Organic LETTERS

Letter

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Highly Enantioselective and *Anti*-Diastereoselective Catalytic Intermolecular Glyoxylate–Ene Reactions: Effect of the Geometrical Isomers of Alkenes

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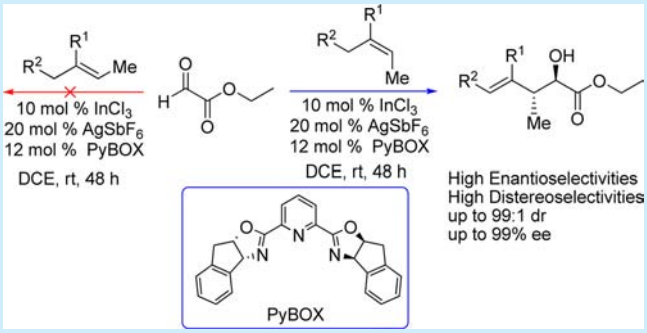
Supporting Information

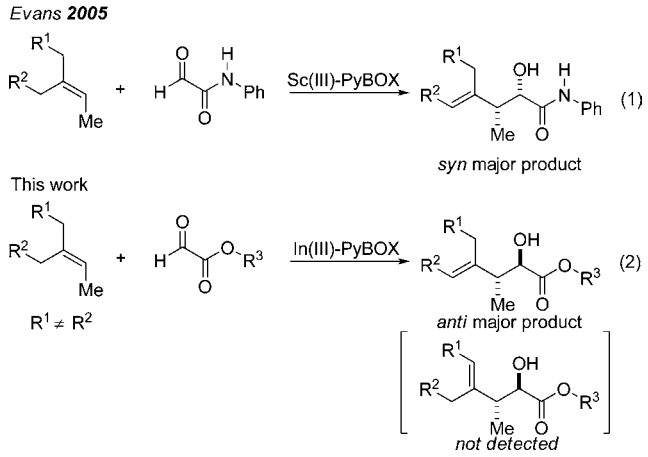
ABSTRACT: An efficient method for the synthesis of homoallylic alcohols with high enantioselectivities and *anti*-diastereoselectivities via an In(III)-catalyzed intermolecular glyoxylate–ene reaction has been developed. The geometrical isomers of alkenes were shown to have different reactivities. Only the isomers of the alkenes having a proton *β*-cis to the substituent reacted in this catalytic system.



Homoallylic alcohols are important building blocks for the synthesis of natural products and biologically active compounds.[1] Among the many methods available, the intermolecular carbonyl–ene reaction[2] is probably one of the best methods for the construction of C–C bonds due the ease of obtaining the starting materials as well as the atom-economic nature of the reaction. Since the first report by Yamamoto on the use of aluminum BINOL complex for the highly catalytic enantioselective carbonyl–ene reaction,[3] many groups have also developed different catalytic systems that afford high enantioselectivies. Elegant work by Mikami on the use of Ti–BINOL complex,[4] Evans' Cu–Box[5] and Sc–Box[6] complex systems, Jacobsen's Cr–Schiff complex,[7] Rawal's Co–Salen complex,[8] Feng's Ni–*N*′*N*′-dioxide complex,[9] and other systems have also been shown to be effective.[10−12] The use of an organocatalyst has also been recently reported by Macmillan's group.[13] In most of these cases, the enantioselective ene reactions studied involved the use of 1,1-disubstituted olefins. In contrast, only sporadic examples of diastereoselective and enantioselective intermolecular carbonyl–ene reactions using trisubstituted olefins to construct two or more stereogenic centers have been reported.[14] For this reaction to be a method of choice for the stereochemical construction of complex molecules, it is essential to access all the possible stereoisomers. While Evans[6] has reported a highly enantioselective *syn*-selective carbonyl–ene reaction, a general method for the highly enantioselective *anti*-diastereoselective carbonyl–ene using simple trisubstituted alkenes is not available. In light of our continuing interest in chiral indium complex catalyzed asymmetric ene reactions,[15] herein we report an indium-catalyzed intermolecular asymmetric glyoxylate–ene reaction between glyoxylates and trisubstituted alkenes with high *anti*-diastereoselectivities and enantioselectivities (Scheme 1). This study also revealed the different reactivities of the geometrical isomers of the alkenes used in this reaction.

To achieve this goal, the model reaction between (*E*)-but-2-en-2-ylbenzene (**1a**) and ethyl glyoxylate was first carried out to test the enantioselectivity and diastereoselectivity of this glyoxylate–ene reaction. The catalytic system of In(OTf)$_3$–

Scheme 1. Transition-Metal-Catalyzed Diastereoselective Carbonyl–Ene Reaction

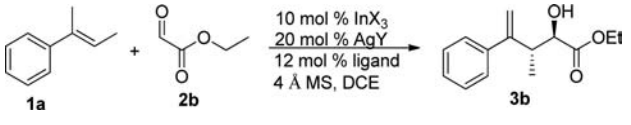


Received: April 20, 2015
Published: May 12, 2015

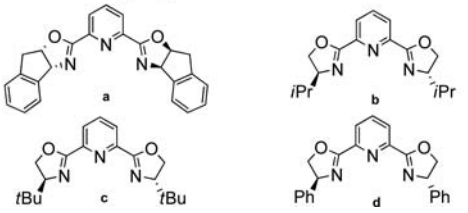
DOI: 10.1021/acs.orglett.5b01151
Org. Lett. 2015, 17, 2736–2739

PyBox developed previously for the carbonyl−ene reaction (entry 1) was first examined. Fortunately, the desired product **3a** could be obtained with good enantioselectivity (ee = 92%) albeit with only 26% yield. Considering the lower reactivity of trisubstituted alkenes as compared with 1,1-disubstituted olefins, a stronger Lewis acid catalyst is required. Therefore, the cationic indium catalysts generated in situ from different InX_3 and $AgSbF_6$ were explored (Table 1, entries 2−5). As expected, the

Table 1. Optimization of the Reaction Conditions[a]



entry	InX_3	AgY	ligand	yield (%)[b]	dr[c]	ee (%)[d]
1	$In(OTf)_3$	_	a	26	85:15	92
2	InF_3	$AgSbF_6$	a	64	75:25	85
3	**$InCl_3$**	**$AgSbF_6$**	**a**	**90**	**94:6**	**95**
4	$InBr_3$	$AgSbF_6$	a	95	87:13	92
5	InI_3	$AgSbF_6$	a	56	85:15	85
6	$InCl_3$	$AgSbF_6$	b	59	80:20	59
7	$InCl_3$	$AgSbF_6$	c	47	77:23	47
8	$InCl_3$	$AgSbF_6$	d	75	95:5	67
9[e]	$InCl_3$	$AgSbF_6$	a	37	94:6	95
10[f]	$InCl_3$	$AgSbF_6$	a	50	92:8	95
11	$InCl_3$	$AgBF_4$	a	49	70:30	90
12	$InCl_3$	$AgPF_6$	a	64	82:18	91
13	$InCl_3$	$AgClO_4$	a	60	87:13	88



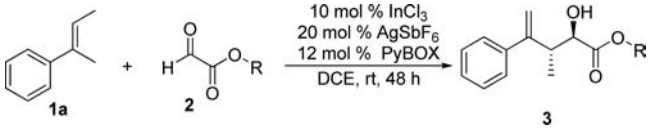
[a]Unless noted otherwise, reactions were carried out on a 0.3 mmol scale of **2b** with 2.0 equiv of olefins in 3.0 mL of anhydrous DCE for 48 h at room temperature. [b]Isolated yield. [c]The values of dr were determined by ^{1}H NMR. [d]The ee values of the major products were determined by chiral-phase HPLC analysis. [e]The reaction ran at 0 °C. [f]5 mol % of $InCl_3$, 6 mol % of PyBox, and 10 mol % of $AgSbF_6$ were used.

"counterion effect"[16] greatly enhanced the reaction's efficiency. Among the indium halides, both $InCl_3$ and $InBr_3$ were found to afford the desired products with good enantioselectivities (95%, 92% respectively), while a better diastereoselectivity was observed in the presence of $InCl_3$ (Table 1, entry 3). When other ligands were examined in this reaction, it was found that ligand **d** afforded the product in the highest diastereoselectivity (95:5) but with lower enantioselectivity (Table 1, entry 8).

Taking the influence of acidity due to the "non-coordinating" anion into account, diverse silver salts were also evaluated (Table 1, entries 11−13). The results indicated that the $AgSbF_6$ was more effective at controlling the enantioselectivity and diastereoselectivity. Finally, either lowering the temperature or reducing the catalyst loading greatly decreased the product yield, without damaging the enantioselectivity. As a result, the optimized reaction conditions were set as follows: 10 mol % of $InCl_3$, 20 mol % of $AgSbF_6$, and 12 mol % of Pybox ligand in the solvent of DCE at room temperature.

With the optimized reaction conditions in hand, different glyoxylates were screened to examine the ester substituent effect for this asymmetric glyoxylate−ene reaction. It was found that glyoxylates with linear ester substituents such as methyl, ethyl, and *n*-butyl groups could furnish the products in high yields with good enantioselectivities and diastereoselectivities. When bulky isopropyl glyoxylate was used, a 93% ee product could be obtained along with a decreased diastereoselectivity and yield (Table 2, entry 3).

Table 2. Screening of Various Glyoxylates[a−d]



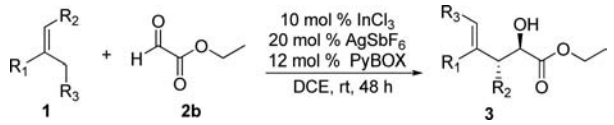
entry	glyoxylate	product	yield (%)	ee (%)	dr(%)
1		3a	85	89	93:7
2		3b	90	95	94:6
3		3c	75	93	85:15
4		3d	84	95	92:8

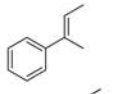
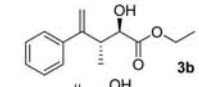
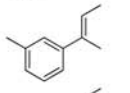
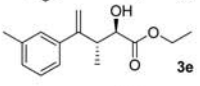
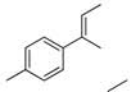
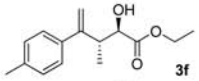
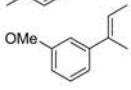
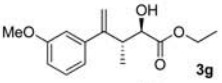
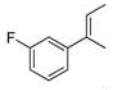
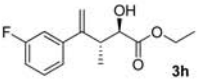
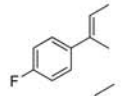
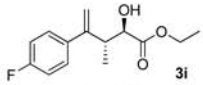
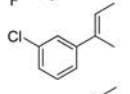
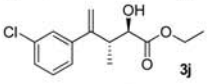
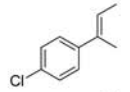
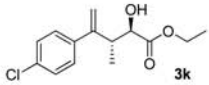
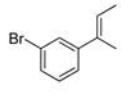
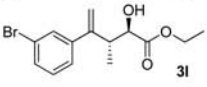
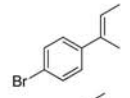
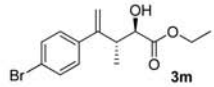
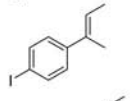
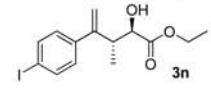
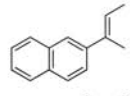
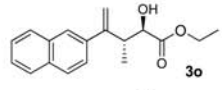
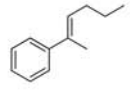
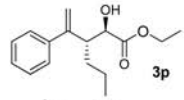
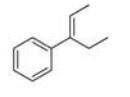
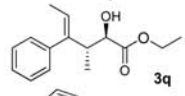
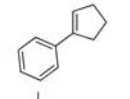
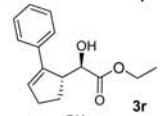
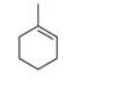
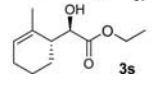
[a]Reactions were carried on 0.3 mmol scale of **2** with 2.0 equiv of olefins in 3.0 mL of anhydrous DCE for 48 h at room temperature. [b]Isolated yield. [c]The dr ratios were determined by ^{1}H NMR. [d]The ee values of the major product were determined by chiral-phase HPLC analysis.

Therefore, ethyl glyoxylate was chosen to test the scope of the trisubstituted alkenes. The results are shown in Table 3. In most cases, the desired homoallylic alcohol products could be obtained in moderate to good yields with high diastereoselectivities and enantioselectivities. Various substituents on the phenyl ring of alkenes were also investigated. The results showed that both the electron-donating and the electron-deficient groups were well tolerated in the substrates to give the corresponding products in good yields and diastereoselectivities and enantioselectivities. More importantly, the homoallylic alcohols with halide atoms such as F, Cl, Br, and even I on the phenyl ring all could be obtained in reasonable to high yields and good stereoselectivities. When (*E*)-2-(but-2-en-2-yl)naphthalene was used in the reaction, an excellent dr ratio (98:2) along with a 95% ee product could be observed. Next, the steric effect of the trisubstituted alkenes with changing R^2 and R^3 groups was examined. When the R^2 was a propyl group, the reaction proceeded smoothly and afforded the desired product in a slightly decreased yield but with high diastereoselectivity (99:1) and enantioselectivity (96% ee). Meanwhile, the selectivities were also good when R^3 was changed to an ethyl group. Furthermore, when cyclopentenylbenzene was employed in this reaction, the product **3r** could be obtained in 75% yield with an excellent enantioselectivity and a slightly diminished dr ratio (88:12). To our delight, this reaction was not only limited to

DOI: 10.1021/acs.orglett.5b01151
Org. Lett. 2015, 17, 2736−2739

Table 3. Screening of Different Trisubstituted Alkenes[a−d]



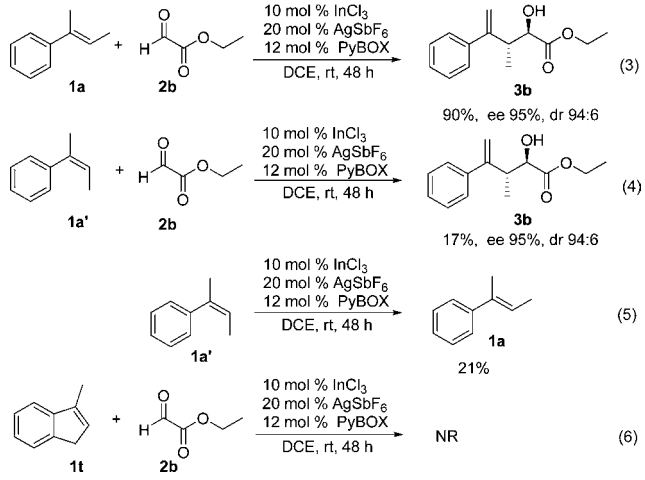
entry	olefin	product	yield (%)	ee (%)	dr(%)
1		 3b	90	95	94:6
2		 3e	86	95	94:6
3		 3f	88	92	88:12
4		 3g	83	95	94:6
5		 3h	57	96	93:7
6		 3i	73	96	91:9
7		 3j	81	95	93:7
8		 3k	78	96	92:8
9		 3l	80	89	92:8
10		 3m	80	97	92:8
11		 3n	55	94	91:9
12		 3o	88	95	98:2
13		 3p	65	96	99:1
14		 3q	65	92	91:9
15		 3r	75	99	88:12
16		 3s	76	97	94:6

[a]Unless noted otherwise, the reactions were carried out under the standard reaction conditions. [b]Isolated yield. [c]The dr ratios were determined by ^{1}H NMR [d]The ee values of the major products were determined by chiral-phase HPLC analysis.

aromatic-substituted alkene derivatives; the 1-methylcyclohex-1-ene was also successfully converted into the corresponding homoallylic alcohol in good yield with 97% ee and 94:6 dr.

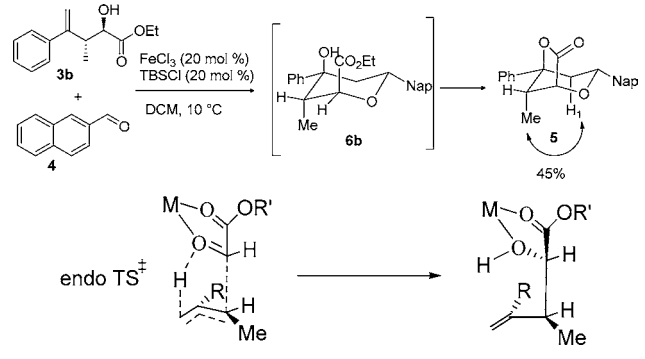
Finally, to understand this diastereoselective glyoxylate−ene reaction pathway, the influence of the steric configuration of olefins was investigated (Scheme 2). Only the alkene with *E*-

Scheme 2. Control Experiments To Investigate the Stereo Effect of Trisubstituted Alkenes for Ene Reaction



configuration **1a** could give the desired product in a high yield and excellent diastereoselectivity and enantioselectivity. When the *Z*-isomer *Z*-**1a**′ was applied in the reaction, only a 17% yield of product was obtained. Interestingly, the product ee and dr were the same as the reaction using ***E*-1a**. We envisage that this reaction proceeds via the *E*-isomer. Indeed, when pure *Z*-**1a**′ was subjected under the same reaction conditions, the isomerized *E*-**1a** was obtained in 21% yield. Next, we used the rigid cyclic alkene **1t** with no proton in the *β-cis* substituent. As expected, no desired product was obtained, further confirming the need to have a proton in the *β-cis* substitutent for this glyoxylate−ene reaction to proceed.

The *anti*-relative configuration of the diastereomers was confirmed by converting one of the products **3b** to the corresponding tetrahydropyran derivative **5** (refer to below).[17] The long-range ^{1}H coupling interaction between the methyl group in the axial position and the indicated proton was identified via 2D NMR spectroscopy analysis. To account for this observed selectivity, we proposed that this indium-catalyzed intermolecular ene reaction proceeded via an *endo* transition state.[5b]



In conclusion, we have developed a simple and efficient method for the synthesis of homoallylic alcohols with high

DOI: 10.1021/acs.orglett.5b01151
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enantioselectivities and *anti*-diastereoselectivities via an In-catalyzed intermolecular glyoxylate−ene reaction. The geometrical isomers of the alkenes were found to have a profound effect on the reactivity of the reaction. In this asymmetric carbonyl−ene reaction, the presence of a proton β-cis to the substituent of the alkene is essential for the high reactivity. This study provides useful information for the design of other ene-type reactions using specific heterosubstituted olefins to obtain homoallylic alcohols in high enantio- and *anti*-diastereoselectivities.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01151.

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Notes

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DOI: 10.1021/acs.orglett.5b01151
Org. Lett. 2015, 17, 2736−2739