Synthetic Methods

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Rhodium(II)- and Copper(II)-Catalyzed Reactions of Enol Diazoacetates with Nitrones: Metal Carbene versus Lewis Acid Directed Pathways**

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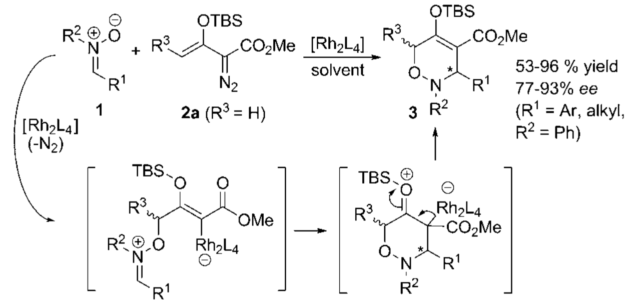
Access to 1,2-oxazines has proven to be highly valuable for the preparation of a multitude of biologically active target compounds,[1] but there are few methods that have been developed for their syntheses.[2] Of particular interest are the 3,6-dihydro-1,2-oxazines, which are available through nitroso hetero-Diels–Alder reactions,[3] gold-catalyzed cycloisomerization with allenes,[4] or (for selected examples) by a one-pot organocatalytic process involving α-oxyamination and an intramolecular Wittig reaction.[5] These oxazines have been valued as synthetic building blocks in organic syntheses,[6] and they are frequently found as structural skeletons in biologically active compounds.[7] We have recently reported an efficient and highly enantioselective formal [3+3] cycloaddition reaction between a variety of nitrones **1** and vinylcarbene intermediates derived from rhodium(II)-catalyzed reactions of TBSO-substituted enol diazoacetate (**2a**, $R^3 = H$).[8] These high-yielding reactions occur by the vinylogous reaction of the electrophilic metal carbene with the nucleophilic nitrone coupled with the intramolecular addition of an iminium ion and dissociation of the catalyst (Scheme 1). In attempts to broaden the scope of this transformation by using **2b** ($R^3 = Ph$) and examine the diastereocontrol we discovered that the rhodium(II) catalysts were inert towards dinitrogen extrusion from **2b** as well as any subsequent reaction. However, a strongly Lewis acidic copper(II) compound catalyzed this reaction efficiently and with complete diastereocontrol.



Scheme 1. Rhodium(II) carbene directed [3+3] cycloaddition of **2a** ($R^3 = H$) with nitrones. TBS = *tert*-butyldimethylsilyl.

Treatment of TBSO-substituted enol diazoacetate **2b** ($R^3 = Ph$) with rhodium(II) acetate in the presence of nitrone **1a** ($R^1 = p\text{-}BrC_6H_4$) at room temperature surprisingly resulted in no observable reaction over 1 h under conditions that resulted in **2a** ($R^3 = H$) forming the corresponding 3,6-dihydro-1,2-oxazine **3** in nearly quantitative yield. Heating the reaction mixture containing $[Rh_2(OAc)_4]$ in dichloromethane to reflux led to a mixture of products, none of which resulted from [3+3] cycloaddition, but a minor component was observed that was generated by oxygen transfer from the nitrone after replacement of the dinitrogen in **2b** by oxygen.[9] Copper(I) catalysts that are alternatives to $[Rh_2(OAc)_4]$ for dinitrogen extrusion[9] were surprisingly limiting: only a trace amount of the [3+3] cycloaddition product was formed with CuI over 24 h (Table 1, entry 2), but this product was obtained as a single diastereoisomer (d.r. > 25:1) in 31 % yield from a reaction catalyzed by $[Cu(MeCN)_4](PF_6)$ (entry 3). Clearly, traditional catalysts for the formation of metal carbenes[10] were not suitable to catalyze this transformation effectively.

Encouraged by the observed high diasterocontrol, we surveyed a variety of Lewis acid catalysts. $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$, and $In(OTf)_3$ were ineffective, but **3a** was formed, albeit as a minor product, on using a catalytic amount of $Zn(OTf)_2$. However, the use of the Lewis acidic copper(II) triflate led to **3a** in 54 % yield (Table 1, entry 5); the yield was further improved to 89 % by using $AgSbF_6$ (entry 6) and a dramatically reduced reaction time of 5 min. Recognizing that the product yield increased and reaction time decreased as the Lewis acidity of the catalyst increased, copper(II) hexafluoroantimonate ($Cu(SbF_6)_2$)[11] was tested, and was found to give superior results (entry 7). Slightly lower yields were obtained by changing the catalyst loading (entries 8–10). Notably, when 4 Å molecular sieves were added to the mixture containing $Cu(SbF_6)_2$, a much lower yield was obtained and a longer reaction time (24 h) was required (entry 10).

The scope of this reaction was evaluated under these optimized conditions by changing the nitrone **1**; as can be seen from Table 2, both high yields and high diastereoselectivities for **3** were obtained. Neither electron-withdrawing (e.g.,

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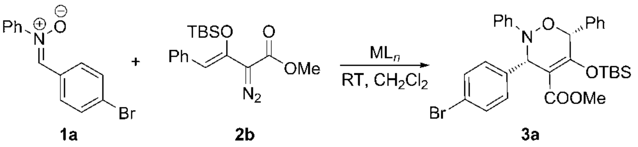
Table 1: Catalyst screening and optimization of reaction conditions.[a]

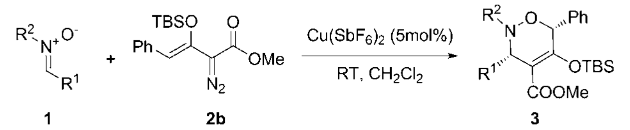


Entry	ML$_n$	t[b]	ML$_n$ [mol %]	**3a** yield [%][c]
1	[Rh$_2$(OAc)$_4$]	1 h	5	mixture
2	CuI	24 h	5	trace
3	[Cu(MeCN)$_4$](PF$_6$)	24 h	5	31
4	Zn(OTf)$_2$	24 h	5	6
5	Cu(OTf)$_2$	24 h	5	54
6	AgSbF$_6$	5 min	5	89
7	**Cu(SbF$_6$)$_2$**	**5 min**	**5**	**95**
8	Cu(SbF$_6$)$_2$	5 min	10	92
9	Cu(SbF$_6$)$_2$	30 min	2	88
10[d]	Cu(SbF$_6$)$_2$	24 h	5	73

[a] Reactions were performed by the dropwise addition of a solution of freshly prepared Cu(SbF$_6$)$_2$ (5.0 mol%) in CH$_2$Cl$_2$ (1 mL) to the mixture of enol diazoacetate **2b** (200 mg, 0.6 mol) and nitrone **1a** (0.5 mmol) in CH$_2$Cl$_2$ (3 mL). [b] The time for complete conversion of **2b** into product(s) was monitored by TLC. [c] Yield of isolated product after column chromatography; the diastereoselectivity was determined by ^{1}H NMR spectroscopic analyses of the unpurified reaction mixture and was greater than 25:1 in all cases. [d] With 4 Å molecular sieves added.

entry 5) nor electron-donating substituents (e.g., entries 4 and 6) on R^1 had an impact on the product yields, although reactions occurred at a faster rate when nitrone **1** contained electron-withdrawing substituents in R^1. Similarly, R^1 can be naphthyl, furyl, or styryl without diminishing the reactivity or selectivity. Changing the substituent on the nitrone nitrogen atom (R^2) from phenyl to substituted phenyl (entries 2, 10, and 11) and to alkyl (entries 12 and 13) similarly had no adverse effect on the reactivity or selectivity. In all cases, only the *syn* diastereomer was observed. The stereochemistry of the product was determined by single-crystal X-ray analysis of **3j**.[12]

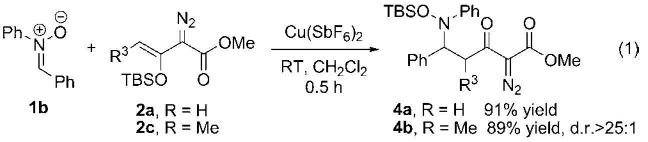
Table 2: Cu(SbF$_6$)$_2$-catalyzed [3+3] cycloaddition reactions of enol diazoacetate **2b** with nitrones.[a]



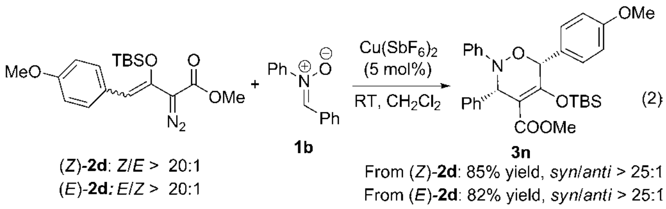
Entry	R^1	R^2	**3**	t [min][b]	Yield [%][c]	d.r. (*syn*/*anti*)[d]
1	4-BrC$_6$H$_4$	Ph	**3a**	5	95	>25:1
2	Ph	Ph	**3b**	5	88	>25:1
3	3-ClC$_6$H$_4$	Ph	**3c**	5	90	>25:1
4	2-MeOC$_6$H$_4$	Ph	**3d**	12 h	95	>25:1
5	2-NO$_2$C$_6$H$_4$	Ph	**3e**	5	96	>25:1
6	3,4-(MeO)$_2$C$_6$H$_3$	Ph	**3f**	60	93	>25:1
7	β-naphthyl	Ph	**3g**	5	80	>25:1
8	2-furyl	Ph	**3h**	5	85	>25:1
9	*trans*-styryl	Ph	**3i**	5	92	>25:1
10	Ph	*p*-BrC$_6$H$_4$	**3j**	5	93	>25:1
11	Ph	PMP	**3k**	5	82	>25:1
12	Ph	Bn	**3l**	30	78	>25:1
13	Ph	Me	**3m**	30	75	>25:1

[a] Reactions were performed as described in Table 1. [b] The time for complete conversion of **2b** into product(s) was monitored by TLC. [c] Yield of isolated product after column chromatography. [d] The diastereoselectivity was determined by ^{1}H NMR spectroscopic analyses of the unpurified reaction mixtures and was greater than 25:1 in all cases. PMP = *p*-methoxyphenyl, Bn = benzyl.

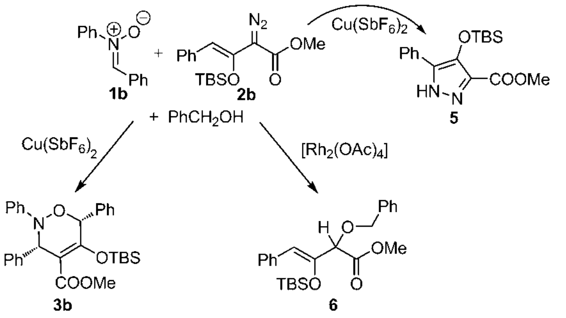
Modification of the vinyl substituent (R^3 in Scheme 1) led to unexpected results in Cu(SbF$_6$)$_2$-catalyzed reactions with diphenylnitrone **1b** [Eq. (1)]. The Mukaiyama–Mannich products **4a** or **4b** were formed in high yields, instead of [3+3] cycloaddition products, when R^3 = H (**2a**) and R^3 = Me (**2c**). This reaction process is characteristic of Lewis acid catalysis and has been observed in reactions between **2a** and nitrones catalyzed by [Cu(MeCN)$_4$](PF$_6$).[13]



The anisyl-substituted aryl enol diazoacetate **2d** was isolated as a mixture of *E* and *Z* isomers (*Z*/*E* = ca. 6:1), instead of the exclusive formation of the *Z* isomers, as observed in the synthesis of **2b** and **2c**. Chromatographic separation of (*Z*)-**2d** from (*E*)-**2d** and treatment of both individually with diphenylnitrone in the presence of a catalytic amount of Cu(SbF$_6$)$_2$ resulted in the exclusive production of the [3+3] cycloaddition product **3n** with high diastereoselectivity. Thus, the stereochemistry of the reactant enol diazoacetate was not retained in the product [Eq. (2)].



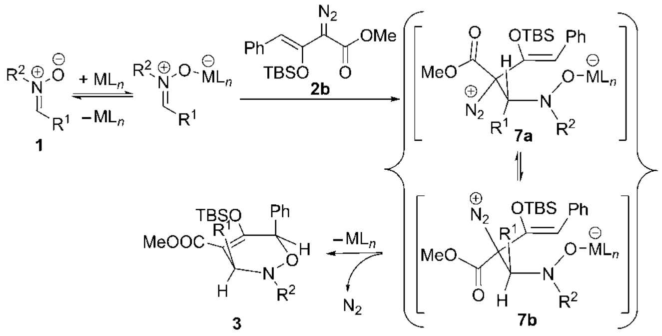
To rule out a metal carbene pathway similar to that shown in Scheme 1 for this [3+3] cycloaddition reaction we initially sought to trap any intermediate metal carbene by cyclopropanation. However, the use of neither [Rh$_2$(OAc)$_4$] nor Cu(SbF$_6$)$_2$ in reactions between diphenylnitrone and **2b** in the presence of styrene led to the production of cyclopropane compounds. The outcome of the reaction with benzyl alcohol as the additive was different in the presence of [Rh$_2$(OAc)$_4$] and Cu(SbF$_6$)$_2$ catalysts: only the [Rh$_2$(OAc)$_4$] catalyst produced the O–H insertion product (Scheme 2), but its yield was less than 30%. The most convincing evidence that Cu(SbF$_6$)$_2$ catalyzed the [3+3] cycloaddition reaction as a Lewis acid came from experiments in which **2b** and Cu(SbF$_6$)$_2$ were combined in dichloromethane, and the nitrone was added last. This approach resulted in **2b** retaining its identity, only undergoing intramolecular dipolar cycloaddition to **5**,[14] and with slow enol hydrolysis observed even



Scheme 2. Catalyst-dependent products.

after 29 hours (see the Supporting Information). However, the addition of nitrone **1b** to the reaction mixture containing **2b** and $Cu(SbF_6)_2$ caused immediate evolution of gas and the formation of the cycloaddition product. Additionally, when the nitrone was combined with an equivalent amount of catalyst, chemical shifts consistent with coordination of the nitrone to the $Cu(SbF_6)_2$ were observed in the NMR spectrum (see the Supporting Information).

On the basis of these determinations the [3+3] cycloaddition reaction between **2b** and nitrones is proposed to occur through Lewis acid catalysis (Scheme 3) rather than via a metal carbene. The catalyst first activates the nitrone through the basic terminal oxygen atom. Electrophilic addition of the resulting iminium ion then occurs directly at the diazo carbon atom of **2b** to generate diazonium ion intermediate **7**, two limiting conformations of which (**7a** and **7b**) are shown. The more stable conformation (**7b**) is that in which the aryl and ester groups are on opposite sides and the diazonium ion and OTBS groups are in proximity, and it is through this conformation that the major isomer is formed. Dissociation of the catalyst from the original nitrone oxygen atom, which occurs with addition to the double bond coupled with loss of dinitrogen (S_N2'), produces **3**.



Scheme 3. Proposed mechanism for the Lewis acid catalyzed formal [3+3] cycloaddition between TBSO-protected enol diazoacetate **2b** and nitrones.

In summary, highly Lewis acidic copper(II) compounds catalyze formal [3+3] cycloaddition of Lewis acid activated nitrones and vinyl diazoacetates. The process is complimentary to its metal carbene counterpart, which is catalyzed by dirhodium(II) species and inhibited from occurring with enol diazoacetate **2b**, and illustrates that a duality of mechanistic pathways can account for the same transformation. Although there are several examples of divergent outcomes from Lewis acid catalysis and metal carbene pathways,[15] the enol diazoacetate/nitrone process reported here is the first in which the same transformation (a formal [3+3] cycloaddition) is reached by both Lewis acids and catalysts that generate metal carbenes, albeit with enol diazoacetates having an aryl (**2b**) rather than a hydrogen (**2a**) substituent.

Experimental Section

General procedure: Nitrone **1a** (137.5 mg, 0.50 mmol), enol diazoacetate **2b** (200 mg, 0.6 mol), and CH_2Cl_2 (3.0 mL) were added under a flow of N_2 to a 10 mL Schlenk flask charged with a magnetic stir bar. The CH_2Cl_2 solution (1 mL) of the freshly prepared $Cu(SbF_6)_2$ (5.0 mol%) was added into the flask. Once the diazo compound was consumed (determined by TLC), the crude products were subjected to ^1H NMR spectroscopic analysis to determine the diastereoselectivity. The reaction mixture was purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 40:1 to 20:1) to give pure product **3a**.

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