Efficient Asymmetric Carbonyl-Ene Reactions Catalyzed by Platinum Metal Lewis Acid Complexes of Conformationally Flexible NUPHOS Diphosphines: A Comparison with BINAP

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A comparative study of the Lewis acid-catalyzed carbonyl-ene reaction of a range of monosubstituted, unsymmetrical 1,1-disubstituted and trisubstituted alkenes with ethyl trifluoropyruvate revealed that platinum complexes of enantiopure conformationally flexible *tropos* NUPHOS diphosphines rival or outperform their atropisomeric enantiopure BINAP counterpart. The stereochemical integrity of these NUPHOS diphosphines remains intact over extended periods, as evidenced by the high ee's obtained for an unreactive substrate requiring >20 h to reach good conversions and the presence of a single diastereoisomer after addition of (*S*,*S*)-DPEN to the reaction mixture. The absolute and relative stereochemistry of a number of the ene products has been determined by single-crystal X-ray crystallography. The sense of asymmetric induction, the regioselectivity, and the *exo* diastereoselectivity are consistent with a stereochemical model based on a square-planar catalyst·pyruvate adduct. The allylbenzene derivatives required for this study were conveniently prepared by the palladium-catalyzed cross-coupling between the corresponding aromatic bromide and allylmagnesium bromide using a catalyst mixture based on $Pd_2(dba)_3$ and a NUPHOS diphosphine.

Introduction

The use of conformationally flexible bidentate ligands for asymmetric catalysis is emerging as a powerful and practical strategy in synthesis, particularly with metal complexes of palladium, platinum, rhodium, and ruthenium.[1] In this approach a conformationally flexible ligand can either (i) magnify the effect of another chiral ligand (asymmetric activation)[2] or (ii) act as the sole source of asymmetry to convey the chiral information in an enantioselective transformation.[3] The former strategy has proven to be highly effective in the ruthenium-catalyzed asymmetric hydrogenation of ketones. For instance, the 3:1 thermodynamic mixture of *S*/*S*,*S* and *R*/*S*,*S* diastereoisomers formed by addition of (*S*,*S*)-DPEN to [$RuCl_2$(DM-BIPHEP)$(dmf)_n$] [(*S*,*S*)-DPEN = (*S*,*S*)-1,2-diphenylethylenediamine; DM-BIPHEP = 2,2′-[(3,5-dimethylphenyl)phosphino]-biphenyl] catalyzes the hydrogenation of 1-acetonaphthone to afford an ee of 84%, slightly higher than that of 80% obtained with its *rac*-DM-BINAP counterpart, which necessarily exists as a 1:1 mixture of diastereoisomers.[4] Although this high ee is clearly due to the favorable diastereoisomeric ratio, since the corresponding 1:1 and 2:1 mixtures of diastereoisomers gave ee's of 63% and 73%, respectively, it could arise from a difference in the enantioselectivities and/or the turnover frequencies of the two diastereoisomers. While the relative contributions of these two factors were not determined, in the case of the *rac*-Tol-BINAP/(*S*,*S*)-DPEN system the more active *R*/*S*,*S*-diastereoisomer catalyzes the enantioselective hydrogenation of cyclohexenone 121 times faster than its *S*/*S*,*S* counterpart.[5] Regardless of the origin of the catalyst performance, this study demonstrated distinct advantages of using a conformationally flexible ligand over its more expensive atropisomeric counterpart. More recently, Mikami[6] and Ding[7] both applied this approach to the use of achiral benzophenone-derived diphosphines, DPBP, for the asymmetric hydrogenation of ketones and achieved ee's up to 99%, and we have reported[8] the use of *rac*-1,2-bis(diphenylphosphinomethyl)cyclohexane as an inexpensive alternative to biaryl-based systems.

In contrast, the use of BIPHEP as the only source of asymmetry in platinum group metal Lewis acid catalysis relies on a chiral auxiliary to resolve the axial chiral conformations. The resolving agent is subsequently liberated to generate an enantiopure Lewis acid fragment that is conformationally stable

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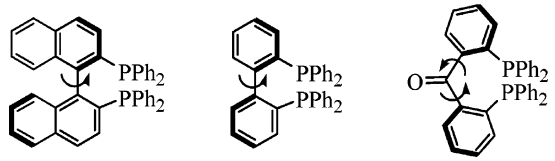
with respect to racemization over the time scale of the reaction. This approach is particularly attractive since it should be possible to convert a racemic metal−BIPHEP complex into a single enantiomer with the desired stereochemistry by using an appropriate chiral resolving agent L*. In this regard, Gagné[9] was first to report that coordination of BIPHEP to a substitutionally inert metal slows atropinterconversion such that its axial chiral conformations can be resolved and used in asymmetric Lewis acid catalysis. In this case, enantiopure (*S*)-BINOL was used as the resolving agent and the resulting 1:1 mixture of δ- and λ-[(BIPHEP)Pt{(*S*)-BINOL}] was interconverted at elevated temperatures to afford δ-[(BIPHEP)Pt{(*S*)-BINOL}] of high diastereopurity (95:5). The Lewis acid generated by liberating the BINOL with triflic acid catalyzed both Diels−Alder and glyoxylate-ene reactions, giving ee's of 94% and 72%, respectively, with no loss of enantiopurity of the catalyst during the reaction. The key to obtaining *complete* control of the axial chirality of BIPHEP, and related diphosphines, appears to be a judicious choice of chiral resolving agent and an appropriate reaction temperature.[10] Ideally, a 1:1 mixture of L* and metal-coordinated BIPHEP should result in selective coordination of L* to a single enantiomer of the [M(BIPHEP)] at room temperature, while at elevated temperatures atropinterconversion of the opposite enantiomer of [M(BIPHEP)] would effect selective coordination of the remaining L* to ultimately afford diastereopure λ- or δ-[M(BIPHEP)(L*)]. Both 3,3′-dimethyl-2,2′-diamino-1,1′-binaphthyl and 2,2′-bis(trifluoromethanesulfonylamino)-1,1′-binaphthyl have proven to be ideal resolving agents for BIPHEP complexes of Rh, Pd, and Pt, and the resulting enantiopure Lewis acid fragments afford high levels of enantiocontrol in the carbonyl-ene,[10b,c] hetero Diels−Alder reactions[10d−f] as well as the ene-type cyclization.[10g,h] Interestingly, there is now increasing evidence that the *tropos*/*atropos* character of rhodium-coordinated BIPHEP depends on the resolving agent, and in one recent development the chiral amino alcohol (*S*)-NOBIN gave [(BIPHEP)Rh{(*S*)-NOBIN}] (NOBIN = 2′-amino-1,1′-binaphthyl-2-ol) as an 82:18 *R*/*S*:*S*/*S* mixture of diastereoisomers instantaneously at room temperature, whereas the corresponding (*R*)-2,2′-diamino-1,1′-binaphthyl/Rh(BIPHEP) system required 17 days to reach complete diastereoselection.[11]

Some time ago we developed an entirely new class of conformationally flexible diphosphines, NUPHOS[12] (Scheme 2), that bears a clear similarity to BIPHEP in that (i) two diphenylphosphino groups are linked by a four-carbon sp^2-tether, (ii) it is *tropos* in nature, and (iii) coordination to platinum slows atropinversion such that enantiopure conformations can be resolved and the resulting enantiopure Lewis acid used in asymmetric catalysis,[13] in some cases giving ee's that rival or exceed those obtained with their atropisomeric counterparts such as MeO-BIPHEP and BINAP. The most appealing feature of NUPHOS diphosphines is their modular, straightforward synthesis from inexpensive and readily available starting materials, in a single-pot reaction. As a result of ongoing studies in this area, we recently had cause to investigate the carbonyl-ene reaction of 1,1-disubstituted and trisubstituted alkenes with ethyl trifluoropyruvate,[14] catalyzed by Lewis acid metal complexes of the type [M{(*R*)-BINAP}]$(SbF_6)_2$ (M = Ni, Pd, Pt), which led to several interesting discoveries relating to subtle differences in the reactivity of these catalysts. In particular, while Lewis acid palladium complexes always gave the expected α-hydroxy ester in good to excellent diastereo- and enantioselectivity, their platinum- and nickel-based counterparts catalyzed isomerization of the methylenecycloalkane and the carbonyl-ene reaction of the resulting isomeric mixture of alkenes at comparable rates to afford a range of α-hydroxy esters in high regioselectivity, good diastereoselectivity, and good to excellent enantioselectivity. The same Lewis acids also catalyzed postreaction isomerization of the ene product as well as consecutive ene reactions to afford a novel double-ene product. As part of a program to evaluate the potential of NUPHOS diphosphines to compete with their BINAP counterparts, we have undertaken a systematic and thorough comparison of their performance in the carbonyl-ene reaction and herein present convincing evidence that these inexpensive and easy-to-prepare diphosphines could offer a practical alternative to the use of enantiopure biaryl-based systems.

Scheme 1. Selected Atropos and Tropos Diphosphines



(*R*)-BINAP (*R*)-BIPHEP (*R*)-DPBP

Scheme 2. Acylic and Monocyclic NUPHOS Diphosphines

1,2,3,4-R_4-NUPHOS
R = Me, **1a**; R = Ph, **1b**

1,4-R_2-cyclo-C_6H_8-NUPHOS
R = Et, **1c**; R = Ph, **1d**

Results and Discussion

The asymmetric carbonyl-ene reaction between an α-keto ester and an alkene is a convenient route to synthetically versatile homoallylic alcohols containing a tertiary stereogenic center (eq 1).[15] While the corresponding reaction with glyoxylate esters

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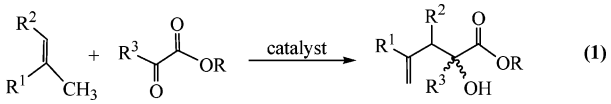
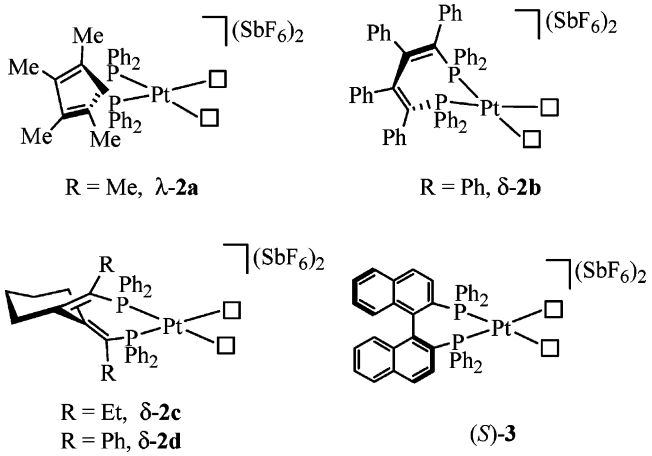


(1)

(R^3 = H) has been thoroughly studied[16] with a range of Lewis acid metal complexes,[17] there are still relatively few reports of asymmetric carbonyl-ene reactions with α-keto esters ($R^3 \neq$ H).[18] Since only a limited number of these involve square-planar Lewis acid platinum metal complexes,[18a−c] the addition of alkenes to ethyl trifluoropyruvate (R = Et, $R^3 = CF_3$) was considered an ideal transformation with which to evaluate the relative merits of platinum-based Lewis acids of NUPHOS diphosphines against their BINAP counterparts. The Lewis acid catalysts used in this study are shown in Chart 1 and were all generated by treatment of a dichloromethane solution of the corresponding enantiopure platinum dichloride complex with 2 equiv of silver hexafluoroantimonate for 30 min immediately prior to addition of substrate. In the case of λ-**2a** and δ-**2b**−**d**, activation was carried out at low temperature to limit/minimize

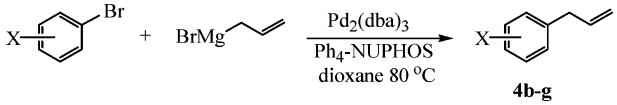
Chart 1. NUPHOS- and BINAP-Based Lewis Acid Catalysts



racemization of the resulting Lewis acid. Reaction mixtures were routinely monitored by quenching with 1 equiv of (*S*,*S*)-DPEN to establish the extent of racemization, and in all cases the resulting ^{31}P NMR spectrum showed the presence of a single diastereoisomer, firm evidence that the NUPHOS stereochemistry remains intact during activation and subsequent reaction, even after extended reaction times (>20 h).

Asymmetric Carbonyl-Ene Reactions with Allylbenzene Derivatives. We began this study by examining the carbonyl-ene reaction between a range of allylbenzene derivatives, substituted at the aromatic ring. Since only a limited number of these substrates are commercially available, **4b**−**g** were prepared via palladium-catalyzed cross-coupling of the corresponding aromatic bromide with allylmagnesium bromide, in dioxane at 80 °C using a catalyst generated *in situ* from $Pd_2(dba)_3$ and Ph_4-NUPHOS (Table 1). Unfortunately, the same procedure could not be used to prepare substrate **4h**, as the reaction between 1-bromo-4-nitrobenzene and allylmagnesium bromide resulted in N-allylation to afford *N*-allyl(4-allylphenyl)-amine as the sole product. However, a high yield of **4h** was obtained from the palladium-catalyzed Suzuki reaction between allylboronic acid pinacol ester and 4-bromonitrobenzene, as previously described.[19]

Table 1. Synthesis of Allyl Benzene Derivatives by the Palladium-Catalyzed Cross-Coupling between Aromatic Bromides and Allylmagnesium Bromide Catalyzed by $Pd_2(dba)_3$/Ph_4-NUPHOS in Dioxane



entry[a]	X	product	yield (%)[b]
1	4-Me	**4b**	60
2	2-Me	**4c**	46
3	3,5-Me_2	**4d**	63
4	4-Cl	**4e**	76
5	2-Cl	**4f**	85
6	3-Cl	**4g**	73
7[c]	4-NO_2	**4h**	0

[a] Reaction conditions: 1 mol % Ph_4-NUPHOS, 0.5 mol % $Pd_2(dba)_3$, aryl bromide (11.4 mmol), and allylmagnesium bromide (12.5 mmol) in 10.0 mL of dioxane at 80 °C. [b] Isolated yields after column chromatography. [c] Prepared in 81% yield following the published procedure.[19]

While the carbonyl-ene reaction between allylbenzene and ethyl trifluoropyruvate has previously been reported,[18a,b] the use of allylbenzene derivatives substituted at the aromatic ring has not been investigated, and as such, each of the products **5b**−**h** was purified by column chromatography and characterized by conventional spectroscopic and analytic techniques. The data in Table 2 show that catalysts λ-**2a** and δ-**2c** gave α-hydroxy ester **5a** in good yield with complete *E*-selectivity and excellent enantioselectivity (98% and 99%, respectively), while δ-**2b**,**d** gave markedly lower conversions, although the enantioselectivities remained high. These results also show that catalyst performance depends on the nature of the C_4-tether and that in general catalyst based on **1c** was consistently the most efficient across all the substrates examined, although excellent ee's and high yields of α-hydroxyester **5b**−**h** were typically obtained with the other NUPHOS diphosphines, with the exception of δ-**2b**, which gave low to poor conversions and thus was tested with only a limited number of substrates. The performance of the corresponding (*S*)-BINAP-based catalyst, (*S*)-**3**, was also

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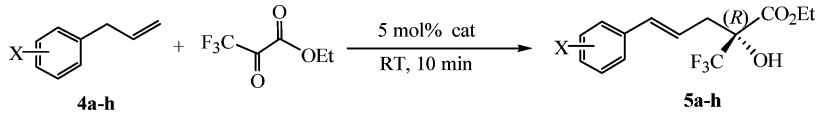
Table 2. Asymmetric Carbonyl-Ene Reaction between Allylbenzene Derivatives and Ethyl Trifluoropyruvate Catalyzed by λ-2a, δ-2b-d, and (*S*)-3 in CH_2Cl_2



4a-h **5a-h**

entry[a]	X	catalyst (mol %)	time (min)	conversion (%)[b]	% ee[c]
1	H	λ-**2a** (5)	10	64	98[d]
2	H	δ-**2b** (5)	10	20	93
3	H	δ-**2c** (5)	10	79	99
4	H	δ-**2d** (5)	10	17	94
5	H	(*S*)-**3** (5)	10	92	99
6	4-Me	λ-**2a** (5)	60	74	95[d]
7	4-Me	δ-**2b** (5)	60	0	nd
8	4-Me	δ-**2c** (5)	60	79	96
9	4-Me	(*S*)-**3** (5)	60	90	93
10	2-Me	λ-**2a** (5)	60	51	97[d]
11	2-Me	δ-**2b** (5)	60	0	nd
12	2-Me	δ-**2c** (5)	60	77	99
13	2-Me	(*S*)-**3** (5)	60	81	96
14	3,5-Me_2	λ-**2a** (5)	60	95	96[d]
15	3,5-Me_2	δ-**2c** (5)	60	89	90
16	3,5-Me_2	(*S*)-**3** (5)	60	94	93
17	4-Cl	λ-**2a** (5)	60	61	98[d]
18	4-Cl	δ-**2b** (5)	60	9	nd
19	4-Cl	δ-**2c** (5)	60	73	>99
20	4-Cl	(*S*)-**3** (5)	60	74	>99
21	2-Cl	λ-**2a** (5)	60	58	96[d]
22	2-Cl	δ-**2c** (5)	60	66	98
23	2-Cl	(*S*)-**3** (5)	60	62	98
24	3-Cl	λ-**2a** (5)	60	83	95[d]
25	3-Cl	δ-**2c** (5)	60	79	99
26	3-Cl	(*S*)-**3** (5)	60	83	>99
27	4-NO_2	δ-**2a** (5)	1440	84	99[d]
27	4-NO_2	δ-**2c** (5)	1440	86	>99
28	4-NO_2	(*S*)-**3** (5)	1440	92	>99

[a] Reaction conditions: 5 mol % catalyst, allylbenzene (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. [d]Opposite enantiomer of that shown in the table figure. Average of three runs. nd = not determined.

investigated for each of the allylbenzene derivatives in order to compare directly the efficacy of an atropisomeric biaryl diphosphine with that of the NUPHOS diphosphines. For each substrate **4a**−**h**, catalyst δ-**2c** gave ee's and conversions that were comparable to those obtained with (*S*)-**3**. While high levels of conversion were reached within 60 min for the vast majority of substrates examined, 1-allyl-4-nitrobenzene required ca. 20 h to achieve a similar level of conversion. The ee of >99% obtained with δ-**2c** is comparable to that obtained with (*S*)-BINAP and strongly suggests that the stereochemical integrity of the catalyst remains intact over the time scale of the reaction. This was confirmed by quenching the reaction mixture with (*S*,*S*)-DPEN, which gave diastereopure δ-[Pt(**1c**){(*S*,*S*)-DPEN}]-$(SbF_6)_2$, as evidenced by a single resonance (δ, −5.9 ppm, $^1J_{Pt-P}$ = 2230 Hz) in the ^{31}P NMR spectrum.

The absolute configuration of α-hydroxy ester **5a** was determined by comparison of the GC retention times and the optical rotation with that reported in the literature,[18] and those of **5b**−**h** were assigned by analogy. As expected, α-hydroxy esters generated from δ-**2b**−**d** and λ-**2a** have opposite absolute configuration, the latter giving product with *S* absolute configuration and confirming that NUPHOS diphosphines with a δ-conformation of the C_4-tether behave in the same manner as (*S*)-BINAP. The sense of asymmetric induction is entirely consistent with the stereochemical models developed for the [M{(*S*)-BINAP}](X)$_2$ (M = Pd, Pt)-catalyzed Diels−Alder reaction between *N*-acryloyloxazolidinones and dienes[20] and the [Cu{(*S*,*S*)-*t*-BuBox}]$(SbF_6)_2$-catalyzed Diels−Alder and aldol reactions of α-dicarbonyl substrates,[21] which involve coordination of the dienophile through both carbonyl oxygen atoms to form a square-planar catalyst·substrate adduct. In the case of a δ-NUPHOS diphosphine the equatorial phenyl rings (Ph_{eq}) are situated in opposite quadrants and prevent approach of the alkene to the *re* face, thereby rendering addition to the *si* face more favorable (Figure 1).

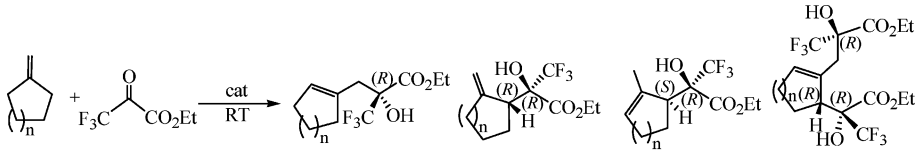
Figure 1. Stereochemical model to rationalize preferential *si* face approach of allylbenzene to afford α-hydroxyester with *R* configuration.

Asymmetric Carbonyl-Ene Reactions with 1,1-Disubstituted and Trisubstituted Alkenes. The comparison has been extended to include the addition of methylenecycloalkane to ethyl trifluoropyruvate, the results of which are listed in Table 3. Qualitatively, the performance of catalysts based on λ-**2a** and δ-**2b**-**d** closely mirrors their BINAP counterpart in terms of (i) the product distribution, (ii) the regioselectivity, (iii) the *exo*:

(20) (a) Oi, S.; Kashiwagi, K.; Inoue, Y. *Tetrahedron Lett.* **1998**, *39*, 6253. (b) Ghosh, A. K.; Matsuda, H. *Org. Lett.* **1999**, *1*, 2157. (c) Oi, S.; Terada, E.; Ohuchi, K.; Kato, T.; Tachibana, Y.; Inoue, Y. *Organometallics* **1999**, *64*, 8660.

(21) (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.

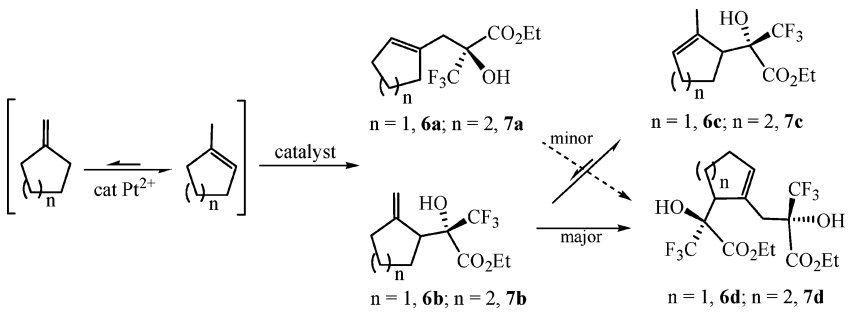
Table 3. Asymmetric Carbonyl-Ene Reaction between Methylenecycloalkane and Ethyl Trifluoropyruvate Catalyzed by *λ*-2a, *δ*-2b−d, and (*S*)-3 in CH_2Cl_2



entry[a]	catalyst (mol %)	n	conv (%)[b]	product ratio[c] 6 or 7 a:b:c:d	*exo*:*endo* ratio[d] 6 or 7 b	6 or 7 c	% ee[e] 6 or 7 a	b	c	%de[f,g] 6 or 7 d
1[h]	*λ*-**2a** (5)	1	100	13:63:18:6	>99:1	5:1	61	>99	83, nd	89
2	*δ*-**2b** (5)	1	99	7:57:36:0	>99:1	9:1	52	80	58, nd	
3	*δ*-**2c** (5)	1	100	11:63:20:6	>99:1	6:1	70	>99	89, nd	91
4[i]	*δ*-**2c** (5)	1	>99	52:47:1:0	>99:1		69	>99	nd, nd	
5	*δ*-**2d** (5)	1	65	6:64:30:0	>99:1	2:1	64	80	52, nd	
6	(*S*)-**3** (5)	1	100	7:68:15:10	>99:1	3:1	72	>99	97, 95	92
7[h]	*λ*-**2a** (5)	2	100	45:49:4:3	>99:1	1:1	63	99	93, nd	nd
8	*δ*-**2b** (5)	2	>99	20:75:5:0	>99:1	1:1	41	92	77, 66	
9	*δ*-**2c** (5)	2	>99	43:55:1:1	>99:1	3:2	70	>99	99,99	89
10	*δ*-**2d** (5)	2	94	26:70:2:0	>99:1	2:1	35	94	64, 55	
11	(*S*)-**3** (5)	2	100	38:47:10:5	>99:1	1:4	77	99	99, 98	91

[a] Reaction conditions: 5 mol % catalyst, methylenecyclohexane (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 X-ray crystal analysis of (1′*R*,2*R*)-**9b**, (1′*R*,2*R*)-**9c**, or by analogy. [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. Relative configuration assigned by X-ray analysis and absolute configuration by analogy with **9b** and **9c**. [g]Minor enantiomers were not detected. [h]Opposite enantiomer of that shown in the table figure. [i]Reaction conducted for 1 min. Average of three runs. nd = not determined.

Scheme 3. Product Distribution of the Carbonyl-Ene Reaction between Methylenecycloalkane and Ethyl Trifluoropyruvate



endo selectivity, and (iv) the enantioselectivity. First, *δ*-**2c** catalyzed the carbonyl-ene reaction with methylenecyclopentane to afford the expected α-hydroxy ester **6a** in good enantioselectivity, together with three additional products, **6b**, **6c**, and **6d**, all of which were also formed with (*S*)-**3** (Scheme 3 and Table 3 entry 3). Products **6b** and **6c** are regioisomers that result from the corresponding ene reaction with 1-methylcyclopentene, generated via the Lewis acid-catalyzed isomerization of the methylenecyclopentane, while **6d** is a double-ene product formed by addition of **6b** to ethyl trifluoropyruvate (Scheme 3), the distribution of these α-hydroxy esters reflecting the relative rates of isomerization versus ene reactivity. Although **6d** could also form by addition of **6a** to ethyl trifluoropyruvate (Scheme 3, minor), we have previously shown that this pathway is much slower than the corresponding addition to **6b** (Scheme 3, major) and is not significant.[14] The parallels in catalyst performance between *λ*/*δ*-**2a**−**d** and (*S*)-BINAP also extend to trends in enantioselectivity and diastereoselectivity in that *λ*-**2a** and *δ*-**2b**−**d** gave α-hydroxy ester **6a** in good to moderate enantioselectivity and for the mono-ene products derived from the isomerized alkene, moderate regioselectivity in favor of the methyl C−H bond to give **6b**, low to high diastereoselectivity, and excellent enantioselectivity for **6b** and **6c** (entries 1−5). A similar distribution of products and comparable levels of regio- and stereocontrol were also obtained with methylenecyclohexane (entries 7−10).

A stereochemical model based on the steric differentiation experienced during *exo* and *endo* approach of 1-methylcycloalkene to a square-planar catalyst·substrate complex adequately accounts for the observed *exo* approach to form (1′*R*,2*R*)-**6b**/**7b** in high diastereoselectivity and (1′*S*,2*R*)-**6c**/**7c** with low diastereoselectivity. However, the moderate level of regiocontrol was somewhat surprising since the catalyst·substrate complex has to discriminate between the methyl substituent (pathway a) and the α-CH_2 of the cycloalkyl ring (pathway b) during *exo* approach of the alkene to the *si* face of the platinum-coordinated pyruvate, the transition state model clearly showing that there would be significant steric differentiation (Figure 2). We have discovered that the regioselectivity measured after 10 min is in fact artificially low due to isomerization of **6b** to **6c**, and the intrinsic regioselectivity measured at much shorter reaction times is significantly higher (Table 3 entry 4 vs 3, *vide infra*). In this regard, Evans has reported exclusive regiocontrol for the α-CH_2 of 1-methylcyclohexene in the ene reaction with ethyl glyoxylate

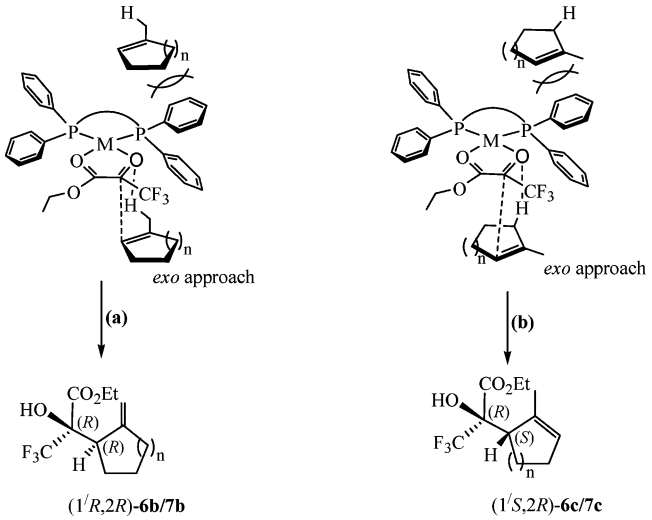


Figure 2. Stereochemical model proposed to account for the high level of regioselectivity obtained in the addition of 1-methylcycloalkene to ethyl trifluoropyruvate.

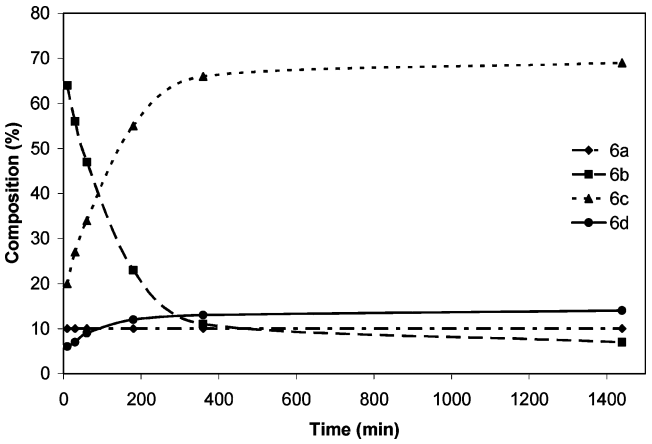


Figure 3. Variation of percent composition for the carbonyl-ene reaction between methylenecyclopentane and ethyl trifluoropyruvate catalyzed by δ-**2c**, in dichloromethane with respect to time at room temperature.

catalyzed by Lewis acid copper complexes of bis(oxazolines), while the corresponding reaction with 1-methylcyclopentene and 1-methylcycloheptene gave multiple regiochemical isomers.[17k]

Further parallels in catalyst performance were also evident in a study of the variation in composition of **6a**−**d** with respect to time for the reaction between methylenecyclopentane and ethyl trifluoropyruvate, in dichloromethane catalyzed by δ-**2c**, which showed that α-hydroxy ester **6c** and double-ene product **6d** increase at the expense of **6b**, while **6a** remains constant (Figure 3), in much the same manner as the reaction catalyzed by (*R*)-**3**.[14] Although isomerization of **6b** to **6c** is relatively slow, the **6b**:**6c** ratio of 47:1 obtained at ca. 1 min (entry 5) is a more reliable measure of the intrinsic regioselectivity, since isomerization of **6b** and its further ene reaction to afford **6d** both contribute to the artificially low regioselectivity described above at long reaction times. Moreover, analysis of the GC retention times and a knowledge of the absolute configurations of **6b** and **6c** (*vide infra*) revealed that this isomerization converts the major *exo* diastereoisomer of **6b**, with (1′*R*,2*R*) configuration, into (1′*R*,2*R*)-**6c**, which corresponds to the minor *endo* diastereoisomer from the ene reaction between 1-methylcycloalkene and ethyl trifluoropyruvate (Scheme 4). Thus, reaction mixtures analyzed after long reaction times (>30 min) result in an artificially high diastereoselectivity in favor of the *endo* diastereoisomer of **6c** due to isomerization of (1′*R*,2*R*)-**6b**, since the major *exo* diastereoisomer of **6c** from the ene reaction of 1-methylcyclopentene has (1′*S*,2*R*) configuration (see Figure 2).

Scheme 4. Isomerization of 1/*R*,2*R*-6b/7b to 1/*R*,2*R*-6c/7c and Formation of Diastereoisomeric Ammonium Salts for Determination of Absolute Configuration

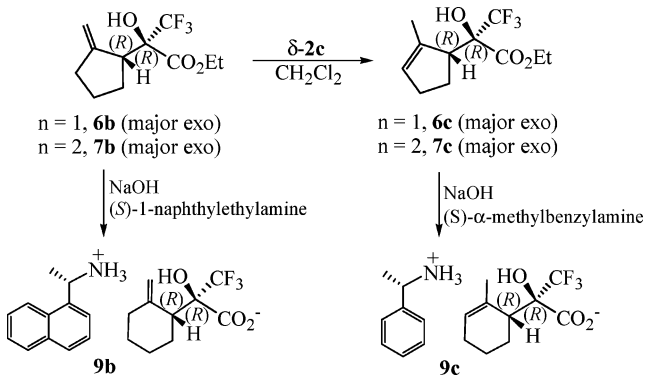


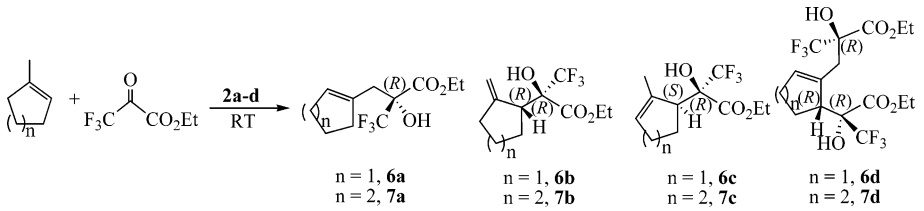
Table 3 also shows that while the trends in catalyst selectivity and activity are qualitatively similar for each catalyst studied, δ-**2c** and λ-**2a** clearly outperform δ-**2b** and δ-**2d**. For instance, δ-**2c** gave α-hydroxy ester **6a** in good yield and moderate enantioselectivity and **6b** and **6c** with a moderate level of regiocontrol, the former in high diastereoselectivity and enantioselectivity, the latter with moderate diastereoselectivity and good enantioselectivity (Table 3 entry 3).

The similarity in catalyst performance between Lewis acid platinum complexes of NUPHOS diphosphines and BINAP also extends to the addition of 1-methylcycloalkene to ethyl trifluoropyruvate, full details of which are presented for comparison in Table 4.

The absolute configuration of **7b** has been determined by hydrolysis to the free acid, **8b**, followed by a singe-crystal X-ray analysis of its (*S*)-1-naphthylethylammonium salt, **9b** (Scheme 4), the structure of which is shown in Figure 4. In the case of (1′*S*,2*R*)-**6c**/**7c** we were unable to isolate sufficient quantities to convert into the corresponding carboxylate salt for crystallization and X-ray structure determination. Fortunately, however, isomerization of a near-enantiopure sample of (1′*R*,2*R*)-**7b** in the presence of δ-**2c** resulted in clean and near-quantitative conversion to (1′*R*,2*R*)-**7c**, which was hydrolyzed to the free acid, **8c**, and successfully crystallized as the corresponding (*S*)-α-methylbenzylammonium salt, **9c** (Scheme 4 and Figure 5). As we know from GC and ^{1}H NMR spectroscopic analysis of the reaction mixture that (1′*R*,2*R*)-**7c** corresponds to the minor *endo* diastereoisomer resulting from regioselective activation of the α-CH_2 of 1-methylcyclohexene, the major *exo* diastereoisomer of **7c** must necessarily be (1′*R*,2*S*) or (1′*S*,2*R*). On the basis that (*S*)-BINAP and δ-NUPHOS favor addition to the *si* face of coordinated pyruvate to generate product with (*R*)-absolute configuration at the tertiary alcohol, we can confidently assign the absolute configuration of the major enantiomer of *exo*-**7c** as (1′*S*,2*R*). While the identity of **6d** and **7d** has been unequivocally established from ^{1}H/^{13}C NMR spectroscopy and mass spectrometry, the relative stereochemistry of the three stereocenters was confirmed by a single-crystal X-ray structure determination of **7d** (Figure 6), and on the basis that it arises from addition of **7b**, with (1′*R*,2*R*)-stereochemistry, to ethyl trifluoropyruvate, it is eminently reasonable to assign the configuration as (2*R*,3′*R*,1″*R*).

Finally, the ability of these catalysts to discriminate between substituents on unsymmetrical 1,1-disubstituted alkenes was explored. For this, we choose 2,4,4-trimethylpent-1-ene as the

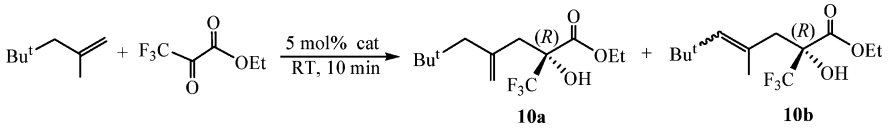
Table 4. Asymmetric Carbonyl-Ene Reaction between 1-Methylcycloalkane and Ethyl Trifluoropyruvate Catalyzed by λ-2a, δ-2b−d, and (*S*)-3 in CH_2Cl_2



entry[a]	catalyst (mol %)	*n*	conv (%)[b]	product ratio[c] **6** or **7** **a**:**b**:**c**:**d**	*exo*:*endo* ratio[d] **6** or **7** **b**	**c**	% ee[e] **6** or **7** **a**	**b**	**c**	% de[f,g] **6** or **7** **d**
1[h]	λ-**2a** (5)	1	100	0:80:19:0	>99:1	8:1		99	79, nd	
2	δ-**2b** (5)	1	65	1:63:36:0	>99:1	3:1	82	80	42, nd	
3	δ-**2c** (5)	1	100	0:75:21:4	>99:1	8:1		>99	93, 94	93
4	(*S*)-**3** (5)	1	99	4:75:16:5	>99:1	3:1	69	>99	96, 95	89
5[h]	λ-**2a** (5)	2	96	4:93:3:0	>99:1	2:1	66	98	88, 87	
6	δ-**2b** (5)	2	25	5:95:0:0	>99:1	2:1	35	93		
7	δ-**2c** (5)	2	98	4:95:1:0	>99:1	2:1	74	>99	92, 95	
8	(*S*)-**3** (5)	2	>99	2:91:7:0	<99:1	2:1	78	>99	99, 96	

[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, 10 min. [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 X-ray crystal analysis of (1′*R*,2*R*)-**9b**, (1′*R*,2*R*)-**9c**, or by analogy. [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. Relative configuration assigned by X-ray analysis and absolute configuration by analogy with **9b** and **9c**. [g]Minor enantiomers were not detected. [h]Opposite enantiomer of that shown in the table figure. Average of three runs.

Table 5. Asymmetric Carbonyl-Ene Reaction between 2,4,4-Trimethylpent-1-ene and Ethyl Trifluoropyruvate Catalyzed by λ-2a, δ-2b−d, and (*S*)-3 in CH_2Cl_2



entry[a]	catalyst (mol %)	time (min)	conv (%)[b]	product ratio[c] **10a**:**10b**	% ee (config)[d] **10a**
1	λ-**2a** (5)	10	>99	88:12	98[e]
2	δ-**2b** (5)	10	98	90:10	93
3	δ-**2c** (5)	10	>99	89:11	99
4	δ-**2d** (5)	10	99	91:9	94
5	(*S*)-**3** (5)	10	99	86:14	99

[a] Reaction conditions: 5 mol % catalyst, 2,2,4-trimethylpent-1-ene (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]Enantiomeric excess determined by chiral GC using a Supelco Beta DEX column. Absolute configuration assigned by analogy. [e]Opposite enantiomer of that shown in the table figure. Average of three runs.

substrate, which requires the catalyst·pyruvate complex to discriminate between a methyl and a neopentyl group. Each of the NUPHOS-based Lewis acids catalyzed the highly regioselective addition of 2,4,4-trimethylpent-1-ene to ethyl trifluoropyruvate to afford α-hydroxy ester **10a**, containing a terminal alkene rather than the more highly substituted alkene. As for all the other substrates investigated, δ-**2c** outperformed each of the other NUPHOS-based catalysts and gave α-hydroxyester **10a** in good yield, high regioselectivity, and excellent enantioselectivity.

Conclusions

This study has demonstrated that the performance of enantiopure Lewis acid platinum catalysts of conformationally flexible NUPHOS diphosphines can rival or outperform their atropisomeric BINAP counterpart in terms of conversion, enantioselectivity, diastereoselectivity, and regioselectivity of reaction. Catalyst performance was found to depend on the substitution pattern of the four-carbon NUPHOS tether, and that based on a 1,4-Et_2-cyclo-C_6H_8 tether was consistently the most efficient over the range of substrates investigated. Moreover, we have also established that the stereochemical integrity of these NUPHOS diphosphines is retained over extended periods since more challenging substrates requiring long reaction times (>20 h) gave good conversions and excellent ee's. Although NUPHOS diphosphines appear to behave in much the same manner as biaryl diphosphines and are prepared from inexpensive starting materials, it will be necessary to improve their synthesis if they are to compete with BINAP. The modular synthesis of these NUPHOS diphosphines will be used to fully optimize catalyst performance and to prepare chiral versions for a comparative study. Further studies are currently underway to develop more cost-effective resolution procedures and explore their applications in a range of late transition metal-catalyzed transformations.

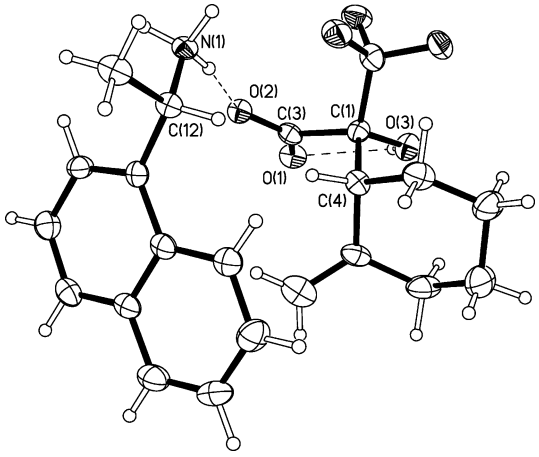


Figure 4. Asymmetric unit of (*S*)-1-(1-naphthyl)ethylammonium ethyl 3,3,3-trifluoro-2-hydroxy-2-(2′-methylenecyclohex-1′-yl)propanoate (**9b**) with 40% probability displacement ellipsoids showing the absolute stereochemistry of C(1) and C(4) to be both of *R*-configuration. Hydrogen bonds within the asymmetric unit are shown as dashed lines.

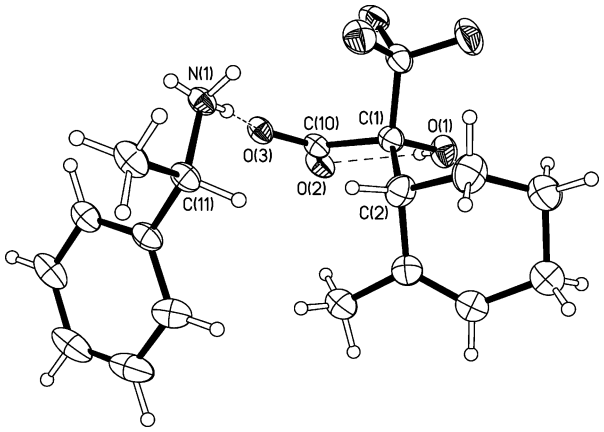


Figure 5. Asymmetric unit of (*S*)-α-methylbenzylammonium ethyl 3,3,3-trifluoro-2-hydroxy-2-(2′-methylcyclohex-2′-en-1′-yl)propanoate (**9c**) with 40% probability displacement ellipsoids showing the absolute stereochemistry of C(1) and C(2) to be both of *R*-configuration. Hydrogen bonds within the asymmetric unit are shown as dashed lines.

Experimental Section

General Comments. All manipulations involving air-sensitive materials were carried out using standard Schlenk line techniques under an atmosphere of nitrogen or argon in oven-dried glassware. Dichloromethane and dioxane were distilled from calcium hydride under an atmosphere of nitrogen. Ethyl trifluoropyruvate, allylmagnesium bromide, aryl bromides, allylbenzene, methylenecyclohexane, 1-methylcyclohexene, 1-methylcyclopentene, methylenecyclopentane, and 2,4,4-trimethylpent-1-ene were purchased from commercial suppliers and used without further purification. [{(*S*)-BINAP}$PtCl_2$] was prepared from [Pt(cycloocta-1,5-diene)Cl_2],[22] and λ- and δ-[(NUPHOS)$PtCl_2$],[13f] 1-allyl-4-nitrobenzene,[19] and 1,2,3,4-Ph_4-NUPHOS[12b] were prepared as previously described. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a JEOL LAMBDA 500 or a Bruker AMX 300 instrument. Optical rotations were measured on a Optical Activity PolAAr 2001 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]^{20}_D$ (*c* g/100 mL, solvent). Thin-layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel 60F 254, and column chromatography was performed using Merck Kieselgel 60. Gas chromatography was performed on a Shimadzu 2010 series gas chromatograph equipped with a split-mode capillary injection system and flame ionization detection using a Supelco Beta DEX column.

(22) Drew, D.; Doyle, J. R. *Inorg. Synth.* **1990**, *28*, 346.

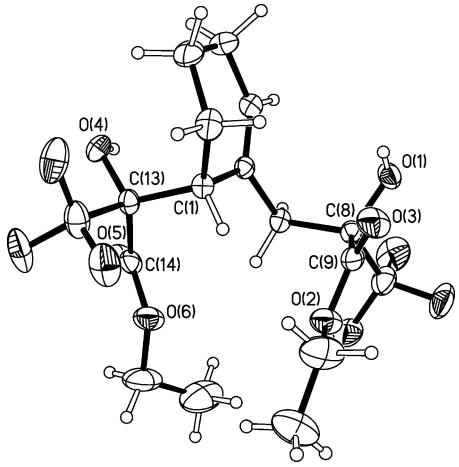


Figure 6. Asymmetric unit of (2*S*,3′*S*,1″*S*)-ethyl 2-(trifluoromethyl)-2-hydroxy-3-[3′-(1″-ethoxycarbonyl-2″,2″,2″-trifluoro-1″-hydroxyethyl)cyclohex-1′-en-2′-yl]propanoate (**7d**) showing the relative stereochemistry of the three stereocenters.

General Procedure for the Synthesis of Allylbenzene Derivatives 4b−g. A flame-dried Schlenk flask was charged with $Pd_2(dba)_3$ (52 mg, 0.057 mmol), 1,2,3,4-Ph_4-NUPHOS (83 mg, 0.114 mmol), and dioxane (10 mL). The resulting red solution was stirred for 30 min at room temperature, after which time the aryl bromide (11.4 mmol) was added followed by allylmagnesium bromide (12.5 mL, 1.0 M in diethyl ether, 12.5 mmol), in a dropwise manner. The flask was fitted with a reflux condenser and heated at 80 °C for 16 h. The resulting mixture was quenched by slow addition of 10% $HCl_{(aq)}$ (40 mL) and the product extracted into diethyl ether (3 × 20 mL). The organic phases were combined and dried over $MgSO_4$, and the solvent was removed to leave a yellow-brown oil, which was purified by column chromatography (SiO_2, 100% hexane) to afford the desired product as a colorless oil.

General Procedure for Platinum-Catalyzed Carbonyl-Ene Reactions between Allyl Benzene Derivatives and Ethyl Trifluoropyruvate. A flame-dried Schlenk flask charged with λ- or δ-[(NUPHOS)$PtCl_2$] (0.02 mmol), $AgSbF_6$ (15.0 mg, 0.044 mmol), and CH_2Cl_2 (2.0 mL) was stirred at room temperature for 30 min, after which time ethyl trifluoropyruvate (80.0 μL, 0.6 mmol) was added followed by the allylbenzene derivative (0.4 mmol). The resulting mixture was stirred for a further 60 min, after which time the solution was flushed through a short plug of silica with CH_2Cl_2, the solvent removed, and the resulting residue purified by column chromatography, eluting with hexane/CH_2Cl_2. The products were analyzed by ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis, and the enantiomeric excess was determined by chiral GC.

General Procedure for Platinum-Catalyzed Carbonyl-Ene Reactions between Methylenecycloalkane and Ethyl Trifluoropyruvate. In a typical procedure a solution of λ- or δ-[(NUPHOS)$PtCl_2$] (0.02 mmol) in dichloromethane (2.0 mL) was treated with $AgSbF_6$ (15.0 mg, 0.044 mmol) and stirred at room temperature for 30 min. Following this, ethyl trifluoropyruvate (80.0 μL, 0.6 mmol) and methylenecyclohexane (48.0 μL, 0.4 mmol) were added. The resulting mixture was stirred for a further 10 min, after which time the solution was filtered through a short plug of silica with CH_2Cl_2, the solvent removed, and the resulting residue purified by column chromatography, eluting with hexane/CH_2Cl_2 (3:2). Each of the products was analyzed by ^1H and ^{13}C NMR spectroscopy, and the data were compared with those previously reported.[14] Enantiomeric excesses were determined by chiral GC as previously described.

Table 6. Summary of Crystal Data and Structure Determination for Compounds 9b, 9c, and 7d

	9b	9c	7d
formula	$C_{12}H_{14}N^+ \cdot C_{10}H_{12}F_3O_3^-$	$C_8H_{12}N^+ \cdot C_{10}H_{12}F_3O_3^-$	$C_{17}H_{22}F_6O_6$
M_r	409.4	359.4	436.4
cryst syst	orthorhombic	monoclinic	orthorhombic
space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$
a, Å	6.862(10)	11.2711(19)	8.6828(18)
b, Å	12.46(2)	6.6473(11)	11.9631(8)
c, Å	24.04(4)	13.145(2)	19.144(3)
β, deg	90	114.252(2)	90
V, Å^3	2056(6)	897.9(3)	1988.5(6)
Z	4	2	4
no. of reflns measd	15 004	9030	36 858
no. of unique reflns	2072	4854	2591
R_{int} (on F^2)	0.110	0.035	0.058
no. of params	280	243	273
R^a [$F^2 > 2\sigma(F^2)$]	0.066	0.065	0.053
$R_w{}^b$ (all data)	0.150	0.194	0.149
GOF^c (S)	1.115	1.045	1.162
max., min. diff map, e Å^{-3}	0.37, −0.34	0.46, −0.34	0.37, −0.30

[a] Conventional $R = \sum||F_o| - |F_c||/\sum|F_o|$ for "observed" reflections having $F_o^2 > 2\sigma(F_o^2)$. [b] $R_w = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$ for all data. [c] GOF = $[\sum w(F_o^2 - F_c^2)^2/(\text{no. unique reflns - no. of params})]^{1/2}$.

Crystal Structure Determinations of 9b, 9c, and 7d. Crystal data are given in Table 6 for **9b**, **9c**, and **7d**. Data for **9b** and **7d** were collected with Mo Kα radiation at 150 K on a Nonius KappaCCD diffractometer, while those for **9c** required synchrotron radiation ($\lambda = 0.6911$ Å) at 120 K, using a Bruker APEX2 diffractometer at Daresbury Laboratory SRS. Procedures for data reduction, structure solution, and refinement were standard. In the absence of significant anomalous scattering effects, Friedel pairs were averaged, and the absolute configuration of each structure was assigned on the basis of known chiral centers and the chemical synthesis. Hydrogen atoms involved in hydrogen bonding were refined freely (but with geometrical restraints for **9c**), while other H atoms were constrained with a riding model.

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Supporting Information Available: Full details of experimental procedures, characterization data, and representative NMR spectra for compounds **4b**−**h**, **5b**−**h**, **8b**, **8c**, **9b**, and **9b** and for compounds **7d**, **9b**, and **9c**, details of crystal data, structure solution and refinement, atomic coordinates, bond distances, bond angles, and anisotropic displacement parameters in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org. Observed and calculated structure factor tables are available from the authors upon request.

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