

Asymmetric Formal [3 + 3]-Cycloaddition Reactions of Nitrones with Electrophilic Vinylcarbene Intermediates

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S Supporting Information

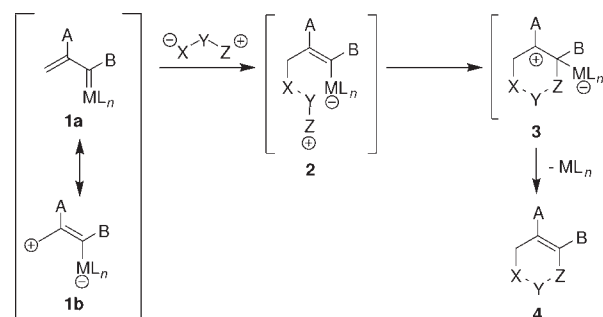
ABSTRACT: With metal carbene access to dipolar intermediates, 3,6-dihydro-1,2-oxazines are produced in high yields by dirhodium(II) carboxylate catalyzed reactions between nitrones and a β -TBSO-substituted vinyl diazoacetate. High enantiocontrol occurs with catalysis by *N*-phthaloyl-(*S*)-(amino acid)-ligated dirhodium carboxylates for [3 + 3]-cycloaddition reactions with both acyclic and cyclic nitrones.

Nitrones are versatile reagents for cycloaddition reactions that produce cyclic hydroxylamine derivatives.¹ Although their catalytic [2 + 3]-dipolar cycloaddition reactions have been studied extensively,² and highly enantioselective reactions with α,β -unsaturated aldehydes have been reported,³ scarce attention has been given to their formal [3 + 3]-cycloaddition reactions. Hayashi reported a palladium-catalyzed [3 + 3]-cycloaddition reaction between an *N*, α -diarylnitron and trimethylenemethane generated from [2-(acetoxymethyl)-2-propenyl]trimethylsilane in high yield,⁴ but nitrones have otherwise been neglected. Greater attention has been given to azomethine imines and their reactions with trimethylenemethane (Pd catalysis),⁴ enals (*N*-heterocyclic carbene catalysis),⁵ and propargyl esters (Au catalysis),⁶ and other pairings for [3 + 3] cycloaddition show broad applicability of this annulation transformation.⁷ However, although there is recognized high potential for [3 + 3]-cycloaddition between 1,3-dipoles and electrophilic vinylcarbenes, only the recent communication by Toste has described a [3 + 3]-annulation process that involves a putative vinylcarbene intermediate.⁶

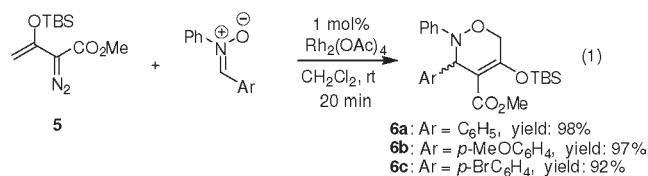
We reasoned that the absence of examples of [3 + 3]-cycloaddition reactions by catalytic dinitrogen extrusion from vinyl diazo compounds was due to the limited ability of structure **1b** of the vinylcarbene intermediate to capture a dipolar species in a stepwise process that is a formal [3 + 3]-cycloaddition (Scheme 1). This problem has now been resolved with the use of TBSO-substituted vinyl diazoacetate **5**⁸ in catalytic reactions with nitrones to form 3,6-dihydro-1,2-oxazine derivatives exclusively and in high yield, and high enantiocontrol has been achieved from the application of a chiral dirhodium carboxylate catalyst.

Treatment of 1.5 equiv of **5** in the presence of *N*, α -diphenylnitron and 1.0 mol % of dirhodium tetraacetate in dichloromethane gave immediate dinitrogen extrusion from **5** and produced 3,6-dihydro-1,2-oxazine **6a** within 20 min in 98% isolated yield (eq 1). No reaction occurred in the absence of catalyst. The installation of the electron-donating MeO substituent or an electron-withdrawing Br substituent on the reactant nitron also

Scheme 1



formed the [3 + 3]-cycloaddition products (**6b** and **6c**) in high yields. Structural confirmation for the 3,6-dihydro-1,2-oxazine products was obtained spectrally and from the X-ray diffraction of a single crystal from **6c** (Figure 1). The core structures of these compounds, which up to now has been mainly available via nitroso hetero-Diels–Alder reactions⁹ and from a tandem one-pot process involving organocatalytic α -oxyamination of an enamine with nitrosobenzene followed by reaction with a vinyl phosphonium salt in an intramolecular Wittig process,¹⁰ are versatile intermediates for the synthesis of α -substituted β -amino acids and related compounds that are not easily accessible by other methods.^{9,11} Substituent groups on **6a** make this 3,6-dihydro-1,2-oxazine particularly suitable for further functionalization.



Only one direct chiral catalytic methodology has been advanced for the synthesis of 3,6-dihydro-1,2-oxazines, and this process is limited to pyridylnitroso compounds that undergo cycloaddition with conjugated dienes.¹² Ley's two-step organocatalytic route¹⁰ provides high enantiocontrol and modest to good yields but is limited thus far to nitrosobenzene. In view of the limited availability of catalytic enantioselective methods with which to access these compounds we sought to employ chiral dirhodium carboxylate catalysts for the reaction between **5** and *N*, α -diphenylnitron depicted in eq 1. As can be seen by the data

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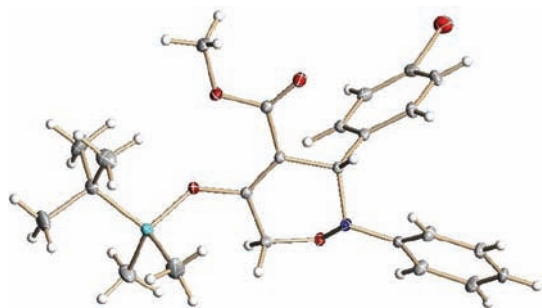
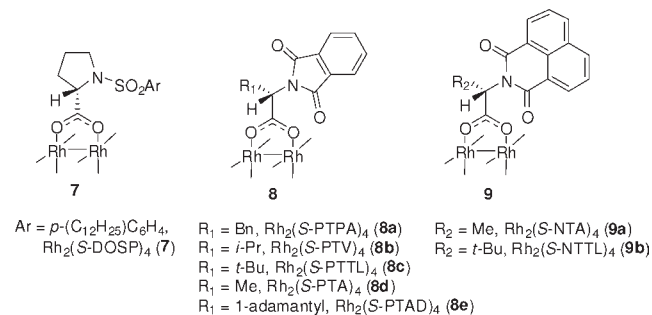


Figure 1. X-ray structure of the formal [3 + 3]-cycloaddition reaction product (**6c**) formed from **5** and *N*-phenyl- α -(*p*-bromophenyl)nitronone.

in Table 1, $\text{Rh}_2(\text{S-DOSP})_4$ (**7**)¹³ catalyzed the formal [3 + 3]-cycloaddition reaction but did not provide evidence of any enantiocontrol. However, the phthalimide-amino acid ligated dirhodium catalysts **8a**–**8d** of Hashimoto and co-workers¹⁴ produced **6a** in good to excellent yields and modest to high enantioselectivities. Surprisingly, the least sterically encumbered catalyst (**8d**) provided the highest level of enantiocontrol; steric interference by R_1 (for **8**) and R_2 (for **9**)¹⁵ appears to be the cause for lowering the % ee, and the absence of **6a** from catalysis by **9b** suggests the absolute limitation for dirhodium carboxylates with this class of chiral ligand. Notably, bulky substituents in ligands also decreased the reaction rate, especially for $\text{Rh}_2(\text{S-PTTL})_4$ (**8c**) and $\text{Rh}_2(\text{S-PTAD})_4$ (**8e**)¹⁶, which only converted a small portion of the nitronone into the [3 + 3]-annulation product **6a** resulting in <20% isolated yield. Both solvent and temperature were varied to reach optimum conditions (entry 14) that included *tert*-butyl methyl ether (TBME) as the solvent and -30°C as the reaction temperature for 95% yield and 93% ee with only 2.0 mol % of **8d** and a reaction time of 2 h.



With the optimal conditions in hand, the generality of this enantioselective formal [3 + 3]-cycloaddition reaction (eq 2) was further investigated, and the results of this investigation are given in Table 2. Product yields were high, and 3,6-dihydro-1,2-oxazines **11** were the sole reaction products; however, enantioselectivities of reactions with nitrones having electron-donating or -withdrawing groups all occurred with a 3–16% lower enantiomeric excess than did *N*, α -diphenylnitronone, indicating little dependence on the electronic nature of aryl substituents. Instead, the size of the α -substituent appears to be a determining factor in the enantioselectivity of these reactions. All substituents on the α -phenyl group decreased the enantioselectivity relative to *N*, α -diphenylnitronone, but 90% ee and 89% ee were achieved with α -2- and α -3-furyl nitrones (entries 9 and 10), albeit in a lower % conversion of **10** and lower isolated yield of **11**. When the

Table 1. Optimization of the Enantioselective Formal [3 + 3] Cycloaddition Reaction between Siloxyvinylidiazooacetate **5** and *N*, α -Diphenylnitronone Catalyzed by Chiral Dirhodium(II) Carboxylates^a

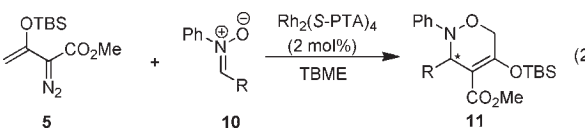
Entry	Rh ₂ L ₄	Solvent	T (°C)	time (h)	yield (%) ^b	ee (%) ^c
1	7	PhMe	23	1	80	0
2	8a	CH ₂ Cl ₂	23	0.5	98	30
3	8a	PhMe	23	0.5	98	70
4	8a	PhMe	-15	2	76	80
5	8b	PhMe	-15	2	80	62
6	8c	PhMe	-15	2	15	60
7	8d	PhMe	-15	2	85	87
8	8e	PhMe	-15	2	18	64
9	9a	PhMe	-15	2	50	53
10	9b	PhMe	-15	2	<3	–
11	8d	PhMe	-30	2	60	89
12	8d	PhMe/hexanes (2:1)	-30	2	70	91
13 ^d	8d	PhMe/hexanes (2:1)	-30	2	95	91
14 ^d	8d	TBME	-30	2	95	93

^a Reactions were performed by addition of a 1.0 mL solution of **5** (0.38 mmol) to the suspension of 0.25 mmol of *N*, α -diphenylnitronone, 0.0025 mmol of catalyst (1.0 mol %), and 100 mg of 4 Å MS with 1.0 mL of solvent. ^b Isolated yield; the only other nitronone-derived material observed in the reaction mixture was unreacted *N*, α -diphenylnitronone. ^c Determined by HPLC (AD-H column). ^d The diazo compound was added dropwise with a syringe pump over a time period of 1 h, and 2.0 mol % catalyst was used.

α -substituent was changed to the aliphatic cyclohexyl group (entry 12), the enantioselectivity was also lower than that with aryl groups as α -substituents.

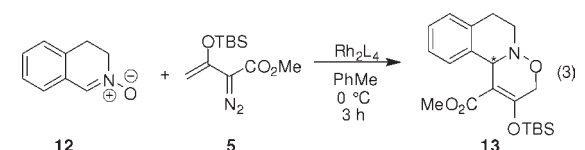
Catalytic reactions of **5** with the cyclic nitronone of 3,4-dihydroisoquinoline *N*-oxide (**12**), which is the geometric equivalent of a *cis*-disubstituted nitronone whose stereochemical requirements would be expected to be different from those of *trans*-disubstituted nitrones such as **10**, were also examined (eq 3 and Table 3). In contrast to reactions with **10**, catalysis of the reaction between **5** and **12** by $\text{Rh}_2(\text{S-PTA})_4$ (**8d**) provided the [3 + 3]-cycloaddition product in high yield but with only a moderate 54% enantiomeric excess. However, the sterically demanding catalyst $\text{Rh}_2(\text{S-PTTL})_4$ (**8c**) improved the enantioselectivity to 80% ee without a significant decrease in product yield. That use of $\text{Rh}_2(\text{S-PTAD})_4$ (**8e**) had the same degree of enantiocontrol as $\text{Rh}_2(\text{S-PTTL})_4$, but the yield of **13** in this case was much lower, suggests the subtle nature of steric influences in this catalytic process. Solvent *tert*-butyl methyl ether was not used because of its poor miscibility with 3,4-dihydroisoquinoline *N*-oxide.

The mechanism of this formal [3 + 3]-cycloaddition (Scheme 2) is in accord with the general process given in Scheme 1. Rhodium carboxylate catalysts activate the vinyl carbene for nucleophilic attack by the nitronone at the γ -position of **14** to form adduct **15**. Vinylogous reactivity in catalytic reactions of vinylidiazooacetates has ample precedent.¹⁷ Intramolecular iminium ion addition to the catalyst-activated vinyl ether functional group of **15** forms, in a stepwise or concerted fashion, the [3 + 3]-cycloaddition product **11**. Iminium ion addition is facilitated by stabilization provided by the TBSO group, and release of the catalyst from **16**

Table 2. Effects of Nitrono Substituents on Enantiocontrol for the Formal [3 + 3]-Cycloaddition Reaction^a


Entry	R	T (°C)	time (h)	yield (%) ^b	ee (%) ^c
1	C ₆ H ₅	-30	2	95	93
2	<i>p</i> -MeC ₆ H ₄	-30	2	95	87
3	<i>p</i> -MeOC ₆ H ₄	-15	3	96	78
4	<i>p</i> -BrC ₆ H ₄	-15	4	65	80
5	<i>p</i> -FC ₆ H ₄	-15	4	92	77
6	<i>m</i> -MeC ₆ H ₄	-30	2	94	90
7	<i>m</i> -ClC ₆ H ₄	-15	3	89	85
8	2-naphthyl	0	3	73	80
9	2-furyl	0	3	53	90
10	3-furyl	0	3	66	89
11	2-thienyl	0	3	81	80
12	cyclohexyl	-30	2	85	77

^a Reactions were performed by slow addition (over 1 h) of 1.0 mL solution of **5** (0.38 mmol) to the suspension of 0.25 mmol of nitrono **10**, 0.0050 mmol of catalyst (2.0 mol %), and 100 mg of 4 Å MS with 1.0 mL of TBME. ^b Isolated yield of **11**; the only other nitrono-derived material observed in the reaction mixture was unreacted **10**. ^c Determined by HPLC (AD-H or OD-H column).

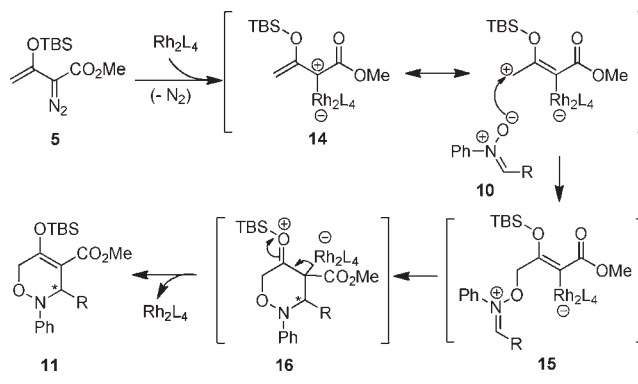
Table 3. Formal [3 + 3]-Cycloaddition Reactions of 3,4-Dihydroisoquinoline N-Oxide with **5^a**


catalyst	yield (%) ^b	ee (%) ^c
Rh ₂ (S-PTA) ₄ (8d)	97	54
Rh ₂ (S-PTTL) ₄ (8c)	86	80
Rh ₂ (S-PTAD) ₄ (8e)	50	80
Rh ₂ (S-NTTL) ₄ (9b)	75	60

^a Reactions were performed by slow addition (over 1 h) of the diazo compound (0.38 mmol) in 1.0 mL of toluene to the suspension of 0.25 mmol of 3,4-dihydroisoquinoline N-oxide, 0.0050 mmol of catalyst (2.0 mol %), and 100 mg of 4 Å MS in 1.0 mL of toluene. ^b Isolated yield; the only other nitrono-derived material observed in the reaction mixture was unreacted **12**. ^c Determined by HPLC (AD-H column).

is a favorable process. As predicted by Scheme 2, methyl styryldiazoacetate, which undergoes dirhodium(II) carboxylate catalyzed [3 + 2] annulation reactions of indoles and vinyl ethers,¹⁸ failed to produce the corresponding [3 + 3]-cycloaddition product with *N*, α -diphenylnitrono with catalysis by either Rh₂(OAc)₄ or Rh₂(S-PTA)₄.

In conclusion, we have developed a general, enantioselective formal [3 + 3]-cycloaddition process between TBSO-activated vinyl diazoacetate **5** and acyclic (**10**) and cyclic (**12**) nitronos that

Scheme 2. Mechanism of the Formal [3 + 3]-Cycloaddition Reaction of Siloxyvinyl diazoacetate **5 and Nitrono **10****

occur in high yields and selectivities. The convenience of this methodology, the absence of a background reaction, and the potential suitability of a spectrum of 1,3-dipoles and β -substituted vinyl diazoacetates for this transformation suggest broad applicability. The high level of dependence of catalyst ligands on enantioselectivity in product formation provides opportunities for new catalyst developments. Further studies exploring these processes are underway.

■ ASSOCIATED CONTENT

S Supporting Information. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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