for the heterocoupling reaction could be further improved to 44% yield and 96% ee by slightly adjusting the reaction conditions (for details, see Tables S8-10). Under this modified reaction conditions, more examples were examined for the heterocoupling reaction of aldehyedes (Table 3). In general, the C-H bond activation occurred on aldehydes with electron-donating groups, followed by coupling with electron-deficient aldehydes to give chiral phthalides with up to 73% yield and up to >99% ee. Heterocoupling of two electron-rich aldehydes could also proceed but was less successful. Intriguingly, 4-methyl benzaldehyde and 3-methyl benzaldehyde could react with [1,1'-biphenyl]-4-carbaldehyde to give the phthalides **2v** (29% yield,

Table 2. Scope of Homocoupling of Aryl Aldehydes

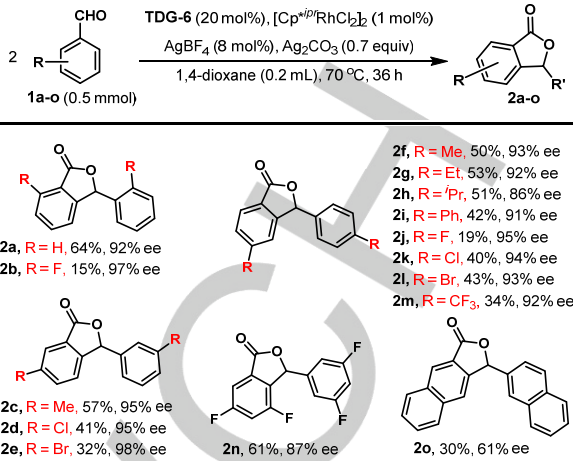
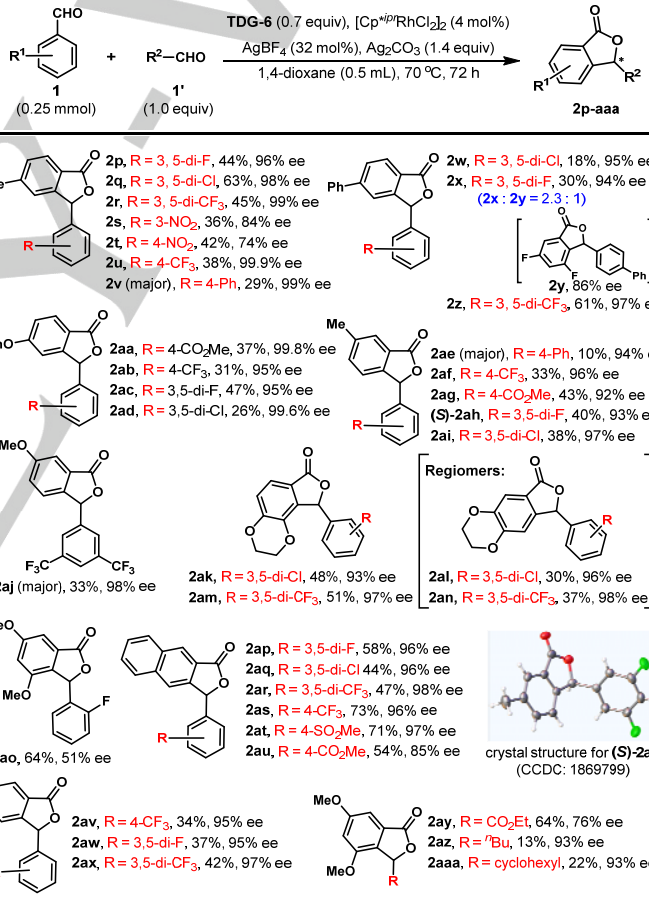
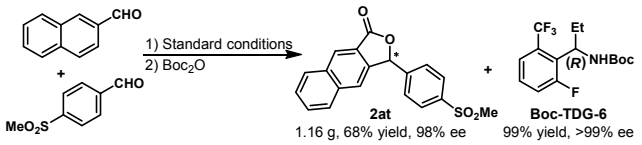


Table 3. Scope of Heterocoupling of Aryl Aldehydes



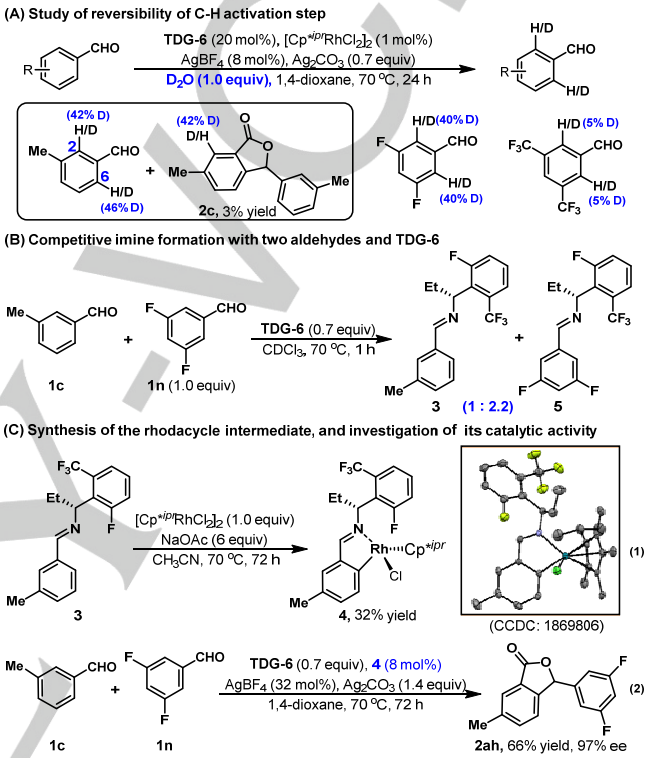
99% ee) and **2ae** (10% yield, 94% ee) as the major products, respectively. In accordance with the homocoupling reaction, no regiomers were detected for the reaction employing 3-methylbenzaldehyde and 2-naphthaldehyde (**2ae**-**2ai**, **2ap**-**2au**). But for reactions with 3-methoxyl benzaldehyde or 1,4-benzodioxan-6-carboxaldehyde, two regiomers were produced in varied ratios (**2aj**-**2an**). Heterocoupling of aromatic aldehydes with aliphatic aldehydes was also possible (**2ay**-**2aaa**). The structure of the product **2ah** was determined by single-crystal X-ray diffraction and the absolute configuration was assigned as *S*.

To examine the practicality of current methodology, a gram-scale heterocoupling reaction of 2-naphthaldehye with 4-(methylsulfonyl)benzaldehyde was carried out. The desired product **2at** was obtained in 68% yield with 98% ee. Remarkably, the chiral amine **TDG-6** could be fully recovered as the form of *N*-Boc-protected amide **Boc-TDG-6** without any loss of enantiopurity (Scheme 2).



Scheme 2. Gram Scale Reaction

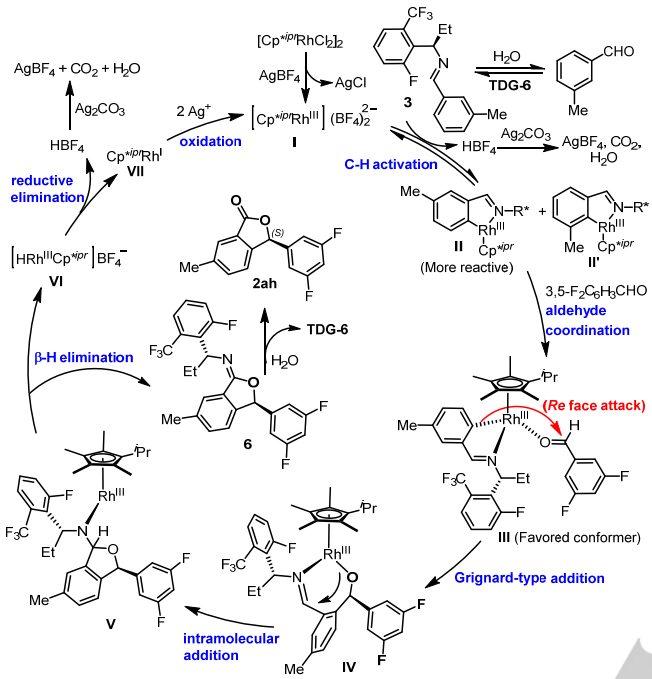
To shed some light on the reaction mechanism, some control experiments were designed. Firstly, when deuteroxide was employed as additive in the homocoupling reaction of 3-methylbenzaldehyde, the deuterated 3-methylbenzaldehyde was generated with 42% D incorporation into the 2-position and 46% D incorporation into the 6-position, suggesting that the C-H activation process is reversible (Scheme 3A). It is noteworthy that there is no significant preference for the deuterium incorporation into the 2- or 6-position of 3-methylbenzaldehyde, implying the 3-methyl group basically don't interfere in the C-H activation process. However, as mentioned earlier, the coupling reactions were highly regioselective and the phthalide products resulted from the C-H activation of 2-C-H bond of 3-methylbenzaldehyde was not detected. It was reasoned that the C-M intermediate II' shown in Scheme 4 generated from the C-H activation of 2-position was unreactive towards the subsequent Grignard-type reaction due to steric reasons. Additionally, the homocoupling product **2c** was also observed with 42% D incorporation into the 7-position, indicating the reverse reaction of C-H activation underwent much faster than the forward Grignard-type reaction from the same C-M intermediate II shown in Scheme 4. To examine the electronic effect on the C-H activation, another two aldehydes including 3,5-difluorobenzaldehyde and 3,5-ditrifluoromethylbenzaldehyde were investigated. Interestingly, while the moderately electron-deficient 3,5-difluorobenzaldehyde could still smoothly undergo the C-H activation, the strongly electron-deficient 3,5-ditrifluoromethylbenzaldehyde could hardly do. This finding was in line with the observed chemoselectivity of heterocoupling reaction. However, the study of competitive imine formation with two electronically different aldehydes (3-methylbenzaldehyde and 3,5-difluorobenzaldehyde) and chiral amine **TDG-6** indicated that the chiral amine preferred the electron-deficient aldehyde to the electron-rich aldehyde with the ratio of 2.2:1 according to ^{1}H NMR analysis (Scheme 3B). Therefore, it was reasoned that although the imine from the electron-rich aldehyde was generated in less amount, it was more reactive towards the C-H activation as well as the subsequent Grignard-type addition to C=O group due to electronic reasons. Evidently, because of significant consumption of chiral amine by electron-deficient aldehyde, higher loadings (0.7 equiv) of the chiral amine **TDG-6** were requisite for the hereocoupling reactions than those for the homocoupling reactions.



Scheme 3. Mechanistic Studies

Secondly, to get a more solid evidence for the C-H activation mechanism, preparation of rhodacyle intermediate was attempted (Scheme 3C). Fortunately, upon treatment of the imine **3** prepared from 3-methylbenzaldehyde and **TDG-6** with $[Cp^{*ipr}RhCl_2]_2$ and sodium acetate, the rhodacylce **4** was isolated in 32% yield (Equation 1).[19] Its structure was determined by single-crystal X-ray diffraction, exhibiting the expected piano-stool type geometry. As there are two C-H bonds in the imine **3** which could possibly undergo C-H activation and the rhodium atom becomes a chiral center in the resulting rhodacycle, regiomers and diastereomers of the rhodacycle **4** may be produced. However, the rhodacycle **4** was the only isomer detected and isolated, indicating it is more thermodynamically stable. It is also assumed that during the C-H activation process the stereochemistry of the chiral rhodium center is fully induced by the chiral imine directing group, with the absolute configuration of rhodium stereogenic center preferring the *R* configuration (assuming the group priority follows the order:

Cp^{*ipr} > Cl > N > C_{aryl}). It is noteworthy that when the pre-catalyst $[Cp^{*ipr}RhCl_2]_2$ was replaced with the chiral rhodacycle **4** to conduct the heterocoupling reaction of aldehydes **1c** and **1n**, the desired product **2ah** was obtained in 66% yield with 97% ee, indicating the dechlorided rhodacycle **4** might be the active intermediate for our described reaction (Equation 2).



Scheme 4. Proposed Reaction Mechanism

According to above mechanistic studies, a proposed catalytic cycle was depicted with the heterocoupling reaction of 3-methylbenzaldehyde and 3,5-difluorobenzaldehyde (Scheme 4). Initially, two aldehydes react competitively with chiral amine **TDG-6** to form the corresponding chiral aldimines, which is a reversible and chemoselective process in favor of forming the electron deficient 3,5-difluorobenzaldimine **5**. However, the rhodium(III) species **I** generated from the pre-catalyst $[Cp^{*ipr}RhCl_2]_2$ and $AgBF_4$ catalyzes the C-H activation of the minor but more reactive chiral 3-methylbenzaldimine **3** to afford the chiral rhodacycle intermediates **II** and **II'**. This C-H activation process is reversible. Owing to the steric hindrance of methyl group, only the intermediate **II** is reactive to undergo further transformations. Based on the single crystal structure of rhodacycle **4**, it is assumed that the coordination of 3,5-difluorobenzaldehyde to rhodium species **II** should occur highly diastereoselectively to give the intermediate **III** with the rhodium adopting the *R* configuration (assuming the group priority follows the order: Cp^{*ipr} > O > N > C_{aryl}). Intramolecular Grignard-type addtiion of aryl to aldehyde from the *Re* face generates the intermediate **IV**, which undergoes an intramolecular attack of imine by the alkoxide to give the intermediate **V**. After β-H elimination, the imine **6** is released, which smoothly hydrolyzes to chiral phthalide **2ah** with the observed (*S*)-configuration. Meanwhile, the rhodium hydride species **VI** is generated, which converts back to the active rhodium(III) catalyst **I** via a sequential reductive elimination and a silver oxidation to close the catalytic cycle. In addition, two molecules of HBF_4 are generated from the whole process, which should react with Ag_2CO_3 to give $AgBF_4$, CO_2 and water.

In summary, a rhodium(III) catalyzed asymmetric C-H activation has been realized by the chiral transient directing group strategy. A series of chiral phthalides have been synthesized in up to 73% yield and >99% ee from very simple and readily available aldehydes. This reaction features high chemoselectivity, regioselectivity, and enantioselectivity. Notably, the rhodacycle intermediate is chiral at rhodium due to its pseudotetrahedral geometry. And the fashion of enantiocontrol is completely different from that of palladium catalysis with chiral TDG.

Acknowledgements

We thank the National Natural Science Foundation of China (Grant 21402244).

Keywords: asymmetric catalysis • C-H activation • rhodium(III) • phthalide • chiral transient directing group

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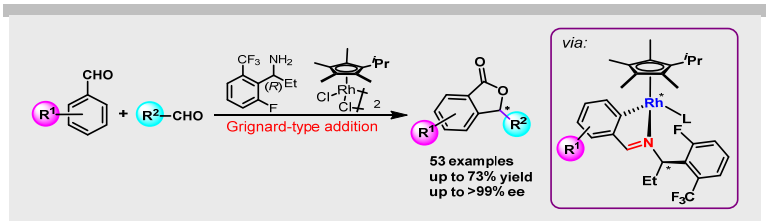

The chiral transient directing group (TDG) strategy has been successfully introduced to the rhodium(III) catalyzed asymmetric C-H activation. In the presence of a catalytic amount of chiral amine and an achiral rhodium catalyst, various chiral phthalides were synthesized from simple aldehydes in high chemoselectivity, regioselectivity, and enatioselectivity (53 examples, up to 73% yield and >99% ee).

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