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An efficient diastereoselective glyoxylate-ene reaction using *N*-glyoxyloyl camphorpyrazolidinone as an enophile

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Abstract—The diastereoselective glyoxylate-ene reaction of *N*-glyoxyloyl camphorpyrazolidinone (**1**) with various alkenes **2a**–**g** in the presence of Lewis acid is described. The corresponding α-hydroxyl carbonyls were generally obtained in moderate to high chemical yields (64–87%) and with high levels of diastereoselectivities (up to 94% de). The predominance of products with the *S* absolute configuration at the newly formed stereogenic center was established by single crystal X-ray analysis and the importance of stereochemical induction is discussed.

The stereoselective formation of carbon–carbon bonds in Lewis acid-promoted ene reactions is one of the most challenging tasks and formidable endeavors of organic synthesis.[1] The glyoxylate variant of this reaction affords α-hydroxyl carbonyls, which are versatile synthons in organic synthesis.[2] In comparison with the well studied Diels–Alder reaction, the less favorable stereoelectronic factors that cause greater activation energies make the carbonyl-ene reactions less well known.[3] Enantioselective glyoxylate-ene reactions promoted by a catalytic amount of chiral Lewis acids have been reported.[4] In cases of a diastereoselective variant bearing a chiral auxiliary, such as reactions of glyoxylate esters derived from 8-phenylmenthol reacts with a broad variety of olefins in the presence of $SnCl_4$, have been investigated.[5] The attachment of an electron-withdrawing group to the carbonyl functionality is beneficial in ene reactions. In continuation of our interest in the development of camphor-based chiral auxiliaries and the synthetic utility thereof,[6] we wish to report on the glyoxylate-ene reaction of *N*-glyoxyloyl camphorpyrazolidinone (**1**) (a chiral 'enophile') with various reactive enes (1,1-disubstituted olefins) in the presence of a Lewis acid. Good to high stereoselectivities and yields were obtained. The mechanistic origin of stereochemical induction is discussed.

The starting*N*-glyoxyloyl camphorpyrazolidinone (**1**) was prepared from camphorpyrazolidinone from this laboratory and has been used in asymmetric synthesis.[7] Various Lewis acids were then screened using 2,4,4-trimethyl-1-pentene (**2a**) as a model ene component. When the reaction was carried out using metal triflates such as $Sm(OTf)_3$, $La(OTf)_3$, $Sn(OTf)_2$, and $Yb(OTf)_3$, the reaction rate was slow (entries 1–4). Reactivity was improved when $Cu(OTf)_2$ and $Eu(OTf)_3$ were used (entries 5 and 6). The diastereoselectivity of the ene product was determined based on ^1H NMR and HPLC analysis and the absolute stereochemistry of the newly generated stereogenic center in the major diastereomer was assigned as an *S* configuration by single crystal X-ray analysis (**3a** and **3g**). To our surprise, the reactivity was significantly improved when $Sc(OTf)_3$ was employed as a Lewis acid (entry 7). An examination of solvent effects revealed CH_2Cl_2 to be the solvent of choice for the reaction (entries 8–10). To further enhance stereoselectivity, the effect of Lewis acid loading was studied (entries 11–13). The optimum conditions involved the use of 0.3 equiv of $Sc(OTf)_3$ in CH_2Cl_2 (Table 1, entry 12).

To further examine the scope and feasibility of the system, various 1,1-disubstituted olefins were used in the reaction. The use of **2b** yielded a product with 74% de (entry 14). The use of methylenecyclopentane and methylenecyclohexane afforded the ene products with high stereoselectivity (entries 16 and 17). Excellent stereoselectivity (94% de) and high chemical yields were

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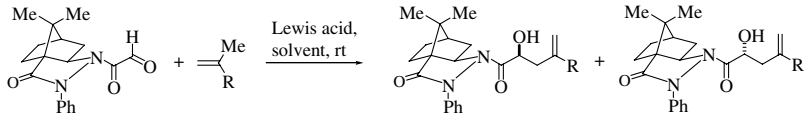
Table 1. Reaction of *N*-glyoxyloyl camphorpyrazolidinone (**1**) with various 1,1-disubstituted alkenes (**2a-g**) catalyzed by a Lewis acid[a]



1 **2a-g** **3a-g** **4a-g**

Entry	R =	Lewis acid (equiv)	Solvent	Time (h)	Yield (%)[b]	**3**:**4**[c]
1	**2a**: $-CH_2{}^tBu$	$Sm(OTf)_3$ (1.0)	CH_2Cl_2	72	<10	—
2	**2a**: $-CH_2{}^tBu$	$La(OTf)_3$ (1.0)	CH_2Cl_2	72	<10	—
3	**2a**: $-CH_2{}^tBu$	$Sn(OTf)_2$ (1.0)	CH_2Cl_2	72	<10	—
4	**2a**: $-CH_2{}^tBu$	$Yb(OTf)_2$ (1.0)	CH_2Cl_2	96	<10	—
5	**2a**: $-CH_2{}^tBu$	$Cu(OTf)_2$ (1.0)	CH_2Cl_2	48	62	76:23
6	**2a**: $-CH_2{}^tBu$	$Eu(OTf)_3$ (1.0)	CH_2Cl_2	48	55	84[d]:16
7	**2a**: $-CH_2{}^tBu$	$Sc(OTf)_3$ (1.0)	CH_2Cl_2	1	80	83:17
8	**2a**: $-CH_2{}^tBu$	$Sc(OTf)_3$ (1.0)	THF	24	39	—
9	**2a**: $-CH_2{}^tBu$	$Sc(OTf)_3$ (1.0)	CH_3CN	48	71	75:25
10	**2a**: $-CH_2{}^tBu$	$Sc(OTf)_3$ (1.0)	Toluene	24	18	—
11	**2a**: $-CH_2{}^tBu$	$Sc(OTf)_3$ (0.5)	CH_2Cl_2	24	71	84:16
12	**2a**: $-CH_2{}^tBu$	$Sc(OTf)_3$ (0.3)	CH_2Cl_2	24	73	89:11
13	**2a**: $-CH_2{}^tBu$	$Sc(OTf)_3$ (0.1)	CH_2Cl_2	24	25	—
14	**2b**: –*n*-Pr	$Sc(OTf)_3$ (0.3)	CH_2Cl_2	24	77	87:13
15	**2c**: $-CH_2OTBDPS$	$Sc(OTf)_3$ (0.3)	CH_2Cl_2	24	64	90:10
16	**2d**: Methylenecyclopentane	$Sc(OTf)_3$ (0.3)	CH_2Cl_2	24	64	95:05
17	**2e**: Methylenecyclohexane	$Sc(OTf)_3$ (0.3)	CH_2Cl_2	24	76	87:13
18	**2f**: $-C_6H_5$	$Sc(OTf)_3$ (0.3)	CH_2Cl_2	24	87	97:03
19	**2g**: $-C_6H_4p$-Cl	$Sc(OTf)_3$ (0.3)	CH_2Cl_2	24	85	97[d]:03

[a] All reactions were carried out using **1** (0.32 mmol) and activated alkene (3 equiv) in the solvent indicated.
[b] Isolated yield.
[c] Determined by both ^1H NMR analysis of the relevant peaks and HPLC analysis of the crude products.
[d] The absolute stereochemistry of the newly generated stereogenic center was determined to have an *S* configuration by single crystal X-ray analysis of **3a** and **3g**.

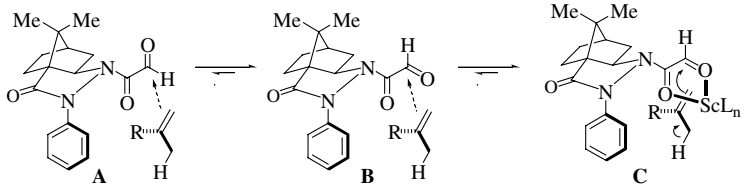


Figure 1. Proposed mechanism for the glyoxylate-ene reaction.

observed when 1,1-arylalkylethylenes were used (entries 18 and 19).

The stereochemical bias of the present study can be rationalized by the conformational preference of the glyoxylate moiety of the enophile in the transition state.[7] Similar to *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam,[8] the CO/CHO *s-cis* planar conformation (**B**) in **1** is electronically favored over its *s-trans* conformer (**A**) with the carbonyl group oriented toward the phenyl moiety (Fig. 1). The coordination of a Lewis acid with the dicarbonyl groups shifts the conformational equilibrium further toward the *s-cis* conformation (**C**).[9] The ene component then attacks the formyl group from the less hindered bottom *si* face, to afford the desired products. The relatively high stereoselectivity observed when 1,1-arylalkylethylenes were used can be attributed by the stabilization of the chiral glyoxylate phenyl group with the ene phenyl group.

In summary, the carbonyl-ene reaction of *N*-glyoxyloyl camphorpyrazolidinone (**1**) with a broad variety of 1,1-disubstituted olefins proceeds smoothly to give the corresponding ene products with high stereoselectivity. This chiral auxiliary provides a simple and efficient approach to the asymmetric synthesis of α-hydroxyl carbonyls in a high diastereomeric excess and in good chemical yields. Further synthetic applications of *N*-glyoxyloyl camphorpyrazolidinone (**1**) and its derivatives are currently underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.10.121.

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