Synthesis of Cyclic Imides from Simple Diols**

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Imide derivatives are widely used organic compounds that have numerous applications in biological, medicinal, synthetic, and polymer chemistry.^[1] In particular, cyclic imides are important building blocks for natural products and drugs, such as palasimide,^[2] salfredins,^[3] thalidomide,^[4] julocrotine,^[5] lamprolobine,^[6] migrastatin,^[7] and phensuximide^[1] (Figure 1).



Figure 1. Examples of bioactive compounds containing a cyclic imide moiety.

Despite their wide applicability, available routes for the synthesis of cyclic imides from readily available starting materials are limited.^[1h] The typical methods are the dehydrative condensation of an anhydride with an amine at high temperatures or with help of Lewis acid,^[1,8] and the cyclization of an amic acid in the presence of acidic reagents,^[1,9] both of which are not atom economical, usually generating stoichiometric amount of by-products.^[10] Some recent approaches include: the iridium-catalyzed multicomponent synthesis of glutarimides;^[11] the ring expansion of 4-formyl- β -lactams for the synthesis of succinimide derivatives;^[12] the iron-catalyzed carbonylative succinimide synthesis using an alkyne, CO, or NH₃;^[13] the ruthenium- or palladium-catalyzed carbonylation of aromatic compounds leading to phthalimides;^[14] and the rhodium-catalyzed 1,4-addition of aryl

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boronic acids to maleimides for the synthesis of chiral 3-substituted succinimide derivatives.^[15] However, each of these routes has its own synthetic problems, especially when applied to syntheses of a range of the cyclic imides, mostly owing to the limited availability of suitably functionalized starting materials. Therefore, the atom-economical synthesis of functionalized imide derivatives from widely used precursors is a challenging goal.

To address this challenge, we postulated that the imides could be synthesized directly from alcohols with amines or amides using a similar strategy to the reported oxidative amide synthesis from alcohols and amines, catalyzed by ruthenium-,^[16,17] rhodium-,^[18] and silver-based^[19] complexes (Scheme 1).^[20] The strategy for the amide synthesis was to oxidize the alcohol to the aldehyde first and then further



Scheme 1. Synthesis of amides and cyclic imides from alcohols and amines.

oxidize a hemiaminal, formed from the aldehyde and the amine, to an amide, with the evolution of two equivalents of hydrogen gas. We focused on identifying an active catalytic system to realize a useful imide synthesis by promoting the further reaction of the less-nucleophilic nitrogen atom of the amide with alcohols. Herein, we report the first direct cyclic imide synthesis from simple diols using an in-situ-generated ruthenium-hydride-based catalyst.

The reaction between 1,4-butanediol (**3a**) and benzylamine (**4a**) to afford *N*-benzylsuccinimide (**5a**) was chosen to screen the catalytic conditions (Table 1). We started our investigation by employing the reported ruthenium catalytic systems used previously in amide synthesis by others^[16] and ourselves.^[17] [{Ru(benzene)Cl₂}] (**1a**)^[17a] and [{Ru(*para*-cymene)Cl₂}] (**1b**)^[17a] showed limited activity, even with the help of an N-heterocyclic carbene (NHC) precursor, 1,3-diisopropylimidazolium bromide (**2**), under basic conditions (Table 1, entries 1 and 2). Unfortunately, use of the previously reported [{Ru(*para*-cymene)Cl₂}] with a diphenylphosphinobutane (dppb) ligand did not exhibit any activity for the imide synthesis (Table 1, entry 3).^[16b] Then, we noticed an early example of the use of [RuH₂(PPh₃)₄] (**1c**) for the synthesis of

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Table 1: Catalyst screening.[a]



[a] Typical reaction conditions: **3a** (0.5 mmol, 1.0 equiv), **4a** (0.55 mmol, 1.1 equiv), a solvent (0.8 mL), reflux, 24 h. [b] Yields are of the isolated product, and represent the average of at least two runs. [c] **1a** (2.5 mol%), **2** (5 mol%), NaH (15 mol%), CH₃CN (5 mol%), toluene.^[17a] [d] **1b** (2.5 mol%), **2** (5 mol%), NaH (15 mol%), NaH (15 mol%), gridine (5 mol%), toluene.^[17a] [e] **1b** (2.5 mol%), Appb (5 mol%), 3-methyl-2-butanone (2.5 equiv), Cs₂CO₃ (10 mol%), tBuOH.^[16b] [f] **1c** (5 mol%), 1-hexyne (2.5 equiv), DME.^[16a] [g] **1c** (5 mol%), **2** (5 mol%), NaH (20 mol%), CH₃CN (5 mol%), toluene.^[17c] [h] **1d** (5 mol%), **2** (5 mol%), PCy₃ (5 mol%), KOtBu (20 mol%), toluene.^[16c] [j] **1e** (5 mol%), toluene.^[16c] DME=1,2-dimethoxyethane.

cyclic lactams from α, ω -aminoalcohols by Naota and Murahashi (Figure 2).^[16a] Although their original conditions, using a hydrogen acceptor, afforded no **5a** product (Table 1, entry 4), [RuH₂(PPh₃)₄] showed good activity (70%) with



Figure 2. Ruthenium catalysts.

the help of NHC precursor **2** (Table 1, entry 5).^[21] The NHCpromoted [RuH₂(PPh₃)₄]-based catalyst was recently reported to be active for the synthesis of amides from either alcohols or aldehydes with amines.^[17c] Other catalytic systems based on $1d^{[16c]}$ and $1e^{[16d]}$ exhibited lower activities in the cyclic-imide synthesis (Table 1, entries 6 and 7).

Having identified our active catalytic system, we tested various amines with 1,4-butandiol to afford N-substituted succinimide derivatives (Table 2). Excellent activities were observed with alkyl and benzyl amines (Table 2, entries 1–5). Noticeably, more-electron-rich benzyl amines favored the cyclization reaction than electron-poor ones (Table 2, entries 4–5; cf. Table 1, entry 5). Pyridine and ether groups were tolerant in this reaction (Table 2, entries 6–9). While 2-aminomethylpyridine (**4g**) exhibited a lower yield, presumably owing to interference of ruthenium binding to **3a**, the reactions of 3-aminomethylpyridine (**4h**) and 4-aminomethylpyridine (**4i**) proceeded smoothly (Table 2, entries 6–8). Moderately hindered amines proceeded well to generate their

Table 2: Synthesis of succinimides from 1,4-butanediol.[a]

Entry	Amine		Amide		Yield [%] ^[b]
1	NH ₂	4b		5 b	81
2	Ph NH2	4c	O N O Ph	5c	76
3	Ph NH ₂	4d	O N O Ph	5 d	88
4	MeO-	4e	O C Me	5 e	87
5	F-	4 f	O N O F	5 f	61
6		4g		5 g	44
7	N-NH ₂	4h		5 h	73
8	N NH ₂	4i		5 i	59
9	H ₂ N OMe	4j		5 j	73
10	NH ₂	4k		5 k	68
11	NH ₂	41		51	57
12	H ₂ N Ph	4m	O N Ph	5 m	36

[a] Reaction conditions: **3a** (0.5 mmol, 1.0 equiv), amine (1.1 equiv), **1c** (5 mol%), **2** (5 mol%), NaH (20 mol%), CH₃CN (5 mol%), toluene (0.5 mL), reflux, 24 h. [b] Yields are of the isolated product, and represent the average of at least two runs.

corresponding succinimides, although it was sensitive to steric hindrance, as reported in the previous amide syntheses (Table 2, entries 10–12).^[16–17] In the case of less-basic aryl amines, such as aniline, the reaction did not proceed as well as observed in the analogous amide synthesis.^[16c,17] γ -Butyrolactone was observed, especially with low yielding substrates (e.g. 5% with **4g**, and 13% with **4m**), along with other

unidentified messy by-products, presumably from possible inter- and intra-molecular amidation and esterification reactions.^[22,23]

Excited by the facile synthesis of succinimide derivatives from **3a**, various diols were screened to synthesize cyclic imides (Table 3). 2-aryl- or alkyl-functionalized 1,4-butanediols generated their corresponding succinimides in good yields (Table 3, entries 1 and 2). A bicyclic succinimide derivative **5p** was also smoothly synthesized from *cis*-1,2cyclohexanedimethanol (**3p**; Table 3, entry 3). Phthalimide derivatives were obtained from 1,2-benzenedimethanol (**3q**) in good yields (Table 3, entries 4–7). At a lower concentration (0.3 M), phthalide (61%) was observed as the major product along with **5q** (21%). The effective phthalide synthesis from **3q** was previously reported with Cp*/ruthenium(II)-catalyst systems.^[22f] Six-membered glutarimides were also formed in

Table 3: Synthesis of cyclic imides from diols.^[a]

Entry	Diol		Amine		Cyclic imide		Yield [%] ^[b]
1	Ph HOOH	3 n	MeO-	4e	Ph OMe	5 n	78
2	но	30	MeO-	4e		50	55
3	ОН	3 p	MeO-	4e	N C OMe	5 p	80
4	ОН	3 q	MeO-	4e		5 q	74
5	ОН	3 q	Ph NH ₂	4d		5r	67
6	ОН	3 q	NH ₂	4s		5 s	61
7	ОН	3 q	N-NH ₂	4h		5t	51
8	но	3 u	MeO	4e	N OMe	5 u	51
9	но он	3 u	Ph ^{NH} 2	4a	N N O Ph	5 v	48
10	Ph HOOH	3 n	CH_3NH_2	4 w	Ph O	5 w	63

[a] Reaction conditions: Diol (0.5 mmol, 1 equiv, 1.0 м), amine (1.1 equiv), **1c** (5 mol%), **2** (5 mol%), NaH (20 mol%), CH₃CN (5 mol%), toluene (0.5 mL), reflux, 24 h. [b] Yields are of the isolated product, and represent the average of at least two runs.

moderate yields (Table 3, entries 8–9). However, the synthesis of a seven-membered cyclic imide from 1,6-hexanediol was not successful. An anticonvulsant drug, phensuximide (5w) was synthesized from the corresponding diol 3n with methylamine in 63% yield (Table 3, entry 10).

The synthesis of linear imides from the intermolecular reaction of amides or amines with alcohols was attempted next (Scheme 2). However, whether the reaction was run from an amide 6 with 1-pentanol (7) or an amine 4e with two equivalents of 7, none of the corresponding linear imide 8 product was detected. Only amide 9 was observed in the reaction of 4e and two equivalents of 7. In the intramolecular reaction of 10, the reaction proceeded well with 70% yield suggesting that the cyclic imide formation may proceed via a stepwise mechanism with a favored intramolecular 5- or 6-membered ring formation.

On the basis of the observations in Scheme 2 and the reasonable previously suggested mechanisms for amide formation from alcohols and amines,^[16,17] we proposed a mechanism involving the formation of an amide intermediate and further cyclization to the imide product by an intramolecular reaction of the amide intermediate (Scheme 3). The observation of lactones, either in low yielding reactions or in lower concentrations, can be explained by an intramolecular reaction of an aldehyde intermediate as reported.^[22] The involvement of a lactone intermediate in the formation of a cyclic imide was ruled out from the reaction of y-butyrolactone with 4e, as a trace amount (<5%) of the corresponding succinimide 5e was observed. The nature of the exact catalyst structure is under investigation to fully understand the mechanism and expand the reaction scope to the synthesis of linear imides, especially in regards of the role of a strong base and possible chelation effect from the intermediates; it has been suggested that a strong base is required to activate precatalysts by reaction with an alkoxide, formed from an alcohol substrate, and the strong base, as well as the generation of an NHC from its precursor.[17]

In conclusion, we have demonstrated that cyclic imides can be synthesized directly from simple diols using an in-situ-generated ruthenium catalytic system. This

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Scheme 2. Attempts to synthesize imides. Conditions: [Ru] 1 c (5 mol%), 2 (5 mol%), NaH (20 mol%), CH₃CN (5 mol%), toluene (0.8 mL), reflux, 24 h.



Scheme 3. Proposed mechanism.

atom economical and operatively simple method will provide an alternative approach for the synthesis of important cyclic imides.

Experimental Section

1c (28 mg, 0.025 mmol), 2 (5.8 mg, 0.025 mmol), NaH (2.4 mg, 0.10 mmol), and CH₃CN (1.2 μ L, 0.025 mmol) were placed in an oven-dried Schlenk tube inside the glove box before toluene (0.5 mL) was added to the mixture. The Schlenk tube was taken out of the glove box and heated to reflux in an oil bath under an argon atmosphere. The flask was removed from the oil bath after 20 min and a diol (0.50 mmol) and an amine (0.55 mmol) were added. The reaction mixture was heated to reflux under a flow of argon to facilitate the removal of hydrogen for 24 h before being cooled down to room temperature. All the volatiles were removed under vacuum. Purification of the crude product was performed by column chromatography on silica gel.

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