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Rhodium(III)-Catalyzed Asymmetric Addition of Inert Arene C−H Bond to Aldehydes To Afford Enantioenriched Phthalides

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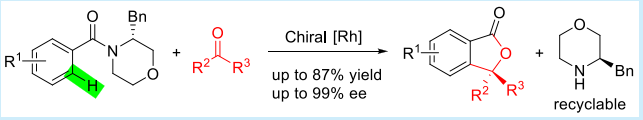
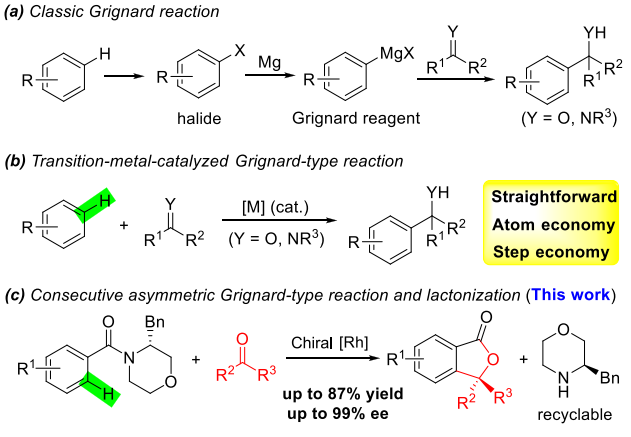
ABSTRACT: An asymmetric rhodium(III)-catalyzed Grignard-type addition of inert arene C−H bond to aldehydes is reported. It provides a new strategy for the synthesis of chiral 3-substituted phthalides in good yields (up to 87%) with high enantiomeric purity (up to 99% ee). Interestingly, a chiral-matching effect between substrate and catalyst was observed, which is crucial to accomplish satisfied reaction outcomes. Mechanistically, the reaction is assumed to proceed via consecutive C(sp^2)−H activation of benzamide, addition to aldehyde, and lactonization.



Transition-metal-catalyzed direct addition of inert hydrocarbon bonds to polar multiple bonds (e.g., C═O and C═N) is known as a Grignard-type reaction.[1] It has gained much interest from chemists because of its appealing advantages in terms of atom economy and step economy (Scheme 1a vs 1b). Though much progress has been made in this field,[1,2] it is still a big challenge to control the stereoselectivity of such reactions.

Scheme 1. Classic Grignard Reaction *versus* Transition-Metal-Catalyzed Grignard-Type Reaction



Regarding asymmetric Grignard-type reactions of aldehydes or ketones, there are rather few reports. In 2009, Shibata et al.[3] revealed the potential of iridium(I)/(*S*)-H_8-BINAP catalyst for the asymmetric intramolecular Grignard-type hydroarylation of ketone, though only one substrate was examined (69% yield, 72% ee). In 2014, Yamamoto et al.[4] successfully developed a highly enantioselective variant of this reaction with an iridium(I)/phosphoramidite catalyst. In 2015, Cramer et al.[5] reported a rhodium(III)-catalyzed asymmetric intramolecular Grignard-type hydroarylation of aldehydes. In contrast to the intramolecular asymmetric Grignard-type reactions, the more challenging intermolecular counterparts are less successful. In 2007, Takai et al.[6] reported a manganese(I)-catalyzed intermolecular Grignard-type hydroarylation of aldehydes, in which promising diastereoselectivities were obtained for some chiral substrates. Recently, we reported an enantioselective rhodium(III) catalyzed Grignard-type homo- and heterocoupling of aldehydes by the chiral transient directing group strategy in high enantioselectivities but low to moderate yields.[7] In addition, examples of asymmetric Grignard-type addition of inert arene C−H bond to imines[8] and polar alkenes[9] are also rare. Evidently, the field of asymmetric Grignard-type additions of inert arene C−H bond to polar multiple bonds is very challenging and still requires more investigation. Encouraged by our previous work on the asymmetric C−H activation reactions,[7,10] we decided to conduct this research and report herein an asymmetric intermolecular Grignard-type addition of an inert arene C−H bond to aldehydes followed by a spontaneous intramolecular lactonization, affording various chiral phthalides in good yields with high enantiopurity (Scheme 1c). It is worth noting that phthalides play a very important role in both total synthesis and pharmaceutical chemistry,[11] and their asymmetric synthesis has attracted much attention from chemists.[5,7,12] However, the asymmetric syntheses of phthalides via inert arene C−H bond addition to aldehyde remains elusive,[7] though the corresponding nonasymmetric counterparts have been well developed.[13]

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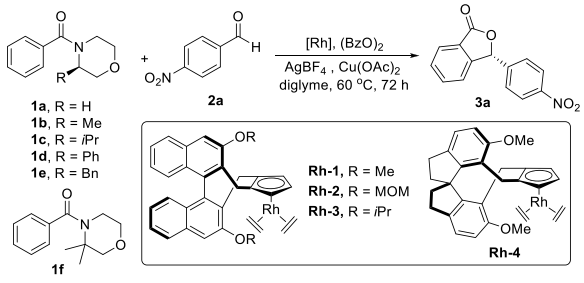
Our preliminary studies indicated that the chiral cyclopentadienyl rhodium catalyst[5,9a,10a,b,14] exhibited high potential for the asymmetric C−H activation reaction of the morpholine benzamide **1a** with *p*-nitrobenzaldehyde **2a** to afford the chiral phthalide product **3a**. Among several structurally tuned chiral cyclopentadienyl rhodium complexes, Cramer's (*R*)-**Rh-1**[14b] proved best, leading to **3a** in 48% yield with 68% ee (Table 1, entries 1−4). Unfortunately, routine optimizations of reaction conditions failed to further improve enantioselectivity. Because the amide structure may greatly impact reaction outcomes, a series of benzamides were investigated (Table S2 in Supporting Information (SI)). Interestingly, when the chiral 3-methylmorpholine amide (*S*)-**1b** was employed as substrate, the enantioselectivity was greatly enhanced to 82% ee (entry 5). However, when the structurally similar but achiral 3,3-dimethylmorpholine amide **1f** was used, only poor enantioselectivity was observed (entry 6). Given the fact that the combined use of chiral substrate and chiral catalyst could significantly improve the enantioselectivity, a series of chiral 3-substituted morpholine amides were studied (entries 7−9). To our delight, the chiral 3-benzylmorpholine amide **1e** provided the best result of 65% yield and 96% ee. The yield could be further enhanced to 80% by simply increasing the catalyst loading to 10 mol % (entry 10). Finally, it was indicated that both the silver and copper additives were indispensible for this reaction (entries 11−13).

Table 1. Reaction Condition Optimizations[a]

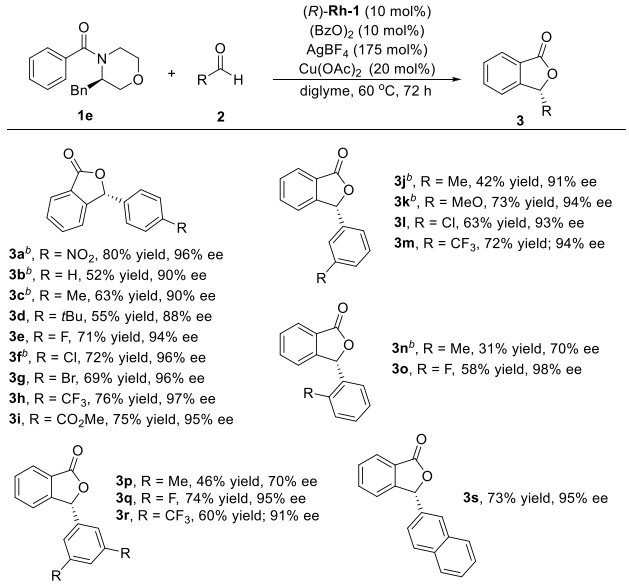


entry	amide	[Rh] (*X* mol %)	yield (%)	ee (%)
1	**1a**	(*R*)-**Rh-1** (5)	48	68
2	**1a**	(*R*)-**Rh-2** (5)	28	52
3	**1a**	(*R*)-**Rh-3** (5)	32	55
4	**1a**	(*S*)-**Rh-4** (5)	40	51
5	(*S*)-**1b**	(*S*)-**Rh-1** (5)	51	82
6	**1f**	(*R*)-**Rh-1** (5)	43	40
7	(*S*)-**1c**	(*S*)-**Rh-1** (5)	45	85
8	(*S*)-**1d**	(*S*)-**Rh-1** (5)	43	69
9	(*R*)-**1e**	(*R*)-**Rh-1** (5)	65	96
10	(*R*)-**1e**	(*R*)-**Rh-1** (10)	80	96
11[b]	(*R*)-**1e**	(*R*)-**Rh-1** (10)	65	89
12[c]	(*R*)-**1e**	(*R*)-**Rh-1** (10)	trace	–
13[d]	(*R*)-**1e**	(*R*)-**Rh-1** (10)	no reaction	–

[a]Amide **1** (0.2 mmol), aldehyde **2a** (0.1 mmol), $(BzO)_2$ (*X* mol %), [**Rh**] (*X* mol %), $AgBF_4$ (175 mol %), $Cu(OAc)_2$ (20 mol %), diglyme (0.1 mL) at 60 °C for 72 h. Isolated yields are reported. [b]In the absence of $Cu(OAc)_2$. [c]In the absence of $AgBF_4$. [d]In the absence of $AgBF_4$ and $Cu(OAc)_2$.

Under the optimized reaction conditions, the scope of aldehyde **2** was examined (Scheme 2). Delightedly, various monosubstituted benzaldehydes bearing electron-donating or electron-withdrawing groups were applicable, affording the corresponding products **3a−o** in moderate to good yields with high ee's. Then, some 3,5-disubstituted benzaldehydes were tested, giving the products **3p−r** in good yields with high enantiomeric purity. 2-Naphthaldehyde also worked well to give the desired product **3s** in 73% yield with 95% ee.

Scheme 2. Substrate Scope for Aldehydes[a]



[a]**1e** (0.2 mmol), **2** (0.1 mmol), (*R*)-**Rh-1** (10 mol %), $(BzO)_2$ (10 mol %), $AgBF_4$ (175 mol %), $Cu(OAc)_2$ (20 mol %), and diglyme (0.1 mL) at 60 °C for 72 h. Isolated yields are reported. The ee values were determined by HPLC. [b]The absolute configuration was assigned to be *R* by comparison of its optical rotation with reported values (see SI).

Then, the scope of benzamide **1** was examined (Scheme 3). It was found that diverse substituted benzamides could be successfully converted to the chiral phthalides **3t−3ad** in good yields with high enantiomeric purity regardless of substitution patterns or electronic properties of substituent. Particularly, when the amides respectively derived from 2-naphthoic acid and 3-methylbenzoic acid were applied, the reactions were found to regioselectively occur at the less hindered sites to give the products **3w** and **3aa**. For the piperonylic acid derived amide, the major regiomer **3x** was obtained in 67% yield with 91% ee, which might be dominated by the electronic effect. Besides, reactions of substituted benzamides with ethyl trifluoropyruvate were also tried, giving the products **3ac−ad** with good enantiomeric purity, albeit in moderate yields.

To check the practicability of this methodology, we attempted to prepare the phthalide **3x** on a large scale (Scheme 4). The product **3x** was obtained in 75% yield with 82% ee. It is worth noting that the chiral morpholine **4** could be recovered in 87% yield without losing any enantiomeric purity (>99% ee). Accordingly, it could be recycled in principle, especially when the reaction is run on a large scale.

To shed some light on the reaction mechanism, some control experiments were conducted. First, chiral matching studies were carried out considering both the amide substrate and rhodium catalyst are chiral in this reaction. By taking the reaction of benzamide (*R*)-**1g** and aldehyde **2b** as the benchmark reaction, as shown in Table 2, it was found that while (*R*)-**Rh-1** led to the product in 57% yield with 96% ee, (*S*)-**Rh-1** resulted in the product in only 14% yield with 4% ee (entries 1−2). Interestingly, when the achiral catalyst

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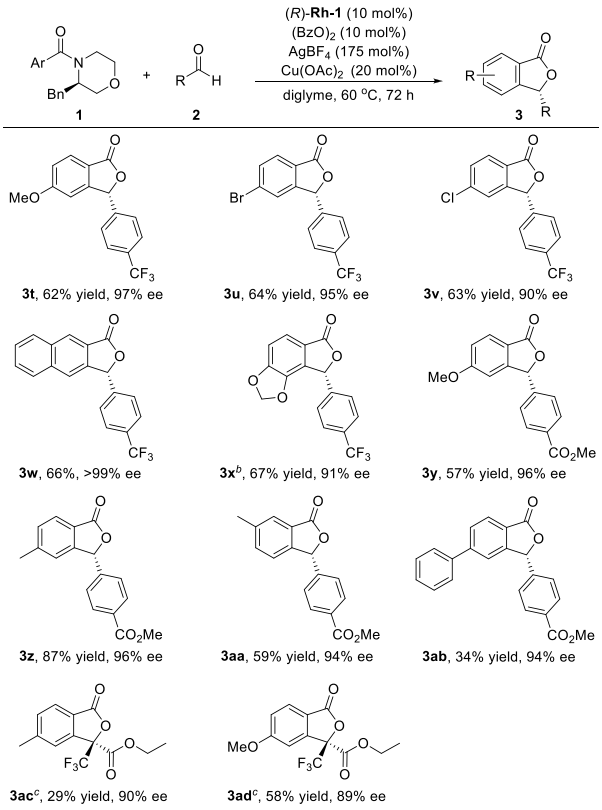
Scheme 3. Substrate Scope for Benzamides[a]



[a]**1** (0.2 mmol), **2** (0.1 mmol), (*R*)-**Rh-1** (10 mol %), $(BzO)_2$ (10 mol %), $AgBF_4$ (175 mol %), $Cu(OAc)_2$ (20 mol %), and diglyme (0.1 mL) at 60 °C for 72 h. Isolated yields are reported. The ee values were determined by HPLC. [b]The regioselectivity is 1:0.3. The major isomer is shown. [c]60 °C, 5 days.

Scheme 4. Large Scale Reaction and Recovery of Chiral Amine

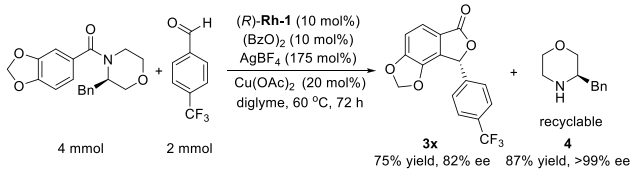
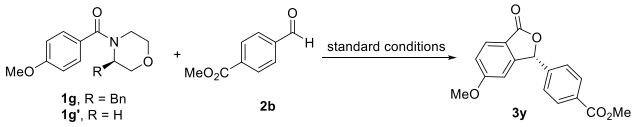


Table 2. Chiral-Matching Experiments[a]



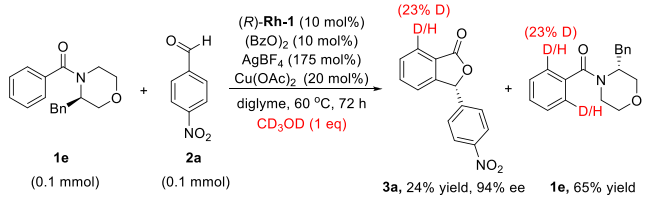
entry	amide	[Rh]	yield (%)	ee (%)
1	(*R*)-**1g**	(*R*)-**Rh-1**	57	96
2	(*R*)-**1g**	(*S*)-**Rh-1**	14	4
3	(*R*)-**1g**	$[Cp^*RhCl_2]_2$	13	59
4	**1g′**	(*R*)-**Rh-1**	32	70

[a]**1** (0.2 mmol), aldehyde **2b** (0.1 mmol), $(BzO)_2$ (10 mol %), [**Rh**] (10 mol %), $AgBF_4$ (175 mol %), $Cu(OAc)_2$ (20 mol %), diglyme (0.1 mL) at 60 °C for 72 h.

$[Cp^*RhCl_2]_2$ was used, the product was obtained with 59% ee, albeit in 13% yield (entry 3). Furthermore, when the achiral amide **1g′** was applied in the presence of (*R*)-**Rh-1**, the product **3y** was obtained in 32% yield with 70% ee (entry 3). Clearly, either the chiral amide or the chiral rhodium catalyst alone was capable of controlling the stereoselectivity of the reaction, though only to a moderate degree. Intriguingly, both the chiral induction and the reactivity were greatly enhanced by combining the chirally matched amide and rhodium catalyst, which might be because a superior chiral environment was created around the catalytic center. In sharp contrast, a chirally mismatched combination only led to an offset of their chiral induction to the reaction.

Second, the reaction of benzamide **1e** with 4-nitrobenzaldehyde **2a** was carried out in the presence of CD_3OD (1 equiv) (Scheme 5). The product **3a** was obtained in 24%

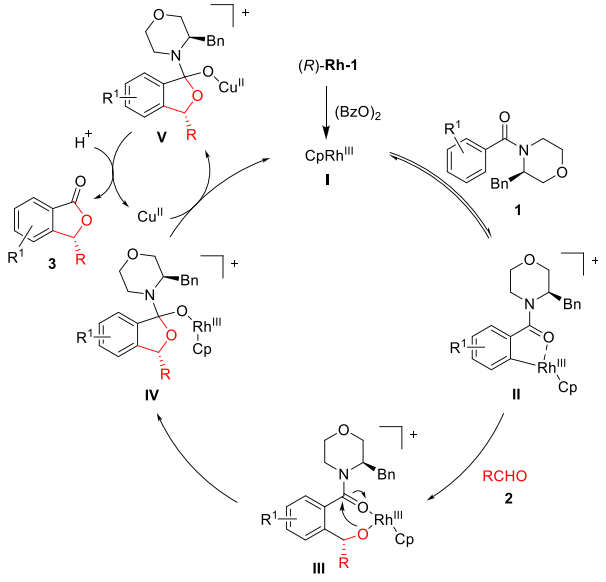
Scheme 5. Deuteration Experiment



yield with a contamination of 23% of **3a**-*d*. Meanwhile, the deuterated benzamide **1e** was recovered in 65% yield. It implied that the C−H activation process was reversible and the rhodacyclic intermediate generated from the C−H activation should react much faster with CD_3OD to regenerate the amide **1e** than with the aldehyde **2a** to deliver the product **3a**.

According to above investigations and previous related studies,[5,7,13] a plausible reaction mechanism is proposed (Scheme 6). First, the chiral precatalyst (*R*)-**Rh-1** is oxidized

Scheme 6. Plausible Reaction Mechanism



to the Rh^{III} complex **I** by $(BzO)_2$. Then, the amide directed C−H activation occurs to give the five-membered rhodacycle **II**, which possibly proceeds via a concerted metalation-deprotonation (CMD) process. Grignard-type addition of **II** to aldehyde **2** affords the intermediate **III**. Although C−H bond additions to unactivated aldehydes are thermodynamically disfavored, **III** is trapped by cyclization upon the amide to

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give the intermediate **IV**. Transmetalation between copper salt and the rhodium alkoxide **IV** might take place to regenerate the catalyst and form the copper alkoxide **V**,[15] which collapses upon protonation to release the product **3**, morpholine and the copper species.

In summary, an asymmetric rhodium(III)-catalyzed intermolecular Grignard-type addition of inert arene C−H bond to aldehydes with subsequent lactonization has been developed, providing an alternative strategy for the synthesis of enantioenriched chiral 3-substituted phthalides (up to 87% yield, 99% ee). Interestingly, a chirally cooperative effect between substrate and catalyst was observed, which proved crucial to accomplish satisfied reaction outcomes. Finally, a plausible reaction mechanism is proposed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01052.

Experimental details, characterization data, ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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