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Rhodium(III)-catalyzed synthesis of phthalides by cascade addition and cyclization of benzimidates with aldehydes†

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Abstract

We herein report the Rh(III)-catalyzed C–H bond activation and addition of benzimidates to aldehydes to afford biologically important phthalides in a single step. The imidate is a novel and unexplored directing group that not only enables C–H bond activation and addition to aldehydes, but also serves to capture the reversibly formed alcohol intermediate. The reaction shows broad scope with a high level of functional group compatibility and is applicable to both aromatic and aliphatic aldehydes.

Introduction

The convergent assembly of alcohols by addition of organometallic reagents to aldehydes is an important and frequently used strategy in synthesis that has been applied extensively to the preparation of drugs, commodity chemicals and materials (eqn (1)). However, significantly greater efficiency with the elimination of stoichiometric metal waste would be accomplished by the transition metal catalyzed direct addition of C–H bonds to aldehydes (eqn (2)). Despite these advantages, relatively few examples of this type of transformation have been reported,^{1,2} particularly when compared to other C–H bond functionalization processes.³ An inherent challenge is the reversible nature of this transformation with the alcohol products only favored when destabilized, highly electron deficient aldehydes are used.^{1b,c}

Organometallic reagent addition

(1)

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(2)

To enable the direct addition of C–H bonds to aldehydes, strategies to overcome the reversibility of this transformation must be explored. Capture of alcohol products as silyl ethers has been accomplished for Ir-, Re-, and Mn-catalyzed additions of specific sp^2 C–H bonds to aldehydes.^{1h–k} More recently, Rh(III)- and Pd-catalyzed additions of selected aromatic C–H bonds to aromatic aldehydes have been achieved by irreversible *in situ* oxidation of the alcohol products to ketones (eqn (3)).^{1a,d,e,g} Here we introduce a new conceptual strategy wherein the directing group for Rh(III)-catalyzed C–H bond functionalization serves an auxiliary role of capturing the alcohol addition products to provide pharmaceutically relevant heterocycles that maintain the alcohol oxidation state (eqn (4)).^{4,5} This approach is specifically demonstrated using the previously unexplored imide directing group to enable efficient and highly functional group compatible coupling of a broad range of aromatic and aliphatic aldehydes to give phthalides, which are present in a variety of bioactive natural products.⁶

(3)

(4)

Results and discussion

We initiated our investigation by testing the Rh(III)-catalyzed addition of methyl benzoate (**1**) to aldehyde **2a** because the ester group is the simplest functionality that might be capable of both directing C–H bond functionalization and accomplishing alcohol capture to give a lactone (Scheme 1). However, even with the very electron-deficient trifluoromethylbenzaldehyde (**2a**), no C–H functionalization product was observed, presumably due to the poor directing ability of the ester group.

We reasoned that it would be necessary to replace the ester group with a more strongly metal coordinating functionality having the ability to capture the alcohol product. The previously unexplored *N*-alkoxy imide (see **3**, Fig. 1) was therefore investigated because it maintains the ester oxidation state and leaving group functionality necessary for alcohol capture while also introducing an oxime directing group, which is particularly effective for Rh(III)-catalyzed C–H functionalization.⁷ We envisioned that reversible addition of **3** to aldehyde **2** would provide alcohol **4**, which would undergo irreversible cyclization *in situ*

with elimination of the methoxy group to give **5**. Hydrolysis would then afford the desired phthalide **6**.

A variety of catalysts and reaction conditions were evaluated for coupling of benzimidate **3a** with 4-chlorobenzaldehyde (**2b**) to afford the phthalide **6a** (Table 1). The cationic rhodium complex, derived from $[\text{Cp}^*\text{RhCl}_2]_2$ and AgSbF_6 , with DCE as solvent efficiently catalyzed the reaction to produce the desired product **6a** in 77% yield (entry 1).⁸ AgBF_4 proved to be as effective as AgSbF_6 (entry 2). Other halide abstractors significantly decreased the yields or gave no desired product (entries 3–7), presumably because coordinating anions compete with the substrates for metal binding. The use of the preformed cationic $\text{Rh}(\text{III})$ precursor $[\text{Cp}^*\text{Rh}(\text{CH}_3\text{CN})_3](\text{SbF}_6)_2$ also was less efficient (entry 8). Additionally, coordinating solvents such as THF resulted in reduced conversion (entry 9). Although *t*-BuOH had previously successfully been employed in $\text{Rh}(\text{III})$ -catalyzed additions of 2-phenylpyridine to imines,^{2c} when this solvent was employed for the preparation of phthalide **6a** no product was observed (entry 10). The reaction is dependent on catalyst loading because the yield dropped to 59% when only 2.5 mol% of $[\text{Cp}^*\text{RhCl}_2]_2$ was employed (entry 11).

Having established the effect of counter anions and solvents on this cascade reaction, we next explored the substrate scope with a diverse set of benzimidates and aromatic aldehydes (Table 2). The reaction shows excellent functional group compatibility, with aldehydes substituted with chloro, fluoro, nitro, ester, and methoxy functional groups all providing 3-aryl phthalides in high yields. While both electron-poor and -rich aromatic aldehydes are suitable for this transformation, the electron-deficient aldehydes afford the products in higher yields (**6d–f** vs. **6c** and **6i**). Moreover, substitution at the *ortho*, *meta*, and *para* positions on aldehydes **2** are all well tolerated.

This reaction is sensitive to the electronic effect of substitution on benzimidates **3**. Electron donating groups result in efficient coupling (**6j**, **k**, **m** and **n**). However, in contrast to the observation that electron-deficient aldehydes result in higher yields, placement of the electron-deficient CF_3 group on the benzimidate reduced the yield to 27% even when the catalyst loading was doubled (**6l**). Importantly, the *meta*-methyl substituted benzimidate exclusively provided the product resulting from C–H activation at the less hindered C–H site (**6o**). Moreover, good yields are maintained even for benzimidates bearing functional groups at the *ortho* position (**6m** and **6n**). The effectiveness of benzimidates with *ortho*-alkoxy substitution is particularly noteworthy, not only because it has previously been reported that an alkoxy group at the *ortho* position can inhibit C–H functionalization *via* chelation,^{2c} but also because a wide range of phthalide natural products incorporate *ortho*-hydroxyl functionality.⁶

We next explored the possibility of extending the substrate scope to unactivated aliphatic aldehydes (Table 3). $\text{Rh}(\text{III})$ -catalyzed additions to this class of aldehydes has not previously been demonstrated even with trapping of the alcohol addition products through oxidation. Conducting the reaction with cyclohexanecarboxaldehyde (**2c**) under the standard conditions afforded the expected phthalide **6q** in only 32% yield (entry 1). Adding 0.5 equiv. of K_2CO_3 to the reaction mixture in an attempt to minimize acid catalyzed aldehyde self-condensation improved the yield to 54% (entry 2). After several failed attempts to further improve the yield, we turned our attention to structural variation of the imidate directing group, in particular, by introducing an *N*-aryl rather than the *N*-methoxy substituent (entries 3–6). The electronic properties of the *N*-aryl substituent had a considerable impact on the reaction yield, with more electron-deficient aryl groups providing the highest yields (entries 5 and 6). The *N*-3,5-bis(trifluoromethyl)phenyl benzimidate (**10a**) proved to be optimal and provided phthalide **6q** in 67% yield (entry 6). Given the success of coupling **10a** with aliphatic aldehyde **2c**, we also examined its coupling to aromatic aldehyde **2a**, and while phthalide

product **6d** was obtained in 71% yield, this was slightly lower than that observed for the corresponding *N*-methoxy benzimidate **3a** (**6d**, Table 2).

With an optimized imidate directing group identified for additions to aliphatic aldehyde **2c**, a range of different aldehydes **2** was surveyed (Table 4). This transformation was found to be very general with linear and sterically hindered aldehydes providing phthalides in good yields (**6t** and **6s**, respectively). Moreover, oxygen functionality could be placed at the α -position of the aldehyde to provide sites for additional synthetic transformations. Both *N*-methoxy benzimidate (**3a**) and *N*-3,5-bis(trifluoromethyl)phenyl benzimidate (**10a**) were evaluated for each of the aliphatic aldehydes with benzimidate **10a** providing higher yields for almost all of the aldehydes examined. The only exception was α -benzyloxyacetaldehyde for which benzimidate **3a** provided phthalide **6u** in a significantly higher yield.

The Rh(III) catalyst used here is stable to air and water, and therefore, the feasibility of performing this novel transformation on the bench top was examined to enhance the practicality of the method (Scheme 2). Coupling reactions between benzimidate **3a** and aldehyde **2a** were carried out with set up on the bench top under an air and also under a N₂ atmosphere (eqn (5)). Both reactions afforded the product **6d** in comparable yields. Furthermore, these reactions proceeded in only slightly lower yield than when the reaction was set up using rigorous inert atmosphere techniques in a glovebox. The bench top reaction between **10a** and the aliphatic aldehyde **2c** under a N₂ atmosphere was similarly successful (eqn (6)). However, a significant reduction in yield was observed when the reaction with the aliphatic aldehyde was carried out in air.

Conclusions

In summary, imidates are a novel and unexplored class of directing groups that not only enable the Rh(III)-catalyzed activation of ortho C–H bonds of benzimidates but also serve to capture the alcohol intermediate formed upon reversible aldehyde addition to provide biologically important phthalides in a single step. The reaction shows broad scope with a high level of functional group compatibility and is applicable not only to aromatic aldehydes but also to aliphatic derivatives for which Rh(III)-catalyzed additions have not previously been demonstrated. We are currently extending this new conceptual strategy for the reversible addition of C–H bonds with directing group capture to other substrate classes and directing group structures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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8. The rate of cyclative capture of the initial alcohol addition product was evaluated by monitoring the reaction of benzimidate **3a** and aldehyde **2a** by ^1H NMR at both early and ~50% conversions. At each time point, the phthalide was the predominant species observed, and little if any alcohol was detected.

Fig. 1.
Proposed capture of C-H addition product **4** to produce phthalide **6**.

Scheme 1.
Attempted reaction of methyl benzoate with aldehyde.

Scheme 2.

Reaction yield comparison under different conditions.

Table 1

Optimization of reaction conditions^a

Entry	Catalyst	Solvent	Catalyst loading (mol%)	Yield ^b (%)
1	(Cp*RhCl ₂) ₂ , AgSbF ₆	DCE	5	77
2	(Cp*RhCl ₂) ₂ , AgBF ₄	DCE	5	76
3	(Cp*RhCl ₂) ₂ , AgPF ₆	DCE	5	15
4	(Cp*RhCl ₂) ₂ , AgOTf	DCE	5	18
5	(Cp*RhCl ₂) ₂ , AgB(C ₆ F ₅) ₄	DCE	5	46
6	(Cp*RhCl ₂) ₂ , AgN(Tf) ₂	DCE	5	36
7	(Cp*RhCl ₂) ₂ , AgOAc	DCE	5	0
8	Cp*Rh(CH ₃ CN) ₃ (SbF ₆) ₂	DCE	10	54
9	(Cp*RhCl ₂) ₂ , AgSbF ₆	THF	5	46
10	(Cp*RhCl ₂) ₂ , AgSbF ₆	<i>t</i> -BuOH	5	0
11	(Cp*RhCl ₂) ₂ , AgSbF ₆	DCE	2.5	59

^a Conditions: **3a** (0.10 mmol), **2b** (0.20 mmol) in 0.5 mL of solvent for 20 h.^b Determined by ¹H NMR relative to 2,6-dimethoxytoluene as internal standard.

Table 2

Substrate scope with aromatic aldehydes^a ^aTabulated values are isolated yields.^bConditions: benzimidate **3** (0.20 mmol), aldehyde **2** (0.40 mmol) in 1.0 mL of DCE for 20 h.^cUsing 10 mol% of (Cp*RhCl₂)₂ and 40 mol% of AgSbF₆.

Table 3Evaluation of different benzimidate directing groups^a

Entry	Benzimidate	R	Yield ^b
1	3a	OMe	32
2	3a	OMe	54 ^c
3	7a	<i>p</i> -OMePh	37
4	8a	Ph	41
5	9a	<i>p</i> -CF ₃ Ph	56
6	10a	3,5-BisCF ₃ Ph	67

^a Conditions: benzimidate (0.10 mmol), **2c** (0.20 mmol) in 0.5 mL of DCE for 20 h.^b Determined by ¹H NMR relative to 2,6-dimethoxytoluene as internal standard.^c Added 0.050 mmol of K₂CO₃ (0.5 equiv.).

Table 4

Substrate scope for aliphatic aldehydes^a

R = OMe (3a) ^c	54%
R = 3,5-bisCF ₃ Ph (10a)	65%
R = OMe (3a) ^c	39%
R = 3,5-bisCF ₃ Ph (10a)	65%

^a Conditions: benzimidate (0.20 mmol), aldehydes (0.40 mmol) in 1.0 mL of DCE for 20 h.^b Isolated yields.^c Added 0.10 mmol of K₂CO₃ (0.5 equiv.).