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Controlling Selectivity in the Synthesis of *Z*- α,β -Unsaturated Amidines by Tuning the *N*-Sulfonyl Group in a Rhodium(II) Catalyzed 1,2-H Shift

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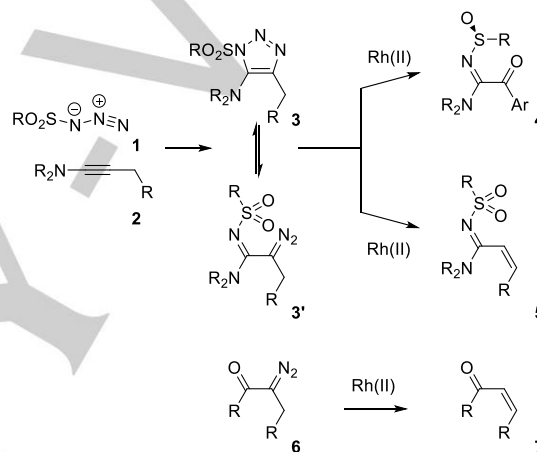
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Abstract: *N*²-Sulfonyl- α -diazo amidines can be synthesized by the reaction of electron rich alkynyl amines with electron poor sulfonyl azides through 1,3-dipolar cycloadditions that proceed with perfect regioselectivity. In the presence of rhodium(II) carboxylate catalysts denitrogenation occurs to give the corresponding metallocarbenes. Then, there is a competition between 1,2-H shift and O-transfer from the sulfonyl group to the metallocarbene center. Using an electron poor nitrobenzenesulfonyl group and large carboxylate rhodium ligands gives complete selectivity for 1,2-H shift, forming α,β -unsaturated amidines in high yield and excellent *Z*-selectivity.

Introduction

Reactions that exploit high energy intermediates are attractive because they can result in the rapid generation of complex molecules.^[1] Rhodium carbenes, readily formed by denitrogenation of diazo starting materials, are an excellent embodiment of this strategy, providing highly interesting and useful reactivity.^[2] However, along with the benefits of using reactive species comes the substantial challenge of control. Once generated, a highly reactive species is poised to react with something and, when this is not the intended target, it can be solvent or result in intramolecular processes. Therefore, careful study of carbene reactivity is not only fascinating but also essential to maximize the value and scope of each transformation. Chemists have deployed various elements of control including tuning rhodium through its ligands,^[3] varying reaction conditions, using additives and varying protecting / directing groups. As a result, rhodium carbenes can provide a wide range of value-added products,^[2] and this has been showcased in the context of complex molecule synthesis^[4] and within biological systems.^[5]

In addition to the performance of a reaction itself, the accessibility of the substrate is a key factor in determining overall value of a process. Diazo starting materials for metallocarbene formation can be derived in number of ways,^[6] including Dimroth^[7] equilibration of 1-sulfonyl-1,2,3-triazoles. The use of triazoles as carbene precursors is a recent development that exemplifies the synergy between easy substrate synthesis and valuable reactivity.^{[8],[9]} The base cycloaddition between an alkyne and an azide to make a triazole is slow and unselective^[10] but approaches

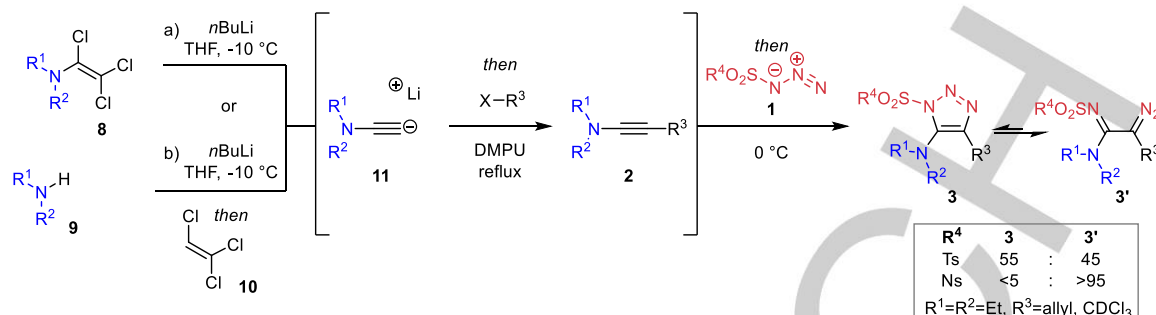


Scheme 1. Preparation and reactivity of 5-aza-1-sulfonyl-1,2,3-triazoles **3** and 1,2-shifts in α -diazo carbonyl species **6**.

have been exploited to improve reaction speed and selectivity: chiefly this involves the use of a catalyst,^[11] but reacting partners can also be selected for a better electronic match. By tuning the electronic properties of the substrates, a close HOMO-LUMO energy results in rapid and selective reaction.^{[10b],[12]} This approach to α -diazo amidines was widely explored by Regitz, Himbert^[13] and Harmon (**1 + 2** \rightarrow **3**, Scheme 1);^[14] and Fokin^[15] capitalised this approach to explore the amidines' reactivity^[16] in styrene cyclopropanation. However, instead of intermolecular reaction, internal O-transfer reaction occurred resulting in sulfur(VI) reduction and the preparation of α -keto sulfinyl amidines **4**. Following optimization, the sulfur(VI) reduction process could be made high-yielding and asymmetric by the use of appropriate chiral rhodium catalysts.

Unsaturation is a key molecular component that has inspired synthetic chemists for over a century, with an alkene adding a defining geometric element to a molecule or providing a functional handle.^[17] Therefore, new methods to create alkenes with high levels of control are valuable. Metallocarbenes with an α -hydrogen atom can undergo 1,2-H shift to form alkenes (**6** \rightarrow **7**, Scheme 1). This can be an excellent approach to the preparation of alkenes because the range of catalysts available allows careful tuning of reactivity and selectivity.^{[18],[19],[20],[21]}

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Scheme 2. Preparation of alkynyl amine and cycloaddition with sulfonyl azides

Here, we report the synthesis of an extended range of α -diazo amidines and describe a method of controlled synthesis of valuable *Z*-alkenes from these diazo compounds under rhodium(II) catalysis (**3** \rightarrow **5**, Scheme 1). The key feature of this work was tuning the electronics of the *N*²-sulfonyl group to control the reactivity of the system and suppress the *O*-transfer process. The products of this work represent novel members of the valuable sulfonyl amidine family of bioactive compounds.^[22]

Results and Discussion

For this study, a range of 5-amino-1-sulfonyl triazoles **3** / α -diazo-*N*²-sulfonyl amidines **3'** was synthesized by the cycloaddition between electron poor sulfonyl azides **1** and electron rich alkynyl amines **2** (Scheme 2). Alkynyl amines are highly reactive and unstable, so they were prepared by one of two different methods and used *in situ* immediately for cycloaddition. Following the research of Regitz, Himbert^[13] and Harmon,^[14] trichloroacetamides **8** (available from trichloroacetamides following treatment with tributyl phosphine^[23]) were treated with 2.0 equivalents of *n*-butyl lithium at -10 °C to promote elimination and lithiation and form the corresponding alkynyl lithium species **11**. Then an electrophile, such as allyl bromide, was added to the reaction mixture along with *N,N*-dimethylpropyleneurea (DMPU) and the reaction was heated to reflux to promote formation of a new C–C bond and complete the generation of the key alkyne **2**. The electron-rich alkyne **2** was cooled to 0 °C and the sulfonyl azide **1** was added. Cycloaddition of the azide with the alkyne occurred rapidly, even at this low temperature, to give the cycloadducts in good yield after only 1 hour. For cyclic substrates: pyrrolidine and piperidine, this method was not successful owing to extreme instability of the intermediates so an alternative method was used.^[24] A lithium amide generated from the amine **9** was added dropwise to trichloroethylene **10** followed by the addition of more *n*BuLi to form the alkynyl lithium species **11** that intersected the above method and went on to deliver the analogous products. Throughout all the reactions studied, complete regioselectivity was observed in the cycloaddition, giving only the products described with no evidence of the isomeric product. Importantly, the presence of the highly electron donating 5-amino substituent combined with the highly electron-withdrawing *N*-sulfonyl substituent meant that the triazole

Table 1. Optimising for the 1,2-H shift.

Entry	Ar	R	Catalyst (5 mol %)	t (min)	5	12	13
1	<i>p</i> -Tol	C ₂ H ₃	Rh ₂ (OAc) ₄	60	45	15	–
2	<i>p</i> -Tol	C ₂ H ₃	Rh ₂ (oct) ₄	60	21	39	–
3	<i>p</i> -Tol	C ₂ H ₃	Rh ₂ (TPA) ₄	60	53 ^a	16 ^a	–
4	<i>p</i> -Tol	C ₂ H ₃	Rh ₂ (esp) ₂	60	31	34	–
5	<i>p</i> -NO ₂ C ₆ H ₄	C ₂ H ₃	Rh ₂ (OAc) ₄	15	37	<5	–
6	<i>p</i> -NO ₂ C ₆ H ₄	C ₂ H ₃	Rh ₂ (oct) ₄	15	50	<5	–
7	<i>p</i> -NO ₂ C ₆ H ₄	C ₂ H ₃	Rh ₂ (TPA) ₄	15	91 ^a	<5	–
8	<i>p</i> -NO ₂ C ₆ H ₄	C ₂ H ₃	Rh ₂ (esp) ₂	15	61	<5	–
9	<i>p</i> -NO ₂ C ₆ H ₄	<i>n</i> Pr	Rh ₂ (TPA) ₄	60	>98 ^a	–	<5
10	<i>p</i> -NO ₂ C ₆ H ₄	Ph	Rh ₂ (TPA) ₄	60	51	–	19
11	<i>p</i> -NO ₂ C ₆ H ₄	Ph	Rh ₂ (OAc) ₄	60	20	–	52
12	<i>p</i> -NO ₂ C ₆ H ₄	Ph	Rh ₂ (oct) ₄	60	41	–	36
13	<i>p</i> -NO ₂ C ₆ H ₄	Ph	Rh ₂ (esp) ₂	60	71	–	<5
14	<i>p</i> -NO ₂ C ₆ H ₄	Ph	Rh ₂ (S- <i>i</i> -PTTL) ₄	60	85 ^a	–	<5

Conditions: 0.2 M in CH₂Cl₂, room temperature; [a] Isolated yield.

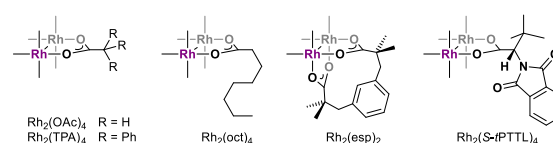


Figure 1. Rhodium(II) catalysts used in this study. One representative carboxylate ligand is shown in each case.

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products significantly populated the α -diazoamidinium form **3'** of the Dimroth equilibrium. This was suggested by a characteristic bright yellow colour and confirmed by the presence of a strong diazo asymmetric stretch in the IR spectra of the compounds. The difference in electronic nature of the substituents on the position of the Dimroth equilibrium was evidenced in toluenesulfonyl (tosyl, Ts) vs 4-nitrobenzenesulfonyl (nosyl, Ns) substituted products: the nosyl-substituted product existed entirely in its diazo form **3'** whereas the tosyl-substituted one had a 55:45 ratio (**3'**:**3**). When the diazo N^2 -tosylamidinium substrate was treated with rhodium(II) acetate at ambient temperature, it was consumed within 1 hour resulting in the formation of two compounds (Table 1, entry 1). The first product was a highly unsaturated product **5** that was formed with exclusive *Z*-selectivity. The second product was a ketone **12** resulting from intramolecular oxygen atom transfer from the sulfur to the carbene position followed by isomerisation of the β,γ -unsaturation into conjugation with the new ketone. The rhodium-catalyzed intramolecular oxygen atom transfer within N^2 -sulfonyl α -diazoamidiniums is an established mode of reactivity^[16] including for the enantioselective synthesis of N^2 -sulfonyl amidines reported by Fokin *et al.*^[15] The effect of a variety of rhodium(II) carboxylates (Figure 1) was studied (entries 1–4) but none showed significant ability to tune the reaction outcome between product families. The key factor in gaining control of the reaction was to consider the electronics of the sulfonyl group. The O-transfer does not occur in *N*-sulfonyl imines derived from triazoles with carbon or hydrogen substituents. The sulfur atom of N^2 -sulfonyl amidiniums is more electron rich than its *N*-sulfonyl imine counterparts because of the additional conjugated nitrogen lone pair. The increase in electron density at sulfur resulted in a weaker sulfur-oxygen double bond and enabled the transfer of oxygen.^[15] In order to suppress oxygen transfer, it was reasoned that switching from tosyl to the more electron-poor nosyl group would increase the S=O bond strength and reduce the propensity for oxygen transfer. Indeed, the use of Ns suppressed oxygen transfer completely in the catalysts evaluated in the benchmark substrate (entries 5–8) as well as accelerating the reaction in general, reducing the time for consumption of starting material to as low as 15 min. Overall, the rhodium carboxylate Rh₂(TPA)₄ (entry 7) with its large ligand size, was selected as the optimum catalyst giving the diene product in 91% yield.

In the more saturated analogue with an alkyl chain included (*n*-propyl, entry 9), the conditions held effective and the *Z*-alkene was also formed in good yield. However, when the substrate scope was extended to a benzyl group, the selectivity for the alkene product (**13**) became an issue once again (entry 12). A rescreen of catalysts showed that the Rh₂(esp)₂^[25] or Rh₂(S-*t*P TTL)₄^[26] ligands could deliver excellent selectivity for the *Z*-alkene product in excellent yield and selectivity (71 and 85%, entries 13 and 14).

The conditions optimized for the allylic *N,N'*-diethyl substrate were evaluated against a panel of other amine substituents (Figure 2). Simple linear alkyl amine substituents all gave the *Z*-alkene products in excellent yield (**5a–d**). When the size of the alkyl substituent was increased, the reaction slowed such that diisobutylamine substrate **5e** required an extended time for the reaction to proceed to completion. It is important to note that leaving the reaction for a longer period was preferable to acceleration of the reaction through heating because at 110 °C the *E*-alkene product was also observed. There was no significant

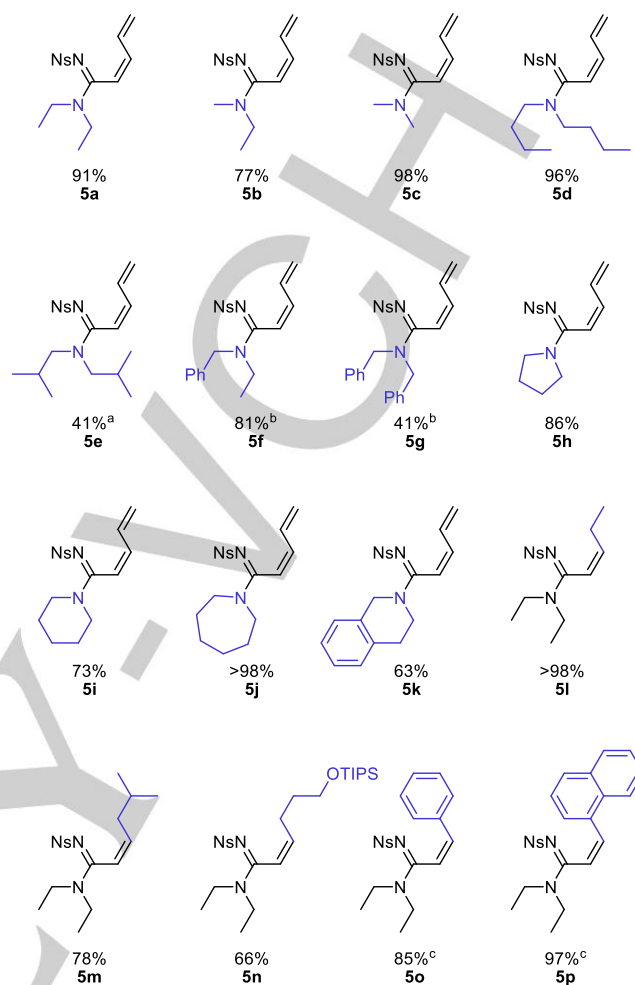
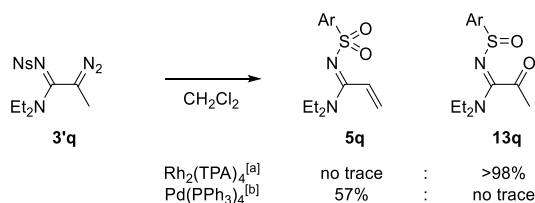


Figure 2. Alkenes accessed through Rh(II) catalyzed denitrogenation and 1,2-H shift. Conditions: 5 mol % Rh₂TPA₄, CH₂Cl₂, 0.2 M; a) 7 days; b) 60 °C (CH₂Cl₂); c) 5 mol % Rh₂(S-*t*P TTL)₄.

drop in yield when switching to a single *N'*-benzyl substituent (**5f**) but there was a significant drop when the *N',N'*-dibenzyl substrate was examined (**5g**). The *N'*-benzyl substrates could be heated to promote reaction without isomerisation of the alkene products. Cyclic amines also performed excellently under the reaction conditions (**5h–j**), although there was reduction in yield for the *N*-benzylic tetrahydroisoquinoline substrate (**5k**). The conditions for the allylic substrate could be directly applied to alkyl substrates giving the *Z*-alkene products **5l–m** with good yield and selectivity. As described during the optimisation, the appearance of some O-transfer in the benzyl substrate (**5o**) necessitated the use of the Rh₂(S-*t*P TTL)₄ catalyst and these conditions also worked well for the larger naphthyl aromatic group (**5p**).

The less-substituted methyl substrate **3'q** resulted in only O-transfer (**13q**) under the conditions attempted using rhodium(II) catalysts (Scheme 3). It is proposed that this was a result of the increased C-H bond strength of the CH₃ group vs alkyl, allylic or benzylic groups,^[20h] slowing the rate of 1,2-H shift such that the O-transfer was the only viable pathway. Switching to a palladium catalyst^[27] was able to overturn the selectivity and the 1,2-H shift

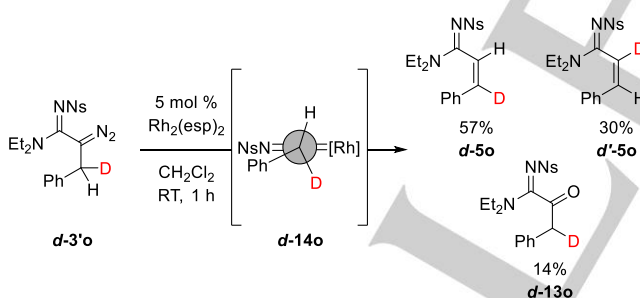
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Scheme 3. Controlling 1,2-H shift for the CH₃ group by choice of transition metal. a) RT, 1 h; b) 100 °C, 18 h.

product **5q** was the only one observed. It is important to note that Pd catalysts were not compatible with other substrates because the catalyst caused isomerisation of the Z-alkene products into a mixture of Z- and E-isomers.

The mechanism of this reaction is proposed to proceed through rhodium(II)-catalyzed loss of nitrogen from the substrate to form the corresponding rhodium carbene (Scheme 4). This is followed by a 1,2-H shift to deliver the product and release the active catalyst. The 1,2-H shift of diazo compounds catalyzed by Rh(II) catalysts is known to be Z-selective for 1-sulfonyl triazoles and α-diazo carbonyl compounds. It has been proposed^[19c] that the large bulk of the rhodium ligands forces the developing double bond to have Z-geometry. In this case, the use of the largest catalysts resulted in the greatest selectivity giving complete selectivity which supports this explanation. A deuterium-containing substrate **d-3'o** was prepared from to explore the proposed mechanism. The substrate underwent denitrogenation and either 1,2-H or 1,2-D shift to form a 1.9:1.0 mixture of the respective products (**d-5o** : **d'-5o**). Interestingly, there was some of the O-transfer product **d-13o**, presumably because deuterium slowed the 1,2-H shift process. This confirmed the mechanism and suggested the 1,2-H shift to be the rate determining step.



Scheme 4. Kinetic isotope effect in the 1,2-H shift.

Conclusion

This work provides a robust method for the preparation of α,β-unsaturated-N²-nosyl amidines with excellent yield and Z-stereoselectivity. The availability of an α-hydrogen on 5-aza-1-STs / α-diazoamidines meant that rhodium(II) carboxylate catalysts promote denitrogenation followed by 1,2-H shift. This mechanism was supported by deuterium labelling experiments. It was found that the use of large carboxylate ligands and—critically—installation of an N²-nosyl group was essential to suppress a competitive O-transfer process. This approach could be highly beneficial in tuning the selectivity of other 1-sulfonyl-1,2,3-triazole derived reactions.

Experimental Section

Representative procedure for rhodium(II) catalyzed 1,2-H shift to form sulfonyl amidine **5a**. Full details, including starting material synthesis procedures for all examples shown and supporting spectra can be found in the Supporting Information.

$\text{Rh}_2(\text{TPA})_4$ (48.0 mg, 0.033 mmol, 5 mol %) was added to a solution of N¹,N¹-Diethyl,N²-(4-nitrobenzenesulfonyl)-2-diazo-pent-4-enamidine **3'a** (240 mg, 0.656 mmol, 1.0 equiv.) in CH_2Cl_2 (3.3 mL) and the mixture was stirred under an argon atmosphere at ambient temperature for 1 hour (TLC monitoring). The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (ethyl acetate in petroleum ether, gradient from 5 to 60%) to give N¹,N¹-diethyl,N²-(4-nitrobenzenesulfonyl)-(Z)-pentadienamidine **5a** (201 mg, 91%) as a pale yellow solid. m.pt. 94–96 °C; $\nu_{\text{max}}(\text{film})$ 3103 (C–H), 2980 (C–H), 2936 (C–H), 1526, 1348, 1292, 1150, 1126 and 1092 cm^{-1} ; δ_{H} (500 MHz, 25.2 °C, CDCl_3): 8.25 (2 H, d, $J = 8.8$ Hz, Ns Ar), 8.04 (2 H, d, $J = 8.8$ Hz, Ns Ar), 6.29 (1 H, dd, $J = 11.5, 11.5$ Hz, 3–H), 6.19 (1 H, d, $J = 11.5$ Hz, 2–H), 5.93 (1 H, ddd, $J = 16.9, 11.5, 10.1$ Hz, 4–H), 5.29 (1 H, dd, $J = 16.9, 1.1$ Hz, 5-H_E), 5.16 (1 H, dd, $J = 10.1, 1.1$ Hz, 5-H_Z), 3.59 (2 H, q, $J = 7.1$ Hz, Et CH₂), 3.38 (2 H, q, $J = 7.2$ Hz, Et' CH₂), 1.23 (3 H, t, $J = 7.1$ Hz, Et CH₃) and 1.13 (3 H, t, $J = 7.2$ Hz, Et' CH₃); δ_{C} (126 MHz, 25.0 °C, CDCl_3): 163.6 (C1=N), 149.3 (Ns Ar), 149.2 (Ns Ar), 134.4 (C3), 131.0 (C4), 128.0 (2 × Ns Ar), 123.7 (2 × Ns Ar), 123.2 (C5), 121.1 (C2), 44.8 (Et' CH₂), 42.8 (Et CH₂), 13.6 (Et' CH₃) and 12.2 (Et CH₃); m/z (ESI) 360.0979 ([M+Na]⁺ = C₁₅H₁₉N₃NaO₄S⁺ requires 360.0988).

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Keywords: Amidine • C–H Shift • Carbenes • Diazo compounds • Rhodium

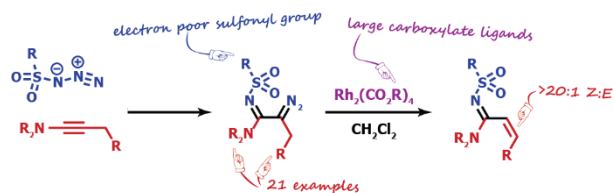
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RESEARCH ARTICLE

Entry for the Table of Contents



α,β -Unsaturated amidines can be synthesized in high yield by rhodium(II) carboxylate catalyzed 1,2-H shift following denitrogenation of α -diazo amidines. Using a large carboxylate rhodium(II) ligand and an electron-poor *N*-sulfonyl group results in exclusive *Z*-selectivity and excellent yield by suppressing side reactions involving intramolecular oxygen transfer.