Enantioselective Synthesis

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Lewis Acid Catalyzed Asymmetric Cycloadditions of Nitrones: α′-Hydroxy Enones as Efficient Reaction Partners**

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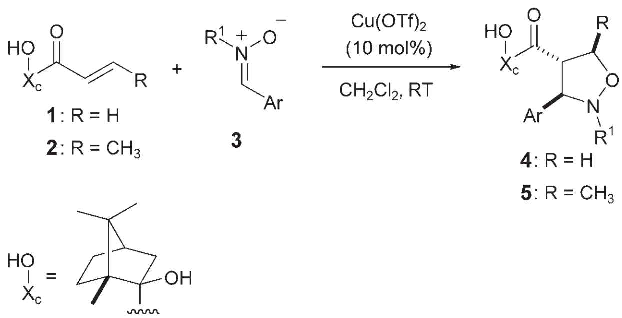
Dedicated to Professor J. Plumet on the occasion of his 60th birthday

The 1,3-dipolar cycloaddition of nitrones to alkenes[1] is an atom-economic method for the construction of isoxazolidines, which are important precursors of, for example, alkaloids, amino acids, β-lactams, and amino sugars.[2] Typically, an electron-deficient alkene is involved, with the interaction between the LUMO of the alkene and the HOMO of the nitrone being the determinant for the relative orientation of the reactants. However, steric factors often counterbalance the electronic preferences, particularly in β-unsubstituted enoyl (acryloyl) systems, and make regiocontrol challenging.[3,4] Additionally, both *endo*/*exo* and π-facial selectivity have to be addressed. Although amine activation of enals[5] has emerged as an attractive approach, most methods rely on the use of Lewis acids to activate the enoyl system toward the nitrone counterpart.[3,4,6] However, despite the many applications, success in asymmetric nitrone cycloadditions remains very scarce compared to that reached in the parent Diels–Alder cycloaddition and only a limited number of alkene templates such as *N*-enoyl derivatives of oxazolidinone,[4a–c,6c–6g] thiazolidinethione,[6a] pyrrolidinone,[6b] and pyrazolidinone,[6h] as well as certain alkylidene malonates[6i] have been employed to fulfill this gap. In metal-catalyzed nitrone cycloadditions, not only are bidentate alkene substrates required but also metal–substrate coordination needs to be notably efficient for optimum selectivity.[7] We report herein that excellent combined levels of regio-, *endo*/*exo*-, and enantioselectivity may be achieved by using α′-hydroxy enones as new partners for this reaction.

Recent observations from these laboratories in the context of Diels–Alder and conjugate addition reactions have shown the role of α′-hydroxy enones in metal-assisted activation, which likely occurs through formation of 1,4-metal-chelated species as the reactive intermediates.[8] It was argued that such a complexation pattern might be effective in nitrone cycloadditions and hence increase the pool of available templates for this reaction. To evaluate this assumption, initial screening reactions were carried out with the chiral α′-hydroxy enone **1**[9] and nitrone **3a** in the presence of several metal triflates (Scheme 1 and Table 1). Data



Scheme 1. Regio- and stereocontrolled 1,3-dipolar cycloadditions of nitrones to α′-hydroxy enones **1** and **2**. OTf = trifluoromethylsulfonyl.

Table 1: Screening of the catalyst for the reaction of enone **1** with nitrone **3a** (R^1 = Bn; Ar = Ph) to give **4a**.[a]

Lewis acid	*t* [h]	Conversion [%]	Regioisomer ratio[b]
$Mg(OTf)_2$	72	68[c]	12:88[d]
$Zn(OTf)_2$	48	81[c]	89:11[e]
$Cu(OTf)_2$	4	> 99	≥ 98:2[e]
$La(OTf)_3$	15	50	98:2[e]
$Yb(OTf)_3$	48	92[c]	85:15[e]

[a] Reactions conducted at room temperature in dry CH_2Cl_2, with 1:1:0.1 molar ratio of enone **1**/**3a**/Lewis acid. [b] Determined by ^1H NMR spectroscopy. [c] By-products from nitrone and enone decomposition were detected. [d] Minor isomer corresponds to **4a**; configuration of the major isomer not established. [e] Configuration of the minor isomer not established.

revealed that $Cu(OTf)_2$ gave the best results and isoxazolidine **4a** could indeed be obtained in high yield and, most notably, with essentially perfect regio- and diastereoselectivity.

Gratifyingly, the chemical efficiency and the high degree of regio- and stereocontrol for this $Cu(OTf)_2$-mediated reaction was found to be quite general over the range of nitrones **3a**–**k** examined (Table 2). Nitrones bearing electron-rich, electron-neutral, or electron-poor aryl substituents were tolerated with almost equal efficiency to give isoxazolidines **4a**–**k** in good yields and with diastereomeric ratios ranging

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Table 2: Asymmetric 1,3-dipolar cycloadditions of enones **1** and **2** with nitrones **3**.[a]

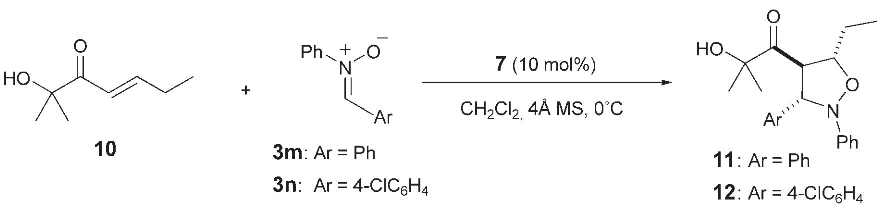
Nitrone 3	Ar	R^1	R	Product	t [h]	Yield [%][b]	d.r.[c]
3a	Ph	$PhCH_2$	H	**4a**	4	88	≥98:2
		$PhCH_2$	CH_3	**5a**	22[d]	84	≥98:2
3b	4-MeO-C_6H_4	$PhCH_2$	H	**4b**	24	68	≥98:2
3c	4-Me-C_6H_4	$PhCH_2$	H	**4c**	30[e]	70	≥98:2
			CH_3	**5c**	50[d]	70	≥98:2
3d	3-Me-4-Me-C_6H_3	$PhCH_2$	H	**4d**	8	83	≥98:2
3e	4-Cl-C_6H_4	$PhCH_2$	H	**4e**	9[e]	89	≥98:2
			CH_3	**5e**	48[d]	71	≥98:2
3f	3-Cl-C_6H_4	$PhCH_2$	H	**4f**	0.5	91	≥98:2
3g	3-Cl-4-MeO-C_6H_3	$PhCH_2$	H	**4g**	2	90	≥98:2
3h	4-CN-C_6H_4	$PhCH_2$	H	**4h**	28	76	94:6[f]
3i	3-NO_2-4-Me-C_6H_3	$PhCH_2$	H	**4i**	2	89	≥98:2
3j	Ph	Ph_2CH	H	**4j**	8	70	90:10[f]
3k	Ph	2-MeO-$PhCH_2$	H	**4k**	10	84	≥98:2

[a] Reactions conducted on 0.5-mmol scale in dry CH_2Cl_2, with 1:1:0.1 molar ratio of enone/nitrone/catalyst. [b] Yield of isolated product after column chromatography. [c] Determined by ^{13}C NMR spectroscopy. [d] In the presence of 4-Å molecular sieves and a 1:2:0.2 molar ratio of enone/nitrone/catalyst. [e] Using 5 mol% of $Cu(OTf)_2$. [f] Configuration of the minor isomer not determined.

from 90:10 to greater than 98:2. The reactions were typically carried out in dichloromethane as solvent using 10 mol% catalyst, although a loading of 5 mol% catalyst led to similar results (products **4c** and **4e**). β-Substituted enones also behaved well in terms of both chemical and stereochemical efficiency, although longer reaction times were required.[10] For example, the reaction of enone **2** with nitrones **3a**, **3c**, and **3e** provided cycloadducts **5a**, **5c**, and **5e** in good yields and with remarkable diastereoselectivity.

The scope of the model is further demonstrated in the catalytic, enantioselective 1,3-dipolar cycloaddition of nitrones to simple α′-hydroxy enone **6**[8] (Table 3). A preliminary survey of combinations of privileged ligands and metal salts[11,12] showed that the Evans bis(oxazoline)–Cu^{II} complex **7** (tBOX/Cu) was most successful in providing the nitrone cycloadducts **8/9** with very high stereoselectivity and with regioisomeric ratios equal to or greater than 90:10. To the best of our knowledge, this represents the highest combined regio- and enantioselectivity observed for β-unsubstituted enoyl substrates.[4,13] As an apparent limitation, however, the reaction of **6** with nitrone **3m** provided low *endo*/*exo* selectivity, although excellent regio- and enantiocontrol were still attained.

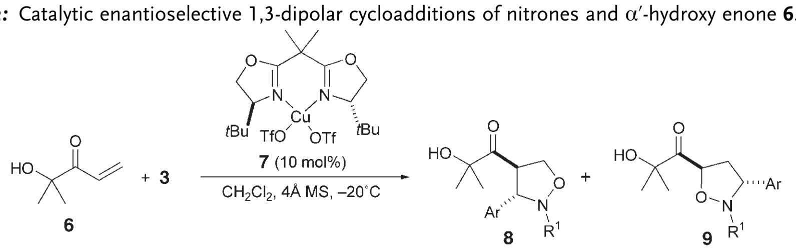
As differently β-substituted, simple hydroxy enones are readily available,[8] the method constitutes a straightforward route to 3,4,5-trisubstituted isoxazolidines of high diastereo- and enantiopurity. For instance, enone **10** reacted with nitrones **3m** and **3n** to give the respective isoxazolidines **11** and **12** with diastereomeric ratios of about 98:2 and enantioselectivities higher than 99% (Scheme 2).



Scheme 2. Enantioselective approach for β-substituted hydroxy enone substrates.

The assigned configuration of adducts **4**, **8**, **5**, and **9** was established by single-crystal X-ray analyses[14] of adducts **4a**, **5a**, **8m**, and **9a** (the configurations of the remaining adducts were assigned by analogy). Additionally, the absolute configuration of **8a** was deduced from comparison of the optical rotation values of elaborated adducts (see below) and by assuming a uniform reaction mechanism.

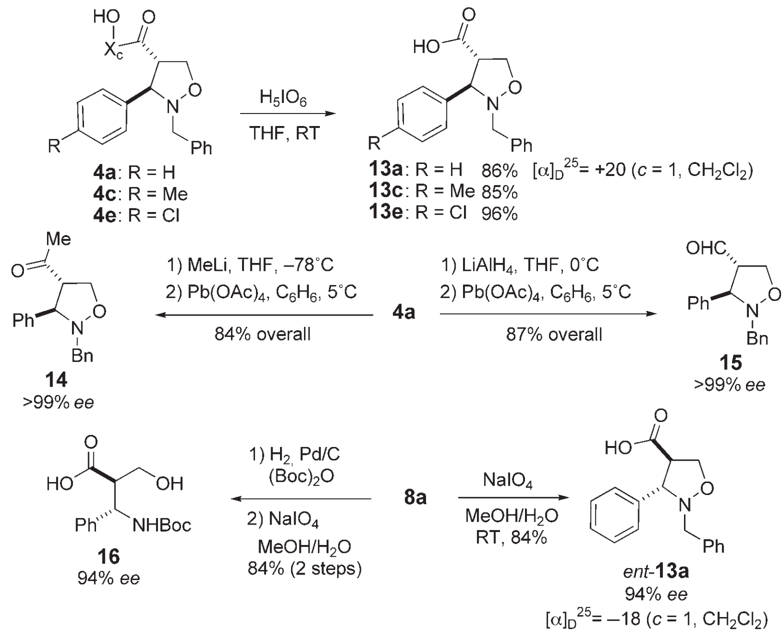
Table 3: Catalytic enantioselective 1,3-dipolar cycloadditions of nitrones and α′-hydroxy enone **6**.[a]



3	Ar	R^1	Yield [%]	Ratio **8**:**9**[b]	Product **8** *endo*/*exo*[c]	*ee* [%][d]
3a	Ph	$PhCH_2$	85	93:7	≥98:2	94
3b	4-MeO-C_6H_4	$PhCH_2$	99	92:8	≥98:2	92
3c	4-Me-C_6H_4	$PhCH_2$	81	92:8	≥98:2	92
3d	3-Me-4-Me-C_6H_3	$PhCH_2$	94	≥98:2	≥98:2	90
3e	Ph	CH_3	55	90:10	≥98:2	96
3f	Ph	Ph	98	≥98:2[e]	76:24	≥99

[a] Reactions conducted at 0.5-mmol scale in CH_2Cl_2 with a 2:1 molar ratio of **6**/**3**. [b] Determined by ^{13}C NMR spectroscopy; absolute configuration of **9** not determined. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC. [e] Reaction conducted at −40°C.

The potential utility of the method is illustrated in Scheme 3. For example, treatment of adducts **4a**, **4c**, and **4e** with periodic acid afforded the corresponding carboxylic acids **13** in high yields and essentially enantiopure form. Likewise, after addition of methyl lithium to **4a** and subsequent cleavage of the diol with lead tetraacetate, enantiopure acetylisoxazolidine **14** was obtained in 84% yield. Similarly, reduction of **4a** and further scission led to isoxazolidine carbal-



Scheme 3. Chemical elaboration of cycloadducts with detachment of the auxiliary X_c–OH. Bn = benzyl; Boc = *tert*-butoxycarbonyl.

dehyde **15**. In all the above examples, the starting (1*R*)-(+)-camphor was recovered after scission, ready for reuse. On the other hand, the oxidative elaboration of adduct **8a** gave *ent*-**13a** along with acetone as the only by-product, whereas hydrogenolytic opening of **8a** with concomitant *N*-protection (Boc) and further cleavage of the ketol afforded homoserine derivative **16** in two high-yielding steps. Of practical interest, both enantiomers of each isoxazolidine product are readily accessible by appropriate choice of the corresponding approach.

In conclusion, α′-hydroxy enones considerably expand the range of metal-catalyzed 1,3-dipolar cycloadditions of nitrones. Conditions have been set that produce the cycloadducts with very high combined levels of regio- and stereoselectivity. The potential of the method has been demonstrated using camphor-derived α′-hydroxy enone **1** in combination with catalytic $Cu(OTf)_2$, or achiral enones **6** and **10** in combination with the Evans bis(oxazoline)–Cu^{II} catalyst, and by the easy elaboration of the cycloadducts to diversely functionalized di- and trisubstituted isoxazolidines in essentially enantiopure form.

Experimental Section

General procedure for Cu^{II}/tBOX (**7**)-catalyzed 1,3-dipolar cycloadditions of nitrones to **6**: A flame-dried flask was charged with 2-hydroxy-2-methylpent-4-en-3-one (**6**; 0.114 g, 1.0 mmol) and dry CH_2Cl_2 (1.5 mL) under N_2. The solution was cooled to −20 °C, and then freshly dried, powdered molecular sieves (4 Å; 250 mg), a solution of the corresponding nitrone (0.5 mmol) in CH_2Cl_2 (1 mL), and a solution of **7** in CH_2Cl_2 (0.05 M, 1 mL) were added consecutively. The resulting mixture was stirred at −20 °C until completion of reaction. The reaction mixture was then diluted with 5 mL of ethyl acetate/hexane (1:1), and the solution was directly applied to a short column of silica gel (1.5 cm × 1.5 cm). Elution with a mixture of ethyl acetate and hexane (1:1), followed by concentration of the collected solution and subsequent purification by column chromatography (silica gel, 1:15 ethyl acetate/hexane), afforded the corresponding cycloadduct.

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[14] CCDC-280037–280040 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.