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Ring-Closing Metathesis/Isomerization/ Pictet–Spengler Cascade *via* Ruthenium/ Chiral Phosphoric Acid Sequential Catalysis

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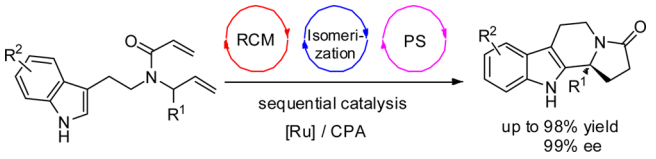
ABSTRACT



Chiral phosphoric acid worked together with Hoveyda–Grubbs II catalyst enabling highly efficient synthesis of enantioenriched tetrahydro-β-carbolines (up to 98% yield, 99% ee) through a ring-closing metathesis/isomerization/Pictet–Spengler cascade reaction *via* sequential catalysis.

The chiral tetrahydro-β-carboline ring system is widely distributed in natural products and pharmaceuticals.[1] The Pictet–Spengler reaction has been recognized as one of the most direct and efficient methods for construction of tetrahydro-β-carboline frameworks.[2] Its catalytically enantioselective version has attracted enormous attention and witnessed significant progress during the past decade.[3] Studies by Jacobsen,[4] List,[5] Hiemstra,[6] and many others[7] have realized highly enantioselective Pictet–Spengler type reactions. Notably, Dixon et al. recently designed a cascade employing gold(I)/chiral phosphoric acid binary catalysts enabling the enantioselective Pictet–Spengler type reaction in a highly efficient manner.[8] However, to date, most of the reported methods are accomplished by the treatment of tryptamine with carbonyl functionality in the presence of a chiral acidic catalyst. Recently, Nielsen et al. reported an alternative route to tetrahydro-β-carboline by devising a Ru-catalyzed tandem ring-closing metathesis

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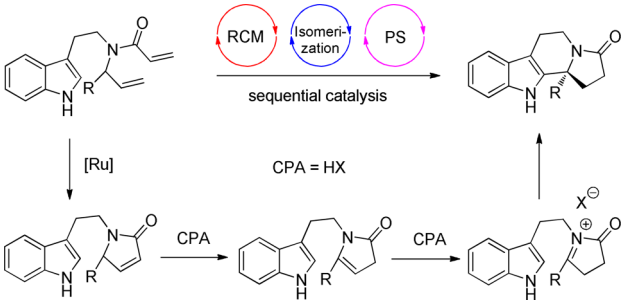
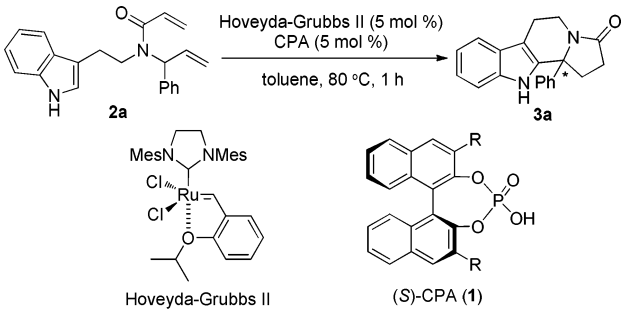
(RCM)/isomerization/*N*-acyliminium cyclization sequence.[9] The tandem reactions provide racemic tetrahydro-*β*-carbolines in good yields from readily available starting materials.

Scheme 1. Enantioselective Synthesis of Tetrahydro-*β*-carbolines *via* Ru/Chiral Phosphoric Acid (CPA) Sequential Catalysis



As we recently succeeded in the development of sequential catalysis where a ruthenium catalyst and chiral phosphoric acid could synergistically catalyze cross-metathesis (CM) and a Friedel–Crafts alkylation reaction,[10,11] we envisioned that a combination of a proper ruthenium catalyst and chiral phosphoric acid could turn the Nielsen reaction into an enantioselective version (Scheme 1). To be noted, Huang et al. recently showed that chiral phosphoric acid could catalyze the isomerization of α, *β*-unsaturated lactam to *N*-acyl iminium in an enantioselective *N*-H functionalization of indoles.[12] In this paper, we report a highly efficient synthesis of enantioenriched indolizinoindoles through a RCM/isomerization/Pictet–Spengler (PS) cascade reaction *via* ruthenium/chiral phosphoric acid sequential catalysis.

Table 1. Screening Chiral Phosphoric Acids for Cascade RCM/Isomerization/PS Reaction



entry[a]	1	R	yield (%)[b]	*ee* (%)[c]
1	**1a**	1-naphthyl	50	28
2	**1b**	2-naphthyl	94	45
3	**1c**	4-NO_2-C_6H_4	46	55
4	**1d**	4-biphenyl	92	46
5	**1e**	9-anthryl	74	43
6	**1f**	9-phenanthryl	82	55
7	**1g**	1-pyrenyl	89	63
8	**1h**	2,4,6-(^{i}Pr)$_3$-C_6H_2	75	38
9	**1i**	4-^{t}Bu-2,6-(^{i}Pr)$_2$-C_6H_2	77	35
10	**1j**	$SiPh_3$	80	86

[a] Reaction conditions: 5 mol % Hoveyda–Grubbs II, 5 mol % (*S*)-**1**, 0.05 mol/L of **2a** in toluene, 80 °C. [b] Isolated yield. [c] Determined by HPLC analysis.

We began our study by using readily available tryptamine derivative **2a** as a model substrate. The Hoveyda–Grubbs II catalyst was used to accomplish the RCM reaction. With chiral phosphoric acid **1a** bearing 1-naphthyl groups, the proposed cascade RCM/isomerization/PS reaction indeed proceeded even at 80 °C, affording cyclization product **3a** in 50% yield and 28% ee (entry 1, Table 1). Inspired by this result, several chiral BINOL-derived phosphoric acids bearing different substituents at 3,3′-positions were further tested. The results are summarized in Table 1. To our great delight, all the tested chiral phosphoric acids could catalyze the cascade reaction together with the ruthenium catalyst, affording the cyclization product generally in good yields and variable enantioselectivity (entries 2–9, Table 1). Notably, chiral phosphoric acid **1j**, bearing triphenyl silyl groups, displayed optimal enantioselective control (80% yield, 86% ee, entry 10, Table 1).

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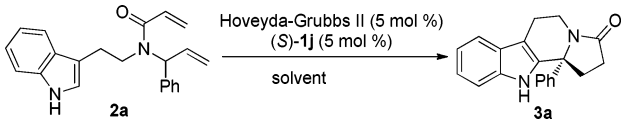
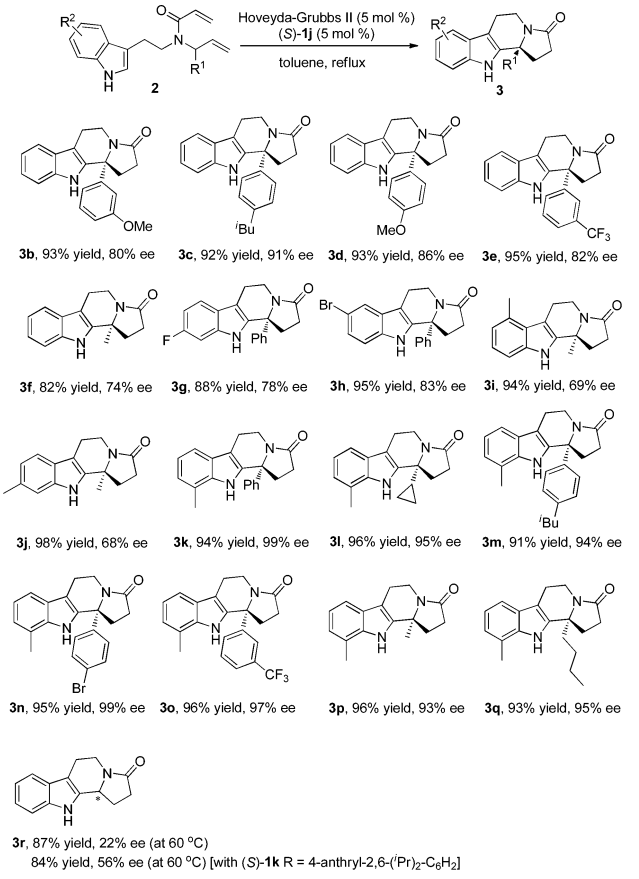
Table 2. Optimization of the Reaction Conditions for Cascade RCM/Isomerization/PS Reaction with CPA **1j**



entry[a]	solvent	additive	t (°C)	yield (%)[b]	ee (%)[c]
1	toluene	none	80	80	86
2	benzene	none	80	48	85
3	*m*-xylene	none	80	60	81
4	$CHCl_3$	none	80	<5	ND
5	DCE	none	80	<5	ND
6	*c*-hexane/ toluene	none	80	90	81
7[d]	toluene	3 Å MS	80	83	86
8[d]	toluene	4 Å MS	80	84	85
9[d]	toluene	5 Å MS	80	60	81
10	toluene	H_2O (1 equiv)	80	80	85
11[e]	toluene	none	80	80	86
12	toluene	none	70	82	85
13	toluene	none	95	86	86
14	toluene	none	reflux	95	84

[a] Reaction conditions: 5 mol % Hoveyda−Grubbs II, 5 mol % (*S*)-**1j**, 0.05 mol/L of **2a**, unless noted otherwise. [b] Isolated yield. [c] Determined by HPLC analysis. [d] With 50 mg of molecular sieves per 0.1 mmol of **2a**. [e] Reaction with 0.1 mol/L of **2a**

Scheme 2. Substrate Scope for Cascade RCM/Isomerization/PS Reaction



It should be noted that this optimal catalyst is consistent with the work of Dixon and co-workers.[8]

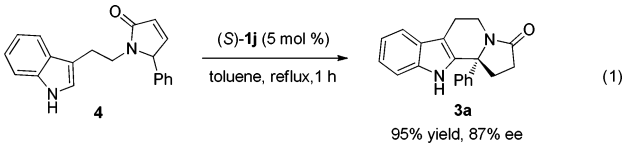
With Hoveyda-Grubbs II and (*S*)-**1j** as the catalysts, the reaction conditions were further optimized as summarized in Table 2. Several conventional solvents were examined. The reactions in benzene and *m*-xylene gave comparable enantioselectivity but decreased yields, while those in $CHCl_3$ and DCE led to no detectable products (entries 1−5, Table 2). The mixed solvents of cyclohexane and toluene (1/1) could be tolerated to afford cyclization product **3a** in excellent yield but with slightly decreased enantioselectivity (90% yield, 81% ee, entry 6, Table 2). When molecular sieves were tested as the additive (entries 7−9, Table 2), both 3 Å and 4 Å MS gave improved yields (83−84%) but 5 Å MS led to a decreased yield (60%). Interestingly, the addition of 1 equiv of water did not show any deteriorative effect (entry 10, Table 2), indicating that the reaction is not sensitive to moisture. Investigation of the reaction temperatures disclosed that the reaction could proceed smoothly ranging from 70 °C to reflux in toluene, without an obvious effect on enantioselectivity (entries 12−14, Table 2). In general a higher temperature leads to a better yield in a shorter reaction time. The reaction in refluxed toluene gave an optimal yield (95%).

Under the optimized reaction conditions (entry 14, Table 2), the substrate scope of this cascade reaction has been examined. The results are summarized in Scheme 2. In general, all the tested substrates with varying substituents on the indole core and amine proceeded well to give cyclization products with excellent yields (82−98%). For the aryl allyl amine moiety, substrates containing substituents such as 3-CF_3, 3-OMe, 4-^{t}Bu, and 4-OMe on the benzene ring could all be tolerated with good enantioselectivity (80−91% ee, **3b**−**3e**, Scheme 2). The substrate derived from methyl allyl amine also gave product **3f** in 82% yield and 74% ee. Substrates bearing different substituents such as 4-Me, 6-Me, 5-Br, 6-F on the indole core all proceeded smoothly under the sequential catalysis (**3g**−**3j**, Scheme 2). Interestingly, when substrates having 7-Me on the indole core were used, the enantioselectivity could be enhanced dramatically. For instance, products **3k**−**q** were obtained in excellent yields (91−96%) and ee (93−99%) with various substituents on the allyl amine such as Ph, 4-^{t}Bu-C_6H_4, 4-Br-C_6H_4, 3-CF_3-C_6H_4, methyl, cyclopropyl, and *n*-butyl groups (**3k**−**3q**, Scheme 2). Notably, when the substrate derived from simple allyl amine (R^1 = H) was used, only moderate enantioselectivity was obtained (**3r**, Scheme 2).[13]

To shed light on the mechanism of this cascade reaction, the α,β-unsaturated lactam **4** was prepared. Treatment of **4** with 5 mol % (*S*)-**1j** in refluxed toluene led to **3a** in 95% yield and 87% ee (eq 1). Similar enantioselectivity between the stepwise and the cascade reaction (entry 14, Table 2)

(13) See the Supporting Information for details.

suggested the *N*-acyl iminium cyclization was mainly catalyzed by chiral phosphoric acid. On the other hand, the high yield and enantioselectivity of the cascade reaction highlight how sequential catalysis is advantageous.



(1)

In conclusion, we have developed a cascade RCM/isomerization/Pictet–Spengler reaction, utilizing a ruthenium complex and chiral phosphoric acid, with excellent yields and enantioselectivity. The synergistic effect of the binary catalytic system allows the enantioselective reaction to proceed under milder reaction conditions compared to the racemic synthesis. This cascade reaction provides a new route for tetrahydro-β-carbolines and concepts in designing transition-metal/chiral Brønsted acid sequential catalysis.

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Supporting Information Available. Detailed experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.