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Asymmetric Platinum Group Metal-Catalyzed Carbonyl-Ene Reactions: Carbon−Carbon Bond Formation versus Isomerization

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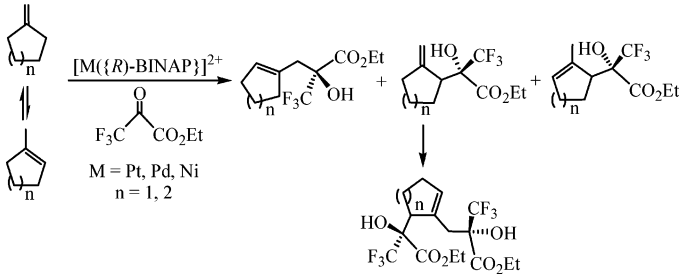

A comparative study of the carbonyl-ene reaction between a range of 1,1′-disubstituted or trisubstituted alkenes and ethyl trifluoropyruvate catalyzed by Lewis acid−platinum group metal complexes of the type [M{(*R*)-BINAP}]$^{2+}$ (M = Pt, Pd, Ni; BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) revealed subtle but significant differences in their reactivity. For instance, the palladium-based Lewis acid [Pd{(*R*)-BINAP}]$^{2+}$ catalyzes the ene reaction between methylene cycloalkane to afford the expected α-hydroxy ester in good yield and excellent diastereo- and enantioselectivity. In contrast, under the same conditions, the corresponding [M{(*R*)-BINAP}]$^{2+}$ (M = Pt, Ni) catalyzes isomerization of methylene cycloalkane and the ene reaction of the resulting mixture of methylene cycloalkane and 1-methylcycloalkene at similar rates to afford a range of α-hydroxy esters in high regioselectivity, good diastereoselectivity, and good to excellent enantioselectivity. In addition, [Pt{(*R*)-BINAP}]$^{2+}$ also catalyzes postreaction isomerization of the ene product as well as consecutive ene reactions to afford a double carbonyl-ene product. The sense of asymmetric induction has been established by single-crystal X-ray crystallography, and a stereochemical model consistent with the formation of (S)-configured α-hydroxy ester has been proposed; the same model also accounts for the observed exo-diastereoselectivity as well as the level of diastereoselectivity.

Introduction

The asymmetric carbonyl-ene reaction between a glyoxylate ester and an α-olefin is a powerful C−C bond forming reaction[1] that provides access to nonracemic synthetically versatile *β*,*γ*-unsaturated α-hydroxy esters (eq 1, R^3 = H).[2] This transformation has traditionally been catalyzed by a high-valent electrophilic early transition metal, a main group or lanthanide metal coordinated by a chiral multidentate protic nitrogen, and/or an oxygen-based ligand.[3] Since the first catalytic enantioselective variant of this reaction,[4] which used a chiral aluminum complex of enantiopure BINOL, a host of Lewis acids including those

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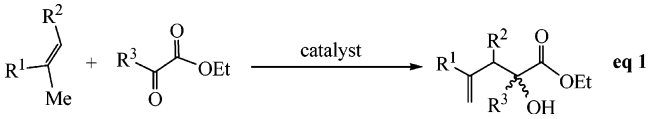
based on Ti,[5] Cr,[6] Co,[7] Cu,[8] various lanthanides,[9] and most recently Sc[1f] have proven to be highly efficient catalysts for this transformation, often giving excellent levels of regio-, enantio-, and diastereocontrol.



eq 1

Recently, square planar cationic metal complexes of the type [(diphosphine)M]$^{2+}$ (M = Pt, Pd, Ni) have emerged as an alternative and highly efficient class of Lewis acid catalyst[10] for a host of important enantioselective transformations including Diels−Alder[11] and hetero Diels−Alder reactions,[12] the enantioselective alkylation of α-imino esters,[13] 1,3-dipolar cycloadditions,[14] asymmetric Prins cyclizations,[15] the Conia-ene reaction,[16] and conjugate addition of amines to α,*β*-unsaturated *N*-alkenylimides,[17] as well as asymmetric reactions via palladium enolates[18] such as Michael reactions with enones,[19] Mannich-type reactions,[20] and the enantioselective fluorination of oxindoles,[21] *β*-ketoesters,[22] and *β*-keto phosphonates.[23] The properties of such complexes are inherently different from those of conventional Lewis acids, unique to the late transition metals, and include well-defined coordination geometries, high carbophilicity, functional group tolerance, slow rates of ligand exchange, and rational control of stereoelectronic properties through ligand modification. In this regard, Gagné et al. have investigated the thermodynamic and kinetic relationship between Lewis acid−Lewis base complexes relevant to the platinum(II)-catalyzed Diels−Alder reaction and have shown that the activity of late transition metal Lewis acid catalysts is controlled by ligand substitution rates rather than electrophilicity and that, despite being considered "soft", the late transition metal Lewis acids are highly electrophilic.[24]

These platinum group metal Lewis acids have also proven to be highly efficient catalysts for the carbonyl-ene reaction. In the first report, Hao et al. examined the influence of ligand, counterion, solvent, and temperature on the palladium-catalyzed glyoxylate-ene reaction and demonstrated that [Pd{(*S*)-Tol-BINAP}(MeCN)$_2$][SbF$_6$]$_2$ (BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, Chart 1) is a highly efficient catalyst at relatively high reaction temperatures.[25] Following this, Gagné reported that the platinum(II)-catalyzed ene reaction between methylene cyclohexane and ethyl glyoxylate was subject to marked anion dependent additive effects and that achiral acidic phenol additives accelerate the reaction of the triflate-based catalyst by disrupting contact ion pairs and sequestering traces of water.[26] While these early examples relied on the use of an enantiopure atropisomeric diphosphine such as BINAP or MeO-BIPHEP (BIPHEP is 2,2′-bis(diphenylphosphino)biphenyl) for efficient control of the stereochemistry, platinum group metal complexes of conformationally flexible diphosphines such as BIPHEP,[27] 1,1′-bis(diphenylphosphino)ferrocene (dppf), and NUPHOS[28] have also been used to control the stereochemical outcome of the carbonyl-ene reaction. For example, the enantiopure Lewis acid *λ*-[(BIPHEP)Pt](OTf)$_2$ catalyzes the carbonyl-ene reaction between methylene cyclohexane and ethyl glyoxylate to afford an enantiomeric excess (ee) of 72% compared to that of 74% obtained with [{(*S*)-MeO-BIPHEP}-Pd](OTf)$_2$.[29] Interestingly, control of axial and helical chirality in palladium complexes of the tropos diphosphine 2,4′,6′,2″-tetrakis(diphenylphosphino)-[1,1′,3′,1″]terphenyl (tetraphos) resulted in higher enantioselectivities and yields compared to those obtained with the corresponding BINAP-based catalyst.[30] In the case of Ni, Pd, and Pt complexes of dppf, which require coordination of enantiopure 2,2′-diamino-1,1′-binaphthyl for control of the axial chirality, the Ni/dppf combination proved to be significantly more efficient and enantioselective than either

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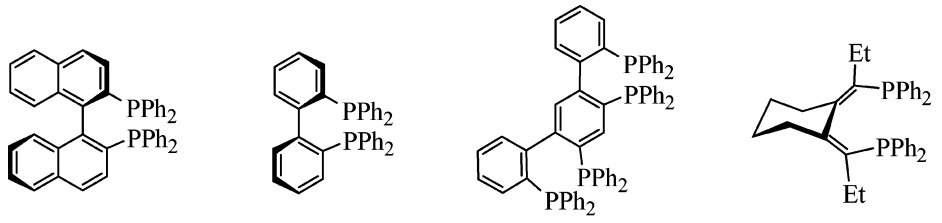
CHART 1



(*R*)-BINAP (*R*)-BIPHEP TETRAPHOS 1,4-Et_2-cyclo-C_6H_8-NUPHOS

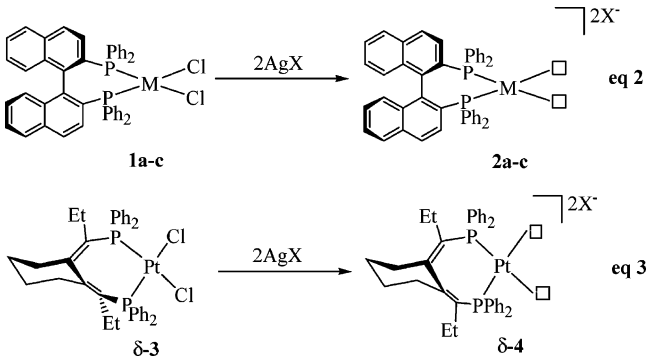
its palladium or its platinum counterparts.[31] In a related approach, we have resolved platinum metal complexes of conformationally flexible NUPHOS-diphosphines[32] [NUPHOS = 1,4-bis(diphenylphosphino)-1,2,3,4-tetrasubstituted-1,3-butadiene] and have shown the corresponding enantiopure Lewis acids δ- or λ-[(NUPHOS)Pt]$(SbF_6)_2$ to be highly efficient catalysts for the carbonyl-ene reaction between various 1,1′-disubstituted alkenes and phenyl glyoxal or ethyl glyoxylate, giving ee's that either rival or exceed those obtained with their atropisomeric counterparts.[33]

Although the carbonyl-ene reaction with glyoxylate esters has been thoroughly studied, the corresponding transformation with α-keto esters is less documented (eq 1, $R^3 = CH_3$, CF_3), which is somewhat surprising since it provides a straightforward route to nonracemic homoallylic tertiary alcohols. Evans et al. has reported that [Cu{(*S*,*S*)-*t*-Bu-box}][SbF_6]$_2$ catalyzes an enantioselective version of the ene reaction with pyruvate esters to afford excellent ee's, although acceptable yields were obtained only after careful optimization.[8a] Interestingly, Mikami and coworkers recently demonstrated that the "soft" Lewis acid [Pd{(*S*)-SEGPHOS}]$^{2+}$ [SEGPHOS = 4,4′-bi-1,3-benzodioxole-5,5′-diylbis(diarylphosphine)] possesses a favorable combination of electrophilicity and ligand substitution rates since it catalyzes the carbonyl-ene reaction of trifluoropyruvate to give high yields, *E*-alkene selectivity, anti-diastereoselectivity, and high enantioselectivities.[34]

During our ongoing investigations into the platinum group chemistry of NUPHOS diphosphines,[35] we had cause to investigate and compare the efficiency of [M(BINAP)]$^{2+}$ (M = Ni, Pd, Pt) as catalysts for the enantioselective carbonyl-ene reaction with ethyl trifluoropyruvate. Herein, we report the results of a systematic and detailed study which led to a number of significant and interesting discoveries including (i) highly efficient Lewis acid catalysis of the carbonyl-ene reaction by each member of the triad [M{(*R*)-BINAP}]$^{2+}$ (M = Ni, Pd, Pt), (ii) competitive Lewis acid-catalyzed isomerization of the ene substrate to afford a mixture of homoallylic products, (iii) Lewis acid-catalyzed isomerization of the resulting α-hydroxy esters, (iv) facile addition of the ene product to a second equivalent of α-keto ester to afford the product of a "double" carbonyl-ene reaction, and (v) highly efficient catalysis of the carbonyl-ene reaction with enantiopure Lewis acid complexes of the conformationally flexible NUPHOS diphosphine 1,2-bis-((1-diphenylphosphino)propylidene)cyclohexane (1,4-Et_2-*cyclo*-C_6H_8−NUPHOS), with ee's and yields that rival those obtained with their BINAP-based counterparts.

Results and Discussion

Since the carbonyl-ene reaction has been catalyzed by a host of Lewis acids, it was considered an ideal transformation to evaluate the relative merits of "soft" late transition metal catalysts. In this study, the addition of a range of mono-, di-, and trisubstituted alkenes to ethyl trifluoropyruvate has been investigated, the results of which are summarized in Tables 1−7. The Lewis acids [M{(*R*)-BINAP}]$^{2+}$ (M = Pt, **2a**; Pd, **2b**; Ni, **2c**) and δ-[Pt(1,4-Et_2-*cyclo*-C_6H_8−NUPHOS}]$^{2+}$ δ-(**4**) were all generated in situ by the addition of 2 equiv of a silver salt to a dichloromethane solution of the corresponding dichloride **1a**−**c** and δ-**3,** respectively (eqs 2 and 3). After stirring for 30 min at ambient temperature, the dienophile and alkene were added, and the progress of the reaction was monitored by GC. Although these reactions proceed in THF, 1,2-dichloroethane, and toluene, the ee's were all consistently lower than those obtained in dichloromethane, which was adopted as the solvent of choice.



In the first instance, the ene reaction between allyl benzene and ethyl trifluoropyruvate to afford α-hydroxy ester **5** was investigated using conditions similar to those developed by Mikami et al.,[34] the results of which are listed in Table 1. Each of the catalysts, **2a**−**c**, gave good conversions (76−92%) which

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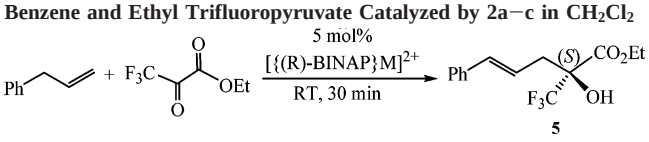
TABLE 1. Asymmetric Carbonyl-Ene Reaction between Allyl Benzene and Ethyl Trifluoropyruvate Catalyzed by 2a−c in CH_2Cl_2



5

entry[a]	catalyst (mol %)	time (min)	conversion[b] (%)	% ee[c] (config)
1	**2a** (5)	30	92	99 (*S*)
2	**2b** (5)	30	76	97 (*S*)
3	**2c** (5)	30	78	92 (*S*)

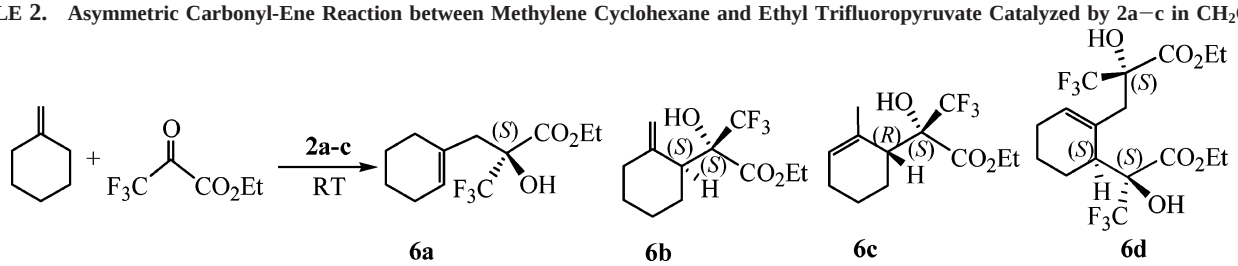
[a] Reaction conditions: 5 mol % catalyst, allyl benzene (0.4 mmol), and ethyl trifluoropyruvate (0.6 mmol) in 2.0 mL of CH_2Cl_2, room temperature. [b] Conversions determined by GC using a Supelco Beta DEX column. [c] Enantiomeric excess determined by chiral GC using a Supelco Beta DEX column. Average of three runs.

increase in the order Pt > Ni ≈ Pd, complete E selectivity, and excellent enantioselectivity (92−99% ee). This order of reactivity is interesting since Gagné et al. have recently commented on the relative activity of $[P_2Pd]^{2+}$ and $[P_2Pt]^{2+}$ (P_2 = dppe, BINAP) Lewis acid catalysts for transformations such as the Diels−Alder reaction and reasoned that catalyst activity is determined by ligand substitution rates rather than by electrophilicity.[24] In such cases, $[P_2Pd]^{2+}$ Lewis acids are more active than their platinum counterparts because ligand substitution rates are faster and not because the metal center is more electrophilic. Therefore, intuitively for reactions in which ligand exchange is rate-limiting, it should be possible to control catalyst activity by reducing the electrophilicity of the Lewis acid and consequently the strength of the metal-product bonding. This appears to be the case for the Lewis acid platinum-catalyzed glyoxylate-ene reaction in which activity was found to increase with increasing phosphine basicity.[26]

Lewis acids **2a**−**c** also catalyze the addition of methylene cyclohexane to ethyl trifluoropyruvate, full details of which are provided in Table 2. Surprisingly, **2a** catalyzed the ene reaction between methylene cyclohexane and ethyl trifluoropyruvate to afford the expected α-hydroxy ester **6a** together with three unanticipated byproducts, **6b**−**d**, which were separated by column chromatography and identified by a combination of ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. While α-hydroxy ester **6a** is the product of an ene reaction between ethyl trifluoropyruvate and methylene cyclohexane, **6b** and **6c** are regioisomers that result from the corresponding ene reaction with 1-methylcyclohexene, generated in situ via Lewis acid-catalyzed isomerization of methylene cyclohexane, and **6d** is a double ene product formed by addition of **6a** and/or **6b** to ethyl trifluoropyruvate (Scheme 1). Thus, the distribution of α-hydroxy esters obtained from the reaction between methylene cyclohexane and ethyl trifluoropyruvate most likely reflects the relative rates of isomerization versus ene reactivity. The data in Table 2 reveal that catalyst **2a** exhibits good enantioselectivity (77% ee) for the expected α-hydroxy ester **6a**. For the mono-ene products derived from the isomerized alkene, catalyst **2a** gives moderate regioselectivity in favor of **6b** (ca. 4.7:1), low to high diastereoselectivity, and excellent enantioselectivity for **6b** and **6c** (Table 2, entry 1). The double ene product, **6d**, is formed in high diastereoselectivity (91% diastereomeric excess (de)). The moderate regioselectivity is not surprising since Evans et al. have demonstrated that steric considerations are an important factor in determining selectivity for copper complexes of bis(oxazolines) with bulkier substituents on the alkene leading to increased selectivities.[8a] In the case of 1-methylcyclohexene, the catalyst−pyruvate complex must discriminate between the methyl substituent and the α-CH_2 of the cyclohexyl ring. High levels of regioselective discrimination of substituents in 1,1-disubstituted alkenes have recently been achieved with Lewis acid scandium catalysts based on pyridine bis(oxazolines), which also gave excellent regio- and diastereoselectivities with trisubstituted alkenes.[1f] Similar levels of regioselectivity have also been obtained for carbonyl-ene reactions catalyzed by optically active cationic cobalt(III) complexes of β-ketoimines.[6]

While the **6b**:**6c** ratio of 4.7:1 may correspond to the regioselectivity of the carbonyl-ene reaction, we must consider that **6b** could subsequently isomerize to **6c** and/or undergo a further ene reaction to afford **6d** (Scheme 1), both of which would lead to an artificially low regioselectivity. To investigate this possibility, a dichloromethane solution of Lewis acid **2a** (5 mol %), α-hydroxy ester **6b** (ca. 0.3 M), and ethyl trifluoropyruvate (1.5 equiv) was stirred at room temperature, and the composition was monitored as a function of time. The 48:7:45 distribution of **6b**−**d** present after 2 h confirms that while **6b** isomerizes to **6c,** it undergoes a much faster addition to ethyl trifluoropyruvate to afford the double ene product **6d**. Since isomerization of **6b** is relatively slow, the reaction between methylene cyclohexane and ethyl trifluoropyruvate was sampled and analyzed after 1 min, and the **6b**:**6c** ratio of 46:1 should be taken as a more reliable measure of the regioselectivity (Table 2, entry 7). Lewis acid **2a** also catalyzed the ene reaction between **6a** and ethyl trifluoropyruvate, albeit much more slowly than **6b** as evidenced by the **6a**:**6d** ratio of 96:4 present after 2 h, thereby confirming that the primary pathway to **6d** is via the addition of **6b** to a second equivalent of ethyl trifluoropyruvate. The (2S,3′S,1″S) configuration of the major diastereoisomer of **6d** (Table 2) is based on approach of (1′*S*,2*S*)-**6b** (an assignment based on the X-ray structure determinations of **10** and **8b**) to the preferred face of the platinum-coordinated ethyl trifluoropyruvate. The composition of a typical reaction mixture, monitored as a function of time (Figure 1), clearly shows that **6b** slowly isomerizes to **6c** and eventually approaches equilibrium and that the double ene product **6d** gradually increases to a maximum level, which presumably corresponds to the complete consumption of ethyl trifluoropyruvate. Examination of the product distribution from this experiment also revealed that the major exo-diastereoisomer of **6b** with (1′S,2S) configuration isomerizes to (1′*S*,2*S*)-**6c**, which corresponds to the minor endo-diastereoisomer from the ene reaction between 1-methylcyclohexene and ethyl trifluoropyruvate (note, the major exo-diastereoisomer of **6c** from the ene reaction of 1-methylcyclohexene has a (1′R,2S) configuration). Thus, the exo:endo ratio of 6:4 determined after 1 min most likely reflects the intrinsic diastereoselectivity of this addition (Table 2, entry 7), whereas the ratio of 1:2 after 30 min (Table 2, entry 1) is artificially high in favor of the endo-diastereoisomer because of the isomerization of (1′*S*,2*S*)-**6b**. In this regard, the relative stereochemistry and absolute configurations of these products, assigned by analogy with the single-crystal X-ray structures of **8b** and **10**, are entirely consistent with the transition state models used to rationalize the stereochemical outcome of these transformations (vide infra). Interestingly, there was no evidence for isomerization of **6b** in the absence of ethyl trifluoropyruvate which suggests that [**2a**-pyruvate]$^{2+}$ is the active isomerization catalyst. As expected, higher yields of the double ene product were obtained when the amount of ethyl trifluoropyruvate was

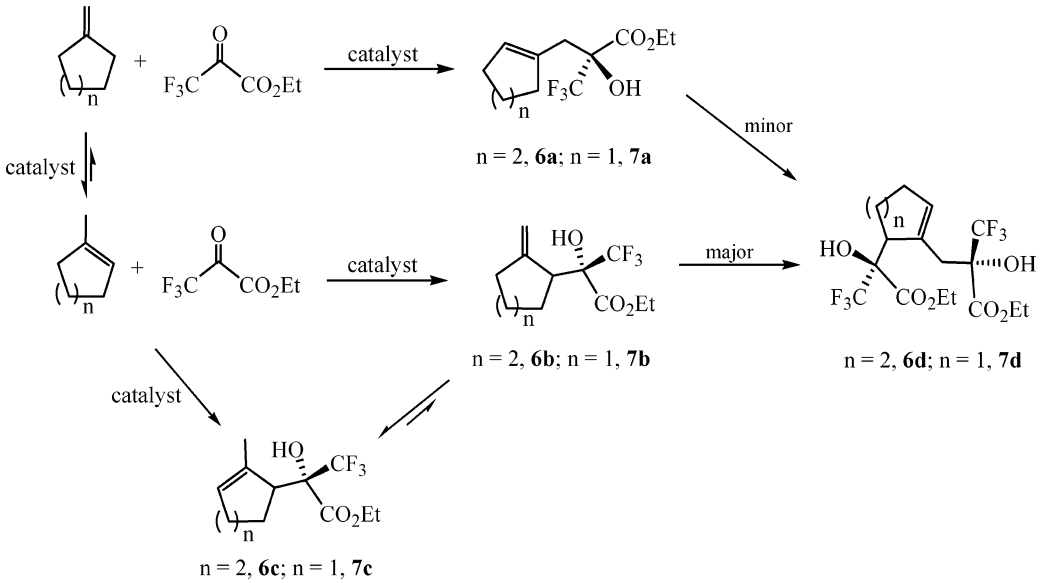
TABLE 2. Asymmetric Carbonyl-Ene Reaction between Methylene Cyclohexane and Ethyl Trifluoropyruvate Catalyzed by 2a−c in CH_2Cl_2



entry[a]	catalyst (mol %)	X^-	time (min)	conv[b] (%)	product ratio[c] **6a**:**6b**:**6c**:**6d**	exo:endo ratio[d] **6b**	**6c**	% ee[e] **6a**	**6b**	**6c**	% de[f,g] **6d**
1	**2a** (5)	SbF_6	30	100	38:47:10:5	>99:1	1:2	77	99	99, 98	91
2	**2b** (5)	SbF_6	30	100	100:0:0:0			93			
3	**2c** (5)	SbF_6	30	100	57:40:2:1	>99:1	1:2	74	99	86, 82	92
4	**2a** (1)	SbF_6	30	79	36:49:10:5	>99:1	2:1	76	99	99, 98	99
5	**2a** (0.5)	SbF_6	30	68	37:48:10:5	>99:1	1:2	76	99	99, 98	99
6	**2a** (0.2)	SbF_6	120	80	36:49:10:5	>99:1	1:1	77	99	99, 96	99
7	**2a** (5)	SbF_6	1	>99	53:46:1:0	>99:1	6:4	77	99	99, 96	
8	**2b** (5)	SbF_6	1	>99	100:0:0:0			94			
8	**2c** (5)	SbF_6	1	>99	59:40:1:0	>99:1	1:1	75	99	86,83	
9	**2a** (5)	BF_4	30	82	61:36:2:0	>99:1	4:6	82	99	99, 87	
10	**2a** (5)	ClO_4	30	8	29:71:0:0	nd	nd	53	99		
11	**2a** (5)	OTf	30	3	nd	nd	nd	nd	nd	nd	nd
12	δ-**4** (5)	SbF_6	10	100	43:55:1:1	>99:1	3:2	70[h]	99[h]	99[h], 99[h]	77[h]

[a] Reaction conditions: 5 mol % catalyst, methylene cyclohexane (0.4 mmol), and ethyl trifluoropyruvate (0.6 mmol) in 2.0 mL of CH_2Cl_2, room temperature. [b] Conversions determined by GC using a Supelco Beta DEX column. [c] Product ratios determined by ^{1}H NMR spectroscopy. [d] exo:endo ratio determined by ^{1}H NMR spectroscopy and chiral GC and assigned by analogy with the X-ray crystal structure of **8b**. [e] Enantiomeric excess determined by chiral GC using a Supelco Beta DEX column and listed either as % ee exo in cases where the ee of the minor endo diastereoisomer was not determined or as % ee exo, % ee endo. [f] Diastereoisomeric excess determined by chiral GC using a Supelco Beta DEX column. [g] Minor enantiomers were not detected. [h] Opposite enantiomer to that shown in the table figure. Average of three runs; nd = not determined.

SCHEME 1



increased, but in general, reactions were performed with 1.5 equiv of enophile.

Table 2 shows that the product distribution also depends on the metal center. Lewis acid **2c** (M = Ni) gave α-hydroxy ester **6a** in good yield and moderate enantioselectivity (74% ee) and gave **6b** in high diastereoselectivity and enantioselectivity, as the major components, together with minor amounts of **6c** as a near 1:1 mixture of diastereoisomers in good enantioselectivity and double addition product **6d** in high diastereoselectivity (Table 2, entry 3). In stark contrast, catalyst **2b** (M = Pd) gave α-hydroxy ester **6a** as the sole product in 93% ee, which is a marked improvement on those of 77 and 74% obtained with **2a** and **2c**, respectively (Table 2, entry 2). The different product distributions obtained with catalyst **2b** compared with **2a**,**c** are most likely associated with a change in the relative rates of isomerization and ene reactivity, particularly since a comparative study has shown Lewis acid **2a** to be a more efficient isomerization catalyst than **2b**. In this regard, [Pd{(*S*)-SEGPHOS}]$^{2+}$ has previously been reported to catalyze the ene reaction between methylene cyclohexane and ethyl trifluoropyruvate to afford **6a** as the sole product in 96% ee.[34] Unfortunately, the corresponding reaction catalyzed by [Pt{(*S*)-

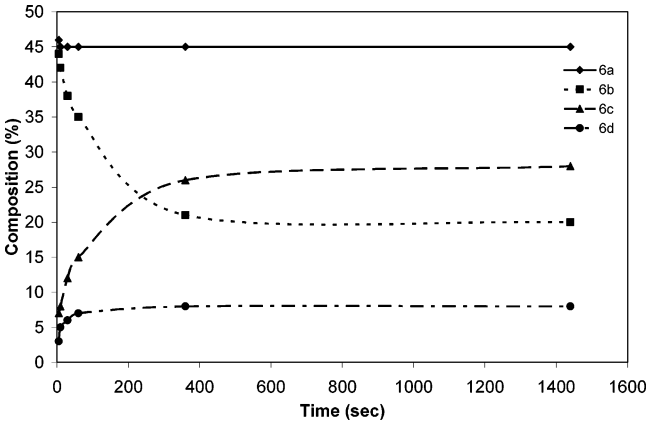


FIGURE 1. Variation of the percent composition for the carbonyl-ene reaction between methylene cyclohexane and ethyl trifluoropyruvate catalyzed by [Pt{(*R*)-BINAP}][SbF_6]$_2$ (**2a**) in dichloromethane with respect to time at room temperature.

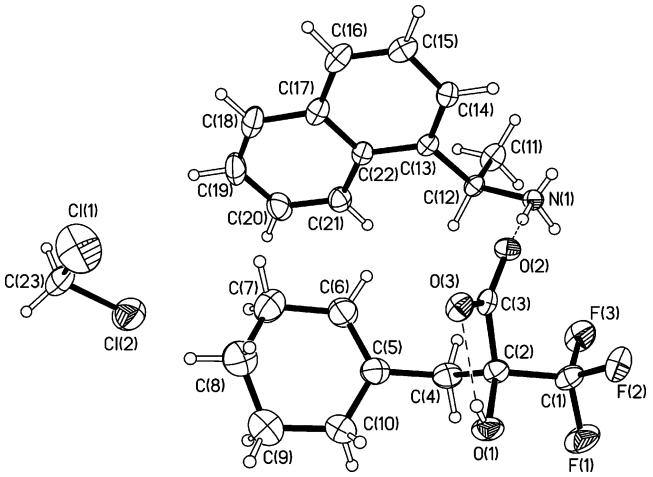


FIGURE 2. Asymmetric unit of (*R*)-1-(1-naphthyl)ethylammonium (2*S*)-3-(cyclohexen-1-yl)-2-(trifluoromethyl)-2-hydroxypropanoate dichloromethane solvate (**10**), with 40% probability displacement ellipsoids, showing the absolute stereochemistry of C(2) to be of S configuration. Hydrogen bonds within the asymmetric unit are shown as dashed lines.

SEGPHOS}]$^{2+}$ was not reported for comparison. The absolute configuration of **6a** was determined by hydrolysis to the free acid (**9**) and a single-crystal X-ray structure determination of its (*R*)-1-naphthylethylammonium salt (**10**), shown in Figure 2.[36] The relative stereochemistry and absolute configurations of α-hydroxy esters **6b**−**d** are based on analogy with this structure and that of **8b**, which was also determined by single-crystal X-ray crystallography (see below).

A limited study of the influence of the counterion on the Lewis acid-catalyzed reaction between methylene cyclohexane and ethyl trifluoropyruvate revealed a marked effect on conversion and enantioselectivity with catalyst performance generally increasing in the order $SbF_6^- \approx BF_4^- > ClO_4^- > TfO^-$ (Table 2, entries 9−11); this is consistent with previous reports including the platinum-catalyzed glyoxylate-ene reaction[26] and the ruthenium-catalyzed Diels−Alder reaction between methacrolein and cyclopentadiene.[37] In an examination of the catalyst loading using methylene cyclohexane and [Pt{(*R*)-BINAP}]-[SbF_6]$_2$ (Table 2, entries 4−6), it was found that loadings as low as 0.2 mol % may be used (80% conversion in 2 h); however, reactions were routinely performed with 5 mol % catalyst, for practical reasons. The effect of temperature on the performance of catalyst **2a** was also investigated since it consistently gave the lowest enantioselectivity in the carbonyl-ene reaction with methylene cyclohexane. The enantioselectivity improved at low temperatures, and at −78 °C, the ee of 80% was marginally higher than that of 77% obtained at room temperature.

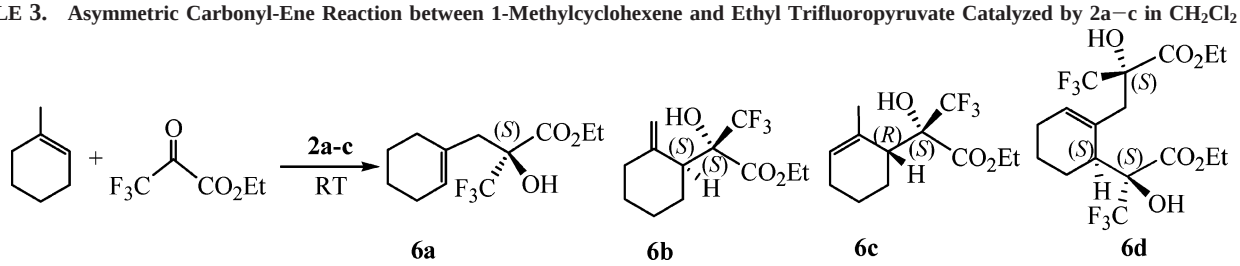
A low temperature ^{31}P and ^{1}H NMR study (213 K) on a dichloromethane solution containing [Pt{(*R*)-BINAP}][SbF_6]$_2$ and 10 equiv of ethyl trifluoropyruvate identified the catalyst−substrate complex [Pt{(*R*)-BINAP}·(pyruvate)]$^{2+}$. Two doublets at 4.8 and 2.7 ppm with a J_{PP} value of 25.0 Hz and Pt−P coupling constants of 4190 and 4039 Hz indicate that the dienophile binds to platinum in the expected κ(O),κ(O) bidentate manner through its carbonyl oxygen atoms and that one of the Pt−O═C bonds is stronger than the other. In addition, two sharp triplets at δ 1.33 and 1.13 in the low temperature ^{1}H NMR spectrum correspond to free and coordinated ethyl trifluoropyruvate, respectively, and confirm that exchange is slow on the NMR time scale. A minor resonance at 1.8 ppm was associated with residual [Pt{(*R*)-BINAP}][SbF_6]$_2$ and corresponds to a K_{eq} of approximately 100 calculated via integration of the ^{31}P resonances. These data are similar to those recently reported[24] for [Pt{(*R*)-BINAP}(acryloyl-*N*-oxazolidinone)]$^{2+}$ and are consistent with activation of the dienophile via a traditional Lewis acid mechanism, as proposed in the transition model used to rationalize the stereochemical outcome of these transformations (vide infra). Addition of methylene cyclohexane to the solution used for these NMR studies resulted in a rapid reaction to afford α-hydroxy esters **6a**−**d** in the same ratio and with enantioselectivities and diastereoselectivities similar to those listed in Table 2, suggesting that we may be observing the active catalyst−substrate complex.

A comparative study between Lewis acid **2a** and the enantiopure NUPHOS-based catalyst δ-[(1,4-Et_2-*cyclo*-C_6H_8−NUPHOS)Pt]$^{2+}$ δ-(**4**) was carried out for the ene reaction between methylene cyclohexane and ethyl trifluoropyruvate to evaluate the relative merits of atropos and tropos diphosphines. Under similar conditions, Lewis acid δ-**4** afforded α-hydroxy ester **6a** in a 71% ee, regioisomeric ene products **6b** and **6c** in moderate-to-high diastereoselectivity and excellent enantioselectivity, and double ene product **6d** in moderate diastereoselectivity (77% de, Table 2, entry 12). Moreover, the regiose-

(36) Crystal data for (*S*)-**6a**: $C_{12}H_{14}N^+ \cdot C_{10}H_{12}F_3O_3^- \cdot CH_2Cl_2$, M_r = 494.4, monoclinic, space group $P2_1$, a = 12.8271(18), b = 6.6780(7), c = 15.6221(18) Å, β = 113.549(8)°, V = 1226.7(3) Å^3, Z = 2, ρ_{calcd} = 1.338 g cm^{-3}, T = 150 K; crystal size 0.42 × 0.10 × 0.10 mm^3, Mo Kα radiation, λ = 0.710 73 Å, μ = 0.31 mm^{-1}, transmission 0.880−0.970 by multi-scan methods, $2\theta_{max}$ = 25°, Nonius Kappa CCD diffractometer, 14 780 measured data, 4155 unique reflections, R_{int} = 0.039; standard direct methods and full-matrix least-squares refinement on all unique F^2 values, NH and OH H atoms freely refined, CH H atoms riding, R (3463 F values with $F^2 > 2\sigma$) = 0.048, R_w (all F^2 values) = 0.121, goodness-of-fit = 1.10, 2-fold disorder resolved for solvent molecule, final difference map extremes +0.30 and −0.28 e Å^{-3}, absolute structure parameter 0.01(9). Programs: Nonius COLLECT and EvalCCD, Bruker SADABS and SHELXTL. CCDC 615959 (*S*-**6a**), CCDC 615960 (*S*,*S*-**8b**), and CCDC 615961 (**1a**) 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 (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax (+44) 1223−336.-033; or deposit@ccdc.cam.uk).

(37) (a) Kündig, E. P.; Suadan, C. M.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1220. (b) Kumar, P. G. A.; Pregosin, P. S.; Vallet, M.; Bernardinelli, G.; Jazzar, R. F.; Viton, F.; Kündig, E. P. *Organometallics* **2004**, *23*, 5410.

TABLE 3. Asymmetric Carbonyl-Ene Reaction between 1-Methylcyclohexene and Ethyl Trifluoropyruvate Catalyzed by 2a−c in CH_2Cl_2



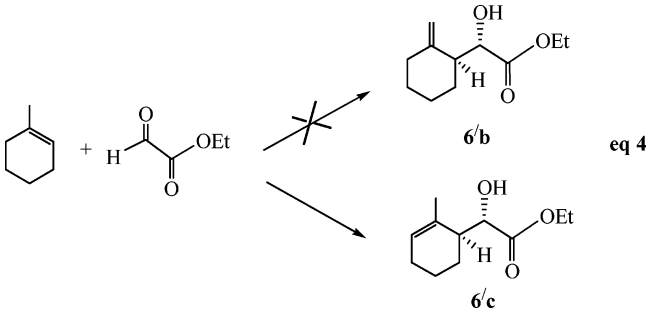
				product ratio[c]	exo:endo ratio[d]		% ee[e]			% de
entry[a]	catalyst (mol %)	time (min)	conv[b] (%)	**6a**:**6b**:**6c**:**6d**	**6b**	**6c**	**6a**	**6b**	**6c**	**6d**
1	**2a** (5)	30	>99	2:91:7:0	> 99:1	1:2	78	>99	99, 96	
2	**2a** (5)	1	98	3:92:5:0	>99:1	2:1	75	>99	99, 97	
3	**2b** (5)	30	93	1:81:18:0	>99:1	3:1	96	99	96, 94	
4	**2c** (5)	30	100	1:98:1:0	>99:1	3:1	77	>99	79, 84	
5	δ-**4** (5)	30	100	4:95:1:0	>99:1	2:1	74[f]	>99[f]	95[f], 92[f]	

[a] Reaction conditions: 5 mol % catalyst, 1-methylcyclohexene (0.4 mmol), and ethyl trifluoropyruvate (0.6 mmol) in 2.0 mL of CH_2Cl_2, room temperature. [b] Conversions determined by GC using a Supelco Beta DEX column. [c] Product ratios determined by ^{1}H NMR spectroscopy. [d] exo:endo ratio determined by ^{1}H NMR spectroscopy and chiral GC and assigned by analogy with the X-ray crystal structure of **8b** [e] Enantiomeric excess determined by chiral GC using a Supelco Beta DEX column and listed either as % ee exo in cases where the ee of the minor endo diastereoisomer was not determined or as % ee exo, % ee endo. [f] Opposite enantiomer to that shown in the table figure. Average of three runs.

lectivity of 55:1 is comparable to that of 46:1 obtained with its (*R*)-BINAP counterpart (Table 2, entry 7). Comparison of the GC retention times revealed that δ-[(1,4-Et_2-*cyclo*-C_6H_8−NUPHOS)Pt]$^{2+}$ δ-(**4**) gave α-hydroxy esters **6a**−**d** with the opposite absolute stereochemistry to that obtained with (*R*)-BINAP; that is, NUPHOS-type diphosphines with a δ conformation behave in much the same manner as (*S*)-BINAP. Gratifyingly, this study shows that Lewis acid catalysts based on conformationally flexible NUPHOS-type diphosphines can compete with their enantiopure BINAP counterparts.

Reasoning that the product distribution obtained from the Lewis acid-catalyzed ene reaction between methylene cyclohexane and ethyl trifluoropyruvate reflected the finely balanced kinetics of alkene isomerization relative to ene reactivity, we also investigated the corresponding reaction with 1-methylcyclohexene, the results of which are summarized in Table 3. Reassuringly, the performance of catalysts **2a**−**c** for the addition of 1-methylcyclohexene to ethyl trifluoropyruvate paralleled that obtained in the corresponding reaction with methylene cyclohexane in that (i) the enantioselectivities of α-hydroxy esters **6a**−**c** are similar to those obtained with methylene cyclohexane, (ii) catalyst **2b** gave α-hydroxy ester **6a** in 96% ee (Table 3, entry 3) whereas its platinum and nickel counterparts gave markedly lower ee's of 78 and 77%, respectively (Table 3, entries 1, 4), and (iii) each of the catalysts gave high levels of regioselectivity to afford **6b** as the dominant product, which corresponds to effective discrimination in favor of the methyl substituent compared to the cyclohexyl α-CH_2. As expected, the performance of δ-**4** for the addition of 1-methylcyclohexene to ethyl trifluoropyruvate compares favorably with that of **2a** in that a similar distribution of α-hydroxy ester **6a** and regioisomers **6b**,**c** was obtained, with comparable levels of enantioselectivity and diastereoselectivity (Table 3, entry 5).

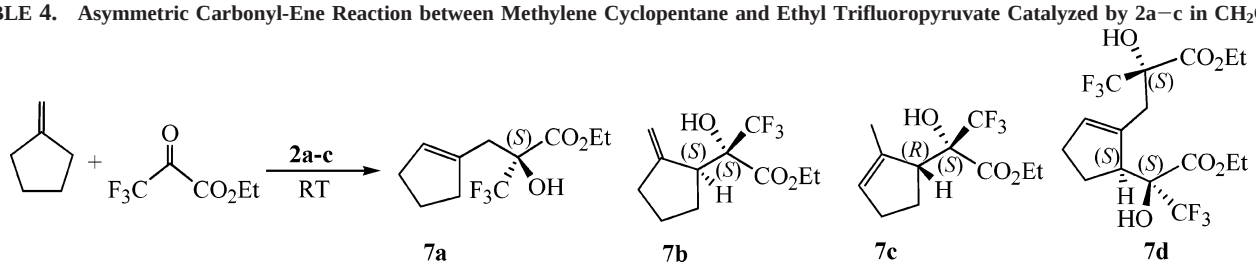
Evans et al. have reported that copper complexes of bis(oxazolines) catalyze the addition of 1-methylcyclohexene to ethyl glyoxylate to afford a single regioisomer, **6′c**, which corresponds to the opposite sense of regioselectivity, that is, discrimination favoring the cyclohexyl α-CH_2 (eq 4).[7] Since it would not be reliable to compare catalyst selectivities for reactions involving different enophiles, the reaction between ethyl glyoxylate and 1-methylcyclohexene was catalyzed by **2a** and afforded regioisomer **6′c** in excellent enantioselectivity (99% ee) and moderate diastereoselectivity (2:1), together with a minor amount of **6′b** (<2%). Thus, since isomerization of α-hydroxy esters has been shown to be relatively slow (vide supra), the Lewis acid-catalyzed addition of 1-methylcyclohexene to ethyl glyoxylate and ethyl trifluoropyruvate must occur with opposing regioselectivity, ethyl glyoxylate forming the thermodynamically favored regioisomer **6′c** while ethyl trifluoropyruvate affords the less favored α-hydroxy ester **6b**. It is reasonable to suggest/speculate that the transition state involving the α-CH_2 is more favored for the less hindered ethyl glyoxylate, whereas the corresponding transition state for pyruvate would experience unfavorable steric interactions between the CF_3 group and the cyclohexyl ring.



eq 4

For comparison, the addition of methylene cyclopentane and 1-methylcyclopentene to ethyl trifluoropyruvate was also catalyzed by **2a**−**c**, details of which are summarized in Tables 4 and 5, respectively. Not surprisingly, the reactivity patterns and trends in catalyst selectivity obtained with these substrates are qualitatively similar to those of their six-membered counterparts. First, Lewis acids **2a**,**c** catalyze the addition of methylene cyclopentane to ethyl trifluoropyruvate to afford mixtures of **7a**−**d** (Table 4, entries 1 and 4), whereas **2b** was highly selective for α-hydroxy ester **7a** (Table 4, entry 3). The similarity in catalyst performance between methylene cyclopentane and methylene cyclohexane also extends to trends in enantioselectivity in that Lewis acid **2b** gave α-hydroxy ester **7a** in excellent

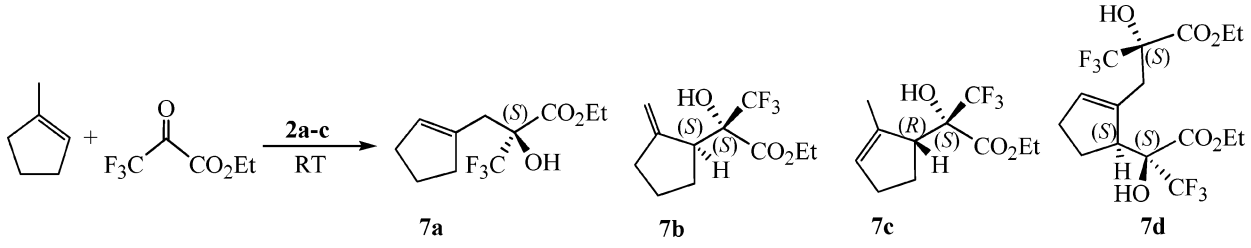
TABLE 4. Asymmetric Carbonyl-Ene Reaction between Methylene Cyclopentane and Ethyl Trifluoropyruvate Catalyzed by 2a−c in CH_2Cl_2



				product ratio[c]	exo:endo ratio[d]		% ee[e]			% de[f,g]
entry[a]	catalyst (mol %)	time (min)	conv[b] (%)	**7a**:**7b**:**7c**:**7d**	**7b**	**7c**	**7a**	**7b**	**7c**	**7d**
1	**2a** (5)	30	100	7:68:15:10	>99:1	3:1	72	>99	97, 95	92
2	**2a** (5)	1	100	10:64:17:9	>99:1	7:1	71	>99	97, 96	91
3	**2b** (5)	30	100	98:2:0:0	>99:1		96	>99		
4	**2c** (5)	30	98	45:26:19:10	>99:1	7:3	73	>99	95, 94	89

[a] Reaction conditions: 5 mol % catalyst, methylene cyclopentane (0.4 mmol), and ethyl trifluoropyruvate (0.6 mmol) in 2.0 mL of CH_2Cl_2, room temperature. [b] Conversions determined by GC using a Supelco Beta DEX column. [c] Product ratios determined by ^{1}H NMR spectroscopy. [d] exo:endo ratio determined by ^{1}H NMR spectroscopy and chiral GC and assigned by analogy with the X-ray crystal structure of **8b**. [e] Enantiomeric excess determined by chiral GC using a Supelco Beta DEX column and listed either as % ee exo in cases where the ee of the minor endo diastereoisomer was not determined or as % ee exo, % ee endo. [f] Diastereoisomeric excess determined by chiral GC using a Supelco Beta DEX column. [g] Minor enantiomers were not detected. Average of three runs.

TABLE 5. Asymmetric Carbonyl-Ene Reaction between 1-Methylcyclopentene and Ethyl Trifluoropyruvate Catalyzed by 2a−c in CH_2Cl_2



				product ratio[c]	exo:endo ratio[d]		% ee[e]			% de[f,g]
entry[a]	catalyst (mol %)	time (min)	conv[b] (%)	**7a**:**7b**:**7c**:**7d**	**7b**	**7c**	**7a**	**7b**	**7c**	**7d**
1	**2a** (5)	30	100	4:75:16:5	>99:1	3:1	69	>99	96, 95	89
2	**2a** (5)	1	100	1:80:19:0	>99:1	9:1	70	>99	96, 95	
3	**2b** (5)	30	100	4:89:8:0	>99:1	4:1	>99	>99	92, 91	
4	**2c** (5)	30	98	1:54:32:14	>99:1	3:1	76	>99	98, 96	80

[a] Reaction conditions: 5 mol % catalyst, 1-methylcyclopentene (0.4 mmol), and ethyl trifluoropyruvate (0.6 mmol) in 2.0 mL of CH_2Cl_2, room temperature. [b] Conversions determined by GC using a Supelco Beta DEX column. [c] Product ratios determined by ^{1}H NMR spectroscopy. [d] exo:endo ratio determined by ^{1}H NMR spectroscopy and chiral GC and assigned by analogy with the X-ray crystal structure of **8b**. [e] Enantiomeric excess determined by chiral GC using a Supelco Beta DEX column and listed either as % ee exo in cases where the ee of the minor endo diastereoisomer was not determined or as % ee exo, % ee endo. [f] Diastereoisomeric excess determined by chiral GC using a Supelco Beta DEX column. [g] Minor enantiomers were not detected. Average of three runs.

enantioselectivity (96% ee), whereas **2a**,**c** gave significantly lower enantioselectivities of 72 and 73%, respectively. A comparison of Tables 4 and 5 reveals that α-hydroxy esters **7b**,**c** are both formed with uniformly high enantioselectivities, >99% and 92−99%, respectively, regardless of the catalyst and substrate. As for methylene cyclohexane, the formation of α-hydroxy esters **7b**,**c** must occur via a rapid Lewis acid-catalyzed isomerization of methylene cyclopentane followed by a moderately regioselective and highly enantioselective and diastereoselective addition of the resulting 1-methylcyclopentene to ethyl trifluoropyruvate (Scheme 1). In addition, the exo:endo ratio of **7c** gradually decreases with increasing reaction time, from 7:1 after 1 min to 3:1 after 30 min (Table 4, entries 1 and 2) because of the isomerization of (1′*S*,2*S*)-**7b** to (1′*S*,2*S*)-**7c**, the product from the minor endo transition state of the direct ene reaction between 1-methylcyclopentene and ethyl trifluoropyruvate (vide infra). This isomerization and the associated artificial change in the exo:endo ratio are clearly evident in Figure 3, which shows the composition of (1′*S*,2*S*)-**7b**, (1′*S*,2*S*)-**7c**, and (1′*R*,2*S*)-**7c** as a function of time for the reaction between methylene cyclopentane and ethyl trifluoropyruvate. The results in Table 5 also show that these parallels in reactivity and selectivity also apply to 1-methylcyclopentene, which is most evident from the catalyst-dependent enantioselectivities of α-hydroxy ester **7a**.

By analogy with our studies on **6b**, a dichloromethane solution of Lewis acid **2a** (5 mol %), α-hydroxy ester **7b**, and ethyl trifluoropyruvate (1.5 equiv) gave a 25:47:28 mixture of **7b**, isomerization product **6c**, and double ene product **7d**, after 2 h. A qualitative comparison with the corresponding ratio of 48:7:45 obtained from **6b** suggests that isomerization of **7b** is faster than that of **6b** while the rates of addition to ethyl trifluoropyruvate remain comparable. In a more detailed study, the variation in composition with respect to time for the reaction between 1-methylcyclopentene and ethyl trifluoropyruvate catalyzed by **2a** (Figure 4) clearly shows that α-hydroxy ester

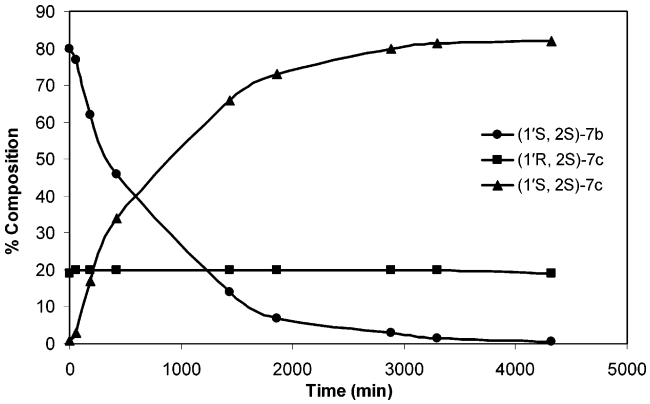


FIGURE 3. Composition of (1′*S*,2*S*)-**7b**, (1′*S*,2*S*)-**7c**, and (1′*R*,2*S*)-**7c** as a function of time for the carbonyl-ene reaction between 1-methylcyclopentene and ethyl trifluoropyruvate catalyzed by [Pt{(*R*)-BINAP}][SbF_6]$_2$ (**2a**) illustrating the artificial change in the exo:endo ratio.

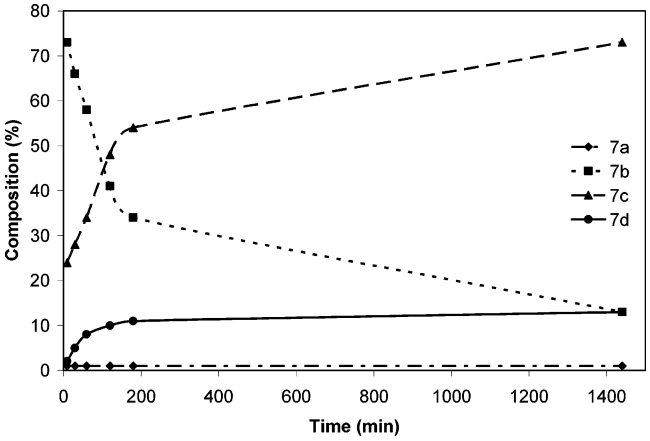


FIGURE 4. Variation of the percent composition for the carbonyl-ene reaction between 1-methylcyclopentene and ethyl trifluoropyruvate catalyzed by [Pt{(*R*)-BINAP}][SbF_6]$_2$ (**2a**) in dichloromethane with respect to time at room temperature.

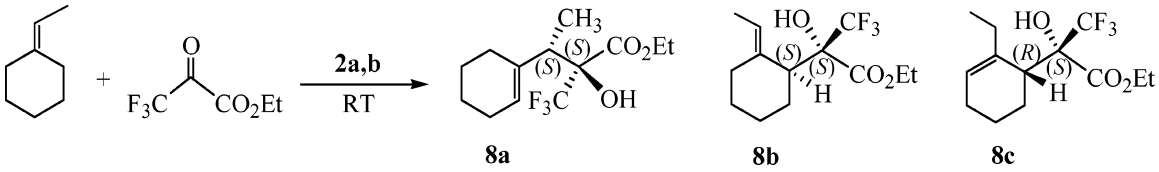
7c and double ene product **7d** gradually increase at the expense of **7b**, while **7a** remains constant. Just as that for **6b**, the change in composition with time, in particular the ratio **7b**:**7c**, suggests that isomerization is relatively slow and that the **7b**:**7c** ratio of 80:19 obtained after 1 min (Table 5, entry 2) corresponds to the intrinsic regioselectivity of the catalyst−pyruvate complex for discrimination between the methyl substituent and the α-CH_2 of the five-membered ring. Reassuringly, the corresponding reaction between methylene cyclopentane and ethyl trifluoropyruvate gave a similar composition−time relationship (Figure S1, Supporting Information), which differed only in the initial distribution of products.

Finally, the addition of ethylidene cyclohexane to ethyl trifluoropyruvate has been investigated since both substrates simultaneously introduce two vicinal stereocenters and the transformation of ethylidene cyclohexane is more challenging than that of methylene cyclohexane as it requires regioselective discrimination between nonequivalent α-CH_2 groups (Table 6). The addition of ethylidene cyclohexane to ethyl trifluoropyruvate catalyzed by **2a** gave α-hydroxy ester **8a** as the dominant product in excellent enantioselectivity and high diastereoselectivity (exo 99%, endo 88% ee; 7:1 exo:endo) together with minor amounts of **8b**,**c** in excellent enantioselectivity and good diastereoselectivity, via the addition of 1-ethylcyclohexene to ethyl trifluoropyruvate (Table 6, entry 1). The identity of each of these α-hydroxy esters was established by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The identity of **8b**, the relative stereochemistry of the two stereocenters, and the stereochemistry of the trisubstituted double bond were unequivocally confirmed by a single-crystal X-ray structure determination.[38] A perspective view of the molecular structure is shown in Figure 5. The structure reveals that **8b** is formed with E stereochemistry and that the carbonyl-ene reaction occurs with exo selectivity (vide infra). The **8b**:**8c** regioselectivity of 17:1 in favor of the ethylidene-based ene product **8b** is significantly lower than that of 44:1 obtained in the corresponding reaction with 1-methylcyclohexene and is consistent with a more difficult discrimination between the ethyl and cyclohexyl α-CH_2 relative to a methyl and the same α-CH_2. In contrast, **2b** catalyzed the ene reaction with ethylidene cyclohexane to afford **7a** exclusively and in an excellent enantioselectivity and high diastereoselectivity (exo 96%, endo 89% ee; exo:endo 9:1). Although 1-ethylcyclohexene is not commercially available, a comparative study of catalyst performance and a scale-up experiment to isolate α-hydroxy ester **8b** for characterization were undertaken using a 10:1 equilibrium mixture of 1-ethylcyclohexene and ethylidene cyclohexane prepared via the acid-catalyzed isomerization of ethylidene cyclohexane (Table 7). Lewis acids **2a**,**b** both catalyze the ene reaction with this mixture to afford α-hydroxy ester **8b** as the major regioisomer (ca. 61:4 and 81:2, respectively) in high diastereoselectivity (exo:endo > 99:1) and excellent enantioselectivity (exo 99% ee), together with minor amounts of **8c**, also in high diastereoselectivity and enantioselectivity (Table 7, entry 1). The reaction also generated α-hydroxy ester **8a** by virtue of the equilibrium mixture of reactants, and as expected, the formation of **8a** by catalysts **2a**,**b** was both highly diastereoselective and enantioselective (93−96% ee). More conveniently, a similar product distribution was obtained when Lewis acid **2a** was used as the catalyst for the in situ isomerization of ethylidene cyclohexane immediately prior to the addition of ethyl trifluoropyruvate. GC analysis of a dichloromethane solution of **2a** (5 mol %) and ethylidene cyclohexane revealed that isomerization was complete within 10 min and that addition of ethyl trifluoropyruvate to this mixture resulted in rapid formation of ene products with diastereo- and enantioselectivities similar to those obtained with the preformed equilibrium mixture.

The sense of asymmetric induction for the carbonyl-ene reaction catalyzed by **2a**−**c** can be accounted for on the basis of a transition state model recently proposed by Oi et al.[10,12b] and Ghosh and Matsuda.[11a] and used to justify the stereochemical outcome of the [M{(*S*)-BINAP}](X_2) (M = Pd, Pt) catalyzed asymmetric Diels−Alder reaction between *N*-acryloyl-*N*-oxazolidinones and various dienes. In this model, the sense

(38) A single-crystal X-ray study established the relative configuration of the stereocenters in **8b**, and the absolute stereochemistry was assigned by analogy with that for (*S*)-**6a**. Crystal data for (*S*,*S*)-**8b**: $C_{13}H_{19}F_3O_3$, M_r = 280.3, orthorhombic, space group $P2_12_12_1$, a = 8.490(5), b = 11.316(5), c = 30.145(17) Å, V = 2896(3) Å^3, Z = 8, ρ_{calcd} = 1.286 g cm^{-3}, T = 150 K; crystal size 0.50 × 0.10 × 0.10 mm^3, Mo Kα radiation, λ = 0.710 73 Å, μ = 0.11 mm^{-1}, transmission 0.945−0.989 by multi-scan methods, $2\theta_{max}$ = 25°, Nonius Kappa CCD diffractometer, 28 215 measured data, 2892 unique reflections (Friedel pairs averaged), R_{int} = 0.093; standard direct methods and full-matrix least-squares refinement on all unique F^2 values, OH H atoms freely refined, CH H atoms riding, R (2308 F values with $F^2 > 2\sigma$) = 0.061, R_w (all F^2 values) = 0.145, goodness-of-fit = 1.15, final difference map extremes +0.35 and −0.34 e Å^{-3}. Programs: Nonius COLLECT and EvalCCD, Bruker SADABS and SHELXTL.

TABLE 6. Asymmetric Carbonyl-Ene Reaction between Ethylidene Cyclohexane and Ethyl Trifluoropyruvate Catalyzed by 2a and 2b in CH_2Cl_2



				product ratio[c]	exo:endo ratio[d]			% ee[e]		
entry[a]	catalyst (mol %)	time (min)	conv[b] (%)	**8a**:**8b**:**8c**	**8a**	**8b**	**8c**	**8a**	**8b**	**8c**
1	**2a** (5)	30	100	82:17:1	7:1	>99:1	nd	99, 88	99	nd
2	**2b** (5)	30	100	100:0:0	9:1			96, 89		

[a] Reaction conditions: 5 mol % catalyst, ethylidene cyclohexane (0.4 mmol), and ethyl trifluoropyruvate (0.6 mmol) in 2.0 mL of CH_2Cl_2, room temperature. [b] Conversions determined by GC using a Supelco Beta DEX column. [c] Product ratios determined by ^{1}H NMR spectroscopy. [d] exo:endo ratio determined by ^{1}H NMR spectroscopy and chiral GC and assigned by analogy with the X-ray crystal structure of **8b**. [e] Enantiomeric excesses determined by chiral GC using a Supelco Beta DEX column and listed either as % ee exo in cases where the ee of the minor endo diastereoisomer was not determined or as % ee exo, % ee endo. Average of three runs; nd = not determined.

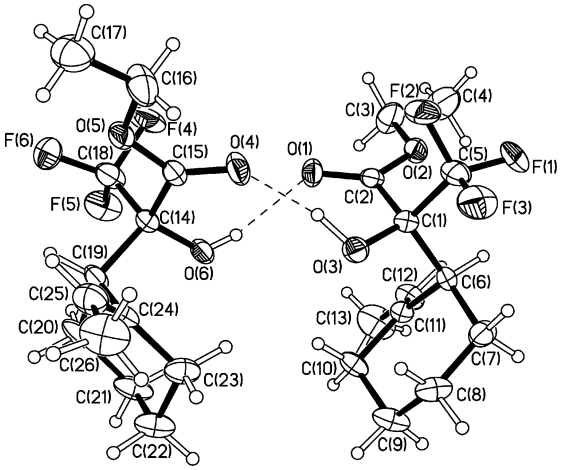


FIGURE 5. Two crystallographically independent molecules of ethyl 2-((*E*)-2-ethylidenecyclohex-1-yl)-3,3,3-trifluoro-2-hydroxypropanoate (**8b**) in the asymmetric unit, illustrating the E stereochemistry of the trisubstituted double bond, the relative stereochemistry of the two stereocenters, and the pair of intermolecular hydrogen bonds between the oxygen atoms of the carbonyls and the hydrogen atoms of the α-hydroxy groups, which link the molecules into a discrete chiral dimer, both molecules being of the same absolute configuration.

of asymmetric induction for the addition of methylene cyclohexane to ethyl trifluoropyruvate catalyzed by [M{(*R*)-BINAP}]$^{2+}$ involves coordination of the dienophile through both carbonyl oxygen atoms to form a square-planar catalyst−substrate adduct similar to that formed between [Cu(*S*,*S*)-*t*-Bu-box)][SbF_6]$_2$ and α-dicarbonyl substrates, proposed by Evans and co-workers and used to explain the high level of enantioface selection in Diels−Alder, hetero Diels−Alder, and aldol reactions.[39] The model illustrated in Figure 6 and the single-crystal X-ray structure of **1a** (Figure 7)[40] both show the asymmetric environment created by the alternating edge−face arrangement of the P−Ph rings which is responsible for controlling the stereochemical outcome of a transformation. It is clear that the pseudo-equatorial phenyl ring on P_A is orientated above the MP_2 plane in such a manner that the Si face of the pyruvate is protected from an attack by the nucleophilic alkene, rendering attack at the more accessible Re face, to afford an α-hydroxy ester with (S)-configuration, more favorable.

The endo/exo selectivity of an ene reaction is commonly accepted to be controlled by steric interactions.[41] In a recent study, Evans and co-workers investigated the [Cu(*S*,*S*)-*t*-Bu-box)][SbF_6]$_2$-catalyzed glyoxylate ene reaction, proposed a model invoking two-point catalyst dienophile binding to form an adduct of the type [Cu(*S*,*S*)-*t*-Bu-box)(glyoxylate)][SbF_6], and speculated that an endo approach of the alkene was favored because approach in an exo manner would result in severe steric interactions between the *tert*-butyl group of the oxazoline and the cyclohexene.[8] By analogy and with reference to the stereochemical model described in Figure 6, it is reasonable to suggest that 1-methylcyclohexene (and ethylidene cyclohexane) will preferentially approach the coordinated ethyl trifluoropyruvate in an exo manner, as shown in Figure 8a, since an endo approach would experience unfavorable steric interactions between the alkene and the pseudo-equatorial phenyl ring attached to P_B (Figure 8b). Thus, the combination of these stereochemical models predicts that 1-methylcyclohexene (and 1-methylcyclopentene) and ethylidene cyclohexane add to ethyl trifluoropyruvate in an exo manner to afford α-hydroxy esters **6b**/**7b** and **8b**, respectively, in high diastereoselectivity (exo:endo > 99:1) and with (S,S) configuration, which is supported by single-crystal X-ray structure determinations of **6a** and **8b**.

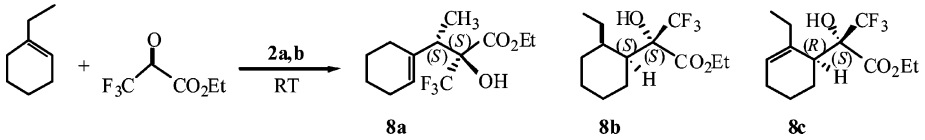
The same model can also be used to rationalize why 1-methylcycloalkenes and 1-ethylcyclohexene add to ethyl trifluoropyruvate to afford **6c**/**7c** and **8c** with much lower diastereoselectivity (2:1 to 4:1 exo:endo) since the corresponding transition state models (Figure 9a,b) clearly show that the steric differentiation associated with exo and endo approach is much less pronounced than that experienced during the formation of

(39) (a) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc*. **1998**, *120*, 5824. (b) Evans, D. A.; Kozlowski, M. C.; Burgeym, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893.

(40) Crystal data for **1a**: $C_{44}H_{32}Cl_2P_2Pt\cdot 2CH_2Cl_2$, M_r = 1058.5, orthorhombic, space group $P2_12_12_1$, a = 12.7463(15), b = 14.9692(17), c = 22.258(3) Å, V = 4253.0(8) Å^3, Z = 4, ρ_{calcd} = 1.653 g cm^{-3}, T = 150 K; crystal size 0.54 × 0.50 × 0.50 mm^3, Mo Kα radiation, λ = 0.710 73 Å, μ = 0.31 mm^{-1}, transmission 0.880−0.970 by multi-scan methods, $2\theta_{max}$ = 25°, Bruker SMART 1K diffractometer, 37 872 measured data, 10 223 unique reflections, R_{int} = 0.037; standard direct methods and full-matrix least-squares refinement on all unique F^2 values, H atoms riding, R (9496 F values with $F^2 > 2\sigma$) = 0.027, R_w (all F^2 values) = 0.056, goodness-of-fit = 1.10, final difference map extremes +1.03 and −1.43 e Å^{-3}, absolute structure parameter 0.004(4). Programs: Bruker SMART, SAINT, SADABS, and SHELXTL.

(41) Snider, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 527−561.

TABLE 7. Asymmetric Carbonyl-Ene Reaction between 1-Ethylcyclohexene[a] and Ethyl Trifluoropyruvate Catalyzed by 2a and 2b in CH_2Cl_2



				product ratio[d]	exo:endo ratio[e]			% ee[f]		
entry[b]	catalyst (mol %)	time (min)	conv[c] (%)	**8a**:**8b**:**8c**	**8a**	**8b**	**8c**	**8a**	**8b**	**8c**
1	**2a** (5)	30	83	35:61:4	7:1	>99:1	3:1	95, 93	99	99, 96
2	**2b** (5)	30	77	17:81:2	11:1	>99:1	11:1	96, 90	98	99, 94

[a] 10:1 ratio of 1-ethylcyclohexane/ethylidene cyclohexane was used. [b] Reaction conditions: 5 mol % catalyst, 1-ethylcyclohexene (0.4 mmol), and ethyl trifluoropyruvate (0.6 mmol) in 2.0 mL of CH_2Cl_2, room temperature. [c] Conversions determined by GC using a Supelco Beta DEX column. [d] Product ratios determined by ^{1}H NMR spectroscopy. [e] exo:endo ratio determined by ^{1}H NMR spectroscopy and chiral GC and assigned by analogy with the X-ray crystal structure of **8b**. [f] Enantiomeric excess determined by chiral GC using a Supelco Beta DEX column. Average of three runs.

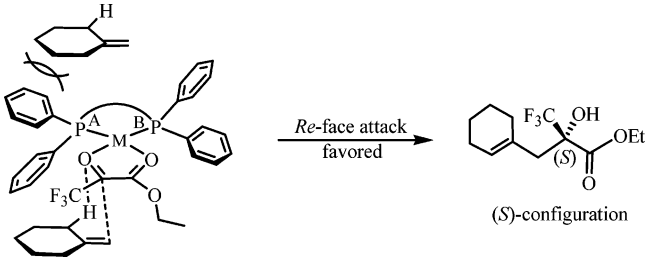


FIGURE 6. Stereochemical model showing the asymmetric environment created by the P−Ph rings of (*R*)-BINAP and the favored Re-face attack of methylene cyclohexane to give α-hydroxy esters with (S)-absolute configuration.

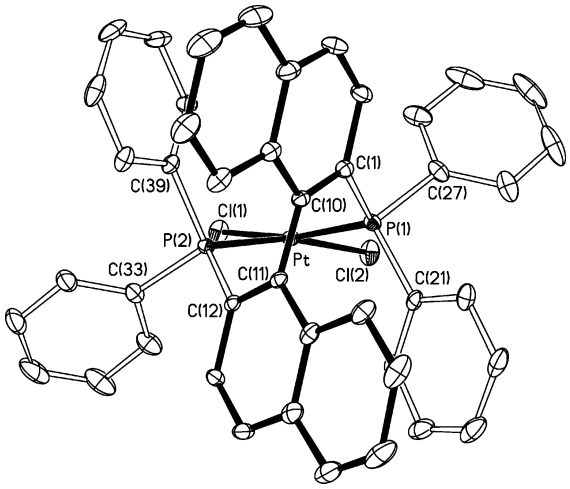


FIGURE 7. Molecular structure of [Pt{(*R*)-BINAP}Cl_2] (**1a**) highlighting the noncrystallographic molecular C_2 axis and the asymmetric environment created by the alternating edge-face arrangement of the P−Ph rings of BINAP. Ellipsoids are at the 30% probability level. Bonds within the dinaphthyl unit and bonds to Pt are shown solid; others are shown hollow.

6b−**8b** (cf. Figure 8). In this case, it is more difficult to predict from the transition state models which diastereoisomer would be favored. However, we are confident that exo approach to afford the (*R,S*)-diastereoisomer will be the dominant pathway since the addition of 1-methylcyclohexene to ethyl trifluoropyruvate monitored as a function of time clearly showed that the major diastereoisomer of **6b** (assumed to be S,S stereochemistry based on the structures of **6a** and **8b**) isomerizes to the minor diastereoisomer of **6c** (vide supra). Provided that isomerization occurs with retention of stereochemistry, this

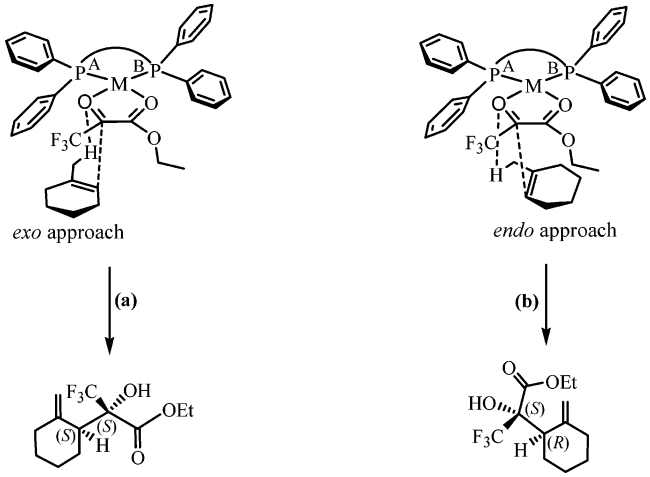


FIGURE 8. Stereochemical model showing exo/endo approaches of 1-methylcyclohexene to [Pt{(*R*)-BINAP}(pyruvate)]$^{2+}$ to account for the high exo-diastereoselectivity to afford (1′*S*,2*S*)-**6b**.

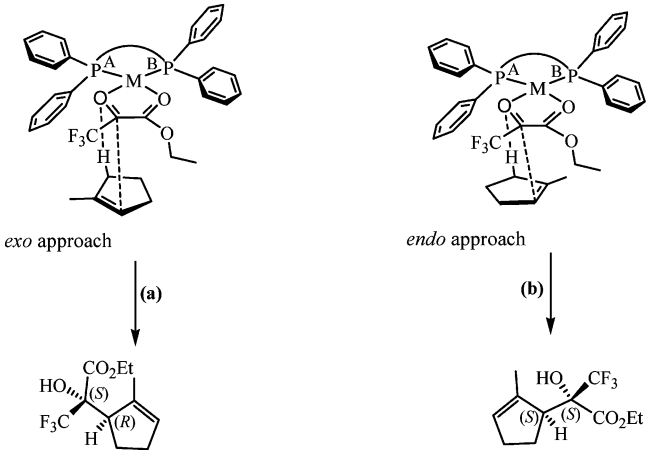


FIGURE 9. Stereochemical model showing exo and endo approaches of 1-methylcyclopentene to [Pt{(*R*)-BINAP}(pyruvate)]$^{2+}$ to explain the low level of exo-diastereoselectivity in favor of (1′*R*,2*S*)-**7c**.

experiment confirms that the minor diastereoisomer of **6c** has S,S stereochemistry, which must result from endo approach, according to the stereochemical model in Figure 9.

In conclusion, soft late transition metal Lewis acids of the type [M{(*R*)-BINAP}]$^{2+}$ are highly active catalysts for the carbonyl-ene reaction between ethyl trifluoropyruvate and a range of methylene cycloalkanes and trisubstituted alkenes.

While [Pd{(*R*)-BINAP}]$^{2+}$ consistently gave the expected α-hydroxy esters in high diastereo- and enantioselectivity, its platinum and nickel counterparts gave a mixture of products resulting from a combination of pathways including (i) alkene isomerization coupled with carbonyl-ene reactivity, (ii) isomerization of the resulting α-hydroxy ester, and (iii) addition of the primary α-hydroxy ester to a second molecule of ethyl trifluoropyruvate to afford a double ene product. On the basis of initial product distributions, the rates of isomerization appear to increase in the order ethylidene cyclohexane < methylene cyclohexane < methylene cyclopentane. Preliminary studies have also shown that enantiopure platinum complexes of the conformationally flexible NUPHOS diphosphine 1,4-Et$_2$-*cyclo*-C$_6$H$_8$−NUPHOS catalyze the carbonyl-ene reaction with trends in reactivity and selectivity patterns that mirror those obtained with its BINAP counterpart, with δ-NUPHOS diphosphines behaving in much the same manner as (*S*)-BINAP. Further studies are currently underway to understand the factors that influence and control the relative rates of isomerization and ene reactivity with the aim of coupling these transformations to develop novel tandem reaction sequences. The application of conformationally flexible NUPHOS diphosphines in a broad range of platinum group metal-catalyzed asymmetric transformations is also being explored with the aim of assessing the relative merits of tropos and atropos diphosphines.

Experimental Section

Typical Procedure for Lewis Acid-Catalyzed Ene Reaction. A flame-dried Schlenk flask charged with [{(*R*)-BINAP)MCl$_2$] (0.02 mmol), AgSbF$_6$ (15 mg, 0.044 mmol), and CH$_2$Cl$_2$ (2.0 mL) was stirred at room temperature for 30 min. After this time, ethyl trifluoropyruvate (80 μL, 0.6 mmol) was added followed by methylene cyclohexane (48 μL, 0.4 mmol). The resulting mixture was stirred for a further 30 min, after which time the solution was flushed through a short plug of silica with CH$_2$Cl$_2$, the solvent was removed, and the resulting residue was purified by column chromatography, eluting with hexane/CH$_2$Cl$_2$ (3:2). The products were analyzed by ^{1}H NMR spectroscopy, and the ee's were determined by chiral GC.

Ethyl *E*-2-(Trifluoromethyl)-2-hydroxy-5-phenylpent-4-enoate (5). A sample was isolated as a colorless oil after purification by column chromatography. $[\alpha]_D^{20} = -46.9$ (*c* 1.0, CH$_2$Cl$_2$); ^{1}H NMR (300.0 MHz, CDCl$_3$, δ) 7.20−7.09 (m, 5H, Ph), 6.41 (d, *J* = 15.8 Hz, 1H, PhC*H*═CH), 5.98 (ddd, *J* = 15.0, 8.1, 6.6 Hz, 1H, CH═C*H*CH$_2$), 4.22 (m, 2H, OC*H*$_2$CH$_3$), 3.82 (s, 1H, O*H*), 2.81−2.67 (m, 2H, CHC*H*$_2$), 1.20 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (125.7 MHz, CDCl$_3$, δ) 169.8 (*C*═O), 137.2 (Ph), 136.1 (Ph), 129.1 (Ph), 126.9 (Ph), 128.3 (*C*═C), 123.9 (q, J_{C-F} = 286 Hz, *C*F$_3$), 121.0 (C═*C*), 78.2 (q, J_{C-F} = 29 Hz, *C*CF$_3$), 64.4 (O*C*H$_2$CH$_3$), 36.1 (═CH*C*H$_2$), 14.6 (OCH$_2$*C*H$_3$); LRMS (EI) *m*/*z* 288 [M]$^+$; HRMS (EI) exact mass calcd for (C$_{14}$H$_{15}$O$_3$F$_3$) [M]$^+$ requires *m*/*z* 288.097329, found *m*/*z* 288.096703; ee determined by GC using a Supelco Beta DEX column (injection temp 170 °C; column conditions 140 °C for 45 min ramp to 180 °C at 3 °C/min, pressure 21 psi) major (*S*)-enantiomer t_R = 37.7 min, minor (*R*)-enantiomer t_R = 35.4 min.

(2*S*)-Ethyl 3-(Cyclohexen-1′-yl)-2-(trifluoromethyl)-2-hydroxypropanoate (6a). A sample was isolated as a colorless oil after purification by column chromatography. $[\alpha]_D^{20} = -19.2$ (*c* 1.0, CH$_2$Cl$_2$); ^{1}H NMR (300.0 MHz, CDCl$_3$, δ) 5.54 (br s, 1H, ═C*H*), 4.40−4.24 (m, 2H, OC*H*$_2$CH$_3$), 3.76 (s, 1H, O*H*), 2.59 (d, *J* = 13.9 Hz, 1H, CH*H*CCF$_3$OH), 2.43 (d, *J* = 14.0 Hz, 1H, C*H*HCCF$_3$OH), 2.12−1.75 (br m, 4H, Cy−C*H*$_2$), 1.60−1.45 (br m, 4H, Cy−C*H*$_2$), 1.33 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (125.7 MHz, CDCl$_3$, δ) 170.2 (*C*═O), 131.4 (CH═*C*CH$_2$), 128.2 (*C*H═CCH$_2$), 123.9 (q, J_{C-F} = 286 Hz, *C*F$_3$), 78.8 (q, J_{C-F} = 28 Hz, *C*CF$_3$), 64.0 (O*C*H$_2$CH$_3$), 40.1 (Cy), 30.3 (Cy), 25.9 (Cy), 23.4 (Cy), 22.5 (*C*H$_2$CCF$_3$OH), 14.4 (OCH$_2$*C*H$_3$); LRMS (EI) *m*/*z* 266 [M]$^+$; HRMS (EI) exact mass calcd for C$_{12}$H$_{17}$O$_3$F$_3$ [M]$^+$ requires *m*/*z* 266.112979, found *m*/*z* 266.113319. Ee determined by GC using a Supelco Beta DEX column (injection temp 135 °C; column conditions 105 °C for 40 min ramp to 175 °C at 5 °C/min; hold 20 min, pressure 21 psi) major (2*S*)-enantiomer t_R = 40.8 min, minor (2*R*)-enantiomer t_R = 38.2 min; 77% ee. Absolute stereochemistry determined by single-crystal X-ray crystallography of the (*R*)-1-(1-naphthyl)ethylammonium salt of the derived carboxylic acid.

(1′*S*,2*S*)-Ethyl 3,3,3-Trifluoro-2-hydroxy-2-(2′-methylenecyclohex-1′-yl)propanoate (6b). A sample was isolated as a single diastereoisomer after purification by column chromatography. $[\alpha]_D^{20}$ = +41.9 (*c* 2.6, CH$_2$Cl$_2$); ^{1}H NMR (300.0 MHz, CDCl$_3$, δ) 4.77 (s, 1H, ═C*H*$_a$H$_b$), 4.64 (s, 1H, ═CH$_a$*H*$_b$), 4.39−4.19 (m, 2H, OC*H*$_2$-CH$_3$), 3.87 (s, 1H, O*H*), 2.95 (t, *J* = 5.2 Hz, 1H, C*H*CCF$_3$OH), 2.41−2.32 (m, 1H, Cy−C*H*$_2$), 2.13−1.85 (br m, 3H, Cy−C*H*$_2$), 1.77−1.63 (m, 2H, Cy−C*H*$_2$), 1.54−1.40 (m, 2H, Cy−C*H*$_2$), 1.31 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (125.7 MHz, CDCl$_3$, δ) 170.9 (*C*═O), 147.8 (*C*═CH$_2$), 124.0 (q, J_{C-F} = 288 Hz, *C*F$_3$), 111.1 (*C*═*C*H$_2$), 82.1 (q, J_{C-F} = 27 Hz, *C*CF$_3$), 64.2 (O*C*H$_2$CH$_3$), 44.4 (Cy), 35.5 (Cy), 28.4 (Cy), 28.3 (Cy), 23.6 (Cy), 14.3 (OCH$_2$*C*H$_3$); LRMS (EI) *m*/*z* 266 [M]$^+$; HRMS (EI) exact mass calcd for C$_{12}$H$_{17}$O$_3$F$_3$ [M]$^+$ requires *m*/*z* 266.112979, found *m*/*z* 266.111816. Anal. Calcd for C$_{12}$H$_{17}$F$_3$O$_3$: C, 54.13; H, 6.44. Found: C, 54.27; H, 6.78. Ee determined by GC using a Supelco Beta DEX column (injection temp 135 °C; column conditions 105 °C for 40 min ramp to 175 °C at 5 °C/min; hold 20 min, pressure 21 psi) major (1′*S*,2*S*)-enantiomer t_R = 27.5 min, minor (1′*R*,2*R*)-enantiomer t_R = 29.5 min; 99% ee. Absolute and relative stereochemistry assigned by analogy.

(1′*R*,2*S*)-Ethyl 3,3,3-Trifluoro-2-hydroxy-2-(2′-methylcyclohex-2′-en-1′-yl)propanoate (6c). A sample was formed as a 3:1 exo:endo mixture of diastereoisomers which can be partially separated by careful column chromatography to afford a 97:3 exo*:* endo mixture. $[\alpha]_D^{20}$ = +12.1 (*c* 0.93, CH$_2$Cl$_2$). Major exo-diastereoisomer: ^{1}H NMR (300.0 MHz, CDCl$_3$, δ) 5.70 (br s, 1H, ═CH), 4.41−4.31 (m, 2H, OC*H*$_2$CH$_3$), 3.69 (s, 1H, O*H*), 2.78 (t, *J* = 5.4 Hz, 1H, C*H*CCF$_3$OH), 2.03−1.99 (m, 2H, Cy−C*H*$_2$), 1.93−1.80 (m, 1H, Cy−C*H*$_2$), 1.77 (br s, 3H, CH═CC*H*$_3$), 1.73−1.71 (m, 1H, Cy−C*H*$_2$), 1.55−1.51 (m, 1H, Cy−C*H*$_2$), 1.50−1.39 (m, 1H, Cy−C*H*$_2$), 1.34 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (125.7 MHz, CDCl$_3$, δ) 170.4 (*C*═O), 130.7 (CH═*C*CH$_3$), 129.8 (*C*H═CCH$_3$), 124.0 (q, J_{C-F} = 287 Hz, *C*F$_3$), 81.1 (q, J_{C-F} = 28 Hz, *C*CF$_3$), 64.1 (O*C*H$_2$CH$_3$), 42.2 (Cy), 31.5 (Cy), 26.4 (Cy), 25.3 (Cy), 25.3 (Cy), 19.6 (CH═C*C*H$_3$), 14.4 (OCH$_2$*C*H$_3$). Minor endo-diastereoisomer: ^{1}H NMR (300.0 MHz, CDCl$_3$, δ) 5.73 (br s, 1H, ═CH), 4.47−4.26 (m, 2H, OC*H*$_2$CH$_3$), 3.50 (s, 1H, O*H*), 2.88−2.86 (m, 1H, C*H*CCF$_3$OH), 2.20−2.13 (m, 2H, Cy−C*H*$_2$), 1.98 (br s, 3H, CH═CC*H*$_3$), 1.94−1.88 (m, 1H, Cy−C*H*$_2$), 1.62−1.43 (m, 3H, Cy−C*H*$_2$), 1.35 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (125.7 MHz, CDCl$_3$, δ)169.9 (*C*═O), 132.8 (CH═*C*CH$_3$), 131.7 (*C*H═CCH$_3$), 124.0 (q, J_{C-F} = 287 Hz, *C*F$_3$), 81.5 (q, J_{C-F} = 28 Hz, *C*CF$_3$), 63.8 (O*C*H$_2$CH$_3$), 40.6 (Cy), 35.8 (Cy), 26.3 (Cy), 24.7 (Cy), 17.6 (CH═C*C*H$_3$), 14.4 (OCH$_2$*C*H$_3$); LRMS (EI) *m*/*z* 266 [M]$^+$; HRMS (EI) exact mass calcd for C$_{12}$H$_{17}$O$_3$F$_3$ [M]$^+$ requires *m*/*z* 266.112979, found *m*/*z* 266.112595. Anal. Calcd for C$_{12}$H$_{17}$F$_3$O$_3$: C, 54.1; H, 6.44. Found: C, 54.44; H, 6.82. Ee's of both diastereoisomers were determined by GC using a Supelco Beta DEX column (injection temp 135 °C; column conditions 105 °C for 40 min ramp to 175 °C at 5 °C/min; hold 20 min, pressure 21 psi). Major exo-diastereoisomer: major (1′*R*,2*S*)-enantiomer t_R = 36.7 min, minor (1′*S*,2*R*)-enantiomer t_R = 35.2 min; 99% ee. Minor endo-diastereoisomer: (1′*S*,2*S*)-enantiomer t_R = 42.9 min, minor (1′*R*,2*R*)-enantiomer t_R = 46.3 min; 98% ee. exo:endo = 3:1. Absolute and relative stereochemistry assigned by analogy.

(2*S*,3′*S*,1″*S*)-Ethyl 2-(Trifluoromethyl)-2-hydroxy-3-[3′-(1″-ethoxycarbonyl-2″,2″,2″-trifluoro-1″-hydroxyethyl)cyclohex-1′-

en-2′-yl]propanoate (6d). A sample was isolated as a single diastereoisomer after purification by column chromatography. $[\alpha]_D^{20} = -51.3$ (*c* 1.45, CH_2Cl_2); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ) 6.09 (br s, 1H, =C*H*), 4.46−4.19 (m, 4H, OCH_2CH$_3$), 3.91 (s, 1H, O*H*), 3.77 (s, 1H, O*H*), 2.74 (m, 1H, C*H*CCF$_3$OH), 2.42 (d, *J* = 14.3 Hz, 1H, C*H*HCCF$_3$OH), 2.17 (d, *J* = 13.7 Hz, 1H, CH*H*CCF$_3$OH), 2.12−1.97 (m, 4H, Cy−CH_2), 1.50−1.39 (m, 2H, Cy−CH_2), 1.35 (t, *J* = 6.9 Hz, 3H, OCH$_2$CH_3), 1.33 (t, *J* = 6.9 Hz, 3H, OCH$_2$CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ) 170.9 (*C*=O), 169.5 (*C*=O), 136.4 (CH=*C*CH$_2$), 124.6 (*C*H=CCH$_2$), 123.8 (q, J_{C-F} = 287 Hz, *C*F$_3$), 123.4 (q, J_{C-F} = 286 Hz, *C*F$_3$), 79.9 (q, J_{C-F} = 28 Hz, *C*CF$_3$), 77.6 (q, J_{C-F} = 27 Hz, *C*CF$_3$), 63.8 (OCH$_2$CH$_3$), 63.7 (OCH$_2$CH$_3$), 41.0 (Cy), 36.7 (Cy), 25.2 (Cy), 24.7 (Cy), 16.9 (*C*H$_2$CCF$_3$OH), 13.6 (OCH$_2$*C*H$_3$), 13.4 (OCH$_2$*C*H$_3$); LRMS (EI) *m*/*z* 437 $[M + H]^+$; HRMS (EI) exact mass calcd for $C_{17}H_{23}O_6F_6$ $[M + H]^+$ requires *m*/*z* 437.139883, found *m*/*z* 437.140808. Anal. Calcd for $C_{17}H_{22}F_6O_6$: C, 46.79; H, 5.08. Found: C, 47.02; H, 5.21. Ee determined by GC using a Supelco Beta DEX column (injection temp 135 °C; column conditions 105 °C for 40 min ramp to 175 °C at 5 °C/min; hold 20 min, pressure 21 psi) major (2*S*,3′*S*,1″*S*)-diastereoisomer t_R = 62.1 min, minor (2*R*,3′*S*,1″*S*)-diastereoisomer t_R = 61.9 min; 91% de.

(2*S*)-Ethyl 3-(Cyclopenten-1′-yl)-2-(trifluoromethyl)-2-hydroxypropanoate (7a). A sample was isolated as a colorless oil after purification by column chromatography. $[\alpha]_D^{20} = -18.8$ (*c* 1.21, CH_2Cl_2); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ) 5.53 (br s, 1H, =C*H*), 4.38−4.28 (m, 2H, OCH_2CH$_3$), 3.79 (s, 1H, O*H*), 2.86 (d, *J* = 14.4 Hz, 1H, CH*H*CCF$_3$OH), 2.67 (d, *J* = 15.0 Hz, 1H, C*H*HCCF$_3$OH), 2.36−2.17 (m, 4H, Cy−CH_2), 1.87−1.77 (m, 2H, Cy−CH_2), 1.33 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$, δ) 170.2 (*C*=O), 137.0 (CH=*C*CH$_2$), 130.6 (*C*H=CCH$_2$), 123.9 (q, J_{C-F} = 286 Hz, *C*F$_3$), 78.3 (q, J_{C-F} = 28 Hz, *C*CF$_3$), 64.2 (OCH$_2$CH$_3$), 36.6 (Cy), 33.6 (Cy), 33.0 (Cy), 24.1 (*C*H$_2$CCF$_3$OH), 14.5 (OCH$_2$*C*H$_3$); LRMS (EI) *m*/*z* 251 $[M - H]^+$; HRMS (EI) exact mass calcd for $C_{11}H_{14}O_3F_3$ $[M - H]^+$ requires *m*/*z* 251.089504, found *m*/*z* 251.090229. Ee determined by GC using a Supelco Beta DEX column (injection temp 135 °C; column conditions 100 °C for 45 min ramp to 170 °C at 5 °C/min; hold 10 min, pressure 21 psi) major (2*S*)-enantiomer t_R = 26.8 min, (2*R*)-minor enantiomer t_R = 24.6 min; 72% ee. Absolute stereochemistry assigned by analogy.

(1′*S*,2*S*)-Ethyl 3,3,3-Trifluoro-2-hydroxy-2-(2′-methylenecyclopent-1′-yl)propanoate (7b). A sample was isolated as a single diastereoisomer after purification by column chromatography. $[\alpha]_D^{20} = +44.4$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ) 4.99 (br s, 1H, =C*H*$_a$H$_b$), 4.55 (br s, 1H, =CH$_a$*H*$_b$), 4.49−4.26 (m, 2H, OCH_2CH$_3$), 3.79 (s, 1H, O*H*), 3.17 (t, *J* = 8.2 Hz, 1H, C*H*CCF$_3$OH), 2.30−2.24 (m, 1H, Cy−CH_2), 2.12−1.92 (m, 1H, Cy−CH_2), 1.55−1.43 (m, 1H, Cy−CH_2), 1.37 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$, δ) 170.6 (*C*=O), 151.2 (*C*=CH$_2$), 124.1 (q, J_{C-F} = 288 Hz, *C*F$_3$), 108.4 (C=*C*H$_2$), 80.3 (q, J_{C-F} = 27 Hz, *C*CF$_3$), 64.1 (OCH$_2$CH$_3$), 45.3 (Cy), 36.0 (Cy), 27.6 (Cy), 25.5 (Cy), 14.4 (OCH$_2$*C*H$_3$); LRMS (EI) *m*/*z* 253 $[M + H]^+$; HRMS (EI) exact mass calcd for $C_{11}H_{16}O_3F_3$ $[M + H]^+$ requires *m*/*z* 253.105154, found *m*/*z* 253.105782. Anal. Calcd for $C_{11}H_{15}F_3O_3$: C, 52.38; H, 5.99. Found: C, 52.46; H, 6.12. Ee determined by GC using a Supelco Beta DEX column (injection temp 135 °C; column conditions 100 °C for 45 min ramp to 170 °C at 5 °C/min; hold 10 min, pressure 21 psi) major (1′*S*,2*S*)-enantiomer t_R = 23.3 min, minor (1′*R*,2*R*)-enantiomer t_R = 29.6 min; 99% ee. Absolute and relative stereochemistry assigned by analogy.

(1′*R*,2*S*)-Ethyl 3,3,3-Trifluoro-2-hydroxy-2-(2′-methylcyclopent-2′-en-1′-yl)propanoate (7c). A sample was formed as a 3:1 exo:endo mixture of diastereoisomers and isolated as a 10:1 exo:endo mixture after purification by column chromatography. $[\alpha]_D^{20}$= +13.4 (*c* 1.17, CH_2Cl_2). Major (1′*R*,2*S*)-diastereoisomer: ^{1}H NMR (300.0 MHz, $CDCl_3$, δ) 5.59 (br s, 1H, =C*H*), 4.38−4.31 (m, 2H, OCH_2CH$_3$), 3.81 (s, 1H, O*H*), 3.18 (t, *J* = 5.8 Hz, 1H, C*H*CCF$_3$OH), 2.38−2.26 (m, 1H, Cy−CH_2), 2.23−2.11 (m, 1H, Cy−CH_2), 2.08−1.99 (m, 2H, Cy−CH_2), 1.78 (br s, 3H, CH=CCH_3), 1.33 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$, δ) 170.6 (*C*=O), 137.9 (CH=*C*CH$_3$), 131.9 (*C*H=CCH$_3$), 124.0 (q, J_{C-F} = 287 Hz, *C*F$_3$), 80.4 (q, J_{C-F} = 28 Hz, *C*CF$_3$), 64.2 (OCH$_2$CH$_3$), 51.5 (Cy), 31.5 (Cy), 27.4 (Cy), 17.2 (CH=*C*CH$_3$), 14.4 (OCH$_2$*C*H$_3$). Minor (1′*S*,2*S*)-diastereoisomer: ^{1}H NMR (300.0 MHz, $CDCl_3$, δ) 5.59 (br s, 1H, =C*H*), 4.47−4.40 (m, 2H, OCH_2CH$_3$), 3.76 (s, 1H, O*H*), 3.36 (t, *J* = 5.8 Hz, 1H, C*H*CCF$_3$OH), 2.35−2.20 (m, 1H, Cy−CH_2), 2.20−2.11 (m, 1H, Cy−CH_2), 2.09−2.03 (m, 2H, Cy−CH_2), 1.75 (br s, 3H, CH=CCH_3), 1.37 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$, δ) 170.5 (*C*=O), 136.7 (CH=*C*CH$_3$), 132.0 (*C*H=CCH$_3$), 123.9 (q, J_{C-F} = 287 Hz, *C*F$_3$), 80.4 (q, J_{C-F} = 28 Hz, *C*CF$_3$), 64.1 (OCH$_2$CH$_3$), 50.7 (Cy), 30.3 (Cy), 26.5 (Cy), 16.0 (CH=*C*CH$_3$), 14.4 (OCH$_2$*C*H$_3$). LRMS (EI) *m*/*z* 252 $[M]^+$; HRMS (EI) exact mass calcd for $C_{11}H_{15}O_3F_3$ $[M]^+$ requires *m*/*z* 252.097329, found *m*/*z* 252.097076. Anal. Calcd for $C_{11}H_{25}F_3O_3$: C, 52.38, H; 5.99. Found: C, 52.67; H, 6.22. Ee's of both diastereoisomers were determined by GC using a Supelco Beta DEX column (injection temp 135 °C; column conditions 100 °C for 45 min ramp to 170 °C at 5 °C/min; hold 10 min, pressure 21 psi). Major exo-diastereoisomer: major (1′*R*,2*S*)-enantiomer t_R = 21.8 min, minor (1′*S*,2*R*)-enantiomer t_R = 22.1 min; 97% ee. Minor endo-diastereoisomer: major (1′*S*,2*S*)-enantiomer t_R = 28.3 min, minor (1′*R*,2*R*)-enantiomer t_R = 34.1 min; 95% ee. exo:endo = 3:1. Absolute and relative stereochemistry assigned by analogy.

(2*S*,3′*S*,1″*S*)-Ethyl 2-(Trifluoromethyl)-2-hydroxy-3-[3′-(1″-ethoxycarbonyl-2″,2″,2″-trifluoro-1″-hydroxyethyl)cyclopent-1′-en-2′-yl]propanoate (7d). A sample was isolated as a single diastereoisomer after purification by column chromatography. $[\alpha]_D^{20} = +1.96$ (*c* 0.92, CH_2Cl_2); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ) 5.73 (br s, 1H, =C*H*), 4.50−4.22 (m, 4H, OCH_2CH$_3$), 3.86 (s, 1H, O*H*), 3.80 (s, 1H, O*H*), 3.51−3.49 (br m, 1H, C*H*CCF$_3$OH), 2.83 (d, *J* = 14.6 Hz, 1H, C*H*HCCF$_3$OH), 2.38 (d, *J* = 13.8 Hz, 1H, CH*H*CCF$_3$OH), 2.44−2.33 (m, 1H, Cy−CH_2), 2.27−2.18 (m, 1H, Cy−CH_2), 2.15−2.04 (m, 1H, Cy−CH_2), 2.02−1.90 (m, 1H, Cy−CH_2), 1.36 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3), 1.32 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$, δ) 171.2 (*C*=O), 169.9 (*C*=O), 137.0 (CH=*C*CH$_2$), 134.2 (*C*H=CCH$_2$), 124.2 (q, J_{C-F} = 287 Hz, *C*F$_3$), 123.7 (q, J_{C-F} = 287 Hz, *C*F$_3$), 79.5 (q, J_{C-F} = 27 Hz, *C*CF$_3$), 79.4 (q, J_{C-F} = 28 Hz, *C*CF$_3$), 64.5 (OCH$_2$CH$_3$), 64.4 (OCH$_2$CH$_3$), 50.7 (Cy), 31.6 (Cy), 31.3 (Cy), 26.7 (*C*H$_2$CCF$_3$OH), 14.5 (OCH$_2$CH$_3$), 14.1 (OCH$_2$*C*H$_3$); LRMS (EI) *m*/*z* 423 $[M + H]^+$; HRMS (EI) exact mass calcd for $C_{16}H_{21}O_6F_6$ $[M + H]^+$ requires *m*/*z* 423.124233, found *m*/*z* 423.122650. Anal. Calcd for $C_{16}H_{20}F_6O_6$: C, 45.50; H, 4.77. Found: C, 45.87; H, 5.03. Ee determined by GC using a Supelco Beta DEX column (injection temp 135 °C; column conditions 100 °C for 45 min ramp to 170 °C at 5 °C/min; hold 10 min, pressure 21 psi) major (2*S*,3′*S*,1″*S*)-diastereoisomer t_R = 65.2 min, minor (2*R*,3′*S*,1″*S*)-diastereoisomer t_R = 64.8 min; 92% ee.

(3*S*,2*S*)-Ethyl 3-(Cyclohexen-1′-yl)-2-(trifluoromethyl)-2-hydroxybutanoate (8a). A sample was isolated as a 98:2 exo:endo mixture of diastereoisomer after purification by column chromatography. $[\alpha]_D^{20} = -18.6$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ) 5.58−5.53 (br s, 1H, =C*H*), 4.37−4.20 (m, 2H, OCH_2CH$_3$), 3.72 (s, 1H, O*H*), 2.86−2.79 (q, *J* = 7.0 Hz, 1H, C*H*CH$_3$), 2.01−1.92 (m, 4H, Cy−CH_2), 1.57−1.47 (br m, 4H, Cy−CH_2), 1.32 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3), 1.21 (dd, *J* = 7.0 Hz, 1.2 Hz, 3H, CHCH_3); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$, δ) 170.9 (*C*=O), 138.1 (*C*=CCHCH$_3$), 126.2 (*C*=CCHCH$_3$), 124.0 (q, J_{C-F} = 288 Hz, *C*F$_3$), 81.2 (q, J_{C-F} = 27 Hz, *C*CF$_3$), 64.0 (OCH$_2$CH$_3$), 43.7 (Cy), 26.8 (Cy), 25.9 (Cy), 23.5 (Cy), 22.8 (*C*HCH$_3$), 14.5 (OCH$_2$*C*H$_3$), 13.8 (CH*C*H$_3$); LRMS (EI) *m*/*z* 279 $[M - H]^+$; HRMS (EI) exact mass calcd for $C_{13}H_{18}O_3F_3$ $[M - H]^+$ requires *m*/*z* 279.120804, found *m*/*z* 279.121300. Ee's of both diastereoisomers were determined by GC using a Supelco Beta DEX column (injection temp 135 °C; column conditions 105 °C for 40 min ramp

to 175 °C at 5 °C/min; hold 20 min, pressure 21 psi). Major exo-diastereoisomer: major (3*S*,2*S*)-enantiomer t_R = 41.6 min, minor (3*R*,2*R*)-enantiomer t_R = 41.1 min; 99% ee. Minor endo-diastereoisomer: major (3*R*,2*S*)-enantiomer t_R = 47.5 min, minor (3*S*,2*R*)-enantiomer t_R = 47.2 min; 88% ee. exo:endo = 7:1. Absolute and relative stereochemistry assigned by analogy.

(1′*S*,2*S*)-Ethyl 2-((*E*)-2′-Ethylidenecyclohex-1′-yl)-3,3,3-trifluoro-2-hydroxypropanoate (8b). A sample was isolated as a single diastereoisomer after purification by column chromatography and crystallized by slow evaporation of a concentrated dichloromethane solution at room temperature. $[\alpha]_D^{20}$ = +39.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ) 5.23 (q, *J* = 6.7 Hz, 1H, =C*H*), 4.37−4.21 (m, 2H, OCH_2CH$_3$), 3.82 (s, 1H, O*H*), 2.88−2.85 (m, 1H, C*H*CCF$_3$OH), 2.39−2.31 (m, 1H, Cy−CH_2), 2.22−2.08 (m, 2H, Cy−CH_2), 2.04−1.89 (m, 1H, Cy−CH_2), 1.79−1.70 (m, 1H, Cy−CH_2), 1.66−1.45 (m, 3H, Cy−CH_2), 1.54 (dd, *J* = 6.7 Hz, 1.2 Hz, 3H, C=CHCH_3), 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ) 170.9 (*C*=O), 138.1 (*C*=CCH$_3$), 124.0 (q, J_{C-F} = 288 Hz, *C*F$_3$), 120.7 (CH=*C*CH$_3$), 82.9 (q, J_{C-F} = 27 Hz, *C*CF$_3$), 63.7 (OCH$_2$CH$_3$), 45.6 (Cy), 28.3 (Cy), 27.2 (Cy), 26.6 (Cy), 23.1 (Cy), 14.1 (OCH$_2$*C*H$_3$), 12.9 (C=CH*C*H$_3$); LRMS (EI) *m*/*z* 280 [M]$^+$; HRMS (EI) exact mass calcd for $C_{13}H_{19}O_3F_3$ [M]$^+$ requires *m*/*z* 280.128629, found *m*/*z* 280.127632. Anal. Calcd for $C_{13}H_{19}F_3O_3$: C, 55.71; H, 6.83. Found: C, 55.97; H, 6.91. Ee determined by GC using a Supelco Beta DEX column (injection temp 135 °C; column conditions 105 °C for 40 min ramp to 175 °C at 5 °C/min; hold 20 min, pressure 21 psi) major (1′*S*,2*S*)-enantiomer t_R = 41.2 min, minor (1′*R*,2*R*)-enantiomer t_R = 45.9 min; 99% ee. Relative stereochemistry determined by single-crystal X-ray crystallography and absolute stereochemistry assigned by analogy.

(1′*R*,2*S*)-Ethyl 2-(2′-Ethylcyclohex-2′-en-1′-yl)-3,3,3-trifluoro-2-hydroxypropanoate (8c). A sample was isolated as a colorless oil after purification by column chromatography. Diastereoisomers can be separated by column chromatography. Major exo-diastereoisomer: $[\alpha]_D^{20}$ = +5.6 (*c* 1.1, CH_2Cl_2). Minor endo-diastereoisomer: $[\alpha]_D^{20}$ = −36.1 (*c* 1.2, CH_2Cl_2). Major exo-diastereoisomer: ^{1}H NMR (300.0 MHz, $CDCl_3$, δ) 5.74 (br s, 1H, =C*H*), 4.44−4.26 (m, 2H, OCH_2CH$_3$), 3.61 (s, 1H, O*H*), 2.86 (t, *J* = 4.5 Hz, 1H, C*H*CCF$_3$OH), 2.18−2.00 (m, 4H, Cy−CH_2), 1.95−1.84 (m, 1H, Cy−CH_2), 1.83−1.72 (m, 1H, Cy−CH_2), 1.70−1.62 (m, 2H, CH=CCH_2CH$_3$), 1.35 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3), 0.99 (t, *J* = 7.3 Hz, 3H, CH=CCH$_2$CH_3). Minor endo-diastereoisomer: ^{1}H NMR (300.0 MHz, $CDCl_3$, δ) 5.71 (br s, 1H, =C*H*), 4.46−4.22 (m, 2H, OCH_2CH$_3$), 3.68 (s, 1H, O*H*), 2.98 (br m, 1H, C*H*CCF$_3$OH), 2.14−1.95 (m, 4H, Cy−CH_2), 1.92−1.82 (m, 1H, Cy−CH_2), 1.71−1.61 (m, 1H, Cy−CH_2), 1.58 (br m, 2H, CH=CCH_2CH$_3$), 1.37 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3), 0.95 (t, *J* = 7.4 Hz, 3H, CH=CCH$_2$CH_3). Major exo-diastereoisomer: ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$, δ) 170.2 (*C*=O), 136.7 (*C*=CH$_2$CH$_3$), 128.1 (*C*=CCH$_2$CH$_3$), 124.0 (q, J_{C-F} = 287 Hz, *C*F$_3$), 81.4(q, J_{C-F} = 28 Hz, *C*CF$_3$), 64.0 (OCH$_2$CH$_3$), 39.5 (Cy), 29.9 (Cy), 26.9 (Cy), 25.0 (Cy), 18.9 (C=C*C*H$_2$CH$_3$), 14.5 (OCH$_2$*C*H$_3$), 13.9 (C=CCH$_2$*C*H$_3$); LRMS (EI) *m*/*z* 279 [M − H]$^+$; HRMS (EI) exact mass calcd for $C_{13}H_{18}O_3F_3$ [M − H]$^+$ requires *m*/*z* 279.120804, found *m*/*z* 279.122101. Ee's of both diastereoisomers determined by GC using a Supelco Beta DEX column (injection temp 135 °C; column conditions 105 °C for 40 min ramp to 175 °C at 5 °C/min; hold 20 min, pressure 21 psi). Major exo-diastereoisomer: major (1′*R*,2*S*)-enantiomer t_R = 45.3 min, minor (1′*S*,2*R*)-enantiomer t_R = 44.2 min; 99% ee. Minor endo-diastereoisomer: major (1′*S*,2*S*)-enantiomer t_R = 45.8 min, minor (1′*R*,2*R*)-enantiomer t_R = 48.6 min; 92% ee. exo:endo = 4:1. Absolute and relative stereochemistry assigned by analogy.

Preparation of (2*S*)-3-(Cyclohexen-1′-yl)-2-(trifluoromethyl)-2-hydroxypropanoic Acid (9). A solution of (2*S*)-ethyl 3-(cyclohexen-1-yl)-2-(trifluoromethyl)-2-hydroxypropanoate (0.100 g, 0.376 mmol) and NaOH (0.300 g, 7.52 mmol) in methanol (3.0 mL) was stirred at room temperature and monitored by TLC until all of the starting materials had been consumed (ca. 18 h). The resulting solution was diluted with water (25 mL) and washed with diethyl ether, and the aqueous layer was acidified to pH 3 using 1 N HCl. The product was extracted into diethyl ether (5 × 15 mL), the organic layers were combined, washed with brine, and dried over Na_2SO_4, and the solvent was removed in vacuo to afford the pure product as an off-white solid in a 95% yield. Mp 121−124 °C; $[\alpha]_D^{20}$ = −16.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300.0 MHz, $CDCl_3$, δ) 6.65 (br s, 2H, O*H*, CO_2*H*), 5.61 (br s, 1H, =C*H*), 2.72 (d, *J* = 14.0 Hz, 1H, CH*H*CCF$_3$OH), 2.53 (d, *J* = 14.0 Hz, 1H, C*H*HCCF$_3$OH), 2.08−1.86 (br m, 4H, Cy−CH_2), 1.60−1.47 (br m, 4H, Cy−CH_2); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, δ) 173.0 (*C*=O), 130.9 (CH=*C*CH$_2$), 129.0 (*C*H=CCH$_2$), 123.6 (q, J_{C-F} = 287 Hz, *C*F$_3$), 78.5 (q, J_{C-F} = 29 Hz, *C*CF$_3$), 40.3 (Cy), 30.1 (Cy), 25.8 (Cy), 23.2 (Cy), 22.2 (*C*H$_2$CCF$_3$OH); LRMS (EI) *m*/*z* 238 [M + H]$^+$; HRMS (EI) exact mass calcd for $C_{10}H_{13}O_3F_3$ [M + H]$^+$ requires *m*/*z* 238.081679, found *m*/*z* 238.082451. Anal. Calcd for $C_{10}H_{13}F_3O_3$: C, 50.42; H, 5.50. Found: C, 50.77; H, 5.81.

Preparation of (*R*)-1-(1-Naphthyl)ethylammonium (2*S*)-3-(Cyclohexen-1-yl)-2-(trifluoromethyl)-2-hydroxypropanoate (10). To a solution of (2*S*)-3-(cyclohexen-1-yl)-2-(trifluoromethyl)-2-hydroxypropanoic acid (0.064 g, 0.27 mmol) in 5 mL of dichloromethane was added (*R*)-1-(1-naphthyl)ethylamine (0.046 mL, 0.27 mmol). After stirring at room temperature for 5 min, the solvent was removed in vacuo to afford a white solid which was washed with 2 × 2 mL of hexane and subsequently crystallized by slow diffusion of a concentrated dichloromethane solution layered with hexane (89%). Mp 137−139 °C; $[\alpha]_D^{20}$ −73.6 (*c* 1.0, acetone); ^{1}H NMR (300.0 MHz, CD_2Cl_2, δ) 7.84−7.73 (m, 3H, C$_{10}H_7$), 7.59−7.57 (m, 1H, C$_{10}H_7$), 7.52−7.36 (m, 3H, C$_{10}H_7$), 7.25 (br s, 3H, NH_3), 5.23 (br s, 2H, =C*H*, O*H*), 5.07 (q, *J* = 6.0 Hz, 1H, C*H*CH$_3$), 2.17 (q, *J* = 13.8 Hz, 2H, CH_aH_bCCF$_3$OH), 1.76 (br s, 4H, Cy−CH_2), 1.60 (d, *J* = 6.6 Hz, 3H, CHCH_3), 1.35−1.33 (m, 4H, Cy−CH_2); ^{13}C{^{1}H} NMR (75.5 MHz, CD_2Cl_2, δ) 174.6 (*C*=O), 135.5 (*C*$_{10}H_7$), 134.8 (*C*$_{10}H_7$), 133.2 (C=*C*CH$_2$), 130.8 (*C*$_{10}H_7$), 130.1 (*C*$_{10}H_7$), 130.0 (*C*$_{10}H_7$), 127.9 (*C*=CCH$_2$), 127.0 (*C*$_{10}H_7$), 126.5 (*C*$_{10}H_7$), 126.2 (*C*$_{10}H_7$), 126.0 (q, J_{C-F} = 287 Hz, *C*F$_3$), 123.9 (*C*$_{10}H_7$), 122.4 (*C*$_{10}H_7$), 78.6 (q, J_{C-F} = 26 Hz, *C*CF$_3$), 47.8 (C*H*CH$_3$), 40.9 (Cy), 30.5 (Cy), 26.2 (CH*C*H$_3$), 23.9 (Cy), 22.9 (Cy), 21.1 (*C*H$_2$CCF$_3$OH); LRMS (EI) *m*/*z* 238 [M + H]$^+$; HRMS (EI) exact mass calcd for $C_{10}H_{13}O_3F_3$ [M + H]$^+$ requires *m*/*z* 238.081679, found *m*/*z* 238.081833. Anal. Calcd for $C_{22}H_{26}F_3NO_3$: C, 64.54; H, 6.40; N, 3.42. Found: C, 64.78; H, 6.66; N, 3.49.

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Supporting Information Available: General experimental procedure, Figure S1, and for compounds **1a**, **8b**, and **10**, details of crystal data, structure solution and refinement, atomic coordinates, bond distances, bond angles, and anisotropic thermal parameters in CIF format. Observed and calculated structure factor tables are available from the authors upon request. This material is available free of charge via the Internet at http://pubs.acs.org.

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