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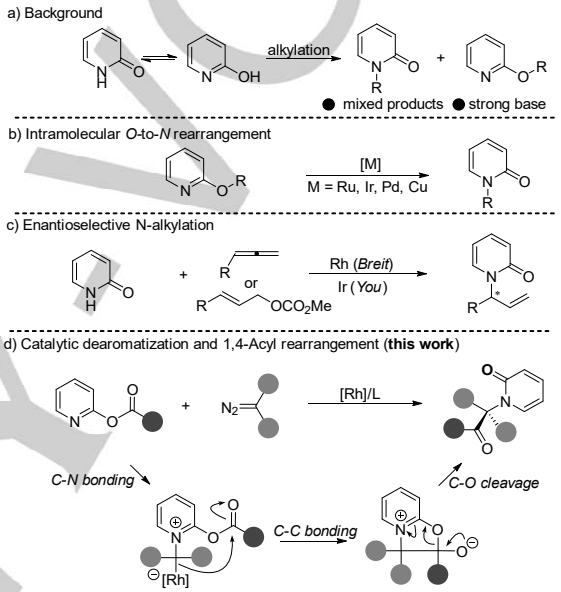
Access to N-Substituted 2-Pyridones by Catalytic Intermolecular Dearomatization and 1,4-Acyl Transfer

Guangyang Xu,[†] Ping Chen,[†] Pei Liu, Shengbiao Tang, Xinhao Zhang* and Jiangtao Sun*

Abstract: *A novel rhodium-catalyzed dearomatization of O-substituted pyridines to access N-substituted 2-pyridones has been developed. Computational study suggested a mechanism involving the formation of a pyridinium ylide followed by an unprecedented 1,4-acyl migratory rearrangement from O-to-C. Furthermore, using chiral dirhodium complexes as the catalyst, the asymmetric transformation has been achieved with excellent enantioselective control. DFT calculations indicate the chirality has been established from axial chirality to central stereogenic centre. The stronger π-π interaction and CH-π interaction accounts for the high enantioselectivity.*

N-Substituted 2-pyridones are key motifs found in many naturally occurring products and biologically active pharmaceuticals.[1] However, the ambident nucleophilic nature of 2-pyridones makes the direct N-alkylation a significant challenge that has intrigued organic chemists for decades (Scheme 1a).[2] Traditional methods for N-substituted 2-pyridone formation often rely on a variety of reaction parameters including solvents, bases, temperature, and the nature of electrophiles.[3] Recently, several elegant approaches have been developed, including intramolecular benzylic/propargylic [1,3]- and allylic [3,3]-rearrangement of *O*-alkylated pyridines (Scheme 1b).[4] Recently, the Breit group[5] and You group[6] independently developed rhodium/iridium-catalyzed intermolecular asymmetric allylic amination reactions to achieve this goal (Scheme 1c). Despite the considerable progress, there are still limitations, including narrow substrate scope, the need of stoichiometric amounts of strong bases and unavoidable *O*-substituted side products. For these reasons, the development of predictable and reliable protocols for the synthesis of N-substituted 2-pyridones is highly desirable.

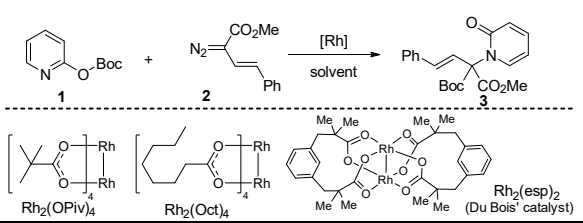
In our continuing research interests in developing novel metal-carbene transformations,[7] we sought to develop an efficient protocol to achieve *N*-alkylated 2-pyridones using diazo compounds as the alkylation reagents. However, a published report[8] and our own investigation[9] disclosed that reaction of 2-pyridones with diazo compounds, catalyzed by rhodium or gold complexes, exclusively led to *O*-alkylated pyridines rather than N-alkylated pyridones. Clearly, the preferred *O*- over *N*-reactivity of 2-pyridones makes this an insuperable problem. Inspired by recent advances in metal-carbene and ylide chemistry,[10] we envisaged that the reaction of 2-O-substituted pyridines with diazo compounds might allow the *in situ* formation of pyridinium ylide,[11] followed by 1,4-acyl rearrangement, the desired N-substituted 2-pyridones would be achieved (Scheme 1d). Moreover, upon the choice of chiral rhodium catalysts, a novel catalytic asymmetric dearomatization (CADA)[12] would be established.



Scheme 1. Previous reports and our new strategy

We commenced our studies using *O*-Boc-pyridine (**1**) and vinyldiazoacetate (**2**) as model substrates to establish the optimal reaction conditions (Table 1). Initially, performing the reaction in dichloromethane at room temperature with 1 mol% of dirhodium catalyst, such as $Rh_2(OAc)_4$, $Rh_2(TFA)_4$, $Rh_2(Oct)_4$ and $Rh_2(OPiv)_4$, delivered **3** in moderate yields (entries 1-4). To our delight, the use of bulky $Rh_2(esp)_2$ (Du Bois′ catalyst) formed **3** in 67% yield and the reaction was completed in five minutes (entry 5). Next, solvent screening showed that the use of 1,2-dichloroethane (DCE), acetonitrile, and hexane failed to give better results (entries 6-8). To improve the reaction further, mixed solvents were tested (entries 9-11). Gratifyingly, after intensively examination, we found that the use of dichloromethane/hexane in a 4:1 ratio afforded **3** in 82% yield (entry 11).

Table 1. Selected optimization[a]



Entry	Catalyst	Solvent	Time (min)	Yield (%)[b]

[a] G. Xu, P. Liu, S. Tang, Prof. Dr. J. Sun
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[†] G. Xu and P. Chen contributed equally to this work.

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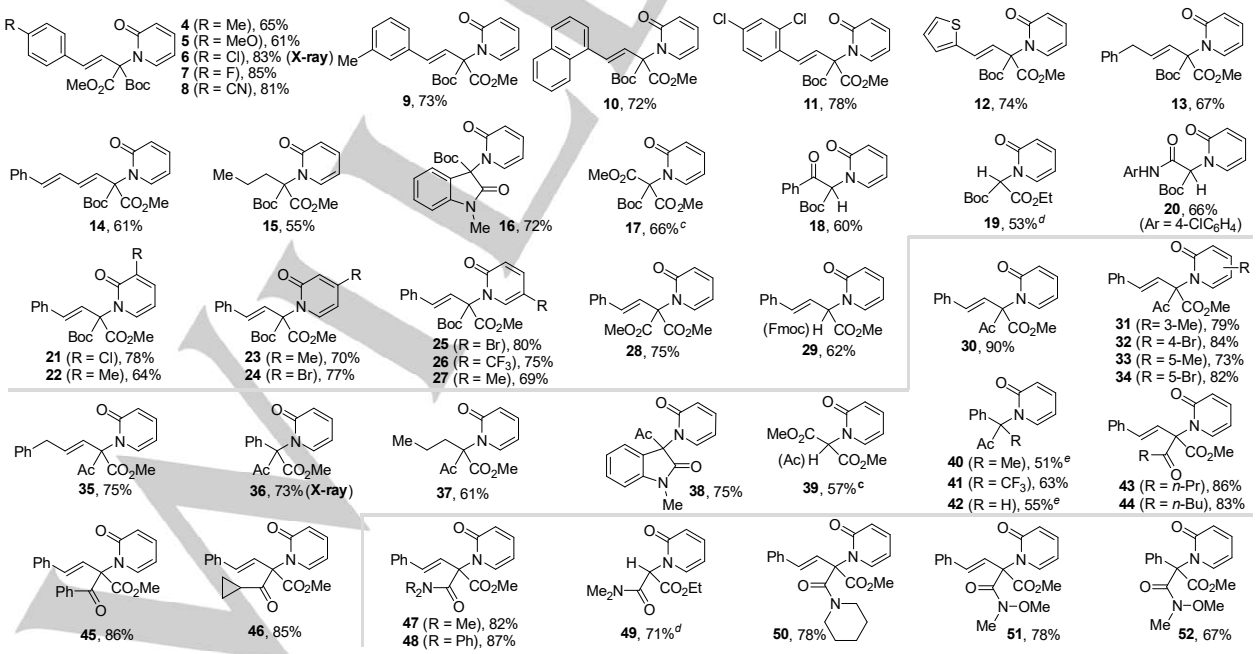
1	$Rh_2(OAc)_4$	CH_2Cl_2	60	31
2	$Rh_2(TFA)_4$	CH_2Cl_2	60	20
3	$Rh_2(Oct)_4$	CH_2Cl_2	60	47
4	$Rh_2(OPiv)_4$	CH_2Cl_2	60	53
5	$Rh_2(esp)_2$	CH_2Cl_2	5	67
6	$Rh_2(esp)_2$	DCE	5	56
7	$Rh_2(esp)_2$	MeCN	20	66
8	$Rh_2(esp)_2$	hexane	20	55
9	$Rh_2(esp)_2$	CH_2Cl_2/hexane (1:1)	20	74
10	$Rh_2(esp)_2$	CH_2Cl_2/hexane (1:4)	20	69
11	$Rh_2(esp)_2$	CH_2Cl_2/hexane (4:1)	20	82

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), catalyst (1 mol%), solvent (5.0 mL) at rt. [b] Isolated yields.

With the optimal reaction conditions in hand, we next explored the substrate scope (Scheme 2). Initially, an array of aryl vinyldiazoacetates bearing various substituents, such as methyl, methoxy, chloro, fluoro and nitrile groups, at the *para* position of phenyl ring, were tested and the products were obtained in moderate to good yields (**4-11**). The use of 2-thienyl vinyldiazoacetate delivered **12** in 74% yield. For benzyl vinyldiazoacetate, **13** was isolated in 67% yield, whereas styryl vinyldiazoacetate gave **14** in 61% yield. The reaction is also amenable to other types of diazo compounds. For instance, use of alkyl and aryl diazo compounds produced **15** and **16** in 55% and 72% yield, respectively. Notably, acceptor/acceptor (malonate diazoacetate) and acceptor/H diazo substrates (α-benzoyl diazo, ethyl diazoacetate and diazo arylacetamide) were all tolerated in this reaction, providing **17-20** in moderate yields. Next, the scope of pyridines was explored. Substitution on the pyridine ring with electron-donating and electron-withdrawing groups had a slight effect on the reaction efficiency (**21-27**). Additionally, other *O*-carboxyl groups, such as methyl ester (**28**) and 9-fluorenylmethyl ester (Fmoc) (**29**) were all tolerated, and the Fmoc group was readily removed upon silica gel chromatography.

Compared with *O*-Boc pyridines, *O*-Ac pyridines exhibited better reactivity, and the desired products (**30-35**) were obtained in good yields. The reaction of *O*-Ac pyridine with phenyl diazoacetate provided **36** in 73% yield, whereas alkyl and cyclic diazo substrates all gave the desired products (**37-38**) in higher yields than the products derived from the *O*-Boc pyridine. The use of malonate diazoacetate afforded **39** with removal of the Ac group in 57% yield after flash chromatography. Notably, the diazo compounds generated *in situ* from the corresponding hydrazones, were also tolerated, although moderate yields were observed (**40** and **42**). Additionally, pyridines bearing different *O*-carbonyl groups, such as propyl, butyl, phenyl and cyclopropanyl were also amenable to this reaction, providing the corresponding products (**43-46**) in good yields. Finally, *O*-amide pyridines bearing NMe_2, NPh_2, piperidine, and Weinreb amide groups were all suitable substrates, delivering the products (**47-52**) in good yields (67%-87%). The structures of **6** and **36** were determined by single crystal X-ray diffraction.[13]

A density functional theory (DFT) study was conducted to understand the reaction mechanism (Figure 1). The process was found to be rather facile with an overall barrier of only 12.7 kcal/mol. The formation of ylide **Int3** is almost energetically neutral referred to **Int1**, indicating the feasibility of pyridine ylide formation. The transition states provide geometrical insights on the large substrate scope. As illustrated in **TS1**, the substituents of rhodium carbene can be easily changed by varying the diazo compounds. The perpendicular orientation of the pyridine allows installation of substituents at 3, 4, or 5-position of pyridine. Due to a significant steric repulsion from the center of the catalyst, the substitution at 6-position of pyridine leads to a much higher barrier for **TS1'**, which is consistent with the experimental observation (Figure S1). Because of the substituents restrict the rotation of C-N bond in the ylide **Int3**, an axial chirality can be constructed. Such an axial chirality may be transformed to a stereogenic center via **TS2**, suggesting the possibility for achieving an asymmetric transformation.



Scheme 2. Substrate scope. [a] Reaction conditions: pyridines (0.2 mmol), diazo compounds (0.3 mmol), $Rh_2(esp)_2$ (1 mol%), CH_2Cl_2/hexane (4:1, 5.0 mL), rt, 20 min. [b] Isolated yields. [c] 60 °C for 2 h. [d] 2 equiv of diazo compound was used. [e] Hydrazone was used as the substrate.

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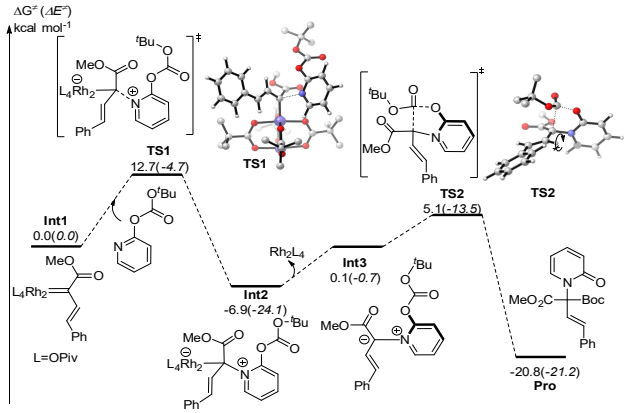
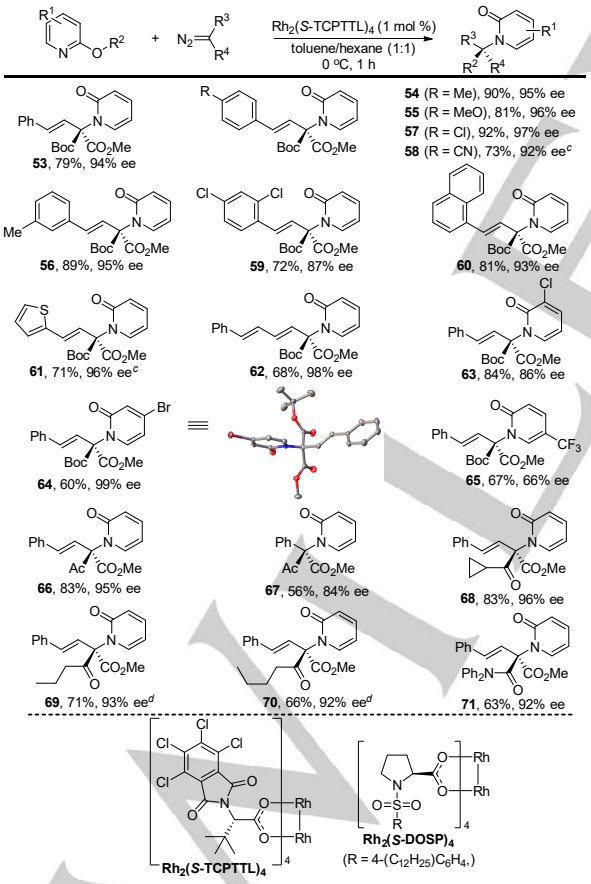


Figure 1. Computational exploration

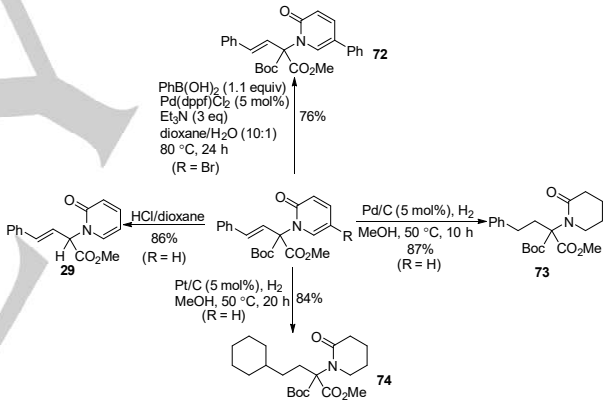
Based on the aforementioned results, we next surveyed the asymmetric version of this reaction (Scheme 3). The reaction of **1** and diazo **2** in the presence of a variety of chiral dirhodium tetracarboxylate catalysts was explored at 0 °C (See Supporting Information for details). After intensively screening, we found the use of toluene/hexane (1:1) in the presence of 1 mol% of Rh_2(*S*-TCPTTL)$_4$[14] furnished **53** in 79% yield and with 94% ee.

Scheme 3. Enantioselective transformation[a,b]



[a] Reaction conditions: pyridine (0.2 mmol), diazo (0.3 mmol), catalyst (1 mol%), toluene/hexane (1:1, 5 mL), 0 °C, 1 h. [b] Isolated yields. Ee was determined by HPLC with a chiral stationary phase. [c] 0 °C for 12 h. [d] 0 °C for 2 h

We next extended this enantioselective protocol to a range of substrates using Rh_2(*S*-TCPTTL)$_4$ as the catalyst. The reaction of pyridine **1** with aryl vinyldiazoacetates bearing either electron-donating or electron-withdrawing groups on the phenyl ring proceeded smoothly to afford the desired products (**54-60**) in good to excellent yields with excellent enantioselectivities (up to 97% ee), whereas thienyl vinyldiazoacetate provided **61** in 71% yield and 96% ee. Also, the use of styryl vinyldiazoacetate delivered **62** in 98% ee albeit with moderate yield. For the scope of pyridines, the pyridine ring bearing a chloro group at the C3 position afforded the desired product **63** in 84% yield and 86% ee. Compound **64** bearing a bromo group at the C4 position was obtained in 60% yield and 99% ee. The absolute configuration of (*S*)-**64** was determined by single crystal X-ray diffraction.[13] However, the 5-CF_3 substituted pyridine provided **65** in moderate enantioselectivity. Next, replacing Boc with Ac group, compound **66** was obtained in 83% yield and 95% ee. It should be noted that the reaction of *O*-Ac-pyridine with α-phenyl diazoacetate provided **67** in 56% yield and 84% ee catalyzed by 1 mol% of Rh_2(*S*-DOSP)$_4$[15] at 0 °C for 5 h. Other acyl groups were also examined, and the desired products (**68-70**) were obtained in good yields and with high ee values. The amide group was also applicable to this reaction, and **71** was obtained in 63% yield and 92% ee.



Scheme 4. Further transformations

Next, further transformations have been conducted to extend the utility of this methodology (Scheme 4). Treatment of compound **3** with HCl in dioxane provided **29** in 86% yield. The reaction of **25** with phenylboronic acid under Suzuki-coupling reaction conditions generated compound **72** in 76% yield. Hydrogenation of **3** with Pd/C gave **73** in 87% yield. However, when Pt/C was used as catalyst for the hydrogenation, the double bond, the pyridone ring and the phenyl moiety were all hydrogenated, delivering **74** in 84% yield.

To gain insights into the origin of the enantioselectivity, a mechanistic study was performed. Rh_2(*S*-TCPTTL)$_4$ carbene was reported to adopt an α,α,α,α-chiral crown conformation in which the carbene binds to the top face.[16] Three optimized carbene isomers were shown in Figure 2a and Figure S2. The staggered conformation **Int1**$_{L2}$ was found to be more stable than the eclipsed **Int1**$_{L2\text{-}a}$. The bottom face **Int1**$_{L2\text{-}b}$ was considered and found to be much less stable than **Int1**$_{L2}$ by 6.1 kcal/mol.[17] Such an energy difference reveals a significant stabilization from the π-π stacking in the TCPT pocket. In both **Int1**$_{L2}$ and **Int1**$_{L2\text{-}a}$ conformations, two

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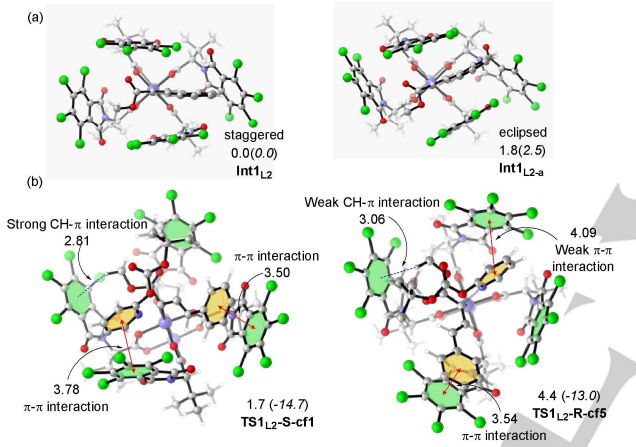
tetrachlorophthalimido (TCPT) groups were twisted to parallel with the carbene, blocking both the *Re* and *Si* faces. Therefore, the origin of enantioselectivity cannot be revealed from the face preference of Rh-carbene.[18] We then calculated full potential energy surface (Figure S3). The nucleophilic attack of pyridine to carbene (**TS1**) is irreversible and supposed to be the enantioselectivity determining step. A systematic conformation search (Figure S4) was conducted to obtain possible conformations. Rotation of three dihedral angles, Ψ1, Ψ2 and Ψ3 leads to 8 conformations (Figure S4 and S5). According to the Boltzmann distribution and Eyring equation, the theoretical ee was calculated to be 99% favoring the *S*-isomer, which is in good agreement with our observations. The most stable structures **TS1$_{L2}$-S-cf1** and **TS1$_{L2}$-R-cf5** were depicted in Figure 2b. The π-π interaction between pyridine and TCPT in **TS1$_{L2}$-S-cf1** (~3.78 Å) is stronger than that in **TS1$_{L2}$-R-cf5** (~4.09 Å). Moreover, **TS1$_{L2}$-S-cf1** also possesses a relatively stronger CH-π interaction. To sum up, the stronger π-π interaction and CH-π interaction are responsible for the enantioselectivity.



Figue 2. DFT calculation on the origin of enantioselectivity

In conclusion, we have developed an unprecedented protocol for the catalytic synthesis of *N*-substituted 2-pyridones from *O*-acyl 2-pyridines and diazo compounds, which proceeded through rhodium-catalyzed pyridinium ylide formation and sequential 1,4-acyl migratory rearrangement under mild reaction conditions. Typically, the reaction is amenable to various carbene precursors. Furthermore, the asymmetric reaction has been realized in the presence of chiral rhodium complexes. DFT calculation disclosed the reaction mechanism and the origin of chiral induction.

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Keywords: dearomatization • carbene • rearrangement• diazo compounds• asymmetric catalysis

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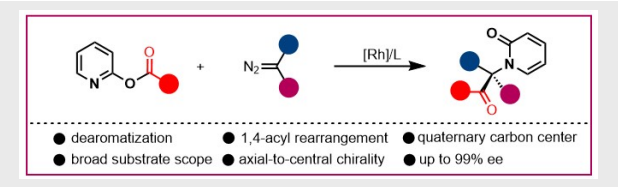

A novel rhodium-catalyzed dearomatization of O-substituted pyridines to access N-substituted 2-pyridones has been developed. Computational study suggested a mechanism involving the formation of a pyridinium ylide followed by 1,4-acyl migratory rearrangement from O-to-C. Furthermore, using chiral dirhodium complexes as the catalyst, the asymmetric transformation has been achieved with excellent enantioselective control.

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