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Synthetic Methods

Ruthenium(II)-Catalyzed C–H Activation with Isocyanates: A Versatile Route to Phthalimides

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Abstract: A cationic ruthenium(II)-complex was utilized in the efficient synthesis of phthalimide derivatives by C–H activation with synthetically useful amides. The reaction proceeded through a mechanistically unique insertion of a cycloruthenated species into a C–Het multiple bond of isocyanate. The novel method also proved applicable for the synthesis of heteroaromatic unsymmetric diamides as well as a potent COX-2 enzyme inhibitor.

Phthalimide derivatives have been largely utilized in medicinal chemistry due to their broad range of applications as anti-inflammatory, anticonvulsant, analgesic, immunomodulatory, and hypolipidimic activities (Figure 1).[1] In addition, phthalimide analogues have found extensive use as agrochemicals, polymers, and in different branches of material sciences.[2]

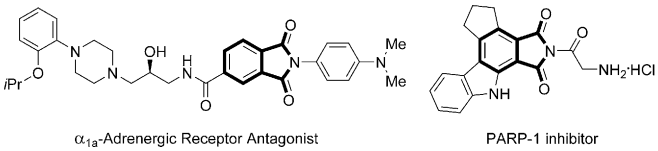
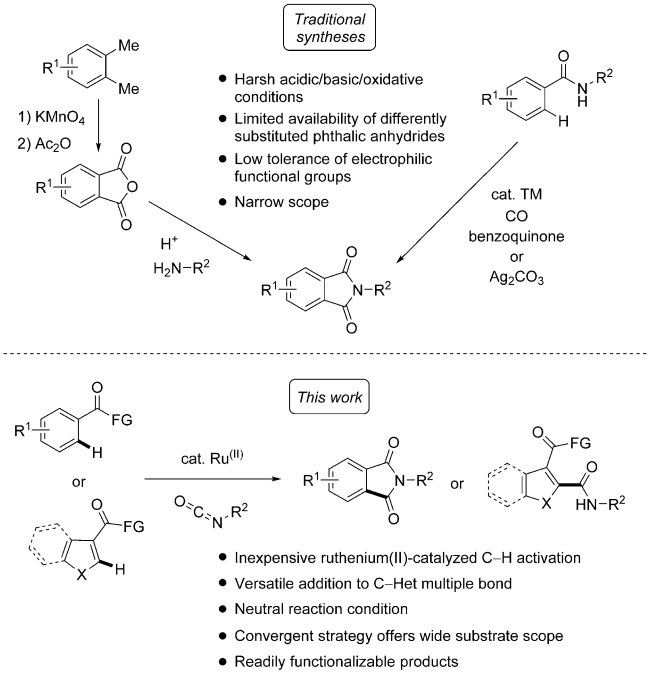


Figure 1. Selected bioactive phthalimide derivatives.

The most commonly used strategy for the synthesis of phthalimide involves reactions between the corresponding phthalic acids or anhydrides and amines.[3] However, the limited availability of differently substituted phthalic acids, mostly due to the harsh reaction conditions in their preparation, calls for alternative protocols. Carbonylative cyclizations of prefunctionalized *ortho*-halo benzoic acid derivatives[4a–c] or *ortho*-dihalo arenes[4d,e] in the presence of amines are thus attractive routes. Formamides were also utilized to construct the phthalimide scaffold by the action of a palladium catalyst.[5] In selected cases, other transition metal catalysts were employed in the carbonylation of secondary benzamides by C–H bond functionalization.[6] Very recently, rhodium(III)-catalyzed imidation of benzoic acid derivatives with isocyanates was reported.[7] This C–H activation-based[8] approach ceased the necessity of prefunctionalized *ortho*-halo benzoic acid derivatives,[9] but was limited to electron-rich substrates.

In recent years, ruthenium complexes have emerged as a versatile, less-expensive alternative to commonly used transition metals in C–H activation chemistry.[10] Along this line, ruthenium(II)-catalyzed cyclometalation followed by migratory insertion of C–C multiple bonds is well-documented in the literature.[10] However, in striking contrast to rhodium or rhenium catalysis,[11] the addition to polar C–Het multiple bonds is extremely rare in ruthenium-catalyzed transformations and was hitherto only accomplished with strongly coordinating arylpyridines, which are unfortunately extremely difficult to remove or modify.[12] In consideration of the practical importance of C–H activations with synthetically useful auxiliaries,[8a] we explored readily available amides for C–H functionalization with isocyanates (Scheme 1). Within our program on sustainable C–H functionalization,[8j] we herein disclose a convergent method for the imidation of easily accessible benzamides by C–H functionalization. Thereby, a novel route to synthetically challeng-



Scheme 1. Strategies for phthalimide synthesis. FG = functional group.

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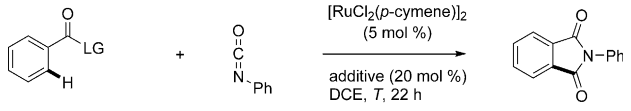
Table 1. Optimization studies.[a]



1 2a 3a

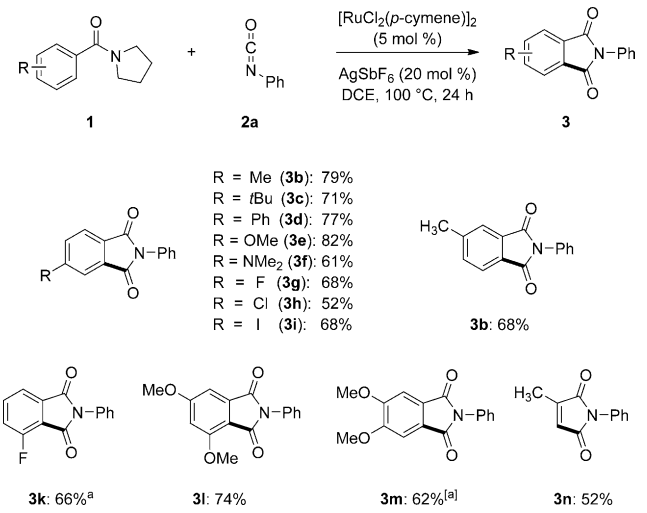
Entry	LG	Additive	**2a** [equiv]	*T* [°C]	Yield [%][b]
1	NMe_2	$AgSbF_6$	2	120	32
2	NMe_2	$AgPF_6$	2	120	26
3	NMe_2	KPF_6	2	120	0
4	NMe_2	$AgSbF_6$	2	100	34
5	NMe_2	$AgSbF_6$	3	100	37
6	OH	$AgSbF_6$	3	100	12
7	OMe	$AgSbF_6$	3	100	0
8	NHMe	$AgSbF_6$	3	100	0
9	$N(iPr)_2$	$AgSbF_6$	3	100	trace
10	N(OMe)Me	$AgSbF_6$	3	100	54
11	**pyrrolidinyl**	**$AgSbF_6$**	**3**	**100**	**71**
12	piperidinyl	$AgSbF_6$	3	100	8
13	morpholinyl	$AgSbF_6$	3	100	trace
14[c]	**pyrrolidinyl**	**$AgSbF_6$**	**3**	**100**	**74**

[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.0–1.5 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (5.0 mol%), additive (20 mol%), solvent (2.0 mL), 22 h, under N_2, LG = leaving group. [b] Isolated yield. [c] 24 h.

ing unsymmetrical heteroaromatic diamides was established as well.

We began our optimization studies (Table 1 and Table S1 in the Supporting Information) by exploring the effect of different co-catalytic additives in the annulation reaction by using dimethylbenzamide as the model substrate (entries 1–3). A cationic ruthenium(II) complex, generated by the addition of co-catalytic amounts of $AgSbF_6$, was found to be more effective than catalysts derived from either $AgPF_6$ or KPF_6. The effect exerted by the leaving group on the catalytic efficiency was studied next (entries 6–14). The free carboxylic acid delivered unsatisfactory results, whereas the ester, the secondary amide, and the bulky tertiary amide were completely inert in the annulation (entries 6–9). The Weinreb amide improved the yield (entry 10), but the most astonishing result was obtained with pyrrolidinyl as the leaving group, and the desired imide was isolated in 71% yield (entry 11). Surprisingly, six-membered heterocyclic amides were ineffective in the imidation process (entries 12 and 13).

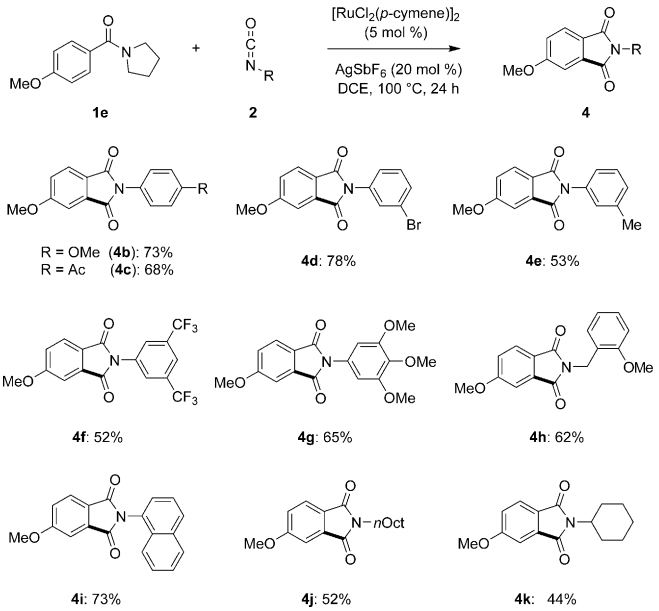
Having the optimized reaction conditions in hand, we explored the substrate scope using differently substituted benzamide derivatives **1** (Scheme 2). Good to excellent yields were obtained with 4-alkyl substituted amides **1b** and **1c**, as well as conjugated biphenyl derivative **1d**. Electron-rich amide **1e** was found to be most reactive and amino derivative **3f** was also efficiently produced. Fortunately, electron-poor substituted arene **1g** was a viable substrate, likewise other halogen substituents were also found to be tolerated by the catalytic system (**1h** and **1i**), which should prove useful for further functionalizations by cross-coupling chemistry. 3-Methyl substituted arene **1j** exclusively underwent the C–H functionalization at the less-hindered position, whereas the opposite regioselectivity was observed with a fluoro-substituted arene **1k**.[13] Di-substituted



Scheme 2. Ruthenium(II)-catalyzed imidation with substituted amides **1**. [a] Corresponding regioisomers were also obtained: **3k′**: 9%; **3m′**: 11%.

aryl amides underwent imidation efficiently, and good yields were obtained with both 3,4- and 3,5-dimethoxy amide derivatives **1l** and **1m**, respectively. Gratifyingly, the new method was not limited to arenes. Indeed, alkenylic C–H activation was found to be suitable for acrylamide **1n**, thereby furnishing product **3n**.

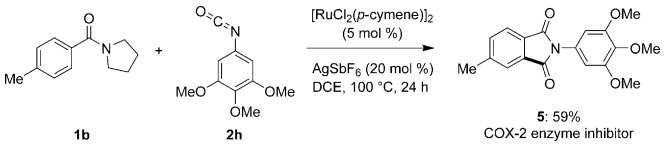
A wide substrate scope was observed when employing differently decorated isocyanates **2** (Scheme 3). Both electron-rich as well as electron-poor aryl isocyanates gave high yields of the desired imides **4b** and **4c**. Halogen substituents (**4d**), as well as alkyl groups, were well-tolerated (**4e**). Highly electron-deficient and electron-rich multiply functionalized aromatic isocyanates delivered the desired products **4f** and **4g**. Benzyl amine derivative **1h** and sterically challenging α-naphthylamine-derived isocyanate **1i** underwent clean imidation. Finally,



Scheme 3. Ruthenium(II)-catalyzed imidation with substituted isocyanates **2**.

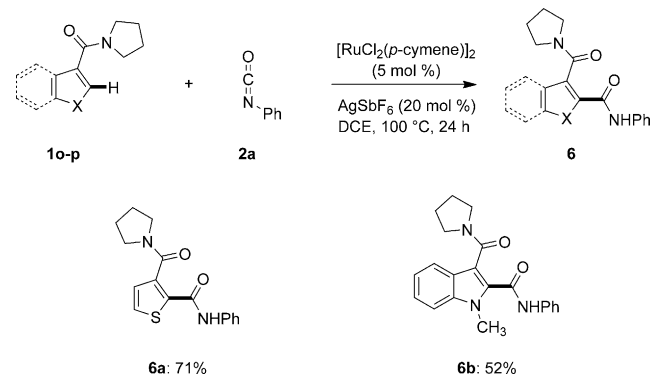
alkyl-substituted isocyanates **1j** and **1k** were tested, delivering the desired products **4j** and **4k**, respectively, in good yields.

Cyclooxygenase (COX) enzyme is responsible for the formation of different biological mediators and pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain.[14] We were pleased to find that our newly developed method proved applicable to the effective and step-economic synthesis of COX-2 enzyme inhibitor **5** possessing $IC_{50} = 0.4$ μM (Scheme 4).[14c]



Scheme 4. Synthesis of COX-2 enzyme inhibitor **5**.

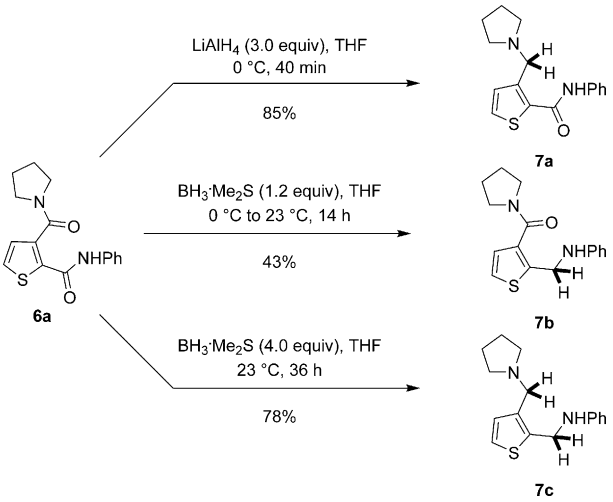
Ruthenium(II)-catalyzed amidation was also successfully applied to different heteroaromatic substrates (Scheme 5). Interestingly, with the five-membered heterocycles **1o** and **1p**, unsymmetrically substituted diamides were obtained, which are challenging to produce using other methods. Notably, the unsymmetrical diamide **6a** can be chemoselectively reduced to the corresponding amines (Scheme 6), giving step-economical access to the products **7a**, **7b,** and **7c**.



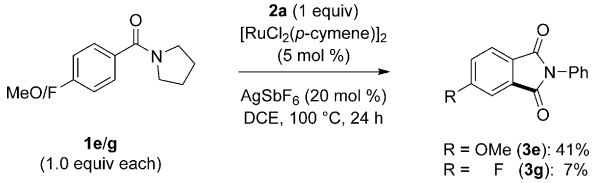
Scheme 5. C–H amidation with heteroaromatic amides.

To understand the catalysts mode of action, we performed an intermolecular competition experiment between amides **1e** and **1g** (Scheme 7). Hence, electron-rich arene **1e** emerged as the more reactive substrate, which could be rationalized in terms of a base-assisted IES-type[15] C–H activation mode. The imidation was also performed in the presence of D_2O (1 equiv), which affirmed a reversible H/D-exchange, as was observed for both the product [D_n]-**3e** and the reisolated starting material [D_n]-**1e** (Scheme 8).

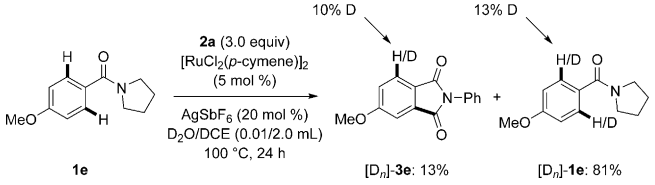
Based on these mechanistic studies, a plausible catalytic cycle is depicted in Scheme 9. Initial reversible C–H ruthenation on amide **1** delivers cationic complex **9**. Coordination of the isocyanate **2**, followed by migratory insertion, forms the C–C bond and produces key intermediate **11**. It is noteworthy that such additions to C–Het multiple bonds are scarce in ruth-



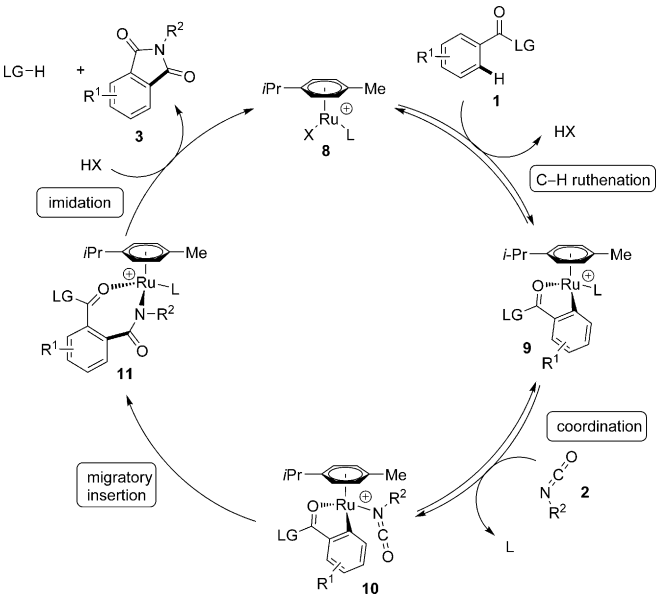
Scheme 6. Chemoselective reduction of the diamide **6a**.



Scheme 7. Intermolecular competition experiments with amides **1**.



Scheme 8. H/D exchange reaction with **1e**.



Scheme 9. Proposed catalytic cycle.

enium(II)-catalyzed C–H activation. Proto-demetalation of intermediate **11** gives rise to diamide **6**, or direct imidation yields product **3** and regenerates the cationic ruthenium species **8**.

In summary, we have developed the first ruthenium(II)-catalyzed direct imide synthesis by C–H bond functionalization. This versatile method proved applicable to a wide variety of easily accessible aromatic amides as well as acrylamide.[16] Importantly, heteroarenes delivered unsymmetrical diamides, which were chemoselectively reduced to a variety of mono- and diamines. The novel strategy provided step-economical access to a potent COX-2 enzyme inhibitor. Mechanistic studies revealed an initial reversible C–H bond metalation by a cationic ruthenium(II)-complex in the amidation process.

Experimental Section

A suspension of amide **1** (0.50 mmol), isocyanate **2** (1.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol%), and $AgSbF_6$ (34.3 mg, 20 mol%) in dichloroethane (DCE, 2.0 mL) was stirred at 100 °C for 24 h under N_2. At RT, the reaction mixture was filtered through a short pad of Celite and eluted with EtOAc (20 mL). The combined solution was concentrated under reduced pressure. The crude products were purified by column chromatography (*n*-hexane/EtOAc) on silica gel to yield the desired products **3**–**6**.

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Keywords: amides · C–H activation · imidation · isocyanate · ruthenium

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[16] Under otherwise identical reaction conditions, methyl 4-(pyrrolidine-1-carbonyl)benzoate has, so far, provided unsatisfactory results.

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Synthetic Methods

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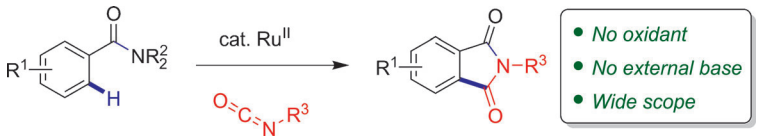
Ruthenium(II)-Catalyzed C–H Activation with Isocyanates: A Versatile Route to Phthalimides



A convenient route to phthalimide: A convergent method for the ruthenium(II)-catalyzed imidation of easily accessible benzamides by C–H functionalization was developed (see scheme). The methodology was successfully applied to the preparation of synthetically challenging unsymmetrical heteroaromatic diamides and proved amenable to a step-economic synthesis of a potent COX-2 enzyme inhibitor.