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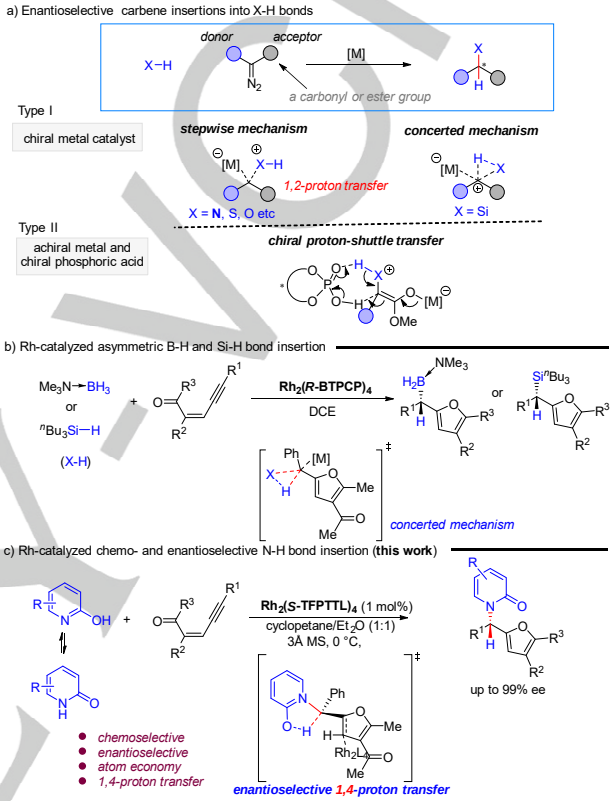
Chemo- and Enantioselective Insertion of Furyl Carbene into the N-H Bond of 2-Pyridones

Kai Wang,[†] Ziye Liu,[†] Guangyang Xu, Ying Shao, Shengbiao Tang, Ping Chen, Xinhao Zhang* and Jiangtao Sun*

Abstract: *Asymmetric carbene insertion reactions represent one of the most important protocols to construct carbon-heteroatom bonds. The use of donor-acceptor diazo compounds bearing an ester group is however a prerequisite for achieving high enantioselectivity. Herein, we report a chemo- and enantioselective formal N-H insertion of 2-pyridones that has been accomplished for the first time with enynones as the donor-donor carbene precursors. DFT calculations indicate an unprecedented enantioselective 1,4-proton transfer from O to C. The rhodium catalyst provides a chiral pocket in which the steric repulsion and the π-π interaction of the propeller ligand play a critical role in determining the selectivities.*

Chiral N-substituted 2-pyridones are key subunits in natural products and pharmaceutical chemicals.[1] However, the ambident nucleophilic nature of 2-pyridones renders their chemo- and enantioselective N-alkylation a significant challenge, and successful examples of such reaction are rare.[2] Metal-carbene mediated alkylation of 2-pyridones with diazo compounds appears to favor O-H over N-H insertion.[3] To finesse this limitation, we have developed an enantioselective, rhodium-catalyzed dearomative N-alkylation of 2-oxypyridines involving ylide formation and O-to-N acyl rearrangement.[4] However, this protocol was also limited in its requirement for donor-acceptor diazoacetates as the alkylation reagents. Thus, the development of a novel insertion reaction, typically the use of donor-donor carbene precursors in chemo- and enantioselective N-alkylation of 2-pyridones is highly desirable.

Enantioselective carbene insertion into X-H bonds (X = N, O, S, B, Si etc.) represents one of the most important strategies to form heteroatom-carbon bonds.[5] To date, many effective approaches, including transition-metal catalysis[6-8] and cooperative catalysis by achiral metal and chiral proton-shuttle transfer,[9] have been established (Scheme 1a). The carbene precursors used in enantioselective X-H insertion (XHI) reactions however are strictly limited to stablized diazo compounds bearing either a carbonyl or an ester group which can delocalize the negative charge on the carbon atom. Furthermore, without an electron-withdrawing group, the donor-donor diazo compounds are easily to form azines, making the enantioselective insertion reaction a formidable challenge.[8f,10] In this respect, the enantioselective transition-metal-catalyzed



Scheme 1. Previous reports and our new strategy

insertion of electronphilic metal carbenes generated *in situ* from readily avalible enynones[11] into X-H bonds offers a different, promising protocol for donor-donor carbene insertion reactions. Recently, Zhu and co-workers reported the first highly enantioselective furyl-carbene insertion into a heteroatom-carbon bond, a reaction useful in the synthesis of organoboron compounds.[12a] Subsequently, they developed an asymmetric rhodium-catalyzed Si-H bond insertion reaction which also used enynones as carbene precursors.[12b] In mechanism, it is commonly accepted that the XHI reactions catalyzed by a chiral metal complex probably proceed by ylide formation and 1,2-proton transfer for heteroatoms such as, N, O, and S, that bear lone-pair electrons, and a concerted mechanism for Si-H bond insertion (Scheme 1a).[5c] Similarly, furyl-carbene insertion into soft nucleophiles (B-H and Si-H) is thought to proceed via a concerted mechanism. Inspired by these seminal research and continuing our interest in metal-carbene chemistry, we report here an unprecedented enantioselective rhodium-catalyzed selective N-alkylation reaction of 2-pyridones with enynones via novel reaction pathway consisting of ylide formation followed by an enantioselective 1,4-proton transfer (Scheme 1c).

We began our study with 2-pyridone (**1a**) and enynone (**2a**) as model substrates to establish the optimal reaction conditions

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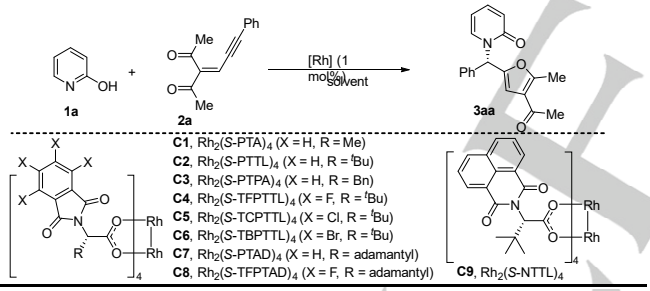
(Table 1). Performing the reactions in diethyl ether at room temperature with 1 mol% of catalyst loading, a range of chiral dirhodium tetracarboxylate catalysts was examined. The first phthalimido catalyst studied, Rh_2(*S*-PTA)$_4$ (**C1**) gave the desired product **3aa** in 52% yield with 82% enantiomeric excess (ee) (entry 1), whereas bulky Rh_2(*S*-PTTL)$_4$ (**C2**) gave **3aa** in higher yield but with a slightly lower ee (entry 2). In contrast, a benzyl substituted phthalimido catalyst Rh_2(S-PTPA)$_4$ (**C3**) gave both a decreased yield and ee (entry 3). The enantioselectivity of **3aa** was improved to 90% ee when Rh_2(*S*-TFPTTL)$_4$ (**C4**) was used as the catalyst (entry 4). Replacement of the fluorine substituents in the phthalimido aryl ring by chlorine (**C5**) or bromine (**C6**) resulted in low yields and decreased ee values, and inversion of the configuration (entries 5 and 6). Attempts to use more bulky rhodium catalysts (**C7** and **C8**) and failed to improve the reaction (entries 7 and 8), while Rh_2(*S*-NTTL)$_4$ (**C9**) exhibited both low catalytic activity and selectivity (entry 9). Solvent screening was conducted using **C4** as the catalyst (entries 10-14). In addition to diethyl ether, dichloroethane (DCE), dichloromethane (DCM), cyclohexane, cyclopentane and methyl *tert*-butyl ether (MTBE) all proved to be suitable solvents, delivering **3aa** in moderate to good yields and with good ee. The enantioselectivity of the reaction with **3aa** was further improved when it was performed in mixed solvents. The use of cyclopentane/Et_2O in a 1:1 ratio furnished **3aa** in 90% yield and with 93% ee (entry 15). Both the yield and ee were slightly increased at low temperatures and with the addition of 3 Å molecular sieves (MS) (entries 16 and 17).

Table 1. Selected optimization[a]



Entry	[Rh]	Solvent	Yield (%)[b]	Ee (%)[c]
1	**C1**	Et_2O	52	82
2	**C2**	Et_2O	86	78
3	**C3**	Et_2O	35	25
4	**C4**	Et_2O	84	90
5	**C5**	Et_2O	50	-20
6	**C6**	Et_2O	41	-40
7	**C7**	Et_2O	63	75
8	**C8**	Et_2O	62	82
9	**C9**	Et_2O	8	-20
10	**C4**	DCE	70	74
11	**C4**	DCM	62	75
12	**C4**	cyclohexane	78	90
13	**C4**	cyclopentane	80	92
14	**C4**	MTBE	82	91
15	**C4**	cyclopentane/Et_2O (1:1)	90	93
16[d]	**C4**	cyclopentane/Et_2O (1:1)	92	96
17[d,e]	**C4**	cyclopentane/Et_2O (1:1)	94	96

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), [Rh] (1 mol%), solvent (2.0 mL) at rt. [b] Isolated yields. [c] The ee values were determined by HPLC analysis. [d] Reactions were performed at 0 °C. [e] 20 mg 3 Å MS was added.

Under the optimal reaction conditions, the substrate scope with respect to the carbonyl-ene-yne (**2**) was evaluated (Scheme 2). Generally, the reaction of aryl terminated carbonyl-ene-ynes (**2**, R^1 = aryl group) with 2-hydroxy pyridine (**1a**) delivers the products (**3aa-3am**) in ≤95% yield and with ≤ 99% enantioselectivity. A variety of electron-donating as well as electron-withdrawing groups at the *ortho*-, *meta*-, and *para*-positions of the aryl ring (R^1) were tolerated. The absolute configuration of **3aa** was unambiguously confirmed by X-ray diffraction analysis.[13] A heteroaryl-terminated substrate was used to give the insertion product (**3an**) in 92% yield and 97% ee. Notably, the reaction of alkyl-terminated substrates (R^1 = alkyl) with **1a** delivered the corresponding products **3ao** and **3ap**, in good yields but with low enantioselectivity under the standard reaction conditions. These results were significantly improved when Rh_2(*S*-PTTL)$_4$ was used as the catalyst. In addition to the acetyl group, alkynes substituted with either a propionyl (**3aq**), an isobutyryl (**3ar**), a benzoyl (**3as**), or ester groups (**3at** and **3au**) at R^2 are all amenable to this reaction, providing the corresponding products in good yields and with good ee values.

Subsequently, the scope of the 2-hydroxy pyridines in this enantioselective Rh-catalyzed dearomative amination was explored. It was found that a range of functional groups on the pyridine ring are tolerated. The electron-rich pyridines bearing 3-methyl (**3ca**), 4-methyl (**3da**), and 5-methyl (**3ha**) performed well in the reaction, affording the corresponding products in high yields (80-92%) and with excellent ee values (93-96%). A 4-benzyloxy substituted pyridine gave the product (**3ga**) in 52% yield and 96% ee. The pyridines substituted with halogen groups such as 3-chloro (**3ba**), 4-bromo (**3ea**), 5-fluoro (**3ia**), 5-bromo (**3ja**) and 5-iodo (**3ka**) were all compatible with the reaction, producing the resulting N-functionalized 2-pyridones which are amenable to further elaboration via common C-X bond coupling reactions. The electron-deficient pyridines bearing 4-methyl formate (**3fa**), 5-methyl formate (**3ma**), and 5-trifluoromethyl (**3la**) groups are all tolerated in this reaction delivering the corresponding products in ≤82% yields and ee values ranging from 89% to 96% ee. Pyridine with an aldehyde group at C5 also reacted well with **2a**, furnishing the desired product (**3na**) in moderate yield and 92% ee.

Further elaboration reactions were conducted and are shown in Scheme 3. Subjecting **3ka** to palladium-catalyzed Suzuki-Miyaura coupling with phenylboronic acid gave **4** in 74% yield and 98% ee. Treatment of **3ka** with phenylacetylene under palladium-catalyzed Sonogashira-coupling, produced **5** in 88% yield and 98% ee. The reaction of the pyridazine (**6**) with **2a** led to the chiral N-alkylated product **7** in 51% yield with 82% ee (Scheme 3b). Moreover, the asymmetric insertion reaction between **1a** and donor/acceptor diazo (**8**) was performed, affording 37% yield of O-alkylated product (**9**) and N-alkylated product (**10**) in 24% yield and 72% ee (Scheme 3c). Moreover, the reaction of **1a** with unsymmetric diaryldiazomethane delivered azine **13** in 83% yield without the detection of insertion product **12** (Scheme 3d). Treatment of enynone **2a** with aniline with this established catalytic system, no reaction occurred under an argon atmosphere, namely, the N-H insertion product **14** was not obtained. Performing the reaction under air led to the formation of imine **15** in 37% yield (Scheme 3e).

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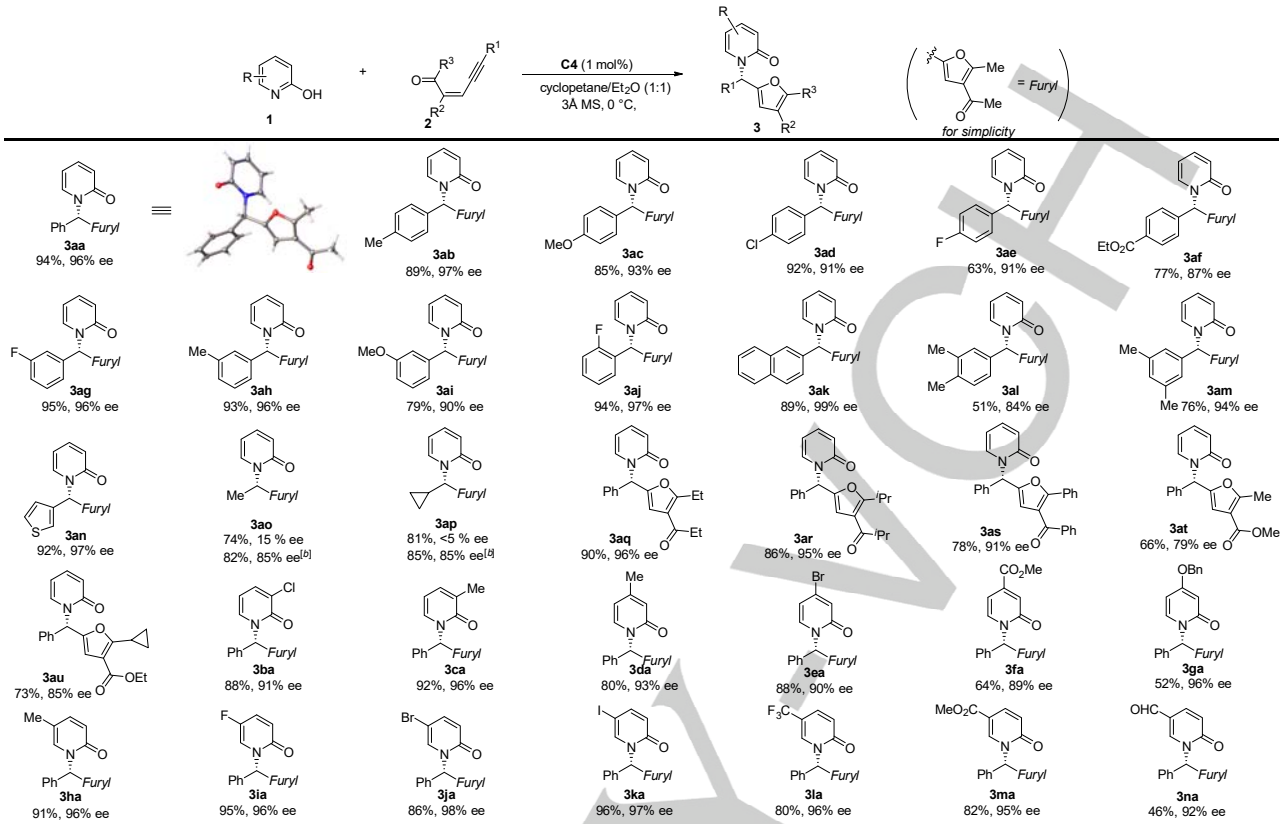
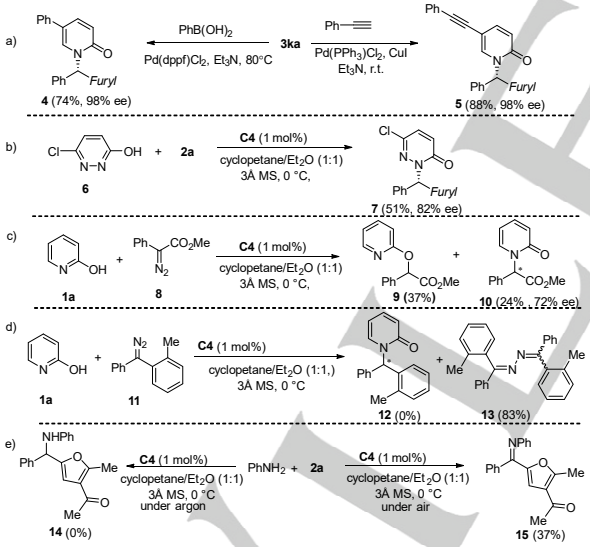


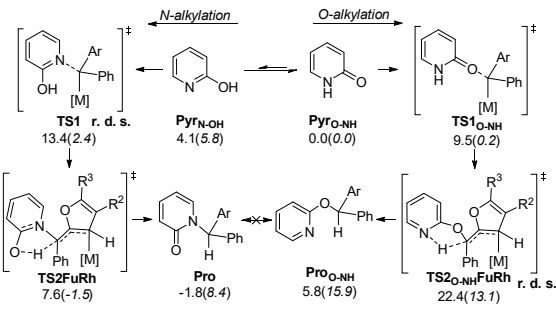
Scheme 2. Substrate scope. [a] Reaction conditions: **1** (0.1 mmol), **2** (0.11 mmol), Rh_2(*S*-TFPTTL)$_4$ (1 mol%) in 2 mL of cyclopentane/Et_2O (1:1), 20 mg 3Å MS, 0 °C, 12-72 h; [b] **1** (0.1 mmol), **2** (0.11 mmol), Rh_2(*S*-PTTL)$_4$ (1 mol%) in 2 mL of cyclopentane/Et_2O (1:1), 20 mg 3Å MS, -20 °C, 12 h; [c] Isolated yields.



Scheme 3. Application and elaboration

DFT calculations were performed in an attempt to understand the reaction mechanism. The calculation began with the 2-furyl-metal carbenoid (**Int1**) whose formation using an enynone as the carbene precursor has been well documented.[14]

Unlike 2-oxypyridines which react with Rh-carbene only at its N-site,[4] 2-pyridone is a more challenging substrate. As shown in Scheme 4 and Figure S1, 2-pyridone (**Pyr$_{O\text{-}NH}$**) is more stable than its isomer 2-hydroxypyridine (**Pyr$_{N\text{-}OH}$**) and its isomerization is feasible. Scheme 4 summarized the most favorable pathways leading to the *N*- or *O*-alkylation products and Figure S2 presented the free energy profile. The relative free energies of **TS1** and **TS1$_{O\text{-}NH}$** almost parallel the relative stabilities of 2-hydroxypyridine and 2-pyridone - a finding which is consistent with the reaction of benzotriazole.[15] Although O-alkylation pathway is preferred at the nucleophilic addition step, the barrier for the subsequent proton-transfer is high due to the steric repulsion in the catalyst pocket. And the N-alkylation with a barrier of 13.4 kcal/mol, is more favorable. Computation with a simplified model $Rh_2(OPiv)_4$ further supports the conclusion (Figures S3-S4).



Scheme 4. *N*- and *O*-alkylation of 2-pyridone with Rh_2(*S*-TFPTTL)$_4$ carbene.

Subsequent analysis focused on origin of the enantioselectivity. The free energy profiles of both the R and S pathways are depicted in Figure 1. The nucleophilic attack of 2-hydroxypyridine on the carbene (**TS1**) forms a chiral center which is then conservatively transformed to a product *via*

TS2FuRh (Figure S5). Dissociation of the Rh catalyst to form **Int3** was found to be energetically unlikely and consequently the chirality determined in **TS1** is not diminished via an achiral transition state (**TS2**). The chiral environment of the catalyst was examined. Rh_2(*S*-TFPTTL)$_4$ carbene was reported to adopt an α,α,α,α-chiral crown conformation in which the carbene binds in the pocket created by the four phthalimido groups (Figure S6).[16,17] A comprehensive conformational search of **TS1** was conducted by rotating the three dihedral angles Ψ1, Ψ2 and Ψ3 (Figures S7).

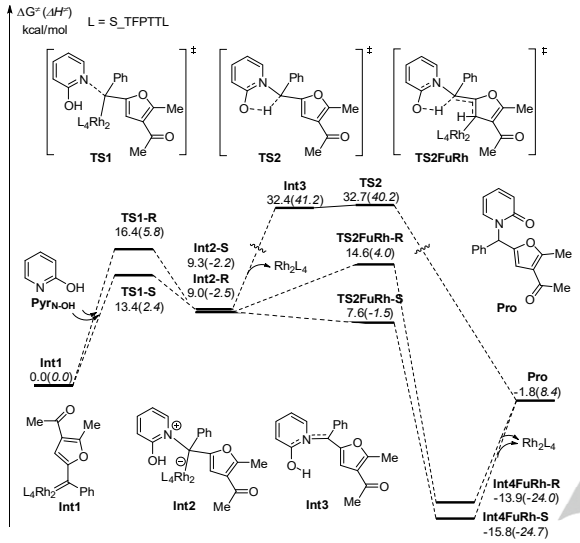


Figure 1. The free energy profile for the favorable pathway.

All the resulting conformations are listed in Figure S7 and the most favorable R/S couple (**TS1-R** and **TS1-S**) are shown in Figure 2. The free energy of **TS1-R** is 3.0 kcal/mol higher than **TS1-S**, again consistent with experimental observation. The phenyl and furan rings in the Rh-carbene and the pyridine ring of 2-pyridone restrict the C-N bond rotation in **TS1**, and these three aryl components form an interesting π-π interaction with the propeller ligand environment. A stronger π-π interaction is found between the furan ring and TFPT in **TS1-S** (~3.72 Å, dihedral angle ~19.78°) than the same interaction is in **TS1-R** (~4.52 Å, dihedral angle ~38.02°) and accounts for the enantioselectivity.

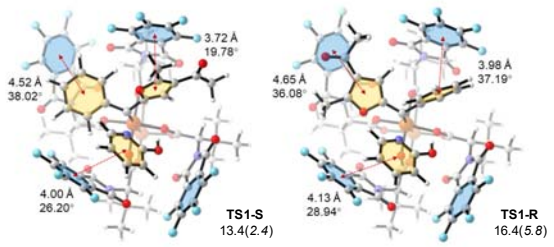


Figure 2. DFT calculations. The origin of enantioselectivity.

In conclusion, we have realized a chemo- and enantioselective formal N-H insertion reaction of 2-pyridones by using enynones as donor-donor carbene precursors, providing the N-alkylated pyridines in moderate to good yields and with excellent enantioselectivity. The reaction represents the first example of formal N-H insertion reaction with donor-donor furyl carbene precursors. DFT calculations revealed that the *N*-alkylation is more favorable than *O*-alkylation of 2-pyridone with Rh_2(*S*-TFPTTL)$_4$ carbene. The reaction proceeds through enantioselective pyridinium ylide formation and sequential 1,4-proton transfer. The steric repulsion and π-π interaction in the catalyst pocket account for the chemo- and enantioselectivity.

Acknowledgements

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Keywords: insertion • carbene • proton transfer• 2-pyridone• asymmetric catalysis

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A chemo- and enantioselective formal N-H insertion has been accomplished for the first time by using enynones as the donor-donor carbene precursors. Distinct with the selective O-H insertion of pyridones for diazo compounds, this reaction occurs exclusively on the desired nitrogen atom. DFT calculations indicate an unprecedented enantioselective O-to-C 1,4-proton transfer.

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Chemo- and Enantioselective Insertion of Furyl Carbene into the N-H Bond of 2-Pyridones