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N-Heterocyclic carbene catalyzed synthesis of oxime esters†

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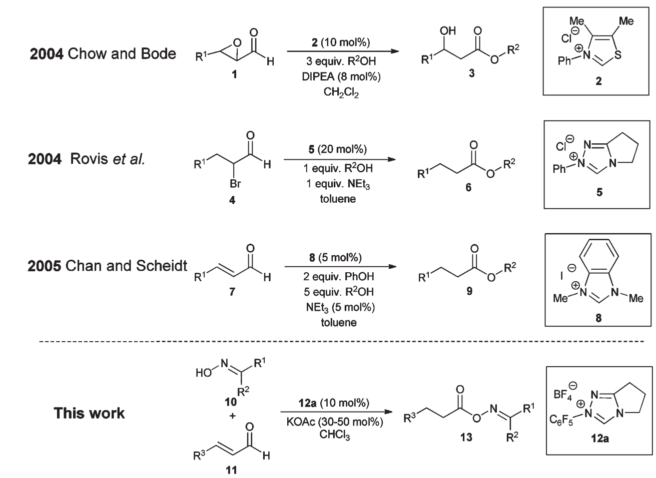
A triazolium salt derived *N*-heterocyclic carbene catalyzes the redox esterification reaction between α–β-unsaturated aldehydes and oximes. The resulting saturated oxime esters were obtained in very good yields for a broad range of aliphatic, aromatic and heteroaromatic substrates.

When designing a synthesis strategy for a complex target molecule through retrosynthetic analysis, the concept of umpolung has turned out to be very useful allowing non-traditional disconnections.[1] In this context *N*-heterocyclic carbenes have evolved into a very successful class of catalysts for the umpolung of aldehydes over the past few decades.[2] Among the vast number of publications on NHC organocatalysis, Chow and Bode[3a] and Rovis *et al.*[3b] independently reported on the conjugate umpolung of α-reducible aldehydes in 2004 (Scheme 1). Thereby, *N*-heterocyclic carbenes react with aldehydes bearing a double bond equivalent or a leaving group in the alpha position to the carbonyl group forming an acyl azolium salt, which subsequently reacts with an alcohol leading to saturated esters *via* internal redox esterification.[3,4]

In comparison with the classic preparation methods of esters *via* substitution reaction of carboxylic acid derivatives[5] this catalytic or sub-stoichiometric approach has, theoretically, the advantage of avoiding stoichiometric amounts of salt waste and/or coupling reagents, therefore being atom[6] and redox economical.[7] In reality, all reports on intermolecular redox esterifications so far do not fulfill these advantages by applying stoichiometric amounts of base, protic additives or large excesses of the *O*-nucleophile (Scheme 1). We now would like to report a highly efficient redox esterification reaction between α–β-unsaturated aldehydes and oximes under very mild, nearly equimolar conditions where no protic additives are necessary. All starting materials and reagents are commercially available and the resulting oxime esters are very useful biologically active molecules for fragrance,[8] medical[9] and agricultural industries.[10]

We started our investigations by utilizing crotonaldehyde (**11a**) and *p*-tolylaldoxime (**10a**) in the presence of the triazolium salt **12a** (5 mol%) and potassium acetate as a base (30 mol%) in chloroform for 24 h. Although crotonaldehyde is thought to be a poor substrate for the redox esterification,[3j] we could successfully isolate the corresponding oxime ester **13a** in 69% yield with 72% converted starting material (Table 1, entry 1). It is noteworthy that no typical by-products *via* the benzoin reaction or dimerization of the aldehyde were observed in the crude reaction mixture. From the range of the tested bases (Table 1, entries 2–8) strong bases such as KO*t*Bu or DBU showed no activity in this reaction while weaker ones, such as amino or acetate bases, could promote the reaction albeit less effectively as compared to potassium acetate. Therefore, in agreement with the literature, only bases whose corresponding acid is strong enough for the protonation of the extended Breslow intermediate **II** (Scheme 2) led to a measurable conversion of the starting material.[3d]

In order to improve the reaction rate we increased the catalyst loading to 10 mol% and tested different solvents (Table 1, entries 9–16). Aprotic solvents and especially chlorinated ones



Scheme 1 Examples of NHC catalyzed redox esterifications; an alcohol is the nucleophile in all three literature cases.

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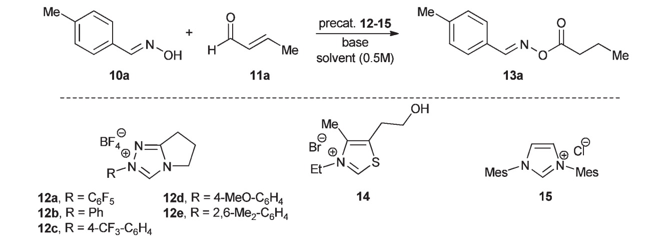
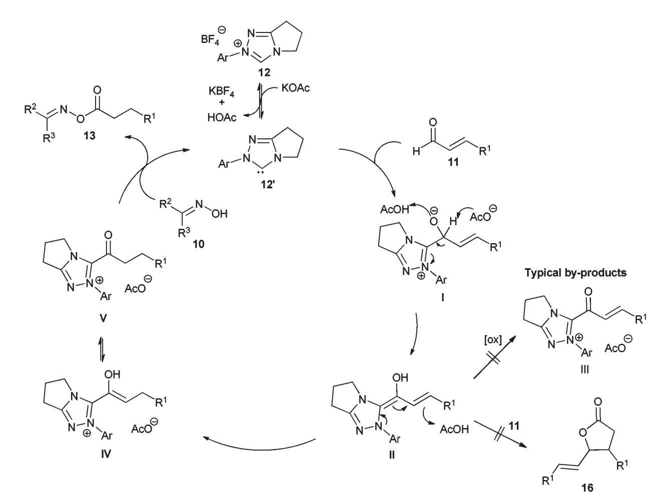
Table 1 Optimization studies of the reaction conditions[a]



Entry	Solvent	Base	Base (mol%)	Precatalyst (mol%)	Conversion[b] (%)
1	$CHCl_3$	KOAc	30	**12a** (5)	72 (69)
2	$CHCl_3$	NaOAc	30	**12a** (5)	53
3	$CHCl_3$	CsOAc	30	**12a** (5)	51
4	$CHCl_3$	DBU	30	**12a** (5)	Trace
5	$CHCl_3$	KOtBu	30	**12a** (5)	Trace
6	$CHCl_3$	$(iPr)_2NEt$	30	**12a** (5)	43
7	$CHCl_3$	NEt_3	30	**12a** (5)	32
8	$CHCl_3$	Cs_2CO_3	30	**12a** (5)	Trace
9	$CHCl_3$	KOAc	30	**12a** (10)	86
10	CH_2Cl_2	KOAc	30	**12a** (10)	83
11	Toluene	KOAc	30	**12a** (10)	73
12	Et_2O	KOAc	30	**12a** (10)	65
13	Acetone	KOAc	30	**12a** (10)	34
14	iPrOH	KOAc	30	**12a** (10)	43
15	MeOH	KOAc	30	**12a** (10)	13
16	EtOAc	KOAc	30	**12a** (10)	55
17	$CHCl_3$	KOAc	30	**12b** (10)	13
18	$CHCl_3$	KOAc	30	**12c** (10)	13
19	$CHCl_3$	KOAc	30	**12d** (10)	10
20	$CHCl_3$	KOAc	30	**12e** (10)	52
21	$CHCl_3$	KOAc	30	**14** (10)	Trace
22	$CHCl_3$	KOAc	30	**15** (10)	Trace
23[c]	$CHCl_3$	KOAc	50	**12a** (10)	91 (90)

[a] Reaction conditions: **10a** (1.0 mmol), **11a** (1.0 mmol), solvent (2.0 mL), 24 h, rt, under air. [b] Conversion of the oxime **10a** in the crude reaction mixture was determined *via* ^{1}H NMR spectroscopy; values in brackets are yields of isolated product **13a**. [c] Excess aldehyde **11a** (1.1 equiv.) was used.



Scheme 2 Proposed mechanism of the NHC catalyzed redox esterification of oximes **10** with enals **11**.

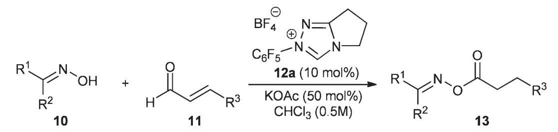
gave the best results, while ethers, esters and primary alcohols led to poor conversion rates. Interestingly, the catalytic system was highly selective concerning the choice of the nucleophile. Even when the reaction was performed in methanol only the desired oxime ester was observed without any by-products such as methylesters resulting from the redox esterification reaction with the solvent. Subsequently, we tested different azolium salts for their catalytic activity (Table 1, entries 9, 17–22). While thiazolium (**14**) and imidazolium salts **15** were catalytically inactive, the triazolium catalyst precursors **12** gave varying results strongly dependent on the aromatic N-substituent. Thereby, only the azolium salts **12a** and **12e** bearing *ortho*-substituents on the *N*-phenyl moiety produced reasonable oxime conversions with triazolium salt **12a** being far superior to **12e**. Finally, using **12a** as a catalyst precursor and increasing the potassium acetate loading to 0.5 equivalents raised the conversion of oxime to 91% and the yield of isolated product to 90% (Table 1, entry 23).

With the optimized conditions in hand we turned our attention to the scope of the oxime and aldehyde substrates. Aliphatic esters of aromatic aldoximes have recently attracted special attention due to their distinct and characteristic aroma of berries making them interesting to the fragrance and food industries.[8] Therefore we prepared a range of these compounds varying the aromatic moiety and utilizing our protocol (Table 2, entries 1–10). Indeed, irrespective of their electronic or steric properties, all these aldoximes performed well with high yields (78–90%). Sole limitations were the solubility and/or the basicity of the aldoxime leading to slightly lower yields for 3,4-dimethoxyphenyl and 4-dimethylaminophenyl substituted aldoximes (Table 2, entries 8, 10). Similarly, heteroaromatic aldoximes gave good results (Table 2, entries 11–13) although their low solubility required a change of solvent in the case of R^1 = 2-pyridinyl and 3-indolyloxime (Table 2, entries 11–12). Since even *ortho*-substituted aldoximes do not inhibit the reaction (Table 2, entry 9), we envisaged that ketoximes could be good substrates as well (Table 2, entries 14–19). In fact, ketoximes irrespective of their aromatic or aliphatic substituents reacted to give the corresponding oxime esters in synthetically useful yields (56–95%). Only some methyl-substituted ketoximes gave moderate results (Table 2, entries 14, 16).

Finally, different α–β-unsaturated aldehydes were tested in this reaction. In comparison to crotonaldehyde the longer chained or bulkier aliphatic aldehydes were all equally active resulting in high yields of 74–90% (Table 2, entries 20–24). Similarly, aromatic aldehydes such as cinnamaldehyde are good substrates as well. The oxime ester formed from cinnamaldehyde and *p*-tolyloxime was isolated in 85% yield (Table 2, entry 25).

The proposed mechanism of the reaction is shown in Scheme 2. First, the triazolium salt **12** is deprotonated by potassium acetate. Considering the low basicity of acetate bases and previous labeling experiments by Sohn and Bode[3d] the concentration of the free carbene **12′** is probably low and the protonation is reversible. Subsequently, the resulting carbene **12′** attacks the aldehyde **11** forming the tetrahedral

Table 2 Scope of the aldehyde and oxime substrates[a]



Entry	R^1	R^2	R^3	**13**	Yield[b] (%)
1	4-MeC_6H_4	H	Me	**a**	90
2	Ph	H	Me	**b**	81
3	1-Naphthyl	H	Me	**c**	93
4	4-BrC_6H_4	H	Me	**d**	90
5	3-ClC_6H_4	H	Me	**e**	90
6	4-$(CF_3)C_6H_4$	H	Me	**f**	83
7	3,4,5-$F_3C_6H_2$	H	Me	**g**	90
8	4-$(Me_2N)C_6H_4$	H	Me	**h**	79
9	2-$(MeO)C_6H_4$	H	Me	**i**	88
10[c]	3,4-$(MeO)_2C_6H_3$	H	Me	**j**	85
11[c]	2-Pyridinyl	H	Me	**k**	73
12[d]	3-Indolyl	H	Me	**l**	84
13	2-Furanyl	H	Me	**m**	87
14	Me	Me	Me	**n**	56
15	Et	Me	Me	**o**	92
16	Ph	Me	Me	**p**	68
17	Ph	Ph	Me	**q**	92
18[e]	1-Indanonyl		Me	**r**	95
19	$-(CH_2)_5-$		Me	**s**	83
20	4-Me-C_6H_4	H	Et	**t**	82
21	4-Me-C_6H_4	H	*n*Pr	**u**	80
22	4-Me-C_6H_4	H	iPr	**v**	90
23	4-Me-C_6H_4	H	CH_2OTIPS	**w**	74
24	4-Me-C_6H_4	H	Bn	**x**	79
25	4-Me-C_6H_4	H	Ph	**y**	85

[a] Reaction conditions: **10** (2.0 mmol), **11** (2.2 mmol), solvent (4.0 mL), 24 h, rt, under air. [b] Yields of isolated product **13**. [c] CH_2Cl_2 (4.0 mL) was used as solvent. [d] A mixture of $CHCl_3$–CH_2Cl_2–Et_2O 2 : 1 : 1 (8.0 mL) was used as solvent. [e] A mixture of $CHCl_3$–CH_2Cl_2 1 : 1 (8 mL) was used as solvent.

intermediate **I**,[11] which rearranges to the Breslow intermediate **II**. Recent DFT calculations showed that such proton transfers are protonation–deprotonation processes more than symmetry forbidden intramolecular [1,2]-H-shifts.[12] In the current case, the acetate base and the corresponding acetic acid predominantly take the role of the proton shuttle agent. Indeed, when the reaction was performed with triethylamine as a base, addition of 30 mol% acetic acid improved the conversion of oxime significantly, up to around 50% (previously 32%, see Table 1 entry 7). The important regioselective step is the subsequent protonation of the Breslow intermediate **II** to the azolium-enol **IV** and its tautomeric acyl-azolium **V**. Taking into account that no significant amounts of by-products were observed, the protonation of the Breslow intermediate occurs faster than the reaction with an additional molecule of the aldehyde **11** preventing C–C bond formation leading to lactones **16**[13] or the oxidation leading to α–β-unsaturated acyl-azolium **III**.[3j,14,15] Finally, the oxime **10** performs a nucleophilic substitution on the carboxyl surrogate **V** yielding the oxime ester **13** and liberating the carbene catalyst **12′** together with acetic acid.

In conclusion we developed a practical, efficient and highly selective redox esterification reaction between enals and oximes. The reaction worked well for all tested aliphatic, aromatic and heteroaromatic substrates with the only limitation being substrate solubility and basicity. In fact, the presented methodology is a good alternative to the classical transesterification processes of carboxylic acid derivatives leading to industrially valuable oxime esters in good to excellent yields.

General procedure for the NHC catalyzed redox esterification

Oxime **10** (2 mmol) and aldehyde **11** (2.2 mmol) were mixed in a flask and subsequently dissolved in chloroform (8 mL). The clear solution was treated with triazolium salt **12a** (0.2 mmol) and potassium acetate (1 mmol). The heterogeneous reaction mixture was stirred at ambient temperature.[16] After 24 h the reaction mixture was transferred onto a small amount of silica gel and purified by column chromatography.

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