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DMF as a Source of Oxygen and Aminomethine: Stereoselective 1,2-Insertion of Rhodium(II) Azavinyl Carbenes into the C═O Bond of Formamides for the Synthesis of *cis*-Diamino Enones

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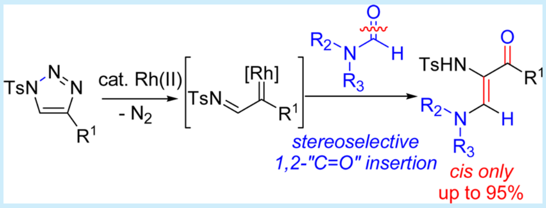
Ⓢ *Supporting Information*

ABSTRACT: A new catalytic reaction in which all the atoms of a formamide are incorporated into the product through a formal stereoselective 1,2-insertion of rhodium(II) azavinyl carbenes, generated in situ from readily available *N*-sulfonylated 1,2,3-triazoles, into the C═O bond of DMF and other *N*,*N*-disubstituted formamides to afford *cis*-diamino enones is described.



N,*N*-Dimethylformamide (DMF) is one of the most commonly employed aprotic polar solvents in various organic reactions. Besides being an effective solvent, DMF has long been used as a reagent, particularly for the introduction of a formyl group in the Vilsmeier–Haack reaction.[1,2] DMF has also been exploited as a convenient source of various functional units such as $-CO$,[3] $-CONMe_2$,[4] $-NMe_2$,[5] and $-H$ (hydride)[6] in transition metal-catalyzed reactions. More recently, it has been reported that DMF can also act as a promising source of $-CN$[7,8] in Pd- or Cu-catalyzed cyanations of aryl halides, organosilanes, or in Pd-catalyzed cyanations of aromatic and heteroaromatic compounds through direct C–H functionalizations (Figure 1).

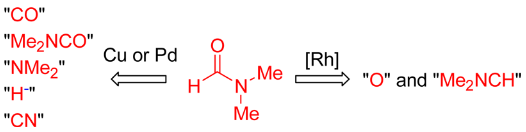
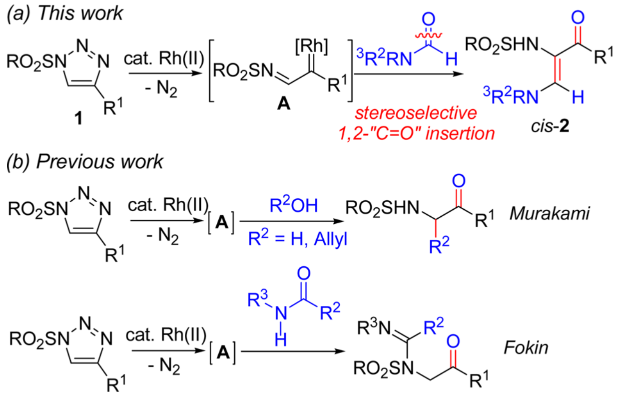


Figure 1. Functional units from DMF incorporated in the product from catalysis.

Despite the utility of DMF as a stable source of various functional units of these catalytic reactions, only one of its fragments is incorporated into the reaction product. On the other hand, Porter and co-workers reported that a rhodium(II)-catalyzed olefination of tertiary formamides with a silylated diazoester afforded vinylogous carbamates, in which all units of amides were incorporated into the product.[9] Herein we report a novel formal stereoselective 1,2-insertion of rhodium(II) azavinyl carbenes **A**, derived from *N*-sulfonyl-1,2,3-triazoles **1**, into the formamide C═O bond to afford *cis*-diamino enones **2**, where DMF and other *N*,*N*-disubstituted formamides are sources of oxygen and aminomethine units (Scheme 1a).

The rhodium(II)-catalyzed denitrogenative transformation of *N*-sulfonylated 1,2,3-triazoles **1**, discovered by Fokin and Gevorgyan,[10] has rapidly taken its place among useful synthetic strategies for various nitrogen-containing cyclic and acyclic comopunds.[11] It has been established that triazole **1**, readily prepared by the copper-catalyzed cycloaddition of a sulfonyl azide and a terminal alkyne,[12] is a convenient progenitor of reactive electrophilic rhodium(II) azavinyl carbene **A**, which reacts with weak unsaturated nucleophiles such as nitriles,[10] alkynes,[13] allenes,[14] isocynates,[15] *α*,*β*-unsaturated aldehydes,[16] furans,[17] indoles,[18] and benzene (intramolecularly)[19] to provide numerous nitrogen heterocycles. Carbene complex **A** was also shown to react with weak protic nucleophiles. For example, Murakami and co-workers reported that the Rh(II) azavinyl carbenes **A** insert into O–H bonds of H_2O and allylic alcohols to afford *α*-amino ketones (Scheme 1b).[20]

Scheme 1. Synthesis of *α*-Amino Ketones from Rh(II) Azavinyl Carbenes



Quite recently Fokin and co-workers reported the stereoselective formal 1,3-insertion of carbenes **A** into the O–H and N–H bonds of primary and secondary amides and carbamates as well as carboxylic acids yielding densely functionalized (*Z*)-enamides or *α*-amino ketones (see Scheme 1b).[21] On the basis

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of these precedents, we anticipated that the *O*-nucleophilic addition of DMF at the electrophilic carbene carbon of **A** may afford rhodium-iminium zwitterionic **B**, which could cyclize to form 2-amino-4-oxazolines **C** as a product (Scheme 2). Much to our surprise, when triazole **1a** (R = tosyl, R^1 = Ph) was reacted with 1.4 equiv of DMF in toluene in the presence of 1.3 mol % $Rh_2(OAc)_4$, the unexpected *cis*-*α*,*β*-diamino vinyl ketone **2a** was isolated in 38% yield (entry 1, Table 1). The structure of **2a** was unambiguously determined by spectroscopic analyses and X-ray crystallography (Figure 2).[22] A cursory inspection of the skeletal framework of the putative carbene **A** and enone **2a** reveals that a stereoselective 1,2-insertion of **A** into the C=O bond of DMF has occurred. We reasoned that formation of **2a** may due to the unstability of *N*,*O*-hemiaminal **C**, which could rearrange to aziridine **D**, and then afford the stable vinylogous enamino ketone **2a** via ring-opening to give the zwitterionic species **E**, followed by deprotonation (Scheme 2).[23]

Scheme 2. Plausible Mechanism for the Formation of 2a

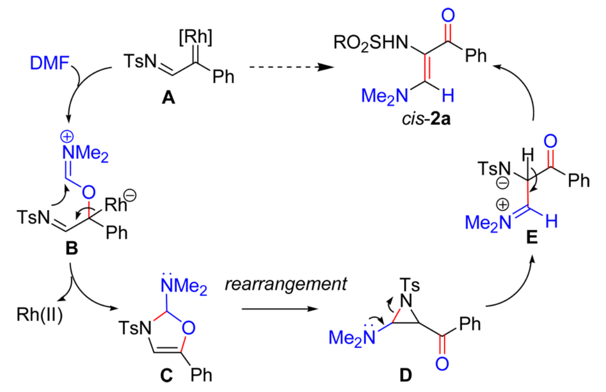


Figure 2. X-ray structure of **2a**.

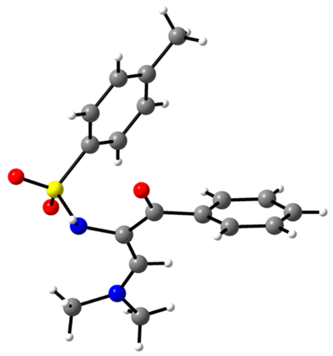
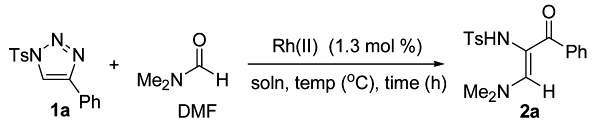
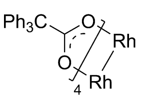


Table 1. Optimization of Reaction Conditions[a]

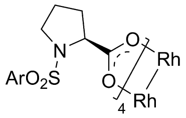


entry	Rh(II)	solvent	*T* (°C)/h	yield (%)[b]
1	$Rh_2(OAc)_4$	toluene	100/4	38
2	$Rh_2(Oct)_4$	toluene	100/4	40
3	$Rh_2(S\text{-}DOSP)_4$	toluene	100/4	53
4	$Rh_2(^tBuCO_2)_4$	toluene	100/4	63
5	$Rh_2(TPA)_4$	toluene	100/4	10
6	$Rh_2(S\text{-}PTPA)_4$	toluene	100/4	57
7	$Rh_2(^tBuCO_2)_4$	toluene	120/4	71
8[c]	$Rh_2(^tBuCO_2)_4$	toluene	120/4	46
9[d]	$Rh_2(^tBuCO_2)_4$	toluene	120/4	62
10	$Rh_2(^tBuCO_2)_4$	$CHCl_3$	72/5	73
11	$Rh_2(^tBuCO_2)_4$	PhCl	142/2.5	57
12	$Rh_2(^tBuCO_2)_4$	1,2-DCE	90/2.5	66
13	$Rh_2(^tBuCO_2)_4$	cyclohexane	90/2.5	<10
14	$Rh_2(^tBuCO_2)_4$	benzene	90/2.5	81

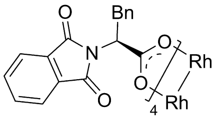
[a] Reaction conditions: **1a** (0.3 mmol), DMF (0.42 mmol), Rh(II) (3.9×10^{-3} mmol), solvent (1.2 mL). [b] Isolated yield after silica column chromatography. [c] Reaction carried out with 0.9 equiv of DMF. [d] Reaction carried out with 5.0 equiv of DMF.



$Rh_2(TPA)_4$



$Rh_2(S\text{-}DOSP)_4$
Ar: $4\text{-}(C_{12}H_{25})C_6H_4$



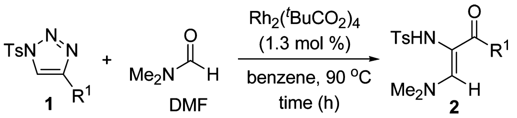
$Rh_2(S\text{-}PTPA)_4$

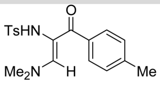
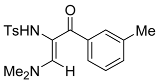
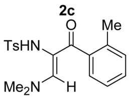
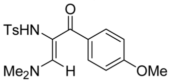
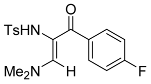
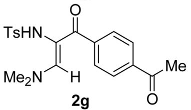
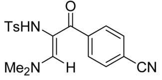
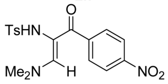
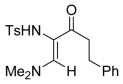
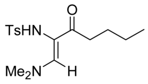
Optimization of the reaction conditions was carried out to make this novel transformation synthetically practical, as summarized in Table 1. Changing the catalyst to $Rh_2(Oct)_4$ and $Rh_2(S\text{-}DOSP)_4$ increased substantially the yields to 40% (entry 2, Table 1) and 53% (entry 3, Table 1), respectively. The yield of **2a** increased further to 63% when $Rh_2(^tBuCO_2)_4$ was used as a catalyst (entry 4, Table 1). However, other catalysts such as $Rh_2(TPA)_4$ and $Rh_2(S\text{-}PTPA)_4$ were not effective (entries 5 and 6, Table 1). With 1.3 mol % $Rh_2(^tBuCO_2)_4$ as a catalyst further optimization of the reaction conditions ultimately led to an optimal protocol in which triazole **1a** is reacted with 1.4 equiv of DMF in benzene solvent at 90 °C for 2.5 h to afford **2a** in 81% yield (entry 14, Table 1).

With optimal reaction conditions in hand, we investigated the generality of these reactions with different triazoles **1**. As shown in Table 2, the reactions with triazoles **1b**−**1d**, prepared from tosyl azide and phenylacetylenes bearing electron-donating methyl at *ortho*-, *meta*-, and *para*-positions suggested the reaction efficiency could be somewhat influenced by steric forces, and thus **2b** and **2c** were formed in higher yields than **2d** obtained from the sterically congested *ortho*-methyl substituted phenyl triazole **1d** (entries 1−3, Table 2). The *para*-methoxy substituted triazole **1e** afforded the corresponding *cis*-diamino vinyl ketones **2e** in good yield (entry 4, Table 2). The triazoles **1f**−**1i**, in which electron-withdrawing groups such as fluorine, ketone, nitrile, and nitro are substituted on the phenyl ring, were also tolerated under the reaction conditions and afforded the corresponding *cis*-diamino vinyl ketones **2f**−**2i** in good yields (entries 5−8, Table 2). Alkyl-substituted triazoles **1j** and **1k** were also tolerated and gave the corresponding *cis*-diamino vinyl ketones **2j** and **2k** in yields of 60 and 64%, respectively (entries 9 and 10, Table 2).

The reaction was extended to other *N*,*N*-disubstituted formamides (Table 3). Thus, triazole **1a** was reacted with *N*,*N*-dibenzyl formamide highly efficiently to afford **2l** in 91% yield (entry 1, Table 3). The reaction with sterically congested *N*,*N*-diisopropyl formamide could produce *cis*-diamino vinyl ketone **2m** in 77% yield (entry 2, Table 3). *N*-Aryl formamides were also reactive, as shown with **2n** obtained in 66% yield (entry 3, Table 3). The reactions with formamides having six-membered cyclic amine moieties such as piperidine and morpholine proceeded smoothly to provide the corresponding vinyl ketones **2o**, **2p** in high yields. Although the yield was slightly decreased, the five-membered pyrrolidine-1-carboxalde-

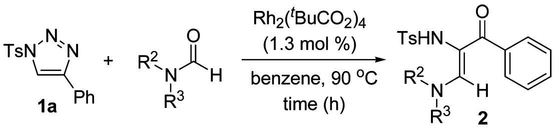
Table 2. Scope with Respect to Triazole 1[a]

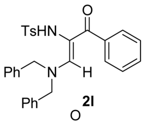
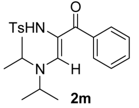
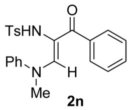
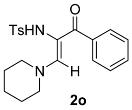
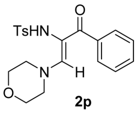
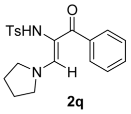


entry	1, R¹	time (h)	2	yield (%)[b]
1	*p*-$CH_3C_6H_4$ 1b	2.0	 2b	73
2	*m*-$CH_3C_6H_4$ 1c	2.5	 2c	80
3	*o*-$CH_3C_6H_4$ 1d	2.0	 2d	63
4	*p*-$CH_3OC_6H_4$ 1e	1.0	 2e	72
5	*p*-FC_6H_4 1f	2.0	 2f	83
6	*p*-AcC_6H_4 1g	2.5	 2g	69
7	*p*-CNC_6H_4 1h	2.5	 2h	91
8	*p*-$NO_2C_6H_4$ 1i	2.5	 2i	55
9	$PhCH_2CH_2$ 1j	2.0	 2j	60
10	$CH_3(CH_2)_2$ 1k	2.5	 2k	64

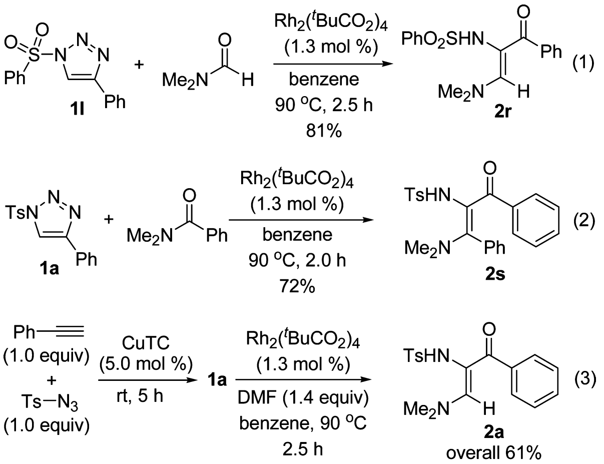
[a]Reaction conditions: **1** (0.3 mmol), DMF (0.42 mmol), Rh(II) (3.9×10^{-3} mmol), solvent (1.2 mL). [b]Isolated yield after silica column chromatography.

Table 3. Reactions of 1a with *N,N*-Disubstituted Formamides[a]



entry	R²R³N	time (h)	2	yield (%)[b]
1	Bn_2N	2.0	 2l	91
2	(*iso*-Pr)$_2$N	1.5	 2m	77
3	Ph(Me)N	1.0	 2n	66
4	1-piperidinyl	2.5	 2o	84
5	1-morpholinyl	2.0	 2p	95
6	1-pyrrolidinyl	2.5	 2q	59

[a]Reaction conditions: **1a** (0.3 mmol), DMF (0.42 mmol), $Rh_2(^tBuCO_2)_4$ (3.9×10^{-3} mmol), solvent (1.2 mL). [b]Isolated yield after silica column chromatography.



hyde can be incorporated to give the *cis*-diamino vinyl ketone **2q**. In sum, these results show that the reaction is highly general with respect to the disubstituted formamides.

When the *N*-tosyl group of **1** was changed to benzenesulfonyl, the reaction efficiency remained high, providing the corresponding *cis*-diamino enone **2r** in 81% yield (eq 1). Under the same reaction conditions, *N,N*-dimethyl benzamide was also successfully incorporated to afford inseparable *E*/*Z* mixture (ca. 8:1, stereochemistry is not assigned) of the trisubstituted vinyl ketone **2s** in high yields (eq 2). However, the reactions either with *N*-methanesulfonyl triazoles or with a *N,N*-dimethylacetamide did not proceed effectively. Finally, along the line with our continuing interest in tandem reactions,[24] a one-pot synthesis of *cis*-diamino vinyl ketone starting from terminal alkyne was carried out to demonstrate the practical convenience of the present method. Treatment of phenylacetylene with tosylazide in the presence of CuTC (5.0 mol %, TC = thiophene-2-carboxylate) in benzene at room temperature generated triazole **1a**. To this reaction mixture was added 1.4 equiv of DMF and $Rh_2(^tBuCO_2)_4$ (1.3 mol %) successively, and the reaction mixture was heated to 90 °C for 2.5 h to afford *cis*-diamino vinyl ketone **2a** in 61% isolated yield (eq 3).

In conclusion, we have developed a new stereoselective 1,2-insertion of Rh(II) azavinyl carbenes into the C═O bond of DMF and other *N,N*-dialkylsubstituted formamides to produce *cis*-diamino enones, in which all the atoms of formamides are incorporated into the product. Although more detailed studies to elucidate the reaction mechanism are warranted, a plausible pathway proceeds via an aziridine intermediate. Further studies on the scope of this novel transformation and on the applications of the *cis*-diamino enones are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, characterization data, and crystal data (CIF) for **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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