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Regioselective lactonization of unsymmetrical 1,4-diols: an efficient access to lactone lignans†

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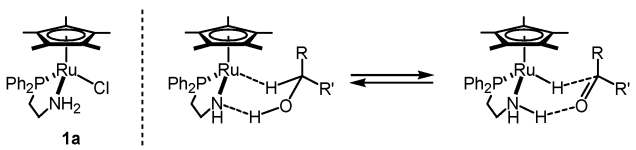
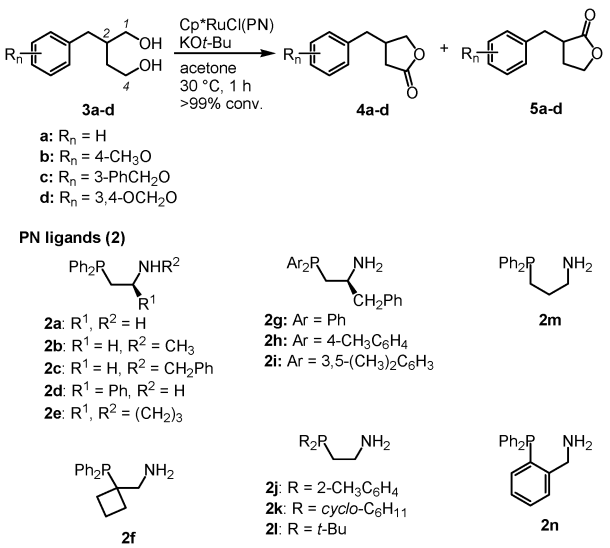
A Cp*Ru-based bifunctional catalyst system (Cp* = η^5-$C_5(CH_3)_5$) with a suitably-designed PN ligand (PN = chelating tertiary phosphine-protic amine ligand) has been developed for a regioselective lactonization of unsymmetrically substituted 1,4-diols, which may provide an expeditious access to a variety of lactone lignans.

We have recently found that a bifunctional catalyst system of Cp*RuCl($Ph_2PCH_2CH_2NH_2$) (**1a**) and KO*t*-Bu effects the reversible hydrogen transfer between alcohols and carbonyls, possibly through a pericyclic transition state as illustrated in Scheme 1.[1–4] This feature was clearly demonstrated by the *intramolecular* hydrogen transfer of secondary alcohols. For example, optically active secondary alcohols undergo rapid racemization,[3a] and allylic secondary alcohols undergo redox isomerization to ketones,[3b] in toluene containing this catalyst system under mild conditions. Notably, primary alcohols are much more susceptible to the similar-type *intramolecular* hydrogen transfer as exemplified with a very rapid H–D scrambling of $PhCD_2OH$ in toluene.[3c] On the other hand, the same catalyst system promotes the *intermolecular* hydrogen transfer when a sacrificial hydrogen acceptor including acetone, methyl vinyl ketone or acrylates is present in the reaction system.[3a,b] Furthermore, a wide range of 1,4-diols with a primary hydroxyl group at one end are very rapidly convertible in acetone as an external hydrogen acceptor to the corresponding γ-lactones under mild conditions.[3c] Encouraged by the marked catalyst performance, we have next examined the lactonization of unsymmetrically substituted 1,4-diols with two primary hydroxyl groups using a diverse array of Cp*Ru catalyst systems with a structurally different PN ligand (**2**), in order to clarify the steric effect of the ligand structure on the regiochemical outcome. Moreover, the high regioselectivity gained by this fine-tuning has proven beneficial in the preparation of lactone lignans that display a substantial range of biological activities.[5] Herein, we wish to report these results.



Scheme 1 Reversible hydrogen transfer between alcohols and carbonyls.

As illustrated in Scheme 2, we initially examined the lactonization of 2-benzyl-1,4-butanediol (**3a**) in acetone as a model reaction,[6] to see if the catalyst molecule can discriminate two primary hydroxyl groups with subtle steric difference in **3a**. The reaction was carried out at 30 °C for 1 h in acetone containing the catalyst system (**3a** : Ru : KO*t*-Bu = 100 : 1 : 1). The binary catalyst system of **1a** and KO*t*-Bu promoted the lactonization of **3a** efficiently to give a mixture of β-benzyl-γ-lactone (**4a**) and α-benzyl-γ-lactone (**5a**) with a molar ratio of 77 : 23 within 1 h (Table 1, entry 1). Almost identical catalyst performance in terms of activity and regioselectivity was observed when the preformed complex **1a** was replaced with *in situ* generated catalyst from the ligand **2a** and



Scheme 2 Cp*Ru(PN)-catalyzed lactonization of **3** in acetone.

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Table 1 Regioselectivity in the lactonization of **3**[a]

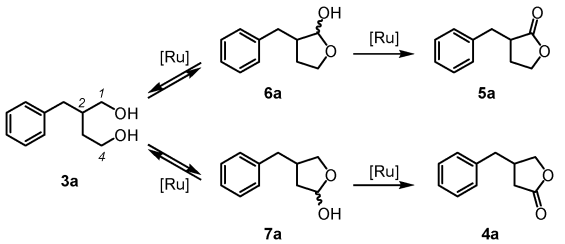
Entry	Substrate	Catalyst system employed[b]	PN ligand	Ratio of products[c]
1	**3a**	A	**2a**	77 : 23
2	**3a**	A	**2b**	82 : 18
3	**3a**	B	**2c**	83 : 17
4	**3a**	A	**2d**	81 : 19
5	**3a**	A	**2e**	80 : 20
6	**3a**	A	**2f**	90 : 10
7	**3a**	A	**2g**	76 : 24
8	**3a**	A	**2h**	78 : 22
9	**3a**	A	**2i**	81 : 19
10	**3a**	B	**2j**	88 : 12
11	**3a**	B	**2k**	96 : 4
12	**3a**	B	**2l**	94 : 6[d]
13	**3a**	A	**2m**	82 : 18
14	**3a**	A	**2n**	92 : 8
15	**3b**	A	**2n**	92 : 8
16	**3c**	A	**2n**	92 : 8
17	**3d**	A	**2n**	92 : 8

[a] Reaction conditions: **3** : Ru : KO*t*-Bu = 100 : 1 : 1, [**3**] = 0.5 M in acetone, 30 °C. All reactions completed within 1 h to give lactones exclusively as a mixture of **4** and **5**. [b] Procedure A: the binary catalyst system of Cp*RuCl(PN) and KO*t*-Bu (Ru : KO*t*-Bu = 1 : 1). Procedure B: the ternary system of Cp*RuCl(isoprene), **2**, and KO*t*-Bu (Ru : **2** : KO*t*-Bu = 1 : 1 : 1). [c] Determined by integration of well-resolved signals of **4** and **5** in ^{1}H NMR spectra of a crude product. [d] 48 h.

Cp*RuCl(isoprene) or [Cp*Ru(CH_3CN)$_3$]OTf. However, the use of a non-methylated cyclopentadienyl congener, [(η^5-C_5H_5)Ru(CH_3CN)$_3$]PF_6, in place of [Cp*Ru(CH_3CN)$_3$]OTf resulted in the moderate regioselectivity (56 : 44). In contrast with the negative impact of a less substituted cyclopentadienyl ligand,[7a] the structural modification of the PN ligand in Cp*RuCl(PN) complexes mostly exerted a positive effect for the preferential formation of **4a**. Although the alkyl substitution at the *N*-α-carbon had no dramatic impact on the regioselectivity (entries 4, 5, 7), *N*-alkyl substitution in the PN ligand slightly improved the regioselectivity for **4a** (entries 2 and 3).

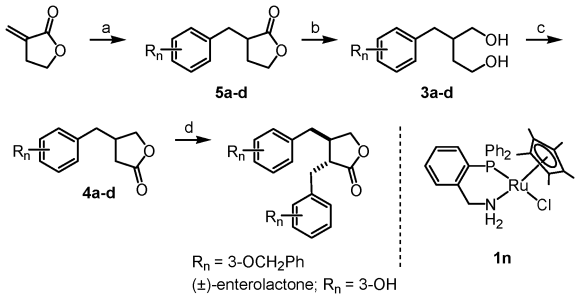
By contrast, the introduction of geminal two substituents at the P-α-carbon improved the regioselectivity reaching to 90 : 10 (entry 6). While the change of substituents on the phosphorous in the PN ligand **2g** from phenyl group to *p*-tolyl (**2h**) or 3,5-xylyl (**2i**) groups resulted in little change in the regioselectivity (entries 7–9), the similar change in the ligand **2a** with *o*-tolyl group (**2j**) or cyclohexyl (**2k**) and *tert*-butyl (**2l**) groups significantly improved the regioselectivity (entries 1, 10–12). Additionally, the replacement of the ethylene linkage in the ligand **2a** with the propylene (**2m**) or the benzylic one (**2n**) gradually improved the regioselectivity for **4a** (entries 13 and 14). The catalyst system of Cp*RuCl[(2-Ph_2P)$C_6H_4CH_2NH_2$] (**1n**) and KO*t*-Bu also promoted the lactonization of structurally similar unsymmetrical 1,4-diols **3b–d** to give β-benzylic-γ-lactones (**4b–d**) in a highly regioselective manner (entries 15–17).[7b] Therefore, the substituents on the aryl group in the substrates **3** may have little effect on the regioselectivity of the lactonization.

Valuable information on the origin of regioselectivity was provided by control experiments using 3-benzyl-2-tetrahydrofuranol (**6a**, Scheme 3), which was separately prepared as a diastereomeric mixture from **5a** by DIBAL reduction.[8] We found that the dehydrogenation of **6a** in acetone containing the catalyst system of **1n** and KO*t*-Bu gave **5a** and a substantial amount of **4a** (**6a** : **1n** : KO*t*-Bu = 100 : 1 : 1, [**6a**] = 0.5 M in acetone, 30 °C, 1 h, **4a** : **5a** = 40 : 60). This result may suggest that the intermediary isomeric lactols, **6a** and **7a**, are interconvertible with each other *via* **3a**, as illustrated in Scheme 3, and hence the regioselectivity in the first dehydrogenation step does not necessarily determine the overall regioselectivity in the present lactonization. In fact, the similar reaction of **6a** *in the absence of acetone* resulted in the formation of **3a** in addition to **4a** and **5a** (**6a** : **1n** : KO*t*-Bu = 100 : 1 : 1, [**6a**] = 0.5 M in toluene, 30 °C, 1 h, **3a** : **4a** : **5a** = 48 : 13 : 39). This result clearly indicated that **6a** can serve not only as a hydrogen donor but also as a hydrogen acceptor, to promote disproportionation into the diol and isomeric lactones. Furthermore, the hydrogen acceptor ability of **6a** should be much higher than that of acetone to allow the formation of **4a** *via* **3a** and **7a** even in acetone. Therefore, the differentiations of the two primary hydroxyl groups in the unsymmetrical diols as well as of two regioisomeric lactols are crucial for determining the overall regioselectivity in the present lactonization.

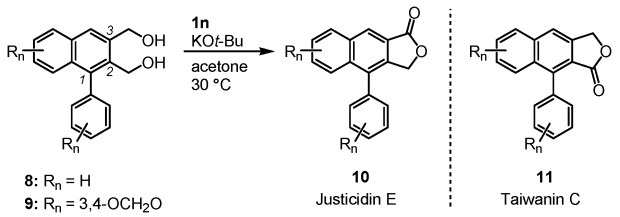


Scheme 3 Reaction course for the lactonization.

Our present method provides a convenient access to biologically important lactone lignans. As illustrated in Scheme 4, the Rh-catalyzed 1,4-addition of suitable arylboronic acids to α-methylene-γ-butyrolactone gave **5a–d** quantitatively. Their catalytic hydrogenation[2f] followed by the present lactonization with **1n** afforded **4a–d**, in which the position of their benzylic groups is switched from α to β. We found that the minor byproducts **5a–d** did not become a major obstacle in the subsequent stereocontrolled C–C bond formation.[9] For example, the deprotonation of the crude **4c** (92 : 8 mixture of **4c** and **5c**) with LDA followed by the reaction with 3-(benzyloxy)-1-(bromomethyl)benzene allowed easy isolation of (±)-*O*,*O*′-dibenzyl enterolactone by silica gel chromatography.



Scheme 4 Preparation of a lactone lignan. *Reagents and conditions*: (a) arylboronic acid (1.1 equiv.), triethylamine (1.1 equiv.), [RhCl(cod)]$_2$ (3 mol%), dioxane–H_2O, 30 °C. (b) See ref. 2f. (c) see Table 1 (entries 14–17). (d) See ESI.†



Scheme 5 Preparation of arylnaphthalene lactone lignans.

The present regioselective lactonization was also applicable to the synthesis of naturally occurring arylnaphthalene lactone lignans. For example, the catalyst system of **1n** and KO*t*-Bu promoted the lactonization of 2,3-bis(hydroxymethyl)-1-arylnaphthalenes **8** or **9** ([**8**] = 0.5 M in acetone, **8** : **1n** : KO*t*-Bu = 100 : 1 : 1, 30 °C, 1 h, >99% yield; [**9**] = 0.1 M in acetone, **9** : **1n** : KO*t*-Bu = 50 : 1 : 1, 30 °C, 15 h, 93% yield) to furnish **10** or Justicidin E, respectively, and no trace of **11** or Taiwanin C was detected[10] (Scheme 5). These results along with the aforementioned preferential formation of **4** from **3** may indicate that the sterically less demanding primary hydroxyl group is favorably susceptible to two-step dehydrogenation by the catalyst system of **1n** and KO*t*-Bu.

In summary, we have developed a Cp*Ru-based bifunctional catalyst system for the regioselective lactonization of unsymmetrical 1,4-diols. The fine-tuning of the skeleton of PN ligands in the catalyst system has proven crucial for the selective dehydrogenation at the sterically less demanding primary hydroxyl group. Further studies to demonstrate the synthetic utility of the present catalytic method are in progress.

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7 (*a*) The use of [(η^5-indenyl)Ru(PPh_3)($Ph_2PCH_2CH_2NH_2$)]Cl in place of **1a** resulted in very sluggish reaction with moderate regioselectivity (3 mol%, 50 °C, 21 h, **4a** : **5a** = 56 : 44). This result also indicated a possible catalyst poisoning by PPh_3; (*b*) Although the regioselectivity proved almost identical, the catalytic activity of the ternary system of [η^5-1,2,3-$(CH_3)_3C_5(CH_2)_4$]RuCl(isoprene), **2n**, and KO*t*-Bu was lower than the binary system of **1n** and KO*t*-Bu possibly due to excessive steric congestion arising from the bicyclic cyclopentadienyl ligand. These results will be reported separately.

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