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Efficient Benzimidazolidinone Synthesis via Rhodium-Catalyzed Double-Decarbonylative C–C Activation/Cycloaddition between Isatins and Isocyanates

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Abstract

The first decarbonylative cycloaddition of less-strained cyclic ketones (isatins) with isocyanates is reported. Initiated by C–C activation, this distinct [5–2+2] transformation provides a rapid entry to access various benzimidazolidinone derivatives, through which a wide range of isocyanates can be efficiently coupled with broad functional group tolerance. A modified one-pot process, combining Curtius rearrangement and C–C activation, was also achieved by using acyl azides as the starting materials. Detailed mechanistic study revealed a surprising double-decarbonylative reaction pathway. The novel reactivity discovered in this basic research is expected to shed light on developing new heterocycle formation methods through a C–C/isocyanate coupling.

Keywords

C–C activation; isocyanate; isatin; cycloaddition; rhodium

Transition metal-catalyzed C–H and C–C activations followed by insertion of a 2π -unsaturated units have emerged as attractive byproduct-free approaches for constructing complex structures from readily available feedstock.^{1–2} Due to the ubiquity and pivotal role of amide bonds in biologically important molecules, isocyanates have been frequently employed as reaction partners for amide synthesis;³ consequently, direct addition of a C–H or C–C bond across isocyanate C=N bonds would offer unique atom-efficient methods to access various nitrogen-containing compounds. In particular, cleavage of a cyclic C–C bond accompanied by annulation with an isocyanate should offer an unusual approach to synthesize lactams (Scheme 1a). While a number of elegant approaches have been reported for coupling of isocyanates with unactivated C–H bonds,⁴ the corresponding couplings involving C–C activation are less common.

In 1987, Tsuji and co-workers developed the first palladium-catalyzed cycloaddition between vinyl cyclopropanes and isocyanates,^{5a} in which the highly reactive donor-acceptor

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Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>. Detailed experimental procedures, characterization of products, and the X-ray analysis.

Notes

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cyclopropanes are needed (Scheme 1b). Later reports disclosed that Lewis acids could also promote this transformation benefiting from significant release of ring strain.^{5b-5c} In 2013, a novel rhodium(I)-catalyzed C–C cleavage of cyclobutanols via β -carbon elimination followed by 1,2-addition with isocyanates was reported by Murakami for preparing linear amides (Scheme 1c).⁶ While strain release offers an important advantage for C–C activation,² to the best of our knowledge, cycloaddition of isocyanates via activation of less strained C–C bonds has not been reported previously. Herein, we describe a decarbonylative regioselective cycloaddition between isatins and isocyanates, which involves a directed C–C activation of isatins with extrusion of two CO molecules (Scheme 1d).⁷⁻⁸ This formal [5–2+2] transformation provides a distinct strategy to convert readily available isatins into various benzimidazolidinone derivatives, a structural motif that has been widely found in pharmaceutical compounds.

Pioneered by Suggs,⁹ Jun,^{2g-2i},¹⁰ Murai,¹¹ Douglas,^{8d-8g} Shi,¹² and Wang,^{13a} the use of directing groups (DGs)^{13b-13f} has been demonstrated as a successful strategy to assist C–C activation of unstrained ketones. Our laboratory has been interested in developing catalytic methods through activation of less-strained cyclic ketones. For example, we recently reported a formal [5+2–1] transformation involving a directed activation of isatins and coupling with alkynes,¹⁴ in which the C3-C4 bond of isatins (e.g. **1a**) was found to be efficiently cleaved by a low valent rhodium complex even at room temperature. Hence, this system provides an excellent platform to study the insertion of isocyanates. Isatin **1a** and isocyanate **2a** were employed as the initial substrates. A variety of metal-ligand combinations were screened. To our surprise, the expected mono-decarbonylative coupling product (**4aa**) was not observed; instead, benzimidazolidinone **3aa** was isolated as the dominating product under various rhodium-catalyzed conditions (Table 1). This result indicated that double decarbonylation (two CO extrusions) occurred when an isocyanate was used as the coupling partner, and the corresponding 2π -insertion was completely regioselective. It was also interesting that no C–H activation coupling product⁴ was observed when 3-methylpyridyl group was used as the DG.

After the reaction was carefully assayed, the benzimidazolidinone (**3aa**) was almost exclusively formed in 98% yield when 5 mol % [Rh(cod)Cl]₂ and 20 mol% AsPh₃ were discovered as the optimal combination (Table 1, entry 1). Control experiments were subsequently conducted to understand the role of each reactant. In the absence of the rhodium catalyst, no desired product was observed (entry 2). The conversion decreased dramatically without the AsPh₃ ligand, and only 34% of **3aa** was obtained (entry 3). Use of Wilkinson's catalyst [Rh(PPh₃)₃Cl] instead gave only 14% of the desired product together with a high recovery of the starting material (entry 4). Employment of other metal, such as Ru₃(CO)₁₂, didn't afford any desired product (entry 5). Bi- or monodentate phosphine ligands, like Xantphos, dppp, dppb, PCy₃, and P(C₆H₂-3,5-(CF₃)₂)₃, which have been proven to be efficient ligands for our previous C–C activation reactions, however, all inhibited this reaction to various extents except P(C₆H₄-4-F)₃, regardless of their electronic properties (entries 7-12). In addition, sterically hindered Xphos and NHC ligand (IMes) decreased the yield to 7% and 29%, respectively (entries 13-14). All these observations suggested that the AsPh₃ ligand played a critical role for the high efficiency of this reaction.

Besides 1,4-dioxane, PhCl also serves a competent solvent (entry 15). Furthermore, decreasing the temperature resulted in lower conversion (entry 16).

With the optimized conditions in hand, the reaction scope was first tested using substrate **1a** with different isocyanates **2** (Table 2). Both aryl and alkyl substituted isocyanates with various electronic properties worked very well affording good to excellent yields of the corresponding benzimidazolidinone derivatives. A broad range of functional groups can be tolerated. Organic halides, such as aryl fluoride (**2a**), bromide (**2c**) and trifluoromethyl groups (**2f**) were compatible; aryl and alkyl substituted esters (**2d** and **2l**) remained untouched due to the near pH and redox neutral conditions. Sterically hindered isocyanates, such as 2,5-dimethoxyl-isocyanate (**2g**) and 1-naphthyl-isocyanate (**2h**), also provided high yields of products. When allylicisocyanate (**2i**) was used, the reaction underwent chemoselective C=N insertion leaving the olefin moiety intact. Furthermore, regular alkyl (**2j**), benzyl (**2k**) and α -ester-isocyanate (**2l**) all gave high yields. X-ray crystal structures of products **3aa** and **3al** have also been obtained.¹⁵ Attempts to couple with other heterocumulenes, such as phenyl isothiocyanates or *N,N'*-dicyclohexylcarbodiimide (DCC), remained unsuccessful.

The scope of the isatins and DGs was next investigated and compared (Table 3). Besides 3-methyl-2-pyridyl-based DGs, other groups, such as 2-pyridyl (**3bk** and **3dk**) and 1*H*-indazol-1-yl (**3ck**), showed good reactivity for the transformation. Isatin substrates with a methyl group at the *C*-5 position led to the corresponding product **3dk** in 84% yield. In addition, the *N*-benzyl protected isatin worked equally well (**3ek**). Finally, the 7-*aza-isatin* compound was also found to be a viable substrate, giving an interesting 1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**3fk**) as the product.

Acyl azides are well-known precursors for preparing isocyanates through Curtius rearrangement.^{3,16} Thus, a one-pot process, which combines Curtius rearrangement and C–C activation, was further developed to access benzimidazolidinone derivatives with a more complex substituent. Acyl azides were first transformed to the isocyanates after heating at 110 °C in PhCl for 2–3 hours, which were then treated with isatin **1a** under the double-decarbonylation conditions (Scheme 2). With this one-pot protocol, the ferrocene derivative (**3am**), acetophenone derivative (**3an**), and Vitamin E derivative (**3ao**) were efficiently synthesized from the corresponding acyl azides. It is not surprising that 4-formyl-benzoyl azide was not a suitable substrate due to the high reactivity of the aryl aldehyde moiety under the Rh catalysis conditions.

To have a better understanding of this transformation, the reaction mechanism was first explored with stoichiometric rhodium. According to our previously reported procedure, treatment of isatin **1a** with $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ led to the cleavage of C3–C4 bond and formation of rhodacycle **Int 1**,¹⁴ which was subsequently examined in the reaction with isocyanate **2k**. Unsurprisingly, the reaction proceeded smoothly and afforded the desired product **3ak** in 81% yield (Eq. 1). This study indicates that the transformation is likely initiated by directed C–C activation of isatins.

Consequently, four possible reaction pathways are proposed as depicted in Scheme 3: (i) the isocyanate inserts into the aryl–Rh bond of **Int 1** to give **Int 2**, which then undergoes a second decarbonylation to give the benzimidazolidinone product (path **A**); (ii) the isocyanate inserts into the acyl–Rh bond of **Int 1** to generate **Int 3**, which is followed by a second decarbonylation and reductive elimination (path **B**); (iii) direct reductive elimination of **Int 3**, followed by a separate decarbonylative C–C activation sequence, would also give product **3** (path **C**); (iv) through **Int 1**, double-decarbonylative C–C activation of the isatin can occur to generate a four-membered rhodacycle **Int 4**, which then undergoes isocyanate insertion to afford product **3** (path **D**).¹⁷

To examine the feasibility of each reaction mechanism, first, 1,3-dimethylquinazoline-2,4(1*H*,3*H*)-dione derivative **4** was prepared and subjected to the standard reaction conditions (Eq. 2). However, no desired benzimidazolidinone **3ap** was observed even after 2 days, which excluded the ‘second separate decarbonylative C–C activation’ mechanism (path **C**). Second, when ¹³C-labeled isocyanate **2b-¹³C**, was subjected to the reaction with **2a** under the standard conditions, the benzimidazolidinone **3ab-¹³C** was isolated in 87% yield with more than 99% of ¹³C incorporation at the carbonyl group (Eq. 3). This result strongly disfavoured both paths **A** and **B**, in which partial or no ¹³C-labeled product should be observed (Scheme 3). Thus, path **D**, involving double decarbonylation first and then isocyanate insertion, should be the most reasonable reaction pathway.

In summary, we have developed a unique Rh-catalyzed [5-2+2] transformation through directed C–C activation of isatins followed by “double decarbonylative cycloaddition” with isocyanates. A broad range of isocyanates can be coupled with high efficiency, and the corresponding benzimidazolidinone derivatives can be obtained in good to excellent yields with high functional group tolerance. In addition, a modified one-pot process combining a Curtius rearrangement and C–C activation was also realized. Furthermore, the mechanistic study disclosed a new mode of reactivity of isatins and strongly supported the proposed double decarbonylation pathway. The novel mode of reactivity discovered here is expected to shed light on developing new heterocycle formation methods through a C–C/isocyanate coupling. Efforts on extending to other systems (e.g. use of a temporary DG) are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Transition metal-catalyzed C–C cleavage and its coupling with isocyanates

Scheme 2.
Curtius Rearrangement/C–C activation/isocyanate insertion

Scheme 3.
Possible reaction pathways

Table 1

Control experiments.

entry	change from standard conditions	conversion / %	3aa / % ^a
1	None	99	98
2	Without Rh catalyst	0	0
3	Without AsPh ₃	34	34
4	RhCl(PPh ₃) ₃ instead of [Rh(cod)Cl] ₂	15	14
5	Ru ₃ (CO) ₁₂ instead of [Rh(cod)Cl] ₂	19	0
6	Xantphos instead of AsPh ₃	7	0
7	dppb instead of AsPh ₃	30	8
8	dppp instead of AsPh ₃	16	9
9	PCy ₃ instead of AsPh ₃	28	16
10	P(C ₆ H ₄ -4-OMe) ₃ instead of AsPh ₃	28	13
11	P(C ₆ H ₄ -4-F) ₃ instead of AsPh ₃	91	78
12	P(C ₆ H ₂ -3,5-(CF ₃) ₂) ₃ instead of AsPh ₃	10	10
13	Xphos instead of AsPh ₃	22	7
14	IMes instead of AsPh ₃	41	29
15	PhCl instead of 1,4-Dioxane	96	72
16	Temperature was 150 °C	31	29

^aDetermined by crude ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

Table 2

The reaction scope of isocyanates^a ^a All the yields are isolated yields.^b The reaction was conducted in PhCl.

Table 3

The reaction scope of isatins