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Single Bifunctional Ruthenium Catalyst for One-Pot Cyclization and Hydration giving Functionalized Indoles and Benzofurans

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Indole^[1] and benzofuran^[1d,2] heterocycles are key structural units in a variety of biologically active natural products and unnatural synthetic materials. Over the last few years, transition-metal catalysts have been extensively used in the cyclization of *o*-alkynylarylamines^[3a–l] and phenols^[3m–p] to construct benzoheterocycles through intramolecular^[3] and intermolecular reactions.^[4] Many of these reactions required the use of a nitrogen protecting group in the case of indoles^[3g,i,k] or stoichiometric amounts of the metal.^[3l] McLory and Trost^[3d] synthesized both unprotected indoles or *N*-benzyl analogues by using rhodium–phosphine complexes, but to optimize the benzofuran synthesis, large amounts of phosphine (0.6 equiv) were needed. Saa and co-workers^[3q] recently reported the use of 10 mol % catalyst and amine solvents in benzofuran synthesis at 90 °C. Herein, we report that the bifunctional ruthenium catalyst **1** which has been used for *anti*-Markovnikov alkyne hydration^[5] emerges as a versatile choice for both indole and benzofuran formation, with a number of unique advantages, including the use of only 2 mol % catalyst in most cases and the unprecedented ability of a cycloisomerization catalyst to perform hydration or deuteration in the same reaction.

We envisioned that the use of alkyne hydration catalyst **1** on substrates, such as **2**, (Scheme 1) would generate the aldehyde **3**, on which cyclization and dehydration would then enable facile synthesis of heterocycles. Indeed, **2a** cyclized to hemiaminal **4a**,^[5a] with some equilibrium amount of **3a**,

Scheme 1. The use of bifunctional catalyst **1** for hydration and cyclization; Cp = cyclopentadienyl.

but elimination of water from **4a** required heating in second step, forming **5a** in 46% overall yield. The same two-step process could be used on the homologous substrate **2b**, to form **5b** in 56% overall yield.

Encouraged by these results, and because of the importance of indoles, we shifted our attention to substrates derived from *o*-ethynylaniline. The first four entries of Table 1 demonstrate that **1** cyclizes a wide range of aniline derivatives; most significantly, the simplest, unprotected parent compound **6** cyclized to indole **17** in 99% yield (Table 1, entry 1). Sulfonamide **7** (Table 1, entry 2) was cyclized to give the *N*-tosyl (Ts) protected indole in just 2 h. Entries 3 and 4 in Table 1 show the ability of the catalyst to form nitrogen analogues with different alkyl substituents. Especially notable is the selectivity of **1**: the *N*-allyl group (Table 1, entry 3) is fully tolerated without the decomposition by isomerization seen when using a Rh-based catalyst.^[3d]

The fact that a wide variety of nucleophilic nitrogen centers could be used in indole formation encouraged us to explore the scope of **1** not only in making more complex indole derivatives, but also in cyclizing phenol derivatives to benzofurans. Gratifyingly, **1** forms both 7-aza- and 6-nitroindoles (Table 1, entries 5 and 6), showing tolerance of various ring substituents, including those that might coordinate to the catalyst. Furthermore, entry 9 (Table 1) shows the ability of **1** to form the benzofuran nucleus in essentially quantita-

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Table 1. Results of heterocycle formation.^[a]

Substrate	Product	Method ^[b]	t [h]	Yield ^[c] [%]
6–9	17–20			
1 6 , R ¹ = H	17 , R ¹ = H	A	17	99
		B	7	87
2 7 , R ¹ = Ts	18 , R ¹ = Ts	A	2	86
		B	7	76
3 8 , R ¹ = allyl	19 , R ¹ = allyl	A	10	74
4 9 , R ¹ = CH ₂ (C ₆ H ₄)CH ₃	20 , R ¹ = CH ₂ (C ₆ H ₄)CH ₃	A	20	82
5 10	21	B	7	94
6 11	22	A	2	91
		B	2	91 (90)
7 12	NR ^[d]	A	40	NR
8 13	17	A	400	84
9 14	23	A	1	99
10 ^[e] 15	24	B ^[f]	1	99 (92)
11 16	25	B ^[f]	1	98 (75)

[a] See Supporting Information for substrate preparation, yield determinations, and product characterization. [b] Method A: with 5 equiv of H₂O, in [D₆]acetone or [D₈]THF. Method B: no water added, in dry [D₈]THF. Reactions were done on a 0.05–0.15 mmol scale with **1** (2 mol %) at 70 °C, unless otherwise noted. [c] Yield calculated from NMR spectroscopy integrations against an internal standard. In parenthesis are the yields for the respective isolated products. [d] NR=no reaction. [e] BR₂=9-borabicyclononane. [f] Reactions done in acetone or [D₆]acetone.

tive yield with the same low catalyst loading as in entries 1–6, and with only 1 h reaction time. The mildness of the cyclization conditions and the tolerance of diverse functional groups in benzofuran formation is highlighted by entries 10 and 11 (Table 1), which show that low catalytic loads are required to convert boryl-protected *o*-ethynyltyrosine (**15**) to its benzofuran derivative **24** and *o*-ethynylated vanillin (**16**) to **25**. Thus, low catalyst loadings of **1** cyclize both ethynylated nitrogen and oxygen analogues to the corresponding indole and benzofuran derivatives in high yields.

Our ongoing mechanistic studies of bifunctional alkyne hydration^[5b] catalysts provide direct evidence for the intermediacy of vinylidenes, such as **B** (Scheme 2). Here, indirect

Scheme 2. Probable mechanism and evidence against protic catalysis (X = NH, O); conditions: a) CF₃SO₃H (5 mol %), 70 °C, 40 h.

evidence for the intermediacy of vinylidenes comes from the inertness of an internal alkyne (Table 1, entry 7) and the sluggish reaction of a silylated alkyne (Table 1, entry 8), in which the latter compound may suffer slow protodesilylation to **6** followed by rapid transformation to **17**. These and all of the other cyclizations discussed below were conducted in NMR spectroscopy tubes to gain the maximum information about the course of the reaction. None of the possible hydration products of general form **E** (Scheme 2) were seen (estimated detection limit usually 1%). This could be a result of initial formation of **E** and its more rapid cyclization and water elimination to give the final product **D** or because of direct cyclization of vinylidene **B**. Evidence for the direct cyclization of **B** includes high yield cyclizations under anhydrous conditions (entries B in Table 1). Moreover, successful reactions of the nitro analogue **11** (entries 6A and 6B) suggest that alkyne hydration via **E** is not a significant pathway, because a previously attempted hydration of 4-nitro(ethynyl)benzene by using **1**^[5a] led to the formation of less than 1% aldehyde and complete catalyst inactivation by pathways known for several other reactions of metals, alkynes, and water.^[6] Control experiments^[7] ruling out protic catalysis by using TfOH (5 mol %, 70 °C, 40 h) on **6** or **14** showed that the aniline formed known^[8a,b] quinoline derivative **Y**, whereas the phenol underwent Markovnikov hydration to give ketone **Z**.^[8c]

To further highlight the unique synthetic potential of catalyst **1**, reactions on doubly ethynylated substrates **26**, **27**, and **28** were performed (Table 2). Of note, except for entry 2, all of the yields in Table 2 refer to isolated and purified products. The case of the nitrogen analogue **26** provides good mechanistic insight: indole formation (**29**) proceeded smoothly (Table 2, entry 1), but hydration of the alkynyl indole to **30**, (Table 2, entry 2) was surprisingly slow and could not be driven to completion. Gratifyingly, the phenolic analogue **28** cyclized to alkyne derivative **33** under anhy-

Table 2. One-pot cyclization and hydration.^[a]

Substrate	Product	Method ^[b]	t [h]	Yield ^[d] [%]
1	26	B	20	60 ^[e]
	29	A	22	11 ^[e]
3	27	B	9	67
4	31	A	24	95 ^[f]
	32	B	10	64
5	28	A	8	74
	33			
	34			

[a] See Supporting Information for substrate preparation, yield determinations, and product characterization. [b] Method A: with 5 equiv of H₂O, in [D₆]acetone or [D₈]THF. Method B: no water added, in dry [D₈]THF. Reactions were done on 0.2–0.5 mmol scale with **1** (4 mol %) at 70 °C, unless otherwise noted. [c] Isolated and purified product. [d] Based on recovered starting material. [e] NMR spectroscopy yield. [f] 20 mol % catalyst used.

drous conditions and also could be hydrated to **34** in the presence of water. It may be noted that the newly formed -CH₂CHO substituent in **34** could be elaborated into a variety of other functionalized side chains.

Because hydration of the sterically similar alkynyl benzofuran **33** to **34** was so much more facile, our hypothesis was that the indole NH must play a role; in putative intermediate **F** (Scheme 2), hydrogen bonding of the pyridinium moiety^[5b] to the acyl could be precluded by competitive interaction with the indole NH. Consistent with this, not only did the *N*-methylated substrate **27** (Table 2, entry 3) cyclize to indole derivative **31** quickly, but also hydration (forming **32**) was more facile, though 20 mol % catalyst was necessary (Table 2, entry 4).

In a further demonstration of the unique features of **1**, the use of D₂O (Scheme 3) resulted in deuteration of indole and benzofuran at position 2 and 3,^[9] which otherwise requires strong base conditions and protecting groups.^[10] Literature on other alkyne hydration catalysts^[11] would suggest that only position 3 would be deuterated, but the bifunctional ligands of **1** promote extensive H/D exchange at the stage

6: X = NH [D₃]**17**: X = ND, 95% deuteration at positions 1–3^[b]
14: X = O [D₂]**23**: X = O, 80% deuteration at positions 2 and 3^[c]

Scheme 3. Synthesis of polydeuterated indole and benzofuran. [a] For **14**: 5 equiv, [D₆]acetone, 1 h; for **6**: 28 equiv, [D₈]THF, 68 h); [b] Maximum deuteration theoretically possible 95% (see Supporting Information for details); [c] Maximum deuteration theoretically possible 80% (see Supporting Information for details).

of vinylidene intermediates, such as **B**,^[12] here allowing for facile deuterium incorporation and cyclization in one pot. Given the recent interest in deuteration of organic molecules^[13] and the attractiveness of using inexpensive and safe-to-handle D₂O as a source of deuterium, these results suggest additional roles for **1** and related species^[14] in the selective labeling of organic molecules.

To summarize, compound **1** is a unique catalyst of broad application because 1) cyclic enamides, indoles, and benzofurans can be made; 2) similar low catalyst loadings are used in each case; 3) several classes of substituents are tolerated on either the benzo ring or on the nitrogen atom involved in the cyclization; 4) one-pot reactions of doubly ethynylated species can lead to significant increases in molecular complexity impossible with other cycloisomerization catalysts incapable of alkyne hydration; 5) both carbons of the newly formed heterocycle can be deuterated simply by adding D₂O. Available evidence rules out protic catalysis, but is consistent with indole and benzofuran formation from direct attack of the heteroatom, rather than water, on a vinylidene intermediate, which suggests additional applications for bifunctional catalyst **1** and its analogues in organic synthesis.

Experimental Section

Preparative procedure for cyclization of 11: In a glove box, a scintillation vial with stir bar was charged with **11** (0.0993 g, 0.6123 mmol), which was dissolved in dry and deoxygenated THF (5 mL). To this was added **1** (0.0131 g, 0.0131 mmol), the vial was sealed with its cap and the reaction mixture was subjected to heating at 70 °C in an oil bath for 2 h. The reaction was monitored by TLC for complete disappearance of starting material following which the solvents were evaporated by rotary evaporation and the product was purified by column chromatography (2:1 hexanes/ethyl acetate) to give **22** as an orange solid (0.092 g, 92 %).

Preparative procedure for cyclization of 16: In a glove box, a scintillation vial with stir bar was charged with **16** (0.0943 g, 0.535 mmol), which was dissolved in deoxygenated acetone (5 mL). To this was added **1** (0.0106 g, 0.0106 mmol), the vial was sealed with its cap and the reaction mixture was subjected to heating at 70 °C in an oil bath for 1 h. The reaction was monitored by TLC for complete disappearance of starting material following which the solvents were evaporated by rotary evaporation and the product was purified by column chromatography (2:1 hexanes/ethyl acetate) to give **25** as an off-white solid (0.071 g, 75 %).

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