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[4+2] Annulation of Vinyl Ketones Initiated by a Phosphine-Catalyzed Aza-Rauhut–Currier Reaction: A Practical Access to Densely Functionalized Tetrahydropyridines

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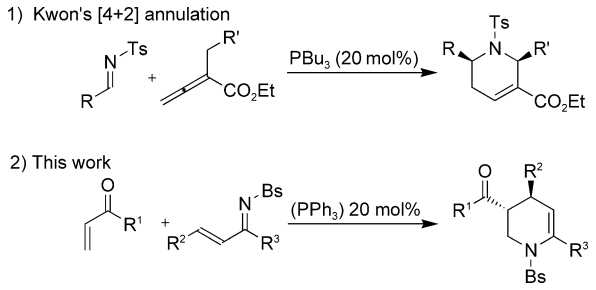
Enolate represents a typical nucleophile in numerous classic C−C bond formation reactions, but generally it inevitably requires additional synthetic steps or stoichiometric base, thus diminishes its synthetic importance. Direct usage of enolate precursor as nucleophile would be of great synthetic efficiency and atom-economy significance. Conceptually, the Rauhut–Currier reaction and Morita–Baylis–Hillman reaction are ideal models, in which activated alkenes are utilized as latent enolate to coupling with Michael acceptor and carbonyl compounds, respectively.[1] Although the Rauhut–Currier reaction was discovered half a century ago, comparing with the Morita–Baylis–Hillman reaction, it did not attract enough attention until recent years, due to lack of selectivity.[2] In 2002, the groups of Krische[2a] and Roush[2b] independently developed a synthetically useful intramolecular Rauhut–Currier reaction to construct five- or six-membered ring systems with high efficiency.[3] In 2007, Miller and Gladysz realized the first intramolecular Rauhut–Currier reaction in an asymmetric manner.[4] Recently, the achievements of Miller, Ruszczycky, and Choi in their natural products and bioactive compounds synthesis further proved the synthetic efficiency of the intramolecular Rauhut–Currier reaction.[5] However, up to date only sporadic intermolecular Rauhut–Currier reactions were documented,[6] and there is no report covering the aza-Rauhut–Currier reaction.

Tetrahydropyridines are intriguing synthetic targets as they can be readily converted into highly functionalized pyridine or piperidine derivatives, which frequently occur in natural products and biologically active compounds.[7] However, existing synthetic methods used to synthesize such highly valuable heterocycles mainly rely on Lewis acid catalyzed aza-Diels–Alder reactions,[8] which require harsh reaction conditions and are limited by relatively narrow substrates scope. In 2003, Kwon and co-workers developed an elegant protocol for the synthesis of highly functionalized tetrahydropyridines, through a phosphine-catalyzed [4+2] annulation reaction of 2-methyl-2,3-butadienoate with aldimines (Scheme 1).[9,10] However, the usage of air sensitive PBu_3 as catalyst partly limited its scale-up potential. Thus, the development of efficient, environmentally benign and practical strategies for the construction of tetrahydropyridines is highly desirable. Herein, we report the first example of aza-Rauhut–Currier reaction initiated [4+2] annulation of readily available vinyl ketones with *N*-sulfonyl-1-aza-1,3-dienes under ambient atmosphere, which provides a practical access to the synthesis of tetrahydropyridine derivatives (Scheme 1).



Scheme 1. Phosphine-catalyzed [4+2] annulation.

Initially, we tested the reaction of (*E*)-1,3-diphenyl-*N*-(tosyl) prop-2-en-1-imine **2a** with methyl vinyl ketone (MVK) **1a** in the presence of PPh_3 (20 mol%) using dichloromethane as solvent. To our delight, the starting materials were consumed completely at room temperature within 24 h, and the desired product was isolated in good yield and diastereoselectivity (Table 1, entry 1). The effects of various sulfonyl protecting groups were subsequently investigated. It was found that benzenesulfonyl (Bs) protected 1,3-azadiene afforded the [4+2] adduct **3a** with the highest yield and diastereoselectivity (Table 1, entry 2). Subsequent catalyst screening indicated that PPh_3 was the best choice in terms of its catalytic performance, low cost, and operational simplicity. Other catalysts examined, such as DABCO, DMAP, and PBu_3 gave unsatisfactory results (Table 1, entries 5–7).[11]

Solvent screening revealed that the solvent significantly influenced the reaction outcome. A dramatic improvement

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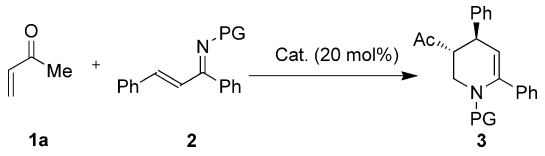
Table 1. Optimization of [4+2] annulation of vinyl ketones with *N*-sulfonyl-1-aza-1,3-dienes.[a]



1a 2 3

Entry	PG	Cat.	Solvent	d.r.[b]	Yield [%][c]
1	Ts	PPh_3	CH_2Cl_2	10:1	74
2	Bs	PPh_3	CH_2Cl_2	10:1	87
3	4-ClPhSO$_2$	PPh_3	CH_2Cl_2	6:1	67
4	4-NO$_2$PhSO$_2$	PPh_3	CH_2Cl_2	8:1	69
5	Bs	DABCO	CH_2Cl_2	5:1	10
6	Bs	DMAP	CH_2Cl_2	4:1	40
7	Bs	PBu_3	CH_2Cl_2	20:1	20
8	Bs	PPh_3	CH_2Cl_2/MeOH (9:1)	18:1	81
9[d]	Bs	PPh_3	CH_2Cl_2	16:1	91
10[e]	Bs	PPh_3	CH_2Cl_2	>20:1	95
11[f]	Bs	–	CH_2Cl_2	n.d.	n.r.

[a] Unless otherwise specified, reactions were performed using **2a** (0.1 mmol) and **1a** (0.3 mmol) in dichloromethane (0.2 mL) at room temperature in the presence of the catalyst (20 mol%) for 24 h. [b] d.r. = trans/*cis*, determined by crude ^{1}H NMR. [c] Yield of isolated *trans* isomer. [d] 4-Methoxyphenol (20 mol%) was added. [e] 4-Methoxyphenol (30 mol%) was added. [f] Reaction was conducted with 4-Methoxyphenol (30 mol%), without PPh_3. n.d. = not determined, n.r. = no reaction.

in diastereoselectivity was observed, when a mixture of dichloromethane and methanol (9:1) was examined for this transformation (Table 1, entry 8). Inspired by this interesting phenomenon, we envisioned that methanol may act as proton source or hydrogen bond donor, which stabilizes the enolate intermediate that is formed by nucleophilic addition of PPh_3 to MVK, thereby driving the reaction forward and accelerating the reaction (Figure 1). A series of Brønsted acids were then tested.[12] Among all the additives examined, 4-methoxyphenol afforded the product with the best yield and diastereoselectivity and in a significantly shorter reaction time (Table 1, entry 9).[11] Notably, when 4-methoxyphenol (30 mol%) was used, the reaction rate was further accelerated and afforded almost exclusive *trans* product in quantitative yield (Table 1, entry 10). A control reaction in absence of PPh_3, was carried out and it was found that the reaction did not proceed when only 4-methoxyphenol was present (Table 1, entry 11). This ruled out the possibility of a Diels–Alder reaction occurring between MVK and *N*-sulfonyl-1-aza-1,3-diene **2a** catalyzed by phenol additive.[13]

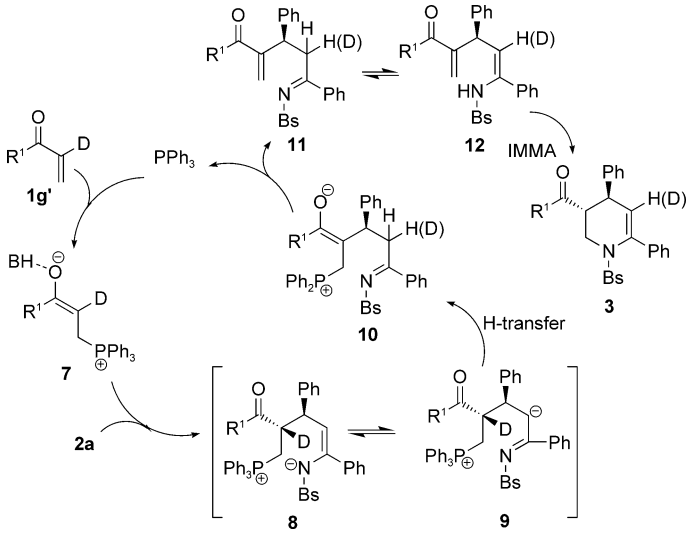
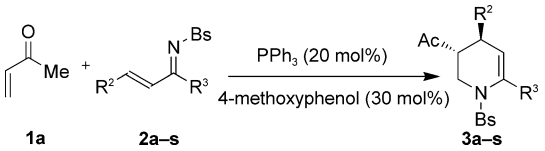


Figure 1. Proposed catalytic cycle of [4+2] annulation between vinyl ketones and *N*-sulfonyl-1-aza-1,3-dienes.

Having established the optimized reaction conditions, the generality of this reaction was then explored (Table 2). This protocol possessed high tolerance to various substituents. *Ortho*-substituted substrates, which usually lead to lower yields or unsatisfactory stereocontrol due to steric hindrance, underwent this process to give products with complete diastereoselectivities, and excellent yields were obtained (Table 2, entries 2 and 3). In addition, *meta*-, and *para*-substituted phenyl-*N*-sulfonyl-1-aza-1,3-dienes also gave the corresponding products with good yields and diastereoselectivities. Regardless of the electronic nature of the phenyl rings, good to excellent chemical yields and diastereomeric ratio (d.r.) values were obtained (Table 2, entries 4–12). 2-Naphthyl and 2,3-dihydrobenzofuran-5-yl substituted aza-1,3-dienes were also well tolerated (Table 2, entries 13 and 14). This protocol could be further extended to heteroaryl *N*-sulfonyl-1-aza-1,3-dienes, although the substrate bearing a 2-thienyl substituent gave a lower diastereo-

Table 2. Generality of [4+2] annulation of vinyl ketones with *N*-sulfonyl-1-aza-1,3-dienes.[a]



1a 2a–s 3a–s

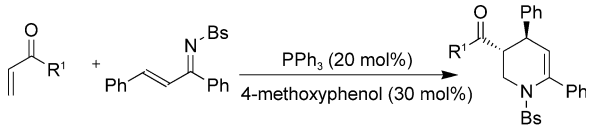
Entry	**2** (R^2, R^3)	**3** (d.r.,[b] yield %[c])
1	**2a** (Ph, Ph)	**3a** (>20:1, 95)
2	**2b** (2-FC$_6$H$_4$, Ph)	**3b** (>20:1, 90)
3	**2c** (2-Cl-5-NO$_2$C$_6$H$_4$,Ph)	**3c** (>20:1, 96)
4	**2d** (3-BrC$_6$H$_4$, Ph)	**3d** (19:1, 95)
5	**2e** (3-MeOC$_6$H$_4$, Ph)	**3e** (13:1, 83)
6	**2f** (3-MeC$_6$H$_4$, Ph)	**3f** (18:1, 81)
7	**2g** (4-NO$_2$C$_6$H$_4$, Ph)	**3g** (>20:1, 94)
8	**2h** (4-BrC$_6$H$_4$, Ph)	**3h** (17:1, 75)
9	**2i** (4-MeC$_6$H$_4$, Ph)	**3i** (13:1, 72)
10	**2j** (4-ClC$_6$H$_4$, Ph,)	**3j** (10:1, 89)
11	**2k** (4-FC$_6$H$_4$, Ph)	**3k** (>20:1, 83)
12	**2l** (4-MeOC$_6$H$_4$, Ph)	**3l** (18:1, 83)
13	**2m** (2-naphthyl, Ph)	**3m** (>20:1, 80)
14	**2n** (2,3-dihydrobenzofuran-5-yl, Ph)	**3n** (18:1, 87)
15	**2o** (2-furyl, Ph)	**3o** (19:1, 91)
16	**2p** (2-thienyl, Ph)	**3p** (7:1, 87)
17	**2q** (styryl, Ph)	**3q** (>20:1, 75)
18	**2r** (Ph, 4-IC$_6$H$_4$)	**3r** (>20:1, 92)
19	**2s** (Ph, styryl)	**3s** (20:1, 93)

[a] Unless otherwise specified, reactions were performed using **2** (0.1 mmol) and **1a** (0.3 mmol) in CH_2Cl_2 (0.2 mL) at room temperature in the presence of PPh_3 (0.02 mmol) and 4-methoxyphenol (0.03 mmol). [b] d.r. = *trans*/*cis*, determined by crude ^{1}H NMR. [c] Yield of isolated *trans* isomer.

selectivity (Table 2, entry 16). Moreover, styryl and 4-iodophenyl substituents on *N*-sulfonyl-1-aza-1,3-dienes, which enabled their adducts more synthetic transformations, had no influence on the reaction outcomes (Table 2, entries 17–19).

It is also noteworthy that the scope of vinyl ketones was not strictly limited to MVK (Table 3). Ethyl vinyl ketone **1b** could also successfully undergo the [4+2] annulation to generate the desired product **3t** in 86% yield and with excellent diastereocontrol. Under the standard reaction conditions, vinyl ketones **1c**, **1d**, **1e**, and **1f** only gave moderate yields (50–70%) due to significant homocoupling. Fortunately, this side reaction can be easily suppressed by the slow addition of a solution of **1c**–**f** in dichloromethane to **2a** through a syringe pump, and the [4+2] annulations adducts could be obtained in good yields and excellent diastereoselectivities (Table 3, entries 2–6).

Table 3. Scope of vinyl ketones.[a]



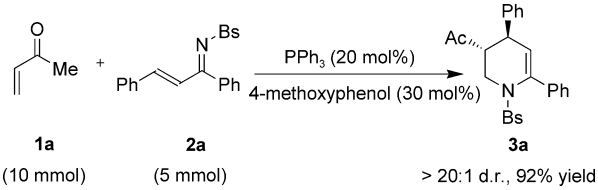
1b–g **2a** **3t–y**

1b R^1 = Et, **1c** R^1 = cyclohexyl, **1d** R^1 = phenyl, **1e** R^1 = 2-furyl, **1f** R^1 = 2-thienyl, **1g** R^1 = *p*-tolyl

Entry	**1**	**3** (d.r.,[b] yield %[c])
1	**1b**	**3t** (>20:1, 86)
2[d]	**1c**	**3u** (10:1, 85)
3[d]	**1d**	**3v** (>20:1, 92)
4[d]	**1e**	**3w** (>20:1, 90)
5[d]	**1f**	**3x** (>20:1, 89)
6[d]	**1g**	**3y** (>20:1, 94)

[a] Unless otherwise specified, reactions were performed using **2a** (0.1 mmol) and **1** (0.3 mmol) in CH_2Cl_2 (0.2 mL) at room temperature in the presence of PPh_3 (0.02 mmol) and 4-methoxyphenol (0.03 mmol). [b] d.r. = *trans*/*cis*, determined by crude ^1H NMR. [c] Yield of isolated *trans* isomer. [d] **1c**–**g** (0.3 mmol) in CH_2Cl_2 (0.2 mL) was added to 0.1 mL of a solution of **2a** (0.1 mmol) and 4-methoxyphenol (0.03 mmol) CH_2Cl_2 during 6 h through a syringe pump.

To demonstrate the ease and feasibility of scaling-up this reaction, this reaction was carried out using 5 mmol of **2a**. The pure crystalline product (**3a**, 1.92 g, 92% yield and >20:1 d.r.) was obtained after single recrystallization from hexane/acetone (8:1), hence proving its scale-up potential (Scheme 2). X-ray crystallographic analysis of **3a** further

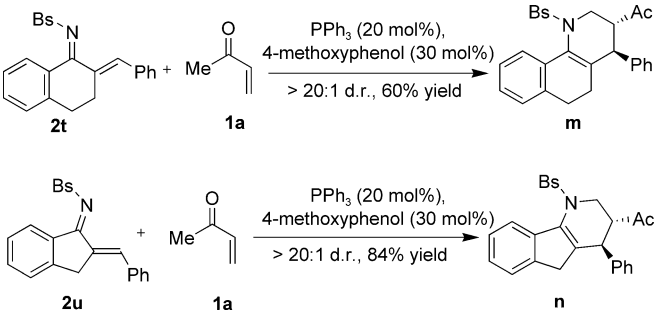


1a (10 mmol) **2a** (5 mmol) **3a** > 20:1 d.r., 92% yield

Scheme 2. Preparative-scale synthesis of tetrahydropyridine.

confirmed the structure of the product established by NMR spectroscopy.[14]

Hydrobenzo[*h*]quinoline is a core substructure which is frequently found in many biologically active natural products, such as *sanguinarine*, *chelerythrine*, *tetrahydroberberine*,[15] and *corynoline*.[16] To highlight the synthetic utility of this method, this molecular complex was efficiently assembled in a single step using the reaction of *N*-sulfonyl-1-aza-1,3-dienes **2t** with methyl vinyl ketone. Alternatively, hydro-1*H*-indeno[1,2-*b*]pyridine derivatives, which are potent antispermatogenic agents,[17] were also synthesized through this protocol, with excellent diastereoselectivity and 84% yield (Scheme 3).

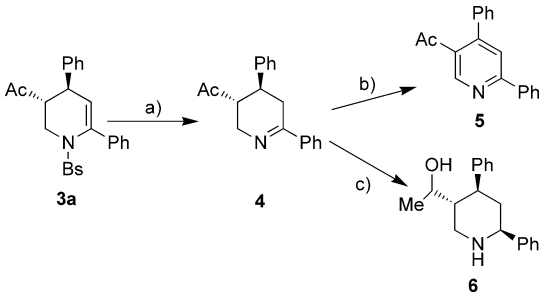


2t **1a** **m**

2u **1a** **n**

Scheme 3. Synthesis of backbone of bioactive compounds.

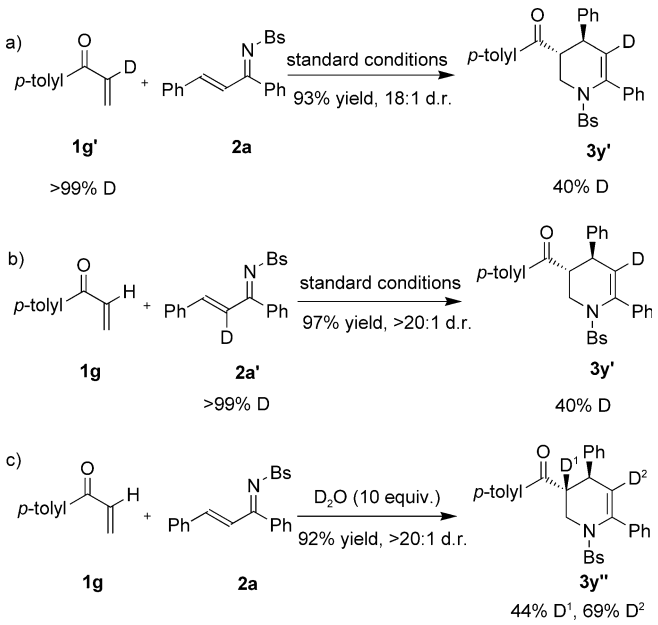
The synthetic utility of this method was further demonstrated (Scheme 4). Deprotection of the benzenesulfonyl group was readily carried out under mild reaction conditions to give imine product **4**, which led to highly substituted pyridine **5** in 88% yield, by oxidation with 2,3-dichloro-5,6-dicyanobenzo-quinone. Furthermore, reduction of imine intermediate **4** with sodium cyanoborohydride afforded piperidine adduct **6** in almost quantitative yield and modest diastereoselectivity.



3a **4** **5** **6**

Scheme 4. Synthesis of pyridine and piperidine from tetrahydropyridine adduct **3a**. a) TFA/thioanisole, *p*-TSA·H_2O, RT, 5 h, 88% yield. b) DDQ, CH_2Cl_2, RT, 2 h, 70% yield. c) $NaBH_3CN$, RT, 0.5 h, 95% yield, 4:1 d.r.

To better understand the reaction pathway, preliminary mechanistic investigations were carried out (Scheme 5). Surprisingly, when deuterium labeled **1g**′ (>99% D) was used



Scheme 5. Preliminary mechanistic investigation.

there was 40% of the deuterium incorporated at the 5-position of **3y′** (experiment a). This interesting phenomenon suggested that a carbanion at the 5-position might be generated during the course of reaction. This hypothesis was further proved by experiment **b**. When deuterium labeled *N*-sulfonyl-1-aza-1,3-diene **2a′** (>99% D) was subjected to the standard reaction conditions, as predicted, similar incorporation of deuterium at the 5-position was observed (experiment b). The erosion of deuterium content probably resulted from the presence of adventitious H_2O and additives. To elucidate our speculation, a reaction between **1g** and **2a** was conducted in the presence of D_2O (10 equiv) under the standard conditions. The reaction proceeded smoothly to deliver the product with similar chemical outcomes, in which 69% deuterium incorporation occurred at the 3-position of **3y″**, accompanied with 44% deuterium incorporation at the 5-position (experiment c).

Based on the above observations, a rational mechanism was proposed (Figure 1). The reaction is initiated by the addition of PPh_3 to the vinyl ketone to generate enolate intermediate **7**, which subsequently undergoes the aza-Rauhut–Currier reaction with *N*-sulfonyl-1-aza-1,3-diene **2a** to form the key intermediate **8**.[18] An equilibrium of enamine **8** and carbanion **9** then affords enolate **10** after an intramolecular proton transfer. This is followed by the formation of imine intermediate **11** and regeneration of the catalyst. Subsequent imine–enamine isomerization affords intermediate **12**, which is believed to undergo an intramolecular Micheal addition (IMMA) with the assistance of phenol additive to finally deliver the desired product **3**.

In summary, the first example of the aza-Rauhut–Currier reaction initiated [4+2] annulation between vinyl ketones and *N*-sulfonyl-1-aza-1,3-dienes has been developed. This protocol furnishes highly functionalized tetrahydropyridines in good to excellent yields (up to 96%) and excellent diastereoselectivities (up to >20:1) using the easily accessible PPh_3 as catalyst. The operation simplicity, broad substrate generality, and low cost of this process apparently proved its potential for industrial application. Preliminary mechanistic study showed this reaction followed an aza-Rauhut–Currier reaction/intramolecular proton transfer/aza-conjugate addition sequence. Additional investigations on the application of this method to construct biologically active molecular complex and its asymmetric manner are currently underway in our laboratory.

Experimental Section

General procedure: Vinyl ketone (**1**, 0.3 mmol) was added to a stirred solution of *N*-sulfonyl-1-aza-1,3-diene (**2**, 0.1 mmol), PPh_3 (5.24 mg, 0.02 mmol), and 4-methoxyphenol (3.72 mg, 0.03 mmol) in CH_2Cl_2 (0.2 mL). After completion of the reaction (monitored by TLC), the reaction mixture was directly applied to column chromatography on silica gel (acetone/hexane 10:1 to 8:1 as eluent) to give the crystalline product **3**.

Acknowledgements

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Keywords: annulation · diene ligands · Rauhut–Currier reaction · tetrahydropyridines · vinyl ketones

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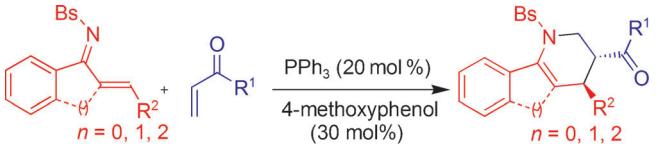
Annulation Reactions



27 examples,
up to 96% yield, > 20:1 d.r.

The first example of phosphine catalyzed aza-Rauhut–Currier reaction initiated [4+2] annulation of vinyl ketones with *N*-sulfonyl-1-aza-1,3-dienes has been disclosed. Under the ambient conditions, this protocol provides a practical access to valuable densely functionalized tetrahydropyridines in good to excellent yields and high diastereoselectivities (see scheme).