Cyclization

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Catalytic Asymmetric [4+2] Annulation Initiated by an Aza-Rauhut–Currier Reaction: Facile Entry to Highly Functionalized Tetrahydropyridines**

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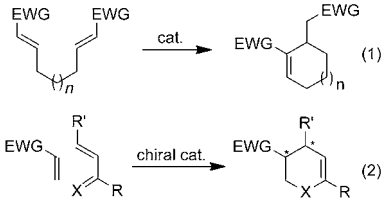
The Rauhut–Currier (RC) reaction, also known as the vinylogous Morita–Baylis–Hillman reaction, was discovered in 1963 by Rauhut and Currier.[1] However, as a result of the low reactivity and selectivity, it did not attract a lot of attention during the last half century. The achievement of Moore and co-workers on the synthesis of the Waihoensene ring system represents the first practical example of utilizing an intramolecular RC reaction as a key step in organic synthesis.[2] Krische and co-workers and Roush and co-workers then independently developed a phosphine-catalyzed intramolecular RC reaction for the synthesis of five- and six-membered ring systems with high efficiency.[3a,b] The first enantioselective intramolecular RC reaction was reported by Miller and co-workers.[4] Shortly thereafter, Seidel and Gladysz realized a catalytic asymmetric version by using a chiral rhenium-containing phosphine catalyst.[5] After such pioneering work, intensive investigations were devoted to this field. Among the remarkable achievements documented, the majority of them focused on the intramolecular reaction [Scheme 1, Eq. (1)],[6] with a few examples



Scheme 1. Catalytic Rauhut–Currier reaction initiated cyclization. EWG = electron-withdrawing group.

reported on the catalytic intermolecular reaction, especially an asymmetric version.[7] Merging an intermolecular RC reaction with subsequent reactions in a cascade reaction, thus forming optically active heterocycles [Eq. (2)], would be of great synthetic importance and significance in terms of atom economy. However, there are only a few reports on using this strategy in a catalytic asymmetric manner.[8]

Chiral tetrahydropyridines are important organic synthons. They can be readily reduced to piperidines, which frequently occur in many natural products of biological relevance.[9] Existing methodologies for their preparation are largely attributed to the aza-Diels–Alder reaction of *N*-sulfonly-1-aza-1,3-butadiene with electron-rich dienophiles,[10] and the [4+2] annulation reaction of 2-methylene-but-3-enoate with imines,[11] which are either limited by a narrow substrate scope or restricted by rigorous reaction conditions. Thus, the development of a more general and efficient protocol is highly desirable. As part of our long-standing interest in organocatalysis,[12] and on the basis of our recent achievement,[13] we report herein an alternative approach to the synthesis of enantioenriched tetrahydropyridines by a catalytic asymmetric [4+2] annulation pathway initiated by an aza-Rauhut–Currier reaction using chiral phosphine catalysts derived from natural amino acids. To the best of our knowledge, this is the first example of the catalytic asymmetric cross-aza-Rauhut–Currier reaction.

The development of chiral phosphine catalysts based on the skeletons of natural amino acids has seen remarkable progress in recent years.[14] Considering their easy accessibility, low cost, and good asymmetric induction, our preliminary studies were carried out using the chiral phosphine catalysts derived from L-leucine (Figure 1). To our delight, 20 mol% of **4a** catalyzed the model reaction of methyl vinyl ketone (**1**; MVK) with the *N*-benzenesulfonyl-1-aza-1,3-diene **2a** to produce the desired product in 64% yield with modest diastereo- and enantioselectivity (Table 1, entry 1). Various N-sulfonyl-1-aza-1,3-dienes were then tested to elucidate the effect of protecting groups on the stereoselective induction, and the *N*-tosyl-1-aza-1,3-diene **2b** proved to be a good choice (entries 2–4).

Other chiral phosphines derived from natural amino acids or chiral α-hydroxy acids were then examined. The catalyst **4b**, which was effective in the [3+2] cycloaddition of chalcones with allenes,[14a] showed no asymmetric induction (Table 1, entry 5). Notably, the TBS-protected catalyst **4e** delivered the product in almost a racemic manner, whereas **4f** bearing a free hydroxy group afforded the corresponding product in 47% *ee* (entries 8 and 9). These results indicated

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that hydrogen bonding between the catalyst and substrate might be crucial to achieve high levels of asymmetric induction. The better *ee* values achieved by the catalysts **4a**, **4c**, and **4d** suggested that the NH group in these catalysts might serve as a hydrogen-bond donor. Inspired by these findings, systematic modification of the catalyst structure was then conducted. Acetyl-, benzoyl-, 4-fluorobenzoyl-, 4-methoxybenzoyl-, and 2-naphthoyl-protected amino phosphines afforded comparable *ee* values to those obtained with **4a** (entries 10–14). Our attempt to increase the acidity of the amide group by introducing a strong electron-withdrawing group resulted in a diminished enantioselectivity (entry 15). Installation of another hydrogen-bond donor, such as the phenol moiety in **4m**, did not lead to any improvement (entry 16). The more-bulky catalyst **4n** showed promising enantioselectivity (68% *ee*), and it was further improved to 71% by using *N*-(4-methoxybenzenesulfonyl)-1-aza-1,3-diene (**2e**; entries 17 and 18). Inspired by the recent work on L-threonine-based dipeptide-containing phosphine catalysts,[15] the catalysts **4o** and **4p** were tested. The catalyst **4o** afforded similar results to that of **4n**, whereas **4p** gave a slightly improved enantioselectivity (entries 19 and 20). Surprisingly, the diastereo- and enantioselectivity were dramatically improved when **2f** was employed as the substrate (entry 21), though a slightly lower yield was obtained. After additional optimization of solvent and the reaction concentration, chloroform was found to be the best choice (entry 22).[16]

With the optimal reaction conditions established, the scope of the 1-aza-1,3-dienes was then explored (Table 2). In the presence of 10 mol% **4p**, *ortho*-, *meta*-, and *para*-substituted aryl 1-aza-1,3-dienes underwent the [4+2] annu-

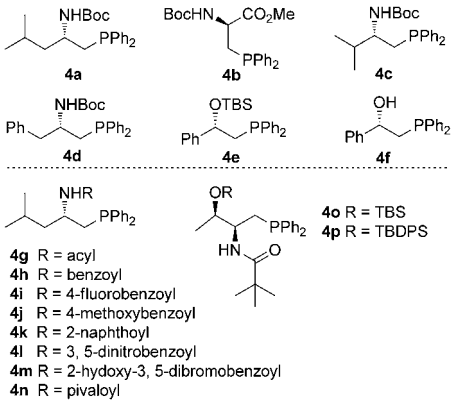
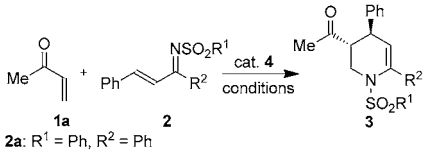


Figure 1. Catalysts examined. Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

Table 1: Optimization of reaction conditions.[a]

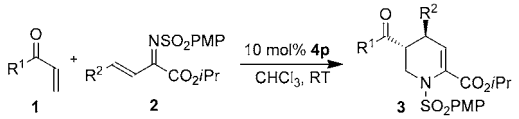


2a: R^1 = Ph, R^2 = Ph
2b: R^1 = *p*-$CH_3C_6H_4$, R^2 = Ph
2c: R^1 = 8-quinolyl, R^2 = Ph
2d: R^1 = *p*-ClC_6H_4, R^2 = Ph
2e: R^1 = *p*-$CH_3OC_6H_4$, R^2 = Ph
2f: R^1 = *p*-$CH_3OC_6H_4$, R^2 = CO_2iPr

Entry	2	Cat. 4 (mol%)	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**2a**	**4a** (20)	64	83:17	55
2	**2b**	**4a** (20)	66	86:14	63
3	**2c**	**4a** (20)	65	83:17	59
4	**2d**	**4a** (20)	60	80:20	56
5	**2b**	**4b** (20)	82	89:11	0
6	**2b**	**4c** (20)	90	67:33	58
7	**2b**	**4d** (20)	68	80:20	60
8	**2b**	**4e** (20)	92	92:8	3
9	**2b**	**4f** (20)	73	93:7	47
10	**2b**	**4g** (20)	80	80:20	56
11	**2b**	**4h** (20)	85	83:17	61
12	**2b**	**4i** (20)	82	83:17	59
13	**2b**	**4j** (20)	81	83:17	58
14	**2b**	**4k** (20)	84	83:17	54
15	**2b**	**4l** (20)	70	67:33	37
16	**2b**	**4m** (20)	70	80:20	40
17	**2b**	**4n** (20)	74	86:14	68
18	**2e**	**4n** (20)	79	80:20	71
19	**2e**	**4o** (20)	87	87:13	71
20	**2e**	**4p** (20)	85	87:13	72
21	**2f**	**4p** (10)	70	>95:5	86
22[e]	**2f**	**4p** (10)	68	>95:5	89

[a] Unless otherwise specified, reactions were performed using 0.1 mmol of **2** and 0.3 mmol of methyl vinyl ketone in 0.2 mL dichloromethane at room temperature in the presence of 20 mol% **4** for 24 h. [b] Yield of isolated *trans* isomer. [c] d.r. = *trans*/*cis*; determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined using a chiral IA-H column. [e] Reaction was performed in chloroform.

Table 2: Generality of [4+2] annulation reaction.[a]



1a: R^1 = methyl
1b: R^1 = ethyl

Entry	1	R^2	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1a**	Ph	68 (**3a**)	>95:5	89
2	**1a**	2-FC_6H_4	59 (**3b**)	>95:5	90
3	**1a**	3-$MeOC_6H_4$	60 (**3c**)	>95:5	92
4	**1a**	3-ClC_6H_4	65 (**3d**)	>95:5	88
5	**1a**	3-BrC_6H_4	74 (**3e**)	>95:5	87
6	**1a**	4-$MeOC_6H_4$	70 (**3f**)	>95:5	99
7	**1a**	4-BrC_6H_4	67 (**3g**)	>95:5	91
8	**1a**	4-MeC_6H_4	72 (**3h**)	>95:5	89
9	**1a**	4-ClC_6H_4	71 (**3i**)	>95:5	90
10	**1a**	4-FC_6H_4	60 (**3j**)	>95:5	90
11	**1a**	2-naphthyl	78 (**3k**)	>95:5	94
12	**1a**	4-PhC_6H_4	55 (**3l**)	>95:5	88
13	**1a**	2-thienyl	85 (**3m**)	>95:5	92
14[e]	**1a**	3-furyl	67 (**3n**)	>95:5	90
15[e]	**1a**	methyl	63 (**3o**)	95:5	86
16	**1b**	3-BrC_6H_4	75 (**3p**)	86:14	86

[a] Unless otherwise specified, reactions were performed using 0.1 mmol of **2** and 0.3 mmol of **1** in 1.0 mL $CHCl_3$ at room temperature in the presence of 10 mol% **4p**. [b] Yield of isolated *trans* isomer. [c] d.r. = *trans*/*cis*; determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined using a chiral IA-H column. [e] Ethyl ester containing 1,3-azadiene was used. PMP = *para*-methoxyphenyl.

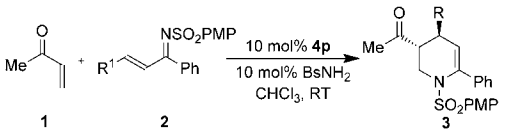
lation process with MVK smoothly, thus generating tetrahydropyridine adducts with exclusively *trans* diastereoselectivity and excellent enantioselectivity in high to excellent chemical yields. Halogenated substrates, which can participate in subsequent transformations such as coupling reactions, were well tolerated in this reaction (entries 4, 5, 7, and 9). Chiral fluorinated heterocycles, which often have superior biological properties relative to their nonfluorinated counterparts, could also be efficiently synthesized (entries 2 and 10). The electronic nature of the ring system slightly influenced the reaction outcome, with electron-rich substrates delivering products under better enantiocontrol (entries 3 and 6). More sterically demanding 2-naphthyl-substituted *N*-4-methoxybenzenesulfonyl-1-aza-1,3-diene proved to be a suitable substrate to give a [4+2] adduct with greater than 95:5 d.r. and 95% *ee* in 78% yield (entry 11). Further exploration revealed that this methodology had remarkable tolerance for the Lewis basic 4-heteroaryl-1-aza-1,3-diene, thus enabling the highly diastereo- and enantioselective synthesis of thienyl- and furyl-substituted tetrahydropyridines (entries 13 and 14). Notably, the reaction could be further extended to aliphatic 1,3-azadienes, for instance, a simple methyl-substituted azadiene participated in this [4+2] annulation process, thus affording product with excellent stereocontrol, in good yield (entry 15). Additionally, ethyl vinyl ketone (**1b**) proved to be a suitable substrate in this transformation (entry 16).

In our previous work, we observed an interesting phenomenon wherein the addition of a Brønsted acid as an additive could accelerate the reaction rate and improve the diastereoselectivity.[13,17] We envisioned that a Brønsted acid additive might assist in the formation of a more-rigid transition state between the catalyst and chalcone-derived 1,3-azadiene substrates, and thus provide better stereocontrol. As expected, we were pleased to find that diastereo- and enantioselectivities were slightly elevated (91:9 d.r. and 74% *ee* in 86% yield) when 10 mol% benzenesulfonamide was added. And the prolonged reaction time could be compensated for by performing the reaction at a higher concentration. Accordingly the enantiomeric excess was further improved to 76% *ee*.[16]

A number of chalcone-derived 1,3-azadienes efficiently underwent the [4+2] annulation reaction, thus giving facile access to 6-aryl-substituted tetrahydropyridines with good diastereo- and enantiomeric excesses in high to excellent yields (Table 3). Chloro-, bromo-, and fluoro-containing 1,3-azadienes were well tolerated in this transformation, thus affording synthetically useful stereocontrols (entries 2–4). Moreover, the *ee* value could be easily increased by a single recrystallization (entry 5). The sterically demanding 2-naphthyl-substituted tetrahydropyridine could be readily prepared under the optimized reaction conditions with 88:12 d.r. and 82% *ee* in 80% yield (entry 6). A heteroaryl-substituted substrate proved to be a suitable reaction component, thus enabling the synthesis of a 2-thienyl-substituted product with acceptable enantiomeric excess (entry 7). The absolute configurations of the products were determined by X-ray crystallography.[18]

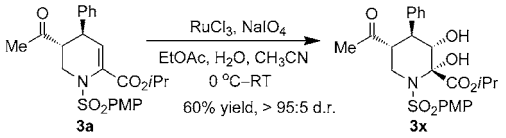
Chiral piperidines are important building blocks in numerous natural products and pharmaceuticals.[9] As demonstrated in Scheme 2, the treatment of **3a** with $RuCl_3$/$NaIO_4$[11b] readily afforded the dihydroxylated piperidine **3x** in 60% yield, with greater than 95:5 diastereoselectivity, thus further demonstrating the synthetic utility of this methodology.

Table 3: [4+2] Annulation of vinyl ketones with chalcones derived N-sulfonyl-1-aza-1,3-dienes.[a]



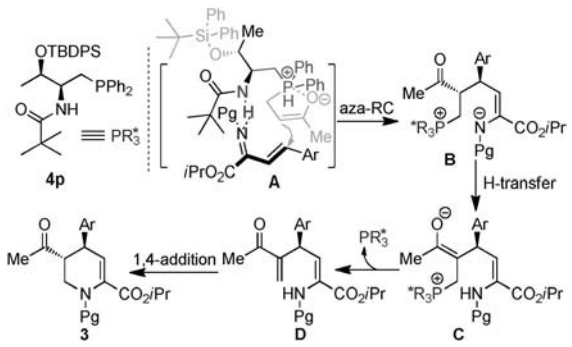
Entry	R^1	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	7	86 (**3q**)	91:9	76
2	3-ClC_6H_4	12	88 (**3r**)	90:10	80
3	3-BrC_6H_4	12	92 (**3s**)	83:17	76
4	4-FC_6H_4	12	87 (**3t**)	89:11	81
5	4-ClC_6H_4	12	70 (**3u**)	91:9	84(99)[e]
6	2-naphthyl	9	80 (**3v**)	88:12	82
7	2-thienyl	24	80 (**3w**)	89:11	78

[a] Unless otherwise specified, reactions were performed using 0.1 mmol of **2** and 0.3 mmol of methyl vinyl ketone in 0.1 mL of $CHCl_3$ at room temperature in the presence of 10 mol% **4p** and benzenesulfonylamide. [b] Yield of isolated product. [c] d.r. = *trans*/*cis*; determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined using chiral IA-H column. [e] Data in parentheses was obtained after single recrystallization.



Scheme 2. Synthesis of dihydroxylated piperidine derivative.

Although the detailed mechanism is not clear at this stage, a transition state is proposed to account for the observed stereochemistry (Scheme 5). The hydrogen bonding between the pivaloyl amide and the 1,3-azadiene could direct the alkene side chain outwards to a sterically less-demanding area and away from the bulky pivaloyl group, thus the enolate generated by nucleophilic addition of the phosphine moiety,



Scheme 3. Plausible transition state and reaction pathway.

preferentially attacks from the Si face (**A**). Subsequent intramolecular proton transfer deliveres the enolate intermediate **C**.[19] After expulsion of the catalyst, an intramolecular Micheal addition occurrs to generate the final [4+2] annulation product.

In summary, an unprecedented catalytic asymmetric [4+2] annulation reaction initiated by an aza-Rauhut–Currier reaction has been developed by utilizing amino phosphine catalysts derived from natural amino acids. This protocol provides a new entry to the synthesis of a broad spectrum of densely functionalized tetrahydropyridines with high stereocontrol in good to excellent yields. Further mechanistic investigations and applications to the synthesis of biologically active molecular complexes are currently underway in our laboratory, and will be reported in due course.

Experimental Section

General procedure: Under ambient conditions, **4p** (6.0 mg, 0.01 mmol) in chloroform (1.0 mL), and vinyl ketone (**1**, 0.3 mmol) were added to a stirred solution of N-sulfonyl-1-aza-1, 3-diene (**2**, 0.1 mmol). The reaction was then stirred at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was directly applied to column chromatography on silica gel (hexanes/ethyl acetate as eluent) to give product **3**.

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