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Catalytic Selective Oxyamidation of Cyclic Enamides using Nitrenes

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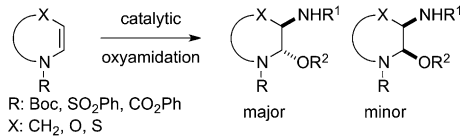
Growing attention has recently been paid to the development of catalytic alkene difunctionalization reactions.[1] These transformations involve the simultaneous installation of two functional groups onto π bonds and offer the most straightforward access to various key motifs such as vicinal diols,[2] amino-alcohols[3] or diamines[4] that are found in a wide range of natural products, drugs, or chiral auxiliaries. However, whereas efficient selective protocols are available for the formation of diols, much work remains to be done in the field of catalytic aminohydroxylation, which raises the additional issue of regioselectivity with non-symmetrical olefins. In particular, poor control of the sense of the addition is observed in many cases thereby limiting its scope.[5] Recent solutions have nevertheless emerged with the design of ligands,[6] the development of tethered reactions,[3a,7] or the discovery of new oxidative conditions.[3a,8]

π-Electron-rich olefins such as enamides are useful scaffolds for the preparation of complex nitrogenated molecules.[9,10] Compared with enamines, enamides have received little attention until recently as a consequence of their decreased nucleophilicity. Their chemistry, initially centered around the application of catalytic hydrogenation for the synthesis of enantiopure amines,[11] has expanded considerably within the last decade following the development of several methodologies for their stereoselective synthesis.[12] Enamides have therefore proved to be efficient nucleophilic agents as well as versatile substrates in radical or pericyclic reactions.[9] The use of transition-metal complexes has also allowed selective transformations such as catalytic cyclopropanation or dihydroxylation.[13] In comparison, the development of an efficient protocol for aminohydroxylation may offer additional synthetic opportunities provided that good regiocontrol of the addition could be achieved. Fundamentally, should the latter allow selective introduction of the O functionality at C2, it will afford the possibility to further functionalize the enamide via the intermediacy of iminium ions.[14] These observations thus prompted us to investigate the oxyamidation of enecarbamates and enesulfonamides within the framework of a program aimed at generating small molecule libraries for biological screening. In this communication, we wish to report the results of our studies that have led to the development of a process occurring with high levels of regio- and stereoselectivity and relying on catalytic nitrene transfers (Scheme 1).



Scheme 1. Catalytic oxyamidation.

Most of the metal-catalyzed aminohydroxylations involve osmium, and to a lesser extent, palladium complexes.[1,3a] However, the sole examples reported with enamides so far are based on the use of manganese and osmium, with the latter surprisingly leading to the formation of diols.[13c] In this context, the use of dirhodium(II) catalysts provides new opportunities since it has been demonstrated that they efficiently catalyze the intramolecular oxyamidation of electron-rich olefins in the presence of iodine(III) oxidants.[15] More recently, one of us has reported that efficient intermolecular oxyamidation of the 2,3-indole π-bond can also be achieved under these conditions.[16] Strikingly, all of these transformations rely on the intermediacy of metallanitrenes better known for giving aziridines from alkenes or C–H aminated products.[17] With the aim of exploring this new type of reactivity for nitrenes in more detail, we therefore decided to study their reaction with enamides that are structurally related to indoles.[18]

Reactivity of simple cyclic enamides **1**[19] under conditions previously optimized for indoles[16] was first investigated with either methanol or acetic acid as nucleophiles. Pleasingly, the combination of the rhodium(II) catalyst $Rh_2(esp)_2$ (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid) with trichloroethylsulfamate ($TcesNH_2$) (both developed by Du Bois and co-workers for catalytic alkene aziridination

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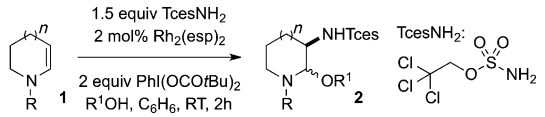
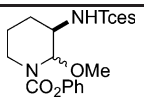
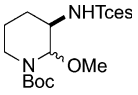
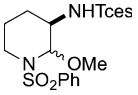
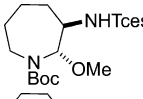
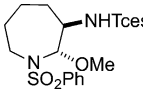
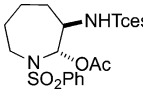
Table 1. Oxyamidation of enamides.



Entry	Substrate		R^1OH	Product		Yield [%][a]	*cis*/*trans*[b]
1		**1a**	MeOH		**2a**	66	42:58
2		**1b**	MeOH		**2b**	71	37:63
3		**1c**	MeOH		**2c**	94	30:70
4		**1d**	MeOH		**2d**	87	0:100
5		**1e**	MeOH		**2e**	88	0:100
6		**1f**	AcOH		**2f**	74[c]	0:100

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Product isolated together with 7% of the 2-OPiv analogue. The same reaction performed with $PhI(OAc)_2$ led to the isolation of only **2f** in 84% yield.

and C–H amination),[20] in the presence of $PhI(OCOtBu)_2$ allowed us to isolate the expected oxyaminated products **2** in very good yields ranging from 66–94% starting from enecarbamates or enesulfonamides (Table 1). More importantly, the reaction proceeds with complete regioselectivity leading to the clean formation of N,O-acetals with the introduction of the amino group at the C3 position. In terms of stereoselectivity, whereas a roughly 2:1 ratio in favor of the *trans* isomer is observed with 6-membered cyclic enamides **1a–c**, this isomer is exclusively obtained in the case of the 7-membered analogues **1d–e**. These conclusions regarding the structures of products **2** were deduced from ^{1}H NMR spectroscopic analysis and then confirmed by X-ray crystallographic analysis of compound **2f** (Figure 1). The picture clearly shows the *trans* arrangement between the OAc group at C2 and the sulfamate at C3. A stabilizing effect induced by the overlap of the nonbonding lone pair n_N with the σ* orbital of the exocyclic C–O bond can also be observed. This can account for the stereoselectivity of the reaction when applied to 7-membered substrates. These excellent results both in terms of efficiency and selectivity then led us to consider other heterocyclic structures such as a benzoxazine.

This type of compound, which combines an enamide with an enol function, raises the issue of regioselectivity since it had previously been shown that glucals also react under these conditions to afford C3 amino acetals.[15] We were thus very pleased to observe that the reaction efficiently takes place starting from substrates **3a–d**[21] in the presence of methanol or acetic acid, to give cleanly the expected oxyaminated products with yields in the 54–98% range and *cis*/*trans* ratio of up to 1:9 (Table 2). Complete regioselectivity was observed as in the previous cases, leading to the formation of a single regioisomer with two N,O-acetal functionalities. Such control in the selectivity was once again secured by X-ray crystallographic analysis of the crystalline compound **5b**. Moreover, it should be pointed out that pyridoxazines can be transformed with good conversions, though the latter are lower than those found with benzoxazines (Table 2, entries 5 and 6 vs. entries 1 and 2).[22] Worthy of note is also the reaction successful with a trisubstituted enamide (Table 2, entry 7), whereas the catalytic sulfide imination of enamide **3e** was not surprising considering the ability of sulfur compounds to react with nitrenes (Table 2, entry 8).[23]

Based on our previous observations with indoles, that is, the replacement of $Rh_2(esp)_2$ by $Rh_2(NHCOCF_3)_4$ favored the formation of *trans* isomers,[16] we performed the reaction in the presence of this catalyst to improve the *cis*/*trans* ratio, however with limited success in the case of benzoxazines **3a** and **3b**. Interestingly, this change, when applied to benzodioxine **7**, proved illuminating because it gave some clues for the hypothetical mechanism of the oxyamidation (Scheme 2). This symmetrical substrate efficiently reacts with acetic acid and methanol, under conditions reported in Table 2, to afford, respectively, the expected products **8a** and **8b** isolated with *cis*/*trans* ratios of 13:87 and 26:74. Replacement of $Rh_2(esp)_2$ by $Rh_2(NHCOCF_3)_4$ then led us to isolate **8a** in 60% yield with a slightly improved ratio of 10:90. Importantly, the ^{1}H NMR spectrum of the crude mixture reveals the presence of the sole *trans* isomer,[24] thereby suggesting that the purification by chromatography on silica gel induces partial epimerization to the *cis* isomer.

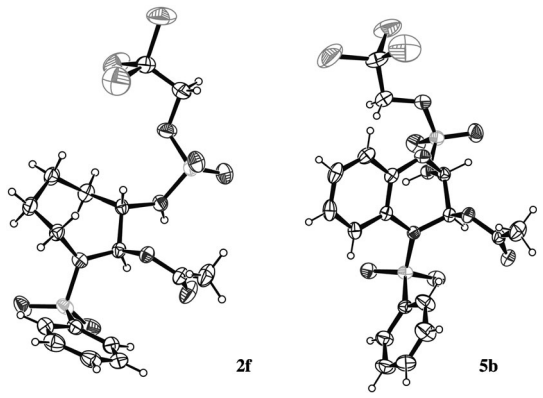
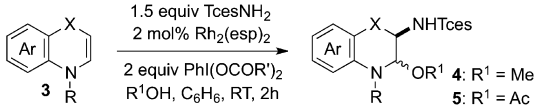
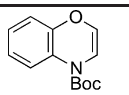
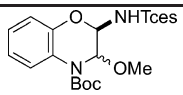
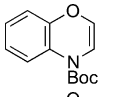
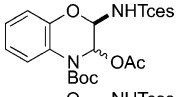
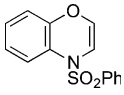
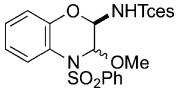
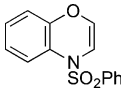
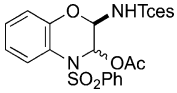
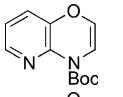
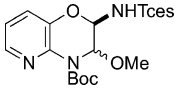
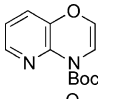
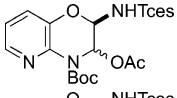
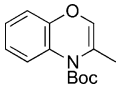
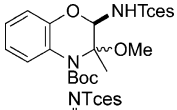
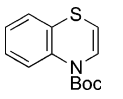
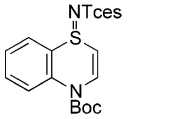


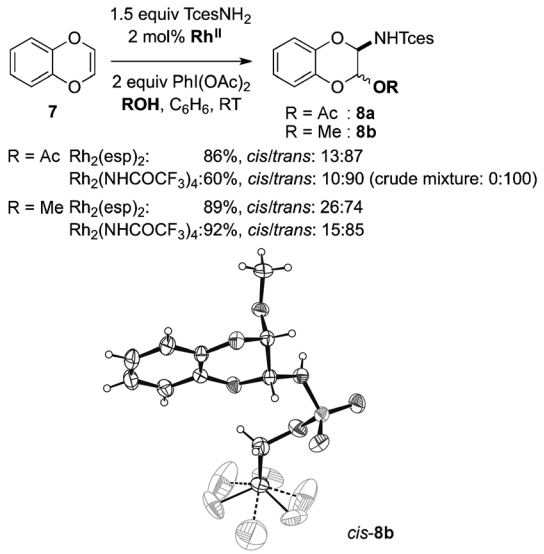
Figure 1. X-ray structure of *trans*-isomers of compounds **2f** and **5b**.

Table 2. Oxyamidation of N,X-heterocycles.



Entry	Substrate		R^1OH	Product		Yield [%][a]	*cis*/*trans*[b]
1		**3a**	MeOH		**4a**	94[c,d]	34:66
2		**3a**	AcOH		**5a**	82[e,f]	23:77
3		**3b**	MeOH		**4b**	98[c]	10:90
4		**3b**	AcOH		**5b**	83[e,g]	30:70
5		**3c**	MeOH		**4c**	61[c]	28:72
6		**3c**	AcOH		**5c**	54[e]	12:88
7		**3d**	MeOH		**4d**	68[c]	36:64
8		**3e**	MeOH		**6**	55	–

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Reaction performed with PhI(OCO*t*Bu)$_2$. [d] Reaction with $Rh_2(NHCOCF_3)_4$ afforded **4a** in 81% yield and a *cis/trans* ratio of 1:4. [e] Reaction performed with PhI(OAc)$_2$. [f] Reaction with $Rh_2(NHCOCF_3)_4$ afforded **5a** in 64% yield and a *cis/trans* ratio of 1:3. [g] Reaction with $Rh_2(NHCOCF_3)_4$ afforded **5b** in 65% yield and a *cis/trans* ratio of 1:2.



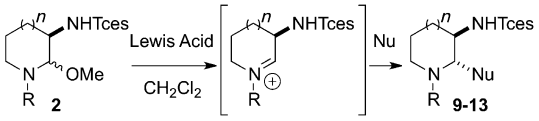
Scheme 2. Oxyamidation of benzodioxine **7** and X-ray structure of *cis*-**8b**.

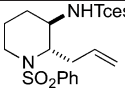
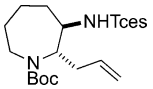
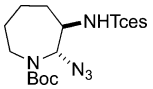
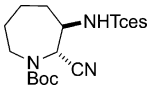
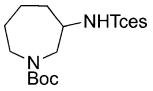
A comparable improvement of the stereoselectivity was seen in the case of methanol since compound **8b** was formed with a *cis/trans* ratio of 15:85. But unexpectedly, with the aim of growing crystals suitable for X-ray crystallographic studies, complete epimerization of the latter occurred after heating in toluene and the *cis* isomer was exclusively obtained as indicated by the X-ray crystal structure (Scheme 2. This phenomenon could be explained by the stabilization provided by the combination of the anomeric effect with the *exo*-anomeric effect as clearly indicated in Scheme 2. All these observations brought us to the hypothesis that catalytic oxyamidation of enamides might involve an initial step of aziridination followed by a S_N2-type ring-opening of the aziridine.[25] The resulting 1,2-*trans*-difunctionalized product would then partly epimerize under the reaction conditions or during the purification on silica gel.

With these N,O-acetals in hand, preliminary experiments were performed to confirm their capacity to act as efficient *N*-(acyl)iminium species likely to undergo nucleophilic displacement (Table 3).[26] We were thus pleased to observe that the *trans* isomer of **2c**, previously separated from its *cis* isomer after careful purification on silica gel, as well as the *N*-(Boc)-derivative **2d** could react with various nucleophiles in the presence of a Lewis acid, that is, boron trifluoride etherate or trimethylsilyl triflate, with yields varying from 58 to 94%. The examples displayed in Table 3 show that very good diastereoselectivities, in favor of the *trans* isomer, can be obtained as a consequence of steric hindrance provided by the C3 amino substituent.[27] This transformation, therefore, gives the opportunity to further functionalize enamides thereby enhancing the synthetic value of this new catalytic oxyamidation.

In conclusion, the application of rhodium-catalyzed nitrene transfers to enamides has allowed us to document a new type of reactivity for nitrenes. Intermolecular addition of nitrene to enecarbamates and enesulfonamides thus affords oxyamidated products with excellent yields of up to 98% and, sometimes, high levels of stereoselectivity. Strikingly, the aminohydroxylation of these non-symmetrical olefins occurs with complete regioselectivity, leading to the formation of N,O-acetals, which can be further transformed following reaction with various C- or N-nucleophiles under acidic conditions. This oxyamidation confirms the synthetic potential of enamides as versatile platforms for the generation of molecular diversity. Work is now in progress to apply these results to the preparation of a library of small bioactive molecules.

Table 3. Reactivity of the N,O-acetals **2c** and **2d**.



Entry	Substrate	Conditions	Product		Yield [%][a]
1	**2c**	Allyl-TMS BF_3·OEt_2 −78 to −40 °C		**9**	61
2	**2d**	Allyl-TMS BF_3·OEt_2 −78 °C to −40 °C		**10**	58
3	**2d**	$TMSN_3$ BF_3·OEt_2 −78 °C		**11**	93
4	**2d**	TMSCN TMSOTf −40 °C		**12**	75
5	**2d**	Et_3SiH BF_3·OEt_2 −78 °C to −30 °C		**13**	94

[a] Yield of isolated product. Allyl-TMS = Allyltrimethylsilane.

Experimental Section

General procedure for the rhodium-catalyzed oxyamidation of enamides: $TcesNH_2$ (1.5 equiv), $Rh_2(esp)_2$ (0.02 equiv) and the nucleophile (12 equiv) were successively added to a solution of enamide **1** or **3** (1 equiv) in benzene ($c = 0.36$ mol L^{-1}). $PhI(OCOR)_2$ (2 equiv) was added to this mixture and the solution was stirred at room temperature for 2 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic extracts were washed twice with brine, and then dried over $MgSO_4$ and concentrated. Products were purified by flash chromatography (silica, petroleum ether/ethyl acetate eluent) to yield the desired products.

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