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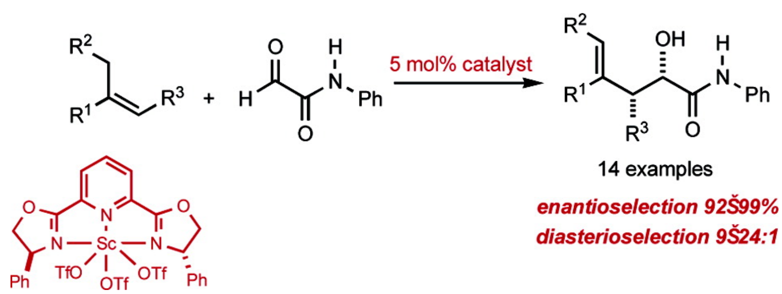

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Enantioselective Syn-Selective Scandium-Catalyzed Ene Reactions

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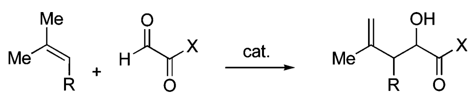
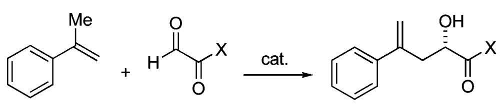
The carbonyl−ene reaction continues to be a powerful C−C bond forming reaction.[1] The first catalytic enantioselective variant using a chiral aluminum BINOL complex was reported by Yamamoto.[2] Subsequently, Mikami and others have reported the use of titanium-based BINOL complexes as efficient catalysts for the carbonyl−ene reaction.[3,4] Other metal cations that have also been used to effectively catalyze the asymmetric carbonyl−ene reaction include complexes derived from Co,[5] Pd,[6] Pt,[7] Cr,[8] Cu,[9] and several lanthanides.[10] The purpose of this Communication is to report that chiral scandium(III) complexes **4** and **5** are effective carbonyl−ene catalysts that afford excellent diastereoselectivities with trisubstituted olefins (eq 1). While there have been isolated reports in the literature of diastereoselective, carbonyl−ene reactions, these transformations have not been systematically explored.[3c,d,8a,11]

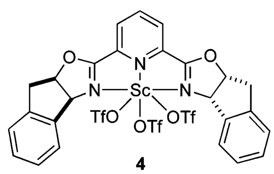


(1)



(2)

1 **2a**, X = OEt **2b**, X = NHPh **3**



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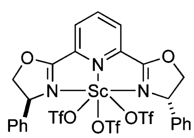
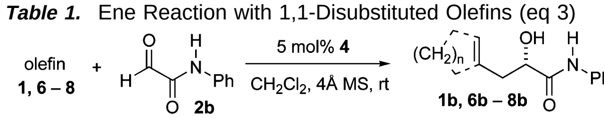


5

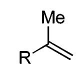
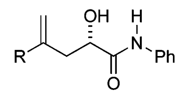
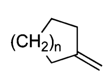
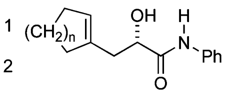
We have previously documented the utility of chiral scandium−pybox[12] complexes as effective Lewis acids exhibiting good chelating potential.[13] More recently, the application of these complexes to the catalysis of the Nazarov reaction has been reported.[14] These results suggested that trivalent scandium−pybox complexes might be effective promoters of the asymmetric, carbonyl−ene reaction. Accordingly, a survey of these complexes was conducted to evaluate the reaction between α-methylstyrene (**1**) with either ethyl glyoxylate (**2a**) or *N*-phenyl glyoxamide (**2b**) (eq 2).[15] From this screen, complexes **4** and **5** surfaced as attractive catalysts for reactions with olefins and glyoxamide **2b**. A benefit of using phenyl glyoxamide as the carbonyl component is that the desired products are routinely isolated as crystalline solids, a desirable attribute for large-scale reactions. This is the principal motivation for using this substrate in the present study.

Under optimized reaction conditions, a representative number of 1,1-disubstituted olefins were evaluated (Table 1). Good yields and high enantiomeric excesses (92−94% ee) were observed for each of the products formed when using α-methylstyrene, isobutylene, methylenecyclohexane, and methylenecyclopentane as nucleophiles. All products were isolated as crystalline solids.

Table 1. Ene Reaction with 1,1-Disubstituted Olefins (eq 3)

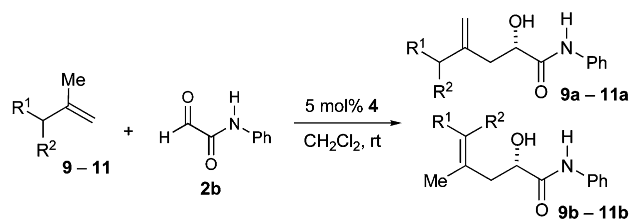


(3)

olefin		product		ee %[a]	yield %	mp °C
	**1**: R = Ph		**1b**	92	73	115
	6: R = Me		**6b**	94[b]	78	68
	**7**: n = 1		**7b**	94	99	80
	8: n = 2		**8b**	94	89	111

[a] Enantiomeric excesses were determined by HPLC using Chiracel OD-H or AD-H columns. [b] Absolute stereochemistry was determined by Mosher ester analysis. Remaining product configurations were assigned by analogy.

Next, we were able to demonstrate that the catalyst was capable of regioselective discrimination of substituents found on unsymmetrical, 1,1-disubstituted olefins (eq 4). Steric considerations seem to be the dominant factor in determining selectivity since the use of bulkier substituents led to increased regioselectivities. In each of these three cases, the product containing a terminal olefin was preferentially formed over the more highly substituted alkene.



(4)

9: R^1 = *i*-Pr, R^2 = H — 94% ee, 78% yield, 4:1 **9a**/**9b**
10: R^1 = R^2 = Me — 96% ee, 60% yield, 5.3:1 **10a**/**10b**
11: R^1 = *t*-Bu, R^2 = H — 94% ee, 81% yield, >99:1 **11a**/**11b**

Trisubstituted olefinic substrates introduce the possibility of simultaneously incorporating a second vicinal stereogenic center (eq 1). We were initially disappointed that the reaction of 2-methyl-2-butene (**12**), under standard conditions with complex **4**, yielded a 5:1 syn:anti mixture of diastereomers (97% ee). However, we were pleased to discover that the related [Sc(*S*,*S*)Phpybox)](OTf)$_3$ complex **5**, in the reaction of **12** with **2b**, afforded the ene product in high diastereoselectivity while simultaneously maintaining excellent enantiomeric excesses (13:1 syn:anti, 94% ee, Table 2). Similarly, the reactions of 3-ethyl-2-pentene, ethylidene cyclohexane, ethylidene cyclopentane, and 2-methyl-2-pentene with **2b**, catalyzed by complex **5**, afforded products with good syn selectivities and high enantiomeric excesses. Once again, all products were isolated as crystalline solids. This present methodology is complementary to the anti-selective, Cu(II)-catalyzed glyoxylate−ene reaction previously reported by our group.[9] This represents one of a

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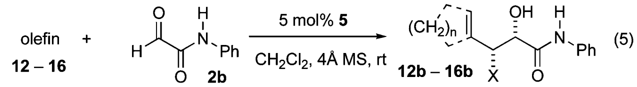
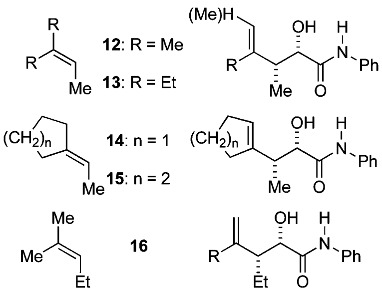
Table 2. Ene Reaction with Trisubstituted Olefins (eq 5)



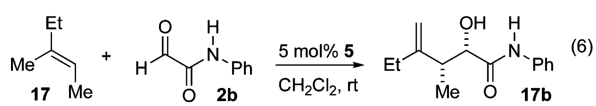


olefin	product	ee %[a]	yield %	dr	mp °C
12: R = Me	**12b**	94[b,c]	78	13:1	104
13: R = Et	**13b**	99	76	24:1	67
14: n = 1	**14b**	98	82	9.3:1	134
15: n = 2	**15b**	98[c]	78	9.3:1	133
16	**16b**	96[c]	58	9:1	87

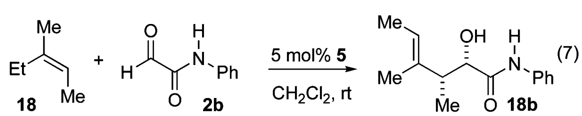
[a] Enantiomeric excesses were determined by HPLC using Chiracel OD-H or AD-H columns. [b] Absolute stereochemistry was determined by Mosher ester analysis. The remaining product configurations were assigned by analogy. [c] Syn stereochemistry was determined by single-crystal X-ray analysis. The remaining product configurations were assigned by analogy.

limited number of examples of enantioselective, syn-selective, ene reactions between glyoxylate derivatives and unactivated olefins.[16]

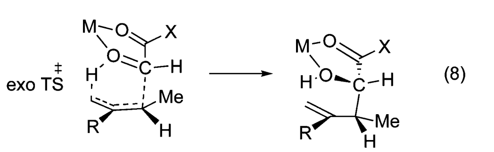
Finally, we were interested in determining if this catalyst was capable of simultaneously providing both regio- and diastereoselectivity. When olefin **17** was subjected to the standard reaction conditions with catalyst **5**, **17b** was produced in excellent enantio- and diastereoselectivity (eq 6). When the same reaction was carried out with its geometric isomer **18**, **18b** was also generated in excellent enantio- and diastereoselectivity (eq 7). In both of these experiments, we did not detect the presence of any regioisomeric products. The major product produced in both cases corresponds to proton transfer from the β-cis substituent through an exo transition state[17] (eq 8). The fact that regioselectivities are significantly enhanced when unsymmetrical trisubstituted olefins (eqs 6 and 7) are utilized suggests that the extra methyl group provides an important stereochemical control element in the transition state. The comparison of these results to the lower regioselectivities observed with 1,1-disubstituted olefins (eq 4) is noteworthy.



95% ee, 83% yield, 10:1 syn/anti

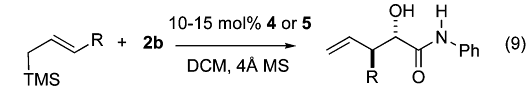


99% ee, 75% yield, 20:1 syn/anti



In our previous study of the glyoxylate ene reaction with the cationic [Cu(*t*-BuBox)](SbF_6)$_2$ complexes, a general preference for endo transition states was observed.[9] It is thus significant that a predisposition for exo transition states has been observed with scandium complex **5**.

As a complement to the present study, we have also found that convenient access to the anti glyoxylate ene-type adducts may be obtained in the Sc(III)-catalyzed reaction between **2b** and acyclic allylsilanes. This transformation affords the anti diastereomers in good yields and selectivities (eq 9). Further studies on both of these processes are ongoing.



19: R = Me — **19b**: 94% ee, 15:1 anti:syn, 71% yield

20: R = Ph — **20b**: 99% ee, >99:1 anti:syn, 68% yield

The *N*-phenylcarboxamides employed in this study may be readily activated for either hydrolysis or transesterification through their derived *N*-Boc imide analogues or through amide nitrosation.[18]

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Supporting Information Available: Experimental details and characterization data for all new compounds (PDF). Crystallographic data for **12b**, **15b**−**18b** and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

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